(19)日本国特許庁(JP)　(12)公表特許公報(A)　(11)特許出願公表番号
特表2005-501840
(P2005-501840A)
(43)公表日　平成17年1月20日(2005.1.20)

(51)Int.Cl.[7]	F I		テーマコード（参考）
A61K 31/4709	A61K	31/4709	4B024
A61P 1/00	A61P	1/00	4B063
A61P 1/18	A61P	1/18	4C050
A61P 11/00	A61P	11/00	4C086
A61P 15/00	A61P	15/00	

審査請求 未請求　予備審査請求 有　（全 355 頁）　最終頁に続く

(21)出願番号	特願2003-518546(P2003-518546)
(86)(22)出願日	平成14年7月23日(2002.7.23)
(85)翻訳文提出日	平成16年1月23日(2004.1.23)
(86)国際出願番号	PCT/EP2002/008218
(87)国際公開番号	WO2003/013537
(87)国際公開日	平成15年2月20日(2003.2.20)
(31)優先権主張番号	01117608.8
(32)優先日	平成13年7月23日(2001.7.23)
(33)優先権主張国	欧州特許庁(EP)
(31)優先権主張番号	02011710.7
(32)優先日	平成14年5月24日(2002.5.24)
(33)優先権主張国	欧州特許庁(EP)

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(54)【発明の名称】癌の改良された治療のための手段および方法

(57)【要約】
本発明は、本発明によるポリヌクレオチドを含む第１、第２、第３および／または第４の変異対立遺伝子をもつ遺伝子型を有する患者において結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌の治療に用いる医薬組成物を調製するためのイリノテカンまたはその誘導体の使用に関する。好ましくは、これらのポリヌクレオチドが含むヌクレオチドの欠失、付加および／または置換は、対応する野生型対立遺伝子と比較して第１、第２、第３および／または第４の変異対立遺伝子の発現を変化させ、あるいは対応する野生型対立遺伝子がコードするポリペプチドと比較してこれらの対立遺伝子がコードするポリペプチドの活性を変化させる。最後に、本発明は、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌または膵癌を患う対象に適した療法を選択する方法に関する。

【特許請求の範囲】
【請求項１】
下記のものよりなる群から選択されるポリヌクレオチドを含む第１の変異対立遺伝子をもつゲノムを有する対象において結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌の治療に用いる医薬組成物を調製するための、イリノテカンまたはその誘導体の使用：
（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：
【化１】

SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422, 425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482, 485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 および／または 641;

（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６０６、６０８、６１０、６１２、６１８、６２０、６２２、６２４および／または６２８のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）多剤耐性１（ＭＤＲ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって、下記の位置に対応する位置において少なくとも１個のヌクレオチドの置換または欠失を有するポリヌクレオチド：
ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の
【化２】

位置 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619

および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の
【化３】

位置 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162

および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１、３０８、
および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１３７、１７６；
（ｄ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８３９４６、７０２００、７０２３７、６５２４１、および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１および／または、ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４１５２９、１７４９０１、１３９１７７、１４０１１８、１４０５６８、１４０７２７、１３９４７９に対応する位置にＡを；ＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置３０８および／または、ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８４７０１、８３９７３、８

４０７４、８４１１９、７８１７０、７０２０４、７０２５３、７０３７１、５０５３７、４３１６２、および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１３７または１７６、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４５９８４、１７１４６６、１７５０６８、１７５０７４、１３９０６４、１３９２７６、１４０５７６に対応する位置にＴを；ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４０８３７、１７１４０４、１７１４５６、１７１５１１、１７１５１２、１３９１１９、１４０４９０、１３９６１９、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置４３２６３に対応する位置にＣを；ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８４０３２、７７８１１、７３２５２、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４１５９０、１７５１４２、１７５１８０、１３９０１５、１４０２１６、１４０５９５に対応する位置にＧを有するポリヌクレオチド；

（ｅ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置２１、１０３、１６８、４００、８９３、９９９、１００１、１１０７および／または１１４１に対応する位置においてアミノ酸置換を含む；

（ｆ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置２１に対応する位置におけるＡｓｎからＡｓｐへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１０３に対応する位置におけるＰｈｅからＬｅｕへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１６８に対応する位置におけるＶａｌからＩｌｅへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００に対応する位置におけるＳｅｒからＡｓｎへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置８９３に対応する位置におけるＡｌａからＳｅｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置９９９に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１００１に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１０７に対応する位置におけるＧｌｎからＰｒｏへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１４１に対応する位置におけるＳｅｒからＴｈｒへの置換。

【請求項２】

対象が、下記のものよりなる群から選択されるポリヌクレオチドを含む第２の変異対立遺伝子をもつゲノムを有する、請求項１に記載の使用：

（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：

【化４】

SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 および／または 334;

（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６００、６０２および／または６０４のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；

（ｃ）多剤耐性タンパク質１（ＭＲＰ１）遺伝子にハイブリダイズしうるポリヌクレオチ

ドであって、ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５７９９８、５７８５３、５３２８２および／または３９５０８に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６６７、１３７６４７、１３７７１０、１２４６６７および／または３８６４６に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７２５８、２７１５９、３４２１８、３４２１５、５５４７２および／または３４２０６－３４２０７に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置２１１３３、１４００８、１８０６７、１７９７０および／または１７９００に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置７９、８８および／または２４９に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５および／または２５９に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２５２７７）の位置１５０７２７および／または３３５５１に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２８）の位置１７４に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２４８および／または２５８に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１８８４、１６２５、１１６３、３８１、２３３、１８９、４４０および／または１７２０－１７２３に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７および／または４３７／４３８に対応する位置における少なくとも１個のヌクレオチドの挿入；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置５５１５６／５５１５７に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド；

（ｄ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置２１１３３、１４００８および／または１８１９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７２５８および／または３４２１８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置７９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５７９９８および／または５７８５３に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６６７および／または１３７６４７に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２５２７７）の位置１５０７２７および／または３３５５１に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２４８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１８８４、１６２５、２３３および／または１８９に対応する位置にＡを；ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置３９５０８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１７９００、１８０６７および／または１８１９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２８）の位置１７４に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置４４０および／または１１６３に対応する位置にＴを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置８８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７１５９、５５４７２および／または３４２１５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７および／または３８６４６に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５３２８２に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７７１０に対応する位置にＣを；ＭＲ

Ｐ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２５８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１に対応する位置にＧを；ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１７９７０に対応する位置におけるＴの欠失を；あるいは、ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置３４２０６－３４２０７に対応する位置におけるＡＴの欠失を；あるいは、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１７２０－１７２３に対応する位置においてＧＧＴＡの欠失を；ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置におけるＴの挿入および／またはその位置４３７／４３８に対応する位置におけるＴＣＣＴＴＣＣの挿入を；ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置５５１５６／５５１５７に対応する位置におけるＴＧＧＧＧＣの挿入を有するポリヌクレオチド；

（ｅ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置２３９に対応する位置におけるＰｈｅからＣｙｓへの置換；または／およびＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置４３３に対応する位置におけるＡｒｇからＳｅｒへの置換；または／およびＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置７２３に対応する位置におけるＡｒｇからＧｌｎへの置換。

【請求項３】

対象が、下記のものよりなる群から選択されるポリヌクレオチドを含む第３の変異対立遺伝子をもつゲノムを有する、請求項１または２に記載の使用：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：１３７、１３８、１４１、１４２、１４５、１４６、１４９および／または１５０のいずれか１つの核酸配列を有するポリヌクレオチド；

（ｂ）シトクロムＰ４５０サブファミリーＩＩＩＡ（ニフェジピンオキシダーゼ）ポリペプチド５（ＣＹＰ３Ａ５）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８および／または９７３６に対応する位置における少なくとも１個のヌクレオチドの置換、あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１および／または１４５９２９に対応する位置における少なくとも１個のヌクレオチドの置換を有するポリヌクレオチド；

（ｃ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８に対応する位置にＣを；ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１および／または１４５９２９に対応する位置にＧを；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置９７３６に対応する位置にＧを有するポリヌクレオチド。

【請求項４】

対象が、下記のものよりなる群から選択されるポリヌクレオチドを含む第４の変異対立遺伝子をもつゲノムを有する、請求項１～３のいずれか一項に記載の使用：

（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：

【化５】

SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 および／または 134;

（ｂ）下記のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレ

オチド：
【化６】

SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550,
552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578,
580, 582, 584, 586, 588, 590, 592, 594, 596 および／または 598;

（ａ）ウリジン二リン酸グリコシルトランスフェラーゼ１メンバーＡ１（ＵＧＴ１Ａ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５９、１６０、２２６、５３９、５４４、６４０、７０１、８４１、８５５、８９０、９３８、１００６、１００７、１０２０、１０８４、１０８５、１１１４、１１１７、１１３９、１１５８、１１７５－１１７６、１２１６、１２９７、１３２４、１４７１、１４７８、３７２－３７３、５２３－５２５および／または８９２－９０５に対応する位置における少なくとも１個のヌクレオチドの置換または欠失、あるいは、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置４７０／４７１および／または１２２２／１２２３に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド；
（ｂ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置２２６、５３９、７０１、８５５、９３８、１０２０および／または１１１７に対応する位置にＡを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１６０、６４０、８９０、１００６、１０８４、１１３９、１１７６、１３２４および／または１４７８に対応する位置にＴを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５４４、８４１および／または１２１６に対応する位置にＣを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：１８１３０３）の位置５９、１００７、１０８５、１１１４、１１５８、１１７５、１２９７および／または１４７１に対応する位置にＧを；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置３７２－３７３に対応する位置におけるＣＴの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５２３－５２５に対応する位置におけるＴＴＣの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置８９２－９０５に対応する位置におけるＴＡＣＡＴＴＡＡＴＧＣＴＴＣの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置４７０／４７１に対応する位置におけるＴの挿入を；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１２２２／１２２３に対応する位置におけるＧの挿入を有するポリヌクレオチド；
（ｃ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１５に対応する位置におけるＬｅｕからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置７１に対応する位置におけるＧｌｙからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１７５に対応する位置におけるＬｅｕからＧｌｎへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１７７に対応する位置におけるＣｙｓからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２０９に対応する位置におけるＡｒｇからＴｒｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２２９に対応する位置におけるＰｒｏからＧｌｎへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２７６に対応する位置におけるＧｌｙからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９２に対応する位置におけるＡｌａからＶａｌへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９３に対応する位置におけるＴｙｒからＴｒｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３０８に対応する位置における

ＧｌｙからＧｌｕへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３３１に対応する位置におけるＧｌｎからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３５７に対応する位置におけるＧｌｎからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３６７に対応する位置におけるＡｒｇからＧｌｙへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３６８に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３８７に対応する位置におけるＰｒｏからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３７５に対応する位置におけるＳｅｒからＰｈｅへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３８１に対応する位置におけるＳｅｒからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４０１に対応する位置におけるＡｌａからＰｒｏへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４２８に対応する位置におけるＬｙｓからＧｌｕへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４８６に対応する位置におけるＴｙｒからＡｓｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４８８に対応する位置におけるＳｅｒからＰｈｅへの置換；

（ｄ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置３７２－３７３に対応する位置におけるＣＴの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１１９に対応する位置におけるアミノ酸Ａｓｐに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置４７０／４７１に対応する位置にＴの挿入を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１５２に対応する位置におけるアミノ酸Ｐｒｏに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置５２３－５２５に対応する位置におけるＴＴＣの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１６８に対応する位置におけるアミノ酸Ｔｈｒに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置８９２－９０５に対応する位置におけるＴＡＣＡＴＴＡＡＴＧＣＴＴＣの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９２に対応する位置におけるアミノ酸Ａｌａに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置１２２２／１２２３に対応する位置におけるＧの挿入を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４０２に対応する位置におけるアミノ酸Ｌｙｓに続く１個以上のアミノ酸が置換、付加および／または欠失するポリヌクレオチド；および

（ｅ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリヌクレオチドはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置４９に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換；および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置２８０に対応する位置におけるＣｙｓから終止コドンへのアミノ酸置換；および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３３１に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換；および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３３５に対応する位置におけるＴｒｐから終止コドンへのアミノ酸置換；および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３５７に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換；および／またはＵＧＴ１Ａ１遺伝子（寄託番号：

Ｇ８８５０２３６）の位置４３７に対応する位置におけるＬｙｓから終止コドンへのアミノ酸置換を含む。
【請求項５】
ポリヌクレオチドが含むヌクレオチドの欠失、付加および／または置換により、対応する野生型対立遺伝子と比較して第１、第２、第３および／または第４の変異対立遺伝子の発現が変化する、請求項１～４のいずれか一項に記載の使用。
【請求項６】
発現の変化が、発現の低下または増大である、請求項５に記載の使用。
【請求項７】
ポリヌクレオチドが含むヌクレオチドの欠失、付加および／または置換により、対応する野生型対立遺伝子がコードするポリペプチドと比較して第１、第２、第３および／または第４の変異対立遺伝子がコードするポリペプチドの活性が変化する、請求項１～７のいずれか一項に記載の使用。
【請求項８】
活性の変化が、活性の低下または増強である、請求項６に記載の使用。
【請求項９】
対象が動物である、請求項１～８のいずれか一項に記載の使用。
【請求項１０】
対象がマウスである、請求項９に記載の使用。
【請求項１１】
対象がヒトである、請求項１～８のいずれか一項に記載の使用。
【請求項１２】
ヒトがアフリカ人種またはアジア人種である、請求項１１に記載の使用。
【請求項１３】
結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、および膵癌を患う対象に適切な療法を選択するための、下記を含む方法：
（ａ）対象から得た試料中の対象のゲノム中における、請求項１～４のいずれか一項に特定した第１、第２、第３および／または第４の変異対立遺伝子の存在または不存在を判定し；そして
（ｂ）（ａ）において得た結果に基づいてその対象に適切な療法を選択すること。
【請求項１４】
癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：
（ａ）患者の遺伝子型をアッセイして、その患者がＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有するかを判定し；そして
（ｂ）前記２以上の遺伝子のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量のイリノテカンをその患者に投与するが、この量は、前記２以上の遺伝子における患者の対立遺伝子を考慮せずに投与する量と比較して増大または減少されること。
【請求項１５】
患者がイリノテカンによる治療に対する中毒反応のリスクを有するかを判定する方法であって、ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子を含む２以上の遺伝子の１以上の変異対立遺伝子を患者が有するかを判定することを含む方法。
【請求項１６】
癌を患う患者にイリノテカンを投与するのに最適な治療方式を判定するための、下記を含む方法：
（ａ）その患者が、ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有するかを判定し；

（ｂ）前記２以上の遺伝子それぞれの１以上のそのような変異対立遺伝子を有する患者において、前記２以上の遺伝子における患者の対立遺伝子を考慮せずにイリノテカンを投与する場合の患者におけるピーク量と比較して、その患者におけるイリノテカンのピーク量を低下させるように方式を変更すること。

【請求項１７】

ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有する患者において癌を治療する方法であって、これら２以上の遺伝子の遺伝子生成物の発現レベルが一般集団のものより低いためイリノテカンに対する高い感受性を示す場合は、その患者に減少された量のイリノテカンを投与することを含む方法。

【請求項１８】

ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有する患者において癌を治療する方法であって、これら２以上の遺伝子の遺伝子生成物の発現レベルが一般集団のものより高いためイリノテカンに対する耐性または耐性素質を示す場合は、その患者に増大された量のイリノテカンを投与することを含む方法。

【請求項１９】

患者において癌を治療する方法であって、患者に有効量のイリノテカンを内部投与することを含み、その際、患者のＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５およびＵＧＴ１Ａ１を含む遺伝子の遺伝子型に基づいて治療方式を改変する方法。

【請求項２０】

癌を患う患者集団を治療するための、下記を含む方法：

（ａ）患者毎に、ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子をその患者が有するかを判定し；

（ｂ）前記２以上の遺伝子の１以上のそのような変異対立遺伝子を有する患者において、そのような対立遺伝子を有する患者の治療に十分な量であって、患者の前記２以上の遺伝子の対立遺伝子を考慮しない場合の量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【請求項２１】

癌を患う患者においてイリノテカンに対する感受性を予測する方法であって、その患者がＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有するかを判定することを含み、これらの対立遺伝子は癌細胞がこれら２以上の遺伝子のタンパク質を低い量または高い量で発現することの指標であり、これにより低発現はイリノテカンに対する感受性が高いことの指標となり、高発現はイリノテカンに対する耐性または耐性素質の指標となる方法。

【請求項２２】

癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＭＤＲ１遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者のＭＤＲ１遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【請求項２３】

癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＭＲＰ１遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺

伝子を有する患者の治療に十分な量であって、患者のＭＲＰ１遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【請求項２４】

癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＵＧＴ１Ａ１遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者のＵＧＴ１Ａ１遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【請求項２５】

癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＣＹＰ３Ａ５遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者のＣＹＰ３Ａ５遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【発明の詳細な説明】

【技術分野】

【０００１】

本発明は、本発明によるポリヌクレオチドを含む第１、第２、第３および／または第４の変異対立遺伝子をもつ遺伝子型を有する患者における結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌の治療に用いる医薬組成物を調製するための、カンプトテシン系薬物、たとえばイリノテカン（ＣＰＴ－１１）またはその誘導体の使用に関する。好ましくは、これらのポリヌクレオチドが含むヌクレオチドの欠失、付加および／または置換により、対応する野生型対立遺伝子と比較して第１、第２、第３および／または第４の変異対立遺伝子の発現が変化し、あるいは対応する野生型対立遺伝子がコードするポリペプチドと比較して前記変異対立遺伝子がコードするポリペプチドの活性が変化する。最後に、本発明は、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌または膵癌を患う対象に適した療法を選択する方法に関する。

【背景技術】

【０００２】

イリノテカンは、東洋の樹木カンプトテカ・アキュミナタ（Ｃａｍｐｔｏｔｈｅｃａ ａｃｕｍｉｎａｔａ）から得られる細胞毒性アルカロイドである、カンプトテシン（ＣＰＴ）の半合成類似体である。カンプトテシンは、可逆的な一本鎖破断を誘発することによりＤＮＡのねじれ歪を解消する酵素トポイソメラーゼＩを特異的に阻害することにより、抗新生物活性を示す［Ｄ’Ａｒｐａ，ｅｔ ａｌ．，１９８９，Ｂｉｏｃｈｉｍ Ｂｉｏｐｈｙｓ Ａｃｔａ ９８９：１６３－７７；Ｈｏｒｗｉｔｚ，ｅｔ ａｌ．，１９７３，Ｃａｎｃｅｒ Ｒｅｓ ３３：２８３４－６］。イリノテカンおよびその活性代謝産物ＳＮ－３８はトポイソメラーゼ１－ＤＮＡ複合体に結合し、これらの一本鎖断片の再結合を阻止する［Ｋａｗａｔｏ，ｅｔ ａｌ．，１９９１，Ｃａｎｃｅｒ Ｒｅｓ ５１：４１８７－９１］。イリノテカンは、カンプトテシン部分とジピペリジノ側鎖の間のカルバメート結合がカルボキシエステラーゼの仲介により開裂することによってイリノテカンから形成される親油性の代謝産物ＳＮ－３８（７－エチル－１０－ヒドロキシカンプトテシン）の水溶性プロドラッグとして作用する［Ｔｓｕｊｉ，ｅｔ ａｌ．，１９９１，Ｊ Ｐｈａｒｍａｃｏｂｉｏｄｙｎ １４：３４１－９］。カルボキシエステラーゼ－２は、薬理学的濃度でこの加水分解に関与する主要な酵素である［Ｈｕｍｅｒｉｃｋｈｏｕｓｅ，ｅｔ ａｌ．，２０００，Ｃａｎｃｅｒ Ｒｅｓ ６０：１１８９－９２］。トポイソメ

ラーゼの阻害およびイリノテカン関連の一本鎖破断は、主にＳＮ－３８により起きる［Ｋａｗａｔｏ，ｅｔ ａｌ．，１９９１，Ｃａｎｃｅｒ Ｒｅｓ ５１：４１８７－９１］。イリノテカンを投与すると、げっ歯類由来の癌を有するマウスおよび組織学的に種々のタイプのヒト癌異種移植片において抗腫瘍活性が生じた［Ｆｕｒｕｔａ，ｅｔ ａｌ．，１９８８，Ｇａｎ Ｔｏ Ｋａｇａｋｕ Ｒｙｏｈｏ １５：２７５７－６０；Ｇｉｏｖａｎｅｌｌａ，ｅｔ ａｌ．，１９８９，Ｓｃｉｅｎｃｅ ２４６：１０４６－８；Ｇｉｏｖａｎｅｌｌａ，ｅｔ ａｌ．，１９９１，Ｃａｎｃｅｒ Ｒｅｓ ５１：３０５２－５；Ｈａｗｋｉｎｓ，１９９２，Ｏｎｃｏｌｏｇｙ（Ｈｕｎｔｉｎｇｔ）６：１７－２３；Ｋｕｎｉｍｏｔｏ，ｅｔ ａｌ．，１９８７，Ｃａｎｃｅｒ Ｒｅｓ ４７：５９４４－７］。

【０００３】

イリノテカンはＣＹＰ３Ａ４およびＣＹＰ３Ａ５によっても酸化される［Ｈａａｚ，ｅｔ ａｌ．，１９９８，Ｄｒｕｇ Ｍｅｔａｂ Ｄｉｓｐｏｓ ２６：７６９－７４；Ｋｕｈｎ，１９９８，Ｏｎｃｏｌｏｇｙ（Ｈｕｎｔｉｎｇｔ）１２：３９－４２；Ｓａｎｔｏｓ，ｅｔ ａｌ．，２０００，Ｃｌｉｎ Ｃａｎｃｅｒ Ｒｅｓ ６：２０１２－２０；Ｒｉｖｏｒｙ，ｅｔ ａｌ．，１９９６，Ｃａｎｃｅｒ Ｒｅｓ ５６：３６８９－９４］。ＳＮ－３８の主な排出経路は、グルクロン酸と抱合して対応するグルクロニド（ＳＮ－３８Ｇ）を形成するものである［Ａｔｓｕｍｉ，ｅｔ ａｌ．，１９９１，Ｘｅｎｏｂｉｏｔｉｃａ ２１：１１５９－６９］。ＳＮ－３８Ｇは腸内細菌叢により脱抱合されてＳＮ－３８を形成すると報告されている［Ｋａｎｅｄａ，ｅｔ ａｌ．，１９９０，Ｃａｎｃｅｒ Ｒｅｓ ５０：１７１５－２０］。ＳＮ－３８のグルクロン酸抱合は、ＵＧＴ１Ａ１およびＵＧＴ１Ａ７により仲介される［Ｌｙｅｒ，ｅｔ ａｌ．，１９９８，Ｊ Ｃｌｉｎ Ｉｎｖｅｓｔ １０１：８４７－５４；Ｃｉｏｔｔｉ，ｅｔ ａｌ．，１９９９，Ｂｉｏｃｈｅｍ Ｂｉｏｐｈｙｓ Ｒｅｓ Ｃｏｍｍｕｎ ２６０：１９９－２０２］。物質収支検討により、全投与量の６４％は糞便中へ排出されることが証明され、胆汁中排出がもつ重要な役割が確認された［Ｓｌａｔｔｅｒ，ｅｔ ａｌ．，２０００，Ｄｒｕｇ Ｍｅｔａｂ Ｄｉｓｐｏｓ ２８：４２３－３３］。以下のことが検討により示唆されている：多剤耐性タンパク質１（ＭＲＰ１）は、イリノテカンおよびその代謝産物の主要なトランスポーターであり［Ｋｕｈｎ，１９９８，Ｏｎｃｏｌｏｇｙ（Ｈｕｎｔｉｎｇｔ）１２：３９－４２；Ｃｈｅｎ，ｅｔ ａｌ．，１９９９，Ｍｏｌ Ｐｈａｒｍａｃｏｌ ５５：９２１－８；Ｃｈｕ，ｅｔ ａｌ．，１９９７，Ｃａｎｃｅｒ Ｒｅｓ ５７：１９３４－８；Ｃｈｕ，ｅｔ ａｌ．，１９９７，Ｊ Ｐｈａｒｍａｃｏｌ Ｅｘｐ Ｔｈｅｒ ２８１：３０４－１４］、それらの胆汁中排出を促進し、そこでそれらは副作用を引き起こすが、Ｐ糖タンパク質もイリノテカンの排出に関与する［Ｃｈｕ，ｅｔ ａｌ．，１９９８，Ｃａｎｃｅｒ Ｒｅｓ ５８：５１３７－４３；Ｃｈｕ，ｅｔ ａｌ．，１９９９，Ｄｒｕｇ Ｍｅｔａｂ Ｄｉｓｐｏｓ ２７：４４０－１；Ｃｈｕ，ｅｔ ａｌ．，１９９９，Ｊ Ｐｈａｒｍａｃｏｌ Ｅｘｐ Ｔｈｅｒ ２８８：７３５－４１；Ｍａｔｔｅｒｎ，ｅｔ ａｌ．，１９９３，Ｏｎｃｏｌ Ｒｅｓ ５：４６７－７４；Ｈｏｋｉ，ｅｔ ａｌ．，１９９７，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ４０：４３３－８；Ｓｕｇｉｙａｍａ，ｅｔ ａｌ．，１９９８，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ４２：Ｓ４４－９］。

【０００４】

カンプトテシンに対する細胞の耐性、および、かくしてイリノテカンに対する療法応答は、細胞内カルボキシエステラーゼ活性およびトポイソメラーゼＩの開裂活性に関連づけられた［ｖａｎ Ａｒｋ－Ｏｔｔｅ，ｅｔ ａｌ．，１９９８，Ｂｒ Ｊ Ｃａｎｃｅｒ ７７：２１７１－６；Ｇｕｉｃｈａｒｄ，ｅｔ ａｌ．，１９９９，Ｂｒ Ｊ Ｃａｎｃｅｒ ８０：３６４－７０］。

【０００５】

そのようなカンプトテシン系薬物、たとえばイリノテカンの使用は、明らかに用量依存性である骨髄抑制および胃腸毒性によって制限される。これらには吐き気、嘔吐、腹痛およ

び下痢が含まれ、これらの副作用は致命的となる可能性がある。イリノテカン療法の用量を制限する主な毒性は下痢であり、これは最高８８％の患者に起き、腸内ＳＮ－３８蓄積に依存する［ｖａｎ　Ａｒｋ－Ｏｔｔｅ，ｅｔ　ａｌ．，１９９８，Ｂｒ　Ｊ　Ｃａｎｃｅｒ　７７：２１７１－６；Ｇｕｉｃｈａｒｄ，ｅｔ　ａｌ．，１９９９，Ｂｒ　Ｊ　Ｃａｎｃｅｒ　８０：３６４－７０；Ａｒａｋｉ，ｅｔ　ａｌ．，１９９３，Ｊｐｎ　Ｊ　Ｃａｎｃｅｒ　Ｒｅｓ　８４：６９７－７０２］；これはＳＮ－３８の胆汁中排出により二次的に起きるものであり、その程度はＳＮ－３８のグルクロン酸抱合により決まる［Ｇｕｐｔａ，ｅｔ　ａｌ．，１９９４，Ｃａｎｃｅｒ　Ｒｅｓ　５４：３７２３－５；Ｇｕｐｔａ，ｅｔ　ａｌ．，１９９７，Ｊ　Ｃｌｉｎ　Ｏｎｃｏｌ　１５：１５０２－１０］。骨髄抑制は、イリノテカンおよびＳＮ－３８両方の濃度－時間曲線下面積に相関していた［Ｓａｓａｋｉ，ｅｔ　ａｌ．，１９９５，Ｊｐｎ　Ｊ　Ｃａｎｃｅｒ　Ｒｅｓ　８６：１０１－１０］。

【０００６】

イリノテカンは、５－フルオロウラシル療法に不応性の転移性結腸直腸癌を患う患者について１９９７年に承認されたが、その療法有益性にはなお疑問がある。最近、国立癌研究所（ＮＣＩ）は、結腸直腸癌に関する２０００人以上の患者に係わる２つの大規模な臨床試験を、ほぼ3倍高いイリノテカン毒性関連死亡率のため、治療の最初の６０日以内で取りやめなければならなかった。死因は下痢と嘔吐に関連する脱水症状および好中球減少関連の敗血症であった［２００１，ａｒｚｎｅｉ－ｔｅｌｅｇｒａｍｍ　３２：５８］。当時イリノテカンは癌自体に有効であることが証明されていたが、短期毒性のため必ずしもすべての患者が長期生存の利益を受けることができるわけではない。したがって、イリノテカン毒性を被る可能性が最も高い患者を同定することが強く望まれている。

【０００７】

現在、患者は大部分の場合、最初はイリノテカン６０～１２５ｍｇ／ｍ^{2}の標準量を他の抗新生物薬と併用して週ごとの投薬で３～４回を数コース投与するという治療計画に従って治療され、治療に対する各患者の耐容性に基づいて後続量を２５～５０ｍｇ／ｍ^{2}漸増量に調整する。イリノテカン関連毒性から回復できるように治療を１～２週間遅らせてもよく、患者が回復していない場合は療法を中止しなければならない。非耐容性毒性が発現しない場合、患者に臨床的有益性がある限り、追加コースの治療を不定期間継続する。応答率は、腫瘍タイプに応じて１０％未満からほぼ９０％まで変動する。しかし、療法応答を評価して代替法を考慮するには少なくとも６～８週間はかかる。このように、その患者に対する適正な投与量を見いだすのは長たらしく、時間がかかり、致命的な有害作用のリスクを生じる。治療による利益のない患者は不必要にこのリスクを受ける可能性があり、さらに、これら患者が適切な治療を受ける前に貴重な時間が浪費される。

【０００８】

さらに、多くの化学療法薬にみられるように、細胞がイリノテカンなどの化学療法薬に最適量を下回る量で曝露されると、療法に対する細胞耐性を発現するリスクは高まる。

胆汁中排出の（たとえばＭＲＰおよびＰ糖タンパク質の）阻害薬およびＵＧＴ１Ａ１の誘発薬による薬物動態調節が、カンプトテシン関連毒性を低下させる手段として示唆された［Ｇｕｐｔａ，ｅｔ　ａｌ．，１９９６，Ｃａｎｃｅｒ　Ｒｅｓ　５６：１３０９－１４；Ｇｕｐｔａ，ｅｔ　ａｌ．，１９９７，Ｃａｎｃｅｒ　Ｃｈｅｍｏｔｈｅｒ　Ｐｈａｒｍａｃｏｌ　３９：４４０－４］。イリノテカンとサイクロスポリンＡおよびフェノバルビタールを併用した臨床試験の予備データは、カンプトテシン関連下痢の抑制に関してある程度有望な結果を示す［Ｒａｔａｉｎ，２０００，Ｃｌｉｎ　Ｃａｎｃｅｒ　Ｒｅｓ　６：３３９３－４］が、サイクロスポリンＡおよびフェノバルビタールなどの薬物による共治療は有害事象および薬物相互作用のリスクを追加する。

【０００９】

ＳＮ－３８およびＳＮ－３８Ｇの薬物動態は両方とも大きな患者間変動性があり［Ｃａｎａｌ，ｅｔ　ａｌ．，１９９６，Ｊ　Ｃｌｉｎ　Ｏｎｃｏｌ　１４：２６８８－９５］、これは患者間のイリノテカン代謝経路の相異によるものと思われる［Ｒｉｖｏｒｙ，ｅｔ

ａｌ．，１９９７，Ｃｌｉｎ Ｃａｎｃｅｒ Ｒｅｓ ３：１２６１－６］。さらに、ギルバート症候群の患者に重篤なイリノテカン毒性が報告された［Ｗａｓｓｅｒｍａｎ，ｅｔ ａｌ．，１９９７，Ａｎｎ Ｏｎｃｏｌ ８：１０４９－５１］。その結果、ＵＧＴ１Ａ１活性の低い患者はイリノテカン毒性のリスクが高いという、イリノテカン代謝に対する遺伝的素質が示唆された［Ｉｙｅｒ，ｅｔ ａｌ．，１９９８，Ｊ Ｃｌｉｎ Ｉｎｖｅｓｔ １０１：８４７－５４；Ａｎｄｏ，ｅｔ ａｌ．，１９９８，Ａｎｎ Ｏｎｃｏｌ ９：８４５－７］。ＵＧＴ１Ａ１プロモーターにおける共通の多型性［Ｍｏｎａｇｈａｎ，ｅｔ ａｌ．，１９９６，Ｌａｎｃｅｔ ３４７：５７８－８１］がインビトロでのＳＮ－３８のグルクロン酸抱合と関連づけられ［Ｉｙｅｒ，ｅｔ ａｌ．，１９９９，Ｃｌｉｎ Ｐｈａｒｍａｃｏｌ Ｔｈｅｒ ６５：５７６－８２］、それを臨床的に利用できる可能性が患者－対照研究から示唆された［Ａｎｄｏ，ｅｔ ａｌ．，２０００，Ｃａｎｃｅｒ Ｒｅｓ ６０：６９２１－６］。しかし、イリノテカン関連毒性はほんの少数の罹患患者（＜１５％）においてＵＧＴ１Ａ１遺伝子型により予測されたにすぎない。

【００１０】

結論として、カンプトテシンをベースとする療法の療法効果および安全性を有意に改善し、かつ療法による死亡を避け、不必要な耐性発現を避け、そして有害事象および療法遅延に関連する医療費を減らすことが、きわめて望ましい。しかし、イリノテカン毒性の低下または療法効果の改善に関して受け入れられている機序は、現在のところない。

【００１１】

したがって、本発明の基礎となる技術的課題は、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌を効果的に治療するための改良された手段および方法を提供し、これにより前記の望ましくない副作用を避けることである。本発明の基礎となる技術的課題は、特許請求の範囲において特徴が明らかにされた態様により解決される。

【発明の開示】

【課題を解決するための手段】

【００１２】

したがって本発明は、下記のものよりなる群から選択されるポリヌクレオチドを含む第１の変異対立遺伝子をもつゲノムを有する対象において、癌、特に結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌の治療に用いる医薬組成物を調製するための、イリノテカンまたはその誘導体の使用に関する：

（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：

【００１３】

【化１】

SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422, 425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482, 485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 および／または 641;

【００１４】

（ｂ）ＳＥＱ ＩＤ ＮＯ：６０６、６０８、６１０、６１２、６１８、６２０、６２２、６２４および／または６２８のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；

（ｃ）多剤耐性１（ＭＤＲ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって

、下記の位置に対応する位置において少なくとも１個のヌクレオチドの置換または欠失を有するポリヌクレオチド：
ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の
【００１５】
【化２】

位置 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619

【００１６】
および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の
【００１７】
【化３】

位置 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162

【００１８】
および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１、３０８、
および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１３７、１７６；
（ｄ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８３９４６、７０２００、７０２３７、６５２４１、および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１および／または、ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４１５２９、１７４９０１、１３９１７７、１４０１１８、１４０５６８、１４０７２７、１３９４７９に対応する位置にＡを；ＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置３０８および／または、ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８４７０１、８３９７３、８４０７４、８４１１９、７８１７０、７０２０４、７０２５３、７０３７１、５０５３７、４３１６２、および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１３７または１７６、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４５９８４、１７１４６６、１７５０６８、１７５０７４、１３９０６４、１３９２７６、１４０５７６に対応する位置にＴを；ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４０８３７、１７１４０４、１７１４５６、１７１５１１、１７１５１２、１３９１１９、１４０４９０、１３９６１９、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置４３２６３に対応する位置にＣを；ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８４０３２、７７８１１、７３２５２、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４１５９０、１７５１４２、１７５１８０、１３９０１５、１４０２１６、１４０５９５に対応する位置にＧを有するポリヌクレオチド；
（ｅ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置２１、１０３、１６８、４００、８９３、９９９、１００１、１１０７および／または１１４１に対応する位置においてアミノ酸置換を含む；
（ｆ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置２１に対応する位置におけるＡｓｎからＡｓｐへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１０３に対応する位置におけるＰｈｅからＬｅｕへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ

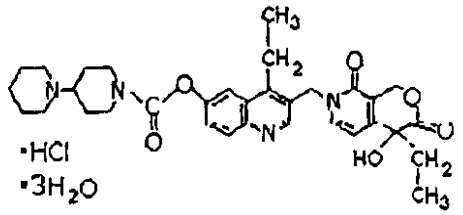
２５０６１１８）の位置１６８に対応する位置におけるＶａｌからＩｌｅへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００に対応する位置におけるＳｅｒからＡｓｎへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置８９３に対応する位置におけるＡｌａからＳｅｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置９９９に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１００１に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１０７に対応する位置におけるＧｌｎからＰｒｏへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１４１に対応する位置におけるＳｅｒからＴｈｒへの置換。

【００１９】

本発明に従って用いる“イリノテカンまたはその誘導体”という用語は、好ましくは下記の一般構造式により特徴付けられ：

【００２０】

【化４】



$C_{33}H_{38}N_4O_8 \cdot HCl \cdot 3H_2O$

【００２１】

さらに米国特許ＵＳ０５１０６７４２、ＵＳ０５３４０８１７、ＵＳ０５３６４８５８、ＵＳ０５４０１７４７、ＵＳ０５４６８７５４、ＵＳ０５５５９２３５およびＵＳ０５６６３１７７に記載された物質を示す。さらに用語“イリノテカンまたはその誘導体”には、カンプトテシンの類似体および誘導体も含まれる。使用できるカンプトテシン類似体のタイプおよび範囲は当業者に周知であり、たとえば、以下の多数の文献に記載されている［Ｈａｗｋｉｎｓ，１９９２，Ｏｎｃｏｌｏｇｙ（Ｈｕｎｔｉｎｇｔ）６：１７－２３；Ｂｕｒｒｉｓ，ｅｔ ａｌ．，１９９４，Ｈｅｍａｔｏｌ Ｏｎｃｏｌ Ｃｌｉｎ Ｎｏｒｔｈ Ａｍ ８：３３３－５５；Ｓｌｉｃｈｅｎｍｙｅｒ，ｅｔ ａｌ．，１９９３，Ｊ Ｎａｔｌ Ｃａｎｃｅｒ Ｉｎｓｔ ８５：２７１－９１；Ｓｌｉｃｈｅｎｍｙｅｒ，ｅｔ ａｌ．，１９９４，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ３４：Ｓ５３－７］。活性なカンプトテシン類似体の具体例は下記のものである：６環式カンプトテシン類似体、９－ニトロ－カンプトテシン、９－または１０－置換アミノ、ハロゲンまたはヒドロキシル基を有する２０Ｓ立体配置のカンプトテシン類似体、７－置換水溶性カンプトテシン、９－置換カンプトテシン、Ｅ環修飾カンプトテシン、たとえば（ＲＳ）－２０－デオキシアミノ－７－エチル－１０－メトキシカンプトテシン、および１０－置換カンプトテシン類似体［Ｅｍｅｒｓｏｎ，ｅｔ ａｌ．，１９９５，Ｃａｎｃｅｒ Ｒｅｓ ５５：６０３－９；Ｅｊｉｍａ，ｅｔ ａｌ．，１９９２，Ｃｈｅｍ Ｐｈａｒｍ Ｂｕｌｌ（Ｔｏｋｙｏ）４０：６８３－８；Ｓｕｇｉｍｏｒｉ，ｅｔ ａｌ．，１９９４，Ｊ Ｍｅｄ Ｃｈｅｍ ３７：３０３３－９；Ｗａｌｌ，ｅｔ ａｌ．，１９９３，Ｊ Ｍｅｄ Ｃｈｅｍ ３６：２６８９－７００；Ｗａｎｉ，ｅｔ ａｌ．，１９８０，Ｊ Ｍｅｄ Ｃｈｅｍ ２３：５５４－６０；Ｋｉｎｇｓｂｕｒｙ，ｅｔ ａｌ．，１９９１，Ｊ Ｍｅｄ Ｃｈｅｍ ３４：９８－１０７］。類似の療法活性をもつ他の多様なカンプトテシン類似体が記載されている［Ｈａｗｋｉｎｓ，１９９２，Ｏｎｃｏｌｏｇｙ（Ｈｕｎｔｉｎｇｔ）６：１７－２３；Ｂｕｒｒｉｓ ａｎｄ Ｆｉｅｌｄｓ，１

９９４，Ｈｅｍａｔｏｌ Ｏｎｃｏｌ Ｃｌｉｎ Ｎｏｒｔｈ Ａｍ ８：３３３－５５；Ｓｌｉｃｈｅｎｍｙｅｒ，ｅｔ ａｌ．，１９９３，Ｊ Ｎａｔｌ Ｃａｎｃｅｒ Ｉｎｓｔ ８５：２７１－９１；Ｓｌｉｃｈｅｎｍｙｅｒ，ｅｔ ａｌ．，１９９４，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ３４：Ｓ５３－７］。カンプトテシン類似体を合成するのに適した方法が記載されている［Ｅｍｅｒｓｏｎ，ｅｔ ａｌ．，１９９５，Ｃａｎｃｅｒ Ｒｅｓ ５５：６０３－９；Ｅｊｉｍａ，ｅｔ ａｌ．，１９９２，Ｃｈｅｍ Ｐｈａｒｍ Ｂｕｌｌ（Ｔｏｋｙｏ）４０：６８３－８；Ｓｕｇｉｍｏｒｉ，ｅｔ ａｌ．，１９９４，Ｊ Ｍｅｄ Ｃｈｅｍ ３７：３０３３－９；Ｗａｌｌ，ｅｔ ａｌ．，１９９３，Ｊ Ｍｅｄ Ｃｈｅｍ ３６：２６８９－７００；Ｗａｎｉ，ｅｔ ａｌ．，１９８０，Ｊ Ｍｅｄ Ｃｈｅｍ ２３：５５４－６０；Ｋｉｎｇｓｂｕｒｙ，ｅｔ ａｌ．，１９９１，Ｊ Ｍｅｄ Ｃｈｅｍ ３４：９８－１０７；Ｓｕｇａｓａｗａ，ｅｔ ａｌ．，１９７６，Ｊ Ｍｅｄ Ｃｈｅｍ １９：６７５－９］。

【００２２】

これらの物質は、次の文献に記載されているように、療法用として、たとえば結腸直腸癌、非－小細胞型および小細胞型の肺癌、食道癌、腎細胞癌、卵巣癌、乳癌、膵癌、扁平上皮癌、白血病およびリンパ腫に有用であることが知られている［Ｋａｗａｔｏ，ｅｔ ａｌ．，１９９１，Ｃａｎｃｅｒ Ｒｅｓ ５１：４１８７－９１；Ｆｕｒｕｔａ，ｅｔ ａｌ．，１９８８，Ｇａｎ Ｔｏ Ｋａｇａｋｕ Ｒｙｏｈｏ １５：２７５７－６０；Ｈａｗｋｉｎｓ，１９９２，Ｏｎｃｏｌｏｇｙ（Ｈｕｎｔｉｎｇｔ）６：１７－２３；Ｓｌｉｃｈｅｎｍｙｅｒ，ｅｔ ａｌ．，１９９３，Ｊ Ｎａｔｌ Ｃａｎｃｅｒ Ｉｎｓｔ ８５：２７１－９１；Ｓｌｉｃｈｅｎｍｙｅｒ，ｅｔ ａｌ．，１９９４，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ３４：Ｓ５３－７；Ｔｓｕｒｕｏ，ｅｔ ａｌ．，１９８８，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ２１：７１－４；Ｗｅｉｓｅｍａｎ，ｅｔ ａｌ．，１９９６，Ｄｒｕｇｓ ５２：６０６－２３；Ｇｏｔｔｌｉｅｂ，ｅｔ ａｌ．，１９７０，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｒｅｐ ５４：４６１－７０；Ｎｅｇｏｒｏ，ｅｔ ａｌ．，１９９１，Ｊ Ｎａｔｌ Ｃａｎｃｅｒ Ｉｎｓｔ ８３：１１６４－８；Ｒｏｗｉｎｓｋｙ，ｅｔ ａｌ．，１９９４，Ｃａｎｃｅｒ Ｒｅｓ ５４：４２７－３６］。同様に本発明による使用に含まれるものは、前記物質の何らかの化学修飾により得られる誘導体であって、本発明の使用にとって療法上同様に好適な誘導体である。本発明物質の誘導体が本発明の使用にとって療法上同様に好適であるかを判定するためには、当技術分野で周知の生物学的アッセイを実施することができる。そのようなアッセイ法は、たとえば次の文献に記載されている［Ｋａｗａｔｏ，ｅｔ ａｌ．，１９９１，Ｃａｎｃｅｒ Ｒｅｓ ５１：４１８７－９１；Ｆｕｒｕｔａ，ｅｔ ａｌ．，１９８８，Ｇａｎ Ｔｏ Ｋａｇａｋｕ Ｒｙｏｈｏ １５：２７５７－６０；Ｇｉｏｖａｎｅｌｌａ，ｅｔ ａｌ．，１９８９，Ｓｃｉｅｎｃｅ ２４６：１０４６－８；Ｇｉｏｖａｎｅｌｌａ，ｅｔ ａｌ．，１９９１，Ｃａｎｃｅｒ Ｒｅｓ ５１：３０５２－５；Ｋｕｎｉｍｏｔｏ，ｅｔ ａｌ．，１９８７，Ｃａｎｃｅｒ Ｒｅｓ ４７：５９４４－７；Ｍａｔｔｅｒｎ，ｅｔ ａｌ．，１９９３，Ｏｎｃｏｌ Ｒｅｓ ５：４６７－７４；Ｔｓｕｒｕｏ，ｅｔ ａｌ．，１９８８，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ２１：７１－４；Ｂｕｒｒｉｓ，ｅｔ ａｌ．，１９９２，Ｊ Ｎａｔｌ Ｃａｎｃｅｒ Ｉｎｓｔ ８４：１８１６－２０；Ｆｒｉｅｄｍａｎ，ｅｔ ａｌ．，１９９４，Ｃａｎｃｅｒ Ｃｈｅｍｏｔｈｅｒ Ｐｈａｒｍａｃｏｌ ３４：１７１－４］。

【００２３】

上記刊行物に記載された化合物はいずれも本発明に使用できるものとする。

イリノテカンは、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌の治療に特に好適であることが示されている。したがって、最も好ましくは本発明に従って使用する物質はイリノテカンである。

【００２４】

本明細書中で用いる用語“医薬組成物”は、本発明物質および所望により１種類以上の医

薬的に許容できるキャリヤーを含む。本発明物質を医薬的に許容できる塩類として配合してもよい。許容できる塩類には、酢酸塩、メチルエステル、塩酸塩、硫酸塩、塩化物などが含まれる。医薬組成物は薬物投与に慣用されるいずれかの経路によっても、たとえば経口、局所、非経口または吸入によっても、都合よく投与され得る。本発明物質は、薬物と標準的な医薬用キャリヤーを常法により混和することによって調製される慣用的な剤形で投与できる。これらの操作は、目的製剤に応じて成分の混合、造粒および圧縮または溶解を患うことができる。医薬的に許容できるキャラクターまたは希釈剤の形状および性質が、混和する有効成分の量、投与経路その他周知の可変要因により支配されることは自明であろう。キャリヤー（１種類以上）は、配合物の他の成分と適合性でありかつそれのレシピエント（recipient）に対して有害でないという意味で“許容できる”ものでなければならない。用いる医薬用キャリヤーは、たとえば固体または液体であってよい。固体キャリヤーの例は、乳糖、白土、ショ糖、タルク、ゼラチン、寒天、ペクチン、アラビアゴム、ステアリン酸マグネシウム、ステアリン酸などである。液体キャリヤーの例は、リン酸緩衝化生理食塩水、シロップ、油、たとえばラッカセイ油およびオリーブ油、水、エマルション、種々のタイプの湿潤剤、無菌溶液などである。同様に、キャリヤーまたは希釈剤は、当技術分野で周知の遅延剤、たとえばモノステアリン酸グリセリルまたはジステアリン酸グリセリルを単独でまたはろうと共に含有してもよい。本発明による物質は、目的効果を達成するために多様な様式で投与できる。本発明物質を単独でまたは医薬製剤として配合して、治療される対象に経口、局所、非経口または吸入により投与することができる。さらに、本発明物質を他の物質と組み合わせ、共通の医薬組成物中において、または別個の医薬組成物として投与することもできる。

【００２５】

希釈剤は、組合わせ物の生物学的活性に影響を与えないように選択される。そのような希釈剤の例は、蒸留水、生理食塩水、リンゲル液、ブドウ糖溶液およびハンクス液である。さらに医薬組成物または配合物は、他のキャリヤー、佐剤、または無毒性、非療法性、非免疫原性である安定剤などを含有することができる。療法有効量とは、症状または状態を改善する本発明物質量を表わす。そのような化合物の療法有効性および毒性は、標準的な医薬的方法により細胞培養または実験動物において判定できる：たとえばＥＤ５０（その集団の５０％において療法的に有効な量）およびＬＤ５０（その集団の５０％に致死的な量）。療法効力と毒性効果の量比が療法指数であり、それを比ＬＤ５０／ＥＤ５０として表わすことができる。

【００２６】

投与方式は、担当医および他の臨床的要因により、好ましくは上記方法のいずれか１つに従って決定される。医療分野で周知のように、いずれの各患者に対する投与量も多数の要因に依存しうる。これには患者の体格、体表面積、年齢、投与する特定の化合物、性別、投与時間および投与経路、全般的健康状態、および併用する他の薬物が含まれる。経過を定期的な評価によりモニターすることができる。

【００２７】

典型的用量はたとえば５～１００ｍｇであるが、特に前記要因を考慮して、この例示範囲を下回るかまたは上回る用量も想定される。一般に医薬組成物の通常の投与としての投与方式は、１日当たり１μｇ～１０ｍｇ単位とすべきである。その方式が連続注入である場合も、体重ｋｇあたり、分（minute）あたり、それぞれ、１μｇ～１０ｍｇ単位とすべきである。経過を定期的な評価によりモニターすることができる。しかし、その対象および投与様式に応じて、約１～約５００ｍｇ／m^2（体表面積）、通常は２０～２００ｍｇ／m^2（体表面積）となるように物質投与量を広範に変更できる。

【００２８】

本明細書に述べられる医薬組成物および配合物を、少なくとも１回、本発明の使用法に従って投与する。しかし、本発明の医薬組成物および配合物を１回より多く、たとえば週１回隔週で、非限定数の週間にわたって投与することができる。

【００２９】

本発明による物質の具体的な配合物は、医薬の分野で周知の方法で調製され、通常は本明細書において上記に述べた少なくとも１種類の有効物質を、医薬的に許容できるそれのキャリヤーまたは希釈剤と混合その他の形で組み合わせて含有する。それらの配合物を調製するためには、有効物質（１種類以上）を通常はキャリヤーと混合し、または希釈剤で希釈し、あるいはカプセル、サッシェ、カシェ、紙その他の適切な容器またはビヒクルに封入またはカプセル化する。キャリヤーは、有効成分に対してビヒクル、賦形剤または媒質として作用する固体状、半固体状、ゲルベースまたは液状の材料であってよい。これらの適切なキャリヤーには、上記のもの、および当技術分野で周知の他のものが含まれる。たとえばＲｅｍｉｎｇｔｏｎ’ｓ　Ｐｈａｒｍａｃｅｕｔｉｃａｌ　Ｓｃｉｅｎｃｅｓ，Ｍａｃｋ　Ｐｕｂｌｉｓｈｉｎｇ　Ｃｏｍｐａｎｙ’（ペンシルベニア州イーストン）参照。配合物を、錠剤、カプセル剤、坐剤、液剤、懸濁液剤などを含む投与様式に適合させることができる。

【００３０】

当該患者群に応じて処方者が用量調整を予測できるように、製品ラベルに推奨投与量を指示する。不適正な薬物を不適正な患者に不適正な量で処方するのを避けるという通告を添える。

【００３１】

用語“治療”または“予防”は、治療した対象または疾患集団において疾病症状が軽減すること、すなわち症状の退行またはそのような症状の進行阻止を意味する。そのような疾病軽減は、疾病に伴う臨床症状の程度（たとえば腫瘍サイズ）によりモニターできる。本発明は治療した患者の１００％に有効ではないかもしれないが、統計的に有意な（ｐ値０．０５未満）人数の患者を治療するのに有効である。その対象人数が有意であるかは、統計学的検定、たとえばスチューデント（Student）のｔ－検定、カイ２乗検定、マン（Ｍａｎｎ）とウィットニー（Ｗｈｉｔｎｅｙ）によるＵ－検定、クラスカル－ウォリス（Ｋｒｕｓｋａｌ－Ｗａｌｌｉｓ）検定（Ｈ－検定）、ジョンケーレ－テルプストラ（Ｊｏｎｃｋｈｅｅｒｅ－Ｔｅｒｐｓｔｒａ）検定またはウィルコクソン（Ｗｉｌｃｏｘｏｎ）検定により判定できる。

【００３２】

本発明は、米国特許ＵＳ０５１０６７４２、ＵＳ０５３４０８１７、ＵＳ０５３６４８５８、ＵＳ０５４０１７４７、ＵＳ０５４６８７５４、ＵＳ０５５５９２３５およびＵＳ０５６６３１７７に医薬組成物に関連して記載したすべての態様をも包含する。

【００３３】

用語“結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌”は、癌に関連する疾患および調節不全（dysregulation）を含む。本発明の使用に包含される好ましい疾患は、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌および膵癌である。これらの疾患および調節不全は当技術分野で周知であり、随伴症状はたとえばステッドマン（Ｓｔｅｄｍａｎ）などの標準的な書籍に記載されている。

【００３４】

本発明の意味において用いる用語“対象”は、動物、好ましくは本明細書において後記に特定するもの、およびヒトを含む。

本明細書中で用いる用語“第１の変異対立遺伝子”は、ＭＤＲ１遺伝子に対応する本明細書において後記に述べられる１以上のポリヌクレオチドを含むポリヌクレオチドを表わす。対象の各個体はＭＤＲ１遺伝子の少なくとも２つの対立遺伝子を保有し、それらの対立遺伝子は区別できるかまたは同一である。本発明の使用によれば、変異対立遺伝子は本明細書において後記に特定するポリヌクレオチドを少なくとも１つ以上含む。そのようなポリヌクレオチドは第１の変異対立遺伝子の調節または機能に対して相乗作用をもつ可能性がある。好ましくは、本発明の使用による変異対立遺伝子は本明細書において特定されたポリヌクレオチドを少なくとも２つ含む。

【００３５】

本発明の文脈において用語“ポリヌクレオチド”または“ポリペプチド”は、本発明の使

用により特定されるポリヌクレオチドまたはポリペプチドの異なる変異体を表わす。そのような変異体は、本明細書において特定されたポリヌクレオチドまたはポリペプチドの基準配列、若しくは野生型配列、並びにそれらと構造または組成の異なる変異体を含む。ポリヌクレオチドの基準配列、若しくは野生型配列は、下記のＧｅｎＢａｎｋ寄託番号のものである：

ポリヌクレオチドについて：

【００３６】

【化５】

GI:8850235, GI:11118740, GI:10281451, GI:11177452, GI:10281451, GI:6706037, U91318, GI:7209451, AC026452, AC003026, U91318, AF022830, GI:7209451, AC026452, AC003026, AC025277, AF022828, AF022829, AF022831, U07050, AC003026, AC002457, AC005068, M29432, M29445 およびGI:11225259

【００３７】

または、ポリペプチドについて寄託番号（Ｐｉｄ　Ｎｏ）：Ｇ８８５０２３６、Ｇ２８２８２０６、Ｇ２５０６１１８またはＧ１２６４４１１８。構造または組成の相異は、通常は１以上のヌクレオチドおよびアミノ酸の置換、付加および／または欠失により起きる。

【００３８】

好ましくは、本発明の使用において述べられる前記ヌクレオチド置換、付加または欠失により、ポリペプチドの対応するアミノ酸１個以上が変化する。変異ポリヌクレオチドには、これらのポリヌクレオチドまたはポリペプチドのフラグメントも含まれる。ポリヌクレオチドまたはポリペプチド並びに前述のフラグメントは、たとえば不十分な、および／または変化した薬物取込みを含めた、ＭＤＲ１の機能不全または調節不全に関連することを特色とする。

【００３９】

本発明は、ＷＯ９９５７３２２、ＷＯ０１０９１８３またはＵＳ５７８６３４４中にポリヌクレオチドに関連して記載したすべての態様をも包含する。

本明細書中で用いる用語“ハイブリダイズする”は、ＭＤＲ１の機能不全または調節不全に関連する上記ポリヌクレオチドまたはその部分にハイブリダイズしうるポリヌクレオチドを示す。したがって、ハイブリダイズするポリヌクレオチドはこれらの機能不全または調節不全にも関連する。好ましくは、ＭＤＲ１の機能不全または調節不全に関連する前述ポリヌクレオチドまたはその部分にハイブリダイズしうるこれらポリヌクレオチドは、ＭＤＲ１の機能不全または調節不全に関連する前記ポリヌクレオチドまたはその部分に対して少なくとも７０％、少なくとも８０％、少なくとも９５％、または少なくとも１００％同一である。したがってそれらのポリヌクレオチドは、ＲＮＡまたはＤＮＡの調製物のノーザンまたはサザンブロット分析におけるプローブとして有用であり得、あるいはそれらの各サイズによってはＰＣＲ分析においてオリゴヌクレオチドプライマーとして使用できるであろう。本発明の使用によれば、たとえば電気泳動移動度シフト分析（ＥＭＳＡ）によるＤＮＡ－タンパク質相互作用の分析に有用な、ハイブリダイズするポリヌクレオチドも含まれる。好ましくは、これらのハイブリダイズするポリヌクレオチドは少なくとも１０、より好ましくは少なくとも１５ヌクレオチドの長さを含み、一方、プローブとして用いるハイブリダイズするポリヌクレオチドは、好ましくは少なくとも１００、より好ましくは少なくとも２００、最も好ましくは少なくとも５００ヌクレオチドの長さを含む。

【００４０】

核酸分子でハイブリダイゼーション実験を行う方法は当技術分野で周知である。すなわち本発明に従って使用すべきハイブリダイゼーション条件は当業者に既知である。そのようなハイブリダイゼーション条件は、標準的な書籍に述べられている。たとえば；Ｍｏｌｅｃｕｌａｒ　Ｃｌｏｎｉｎｇ，Ａ　Ｌａｂｏｒａｔｏｒｙ　Ｍａｎｕａｌ，Ｃｏｌｄ　Ｓｐｒｉｎｇ　Ｈａｒｂｏｒ　Ｌａｂｏｒａｔｏｒｙ（１９８９）ニューヨーク。本発明の

使用に関して好ましいものは、ＭＤＲ１の機能不全または調節不全に関連する上記ポリヌクレオチドまたはその部分に、ストリンジェントなハイブリダイゼーション条件下でハイブリダイズしうるポリヌクレオチドである。すなわちこれらは、無関係なポリヌクレオチド、たとえば本発明のＭＤＲ１ポリペプチドとは異なるポリペプチドをコードするポリヌクレオチドに交差ハイブリダイズしない。

【００４１】

さらに、ある対象が本明細書に上記に述べられたポリヌクレオチドを含むかを判定する方法は当技術分野で周知である。この方法を実施するためには、生物学的材料を含む試料、たとえば単離した細胞または組織を、その対象から採取することが必要であろう。さらに、当技術分野で既知の方法には、たとえばＰＣＲをベースとする方法、ＲＦＬＰをベースとする方法、ＤＮＡ配列決定をベースとする方法、ハイブリダイゼーション方法、一本鎖コンホメーション多型（ＳＳＣＰ）、変性剤濃度勾配ゲル電気泳動（ＤＧＧＥ）、ミスマッチ開裂検出、ヘテロ二本鎖分析、質量分析に基づく方法、ＨＰＬＣをベースとする方法、プライマー延長をベースとする方法、および５’－ヌクレアーゼアッセイをベースとする方法が含まれる。上記に特定した１以上のポリヌクレオチドの存在または不存在を判定するために用いるのに好ましい好都合な方法は、対象から血球を単離し、これらの血球から単離したゲノムＤＮＡについてＰＣＲベースのアッセイを実施するものである。これにより、本明細書において特定した上記ポリヌクレオチドまたはその部分が存在するかしないかを、ＰＣＲを利用して判定する。この方法については後記および実施例に詳述する。

【００４２】

本明細書中で用いる用語“対応する”は、ある位置がそれぞれ先行するヌクレオチドおよびアミノ酸の個数だけで決定されるわけではないことを意味する。本発明の使用における所与のヌクレオチドまたはアミノ酸（欠失、置換されていてもよく、または１以上の追加のヌクレオチドを含んでもよい）の位置は、その遺伝子またはポリペプチドの他の位置における欠失もしくは追加のヌクレオチドまたはアミノ酸のため、変動する可能性がある。したがって本発明による“対応する位置”のもとでは、ヌクレオチドまたはアミノ酸を指示する数字が異なる可能性はあるが、依然として類似の隣接ヌクレオチドまたはアミノ酸をもつと理解すべきである。交換、欠失していてもよく、または追加のヌクレオチドもしくはアミノ酸を含んでもよいそれらのヌクレオチドまたはアミノ酸も、“対応する位置”という用語に含まれる。それらのヌクレオチドまたはアミノ酸は、たとえばそれらに隣接するものと一緒になって、遺伝子の発現、対応するＲＮＡもしくはＲＮＡ編集の安定性の調節などに関与し並びに本発明タンパク質の機能ドメインもしくは機能モチーフをコードする配列を形成することができる。

【００４３】

たとえば“位置１７９７０－１７９７０”は、そのポリヌクレオチドがそのポリヌクレオチドの対応する野生型バージョンの位置１７９７０と位置１７９７０の間で欠失した１個以上の欠失ヌクレオチドを含むことを意味する。同じことが、上記態様において述べられたその同じ方式で記載された他のすべての位置数字に、必要に応じて変更を加えて適用される。

【００４４】

たとえば“位置１２２２／１２２３”は、そのポリヌクレオチドがそのポリヌクレオチドの対応する野生型バージョンの位置１２２２と位置１２２３の間に挿入された１個以上の追加のヌクレオチドを含むことを意味する。同じことが、上記態様において述べられたその同じ方式で記載された他のすべての位置数字に、すなわち斜線（／）で分離した２つの連続位置数字に、必要に応じて変更を加えて、適用される。

【００４５】

本発明に従って、ＭＤＲ１遺伝子の遺伝子変動の様式および集団内分布－ＭＤＲ１遺伝子の異なる対立遺伝子－を、多数の異なる個体に由来するヒトのこの遺伝子の関連領域の配列分析により分析した。個体のゲノムＤＮＡ、すなわちＭＤＲ１遺伝子を含む全遺伝子の個体の遺伝的素質を保有するものを個体の血液試料から容易に精製できることは、周知の

事実である。次いでこれらの個体のＤＮＡ試料を、その血液試料を提供した個体に存在するＭＤＲ１遺伝子の対立遺伝子の配列組成を分析するのに用いる。配列分析は、それらの遺伝子の関連領域をＰＣＲ増幅した後、ＰＣＲ生成物を精製し、続いて確立されている方法で自動ＤＮＡ配列決定する（たとえばＡＢＩ　ｄｙｅｔｅｒｍｉｎａｔｏｒ　ｃｙｃｌｅ　ｓｅｑｕｅｎｃｉｎｇ）ことにより行われた。

【００４６】

ヒトの血液ゲノムＤＮＡからのＰＣＲ生成物の直接ＤＮＡ配列決定法により個体の遺伝子型を決定してＭＤＲ１遺伝子の新規な変異体を同定する試みに際して、考慮しなければならない１つの重要なパラメーターは、それぞれのヒトが（通常は；異常な例外はきわめて少ない）常染色体遺伝子の遺伝子コピーを２つもつ（二倍性）という事実である。このため、ホモ接合配列変異だけでなくヘテロ接合変異をも明確に同定できるように、配列を評価する際にはきわめて慎重でなければならない。ＭＤＲ１遺伝子の多型性（ホモ接合性およびヘテロ接合性）を同定および解明する際の異なる工程の詳細を、後記の実施例に記載する。

【００４７】

この２０年間で、薬物応答における変動性の重要な原因として遺伝子の不均一性が次第に認識されるようになった。多くの科学情報（Ｍｅｙｅｒ，Ａｎｎ．Ｒｅｖ．Ｐｈａｒｍａｃｏｌ．Ｔｏｘｉｃｏｌ．３７（１９９７）２６９－２９６およびＷｅｓｔ，Ｊ．Ｃｌｉｎ．Ｐｈａｒｍａｃｏｌ．３７（１９９７）６３５－６４８）が、ある薬物はある患者においては他の患者より有効であるか、または、著しく有毒となる可能性すらあること、そして薬物に対する患者の応答におけるそのような変動が分子的基礎と相関している可能性があることを明確に示している。この“ファーマコゲノミクス”の概念では、薬物に対する応答性と患者の遺伝子プロフィルの相関性に注目している（Ｍａｒｓｈａｌｌ，Ｎａｔｕｒｅ　Ｂｉｏｔｅｃｈｎｏｌｏｇｙ，１５（１９９７）９５４－９５７；Ｍａｒｓｈａｌｌ，Ｎａｔｕｒｅ　Ｂｉｏｔｅｃｈｎｏｌｏｇｙ，１５（１９９７）１２４９－１２５２）。薬物療法に関するこの集団変動性の文脈において、ファーマコゲノミクスは特定の薬物に副作用なしに応答しうる患者を同定および選択するのに有用な手段として提唱された。この同定／選択は、たとえば患者の血液中の白血球に由来するＤＮＡを遺伝子型特定することにより遺伝子多型性を分子診断して、疾患の特性を判定することに基づくことができる（Ｂｅｒｔｚ，Ｃｌｉｎ．Ｐｈａｒｍａｃｏｋｉｎｅｔ．３２（１９９７）２１０－２５６；Ｅｎｇｅｌ，Ｊ．Ｃｈｒｏｍａｔｏｇｒａ．Ｂ．Ｂｉｏｍｅｄ．Ａｐｐｌ．６７８（１９９６）９３－１０３）。保健関係機関、たとえば米国の保健機構および欧州諸国の政府公衆衛生局にとって、このファーマコゲノミクスアプローチは、保健を向上させ、かつ不必要な薬物の開発、無効な薬物、および薬物投与による副作用のため生じる保健関連経費を低減する方策となる可能性をもつ。

【００４８】

本発明の変異遺伝子の変異は、時には１個以上のアミノ酸の欠失、挿入、特に置換を単独で、または合わせて生じる。野生型遺伝子または他の変異形にそのような変異を遺伝子工学的に導入することももちろん可能である。それらの遺伝子のＤＮＡ配列にそのような修飾を導入する方法は当業者に周知である；たとえばＳａｍｂｒｏｏｋ，Ｍｏｌｅｃｕｌａｒ　Ｃｌｏｎｉｎｇ，Ａ　Ｌａｂｏｒａｔｏｒｙ　Ｍａｎｕａｌ，Ｃｏｌｄ　Ｓｐｒｉｎｇ　Ｈａｒｂｏｒ　Ｌａｂｏｒａｔｏｒｙ（１９８９）ニューヨークを参照。

【００４９】

本発明のポリペプチドのアミノ酸配列の変化の性質を調べるためには、インターネットから入手可能なＢＲＡＳＭＯＬを使用できる。さらに、他の適切なコンピュータープログラムを用いて、構造モチーフのフォールディングシミュレーション（folding simulation）およびコンピューター再設計を実施できる（Ｏｌｓｚｅｗｓｋｉ，Ｐｒｏｔｅｉｎｓ　２５（１９９６）２８６－２９９；Ｈｏｆｆｍａｎ，Ｃｏｍｐｕｔ．Ａｐｐｌ．Ｂｉｏｓｃｉ．１１（１９９５）６７５－６７９）。詳細なタンパク質モデルのコンホメーション分析およびエネルギー分析のために、コンピューターを利用できる（Ｍｏｎｇｅ，Ｊ．Ｍｏ

ｌ．Ｂｉｏｌ．２４７（１９９５）９９５－１０１２；Ｒｅｎｏｕｆ，Ａｄｖ．Ｅｘｐ．Ｍｅｄ．Ｂｉｏｌ．３７６（１９９５）３７－４５）。これらの分析を、特定の変異が薬物の代謝、結合、阻害、療法作用の仲介および／または輸送に及ぼす影響を同定するために利用できる。さらに、本発明の使用において特定されるポリヌクレオチドがコードするポリペプチドの構造の変化の知見に基づいて、より効果的に代謝、修飾、輸送、排出および／または結合する前記物質の誘導体を設計および合成することができる。これにより、本明細書に述べられる物質に基づいて、１以上の本発明のポリヌクレオチドの存在を特色とする遺伝子型をもつ対象における結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、特に膵癌の療法において、より効果的な薬物またはプロドラッグを設計できる。

【００５０】

通常は、本発明の使用において述べられるポリヌクレオチドがコードするタンパク質のアミノ酸配列のアミノ酸の欠失、付加または置換は、１以上のヌクレオチドの置換、挿入もしくは欠失またはそのいずれかの組合わせによるものである。好ましくは、そのヌクレオチド置換、挿入または欠失により、下記のアミノ酸置換が起きる：ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置２１に対応する位置におけるＡｓｎからＡｓｐへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１０３に対応する位置におけるＰｈｅからＬｅｕへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１６８に対応する位置におけるＶａｌからＩｌｅへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００に対応する位置におけるＳｅｒからＡｓｎへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置８９３に対応する位置におけるＡｌａからＳｅｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置９９９に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１００１に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１０７に対応する位置におけるＧｌｎからＰｒｏへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１４１に対応する位置におけるＳｅｒからＴｈｒへの置換。本明細書に記載する使用において述べられるポリヌクレオチドがコードするポリペプチドは、本発明により述べられる変異のため変化した生物学的特性をもつ。それらの変化した特性の例は、影響を受けるポリペプチドの安定性またはポリペプチドの量であり、その結果たとえば下記の変化が起きる：薬物代謝の変化もしくは薬物輸送の変化または基質特異性の変化もしくは触媒活性の変化：例えばこれらは不十分な薬物代謝もしくは薬物代謝能の完全な喪失または薬物代謝能の増強を特色とする；あるいは輸送活性の変化：これはたとえば不十分な薬物輸送または薬物輸送能の完全な喪失を特色とする；あるいは基質結合性の変化：これはたとえば薬物作用の変化を特色とする；あるいは輸送阻害もしくは輸送誘導の変化または受容体もしくは他のターゲット分子への結合性の変化：これらはたとえば信号伝達経路の活性化の変化またはタンパク質もしくは酵素の機能の変化を特色とする。これらの特性変化は、本発明の使用により治療される対象の、前記物質に対する薬理学的応答性を損なう。さらに、本明細書において特定する変異対立遺伝子がコードするポリペプチドのこれらの特性変化のため、対象に対して有害もしくは有毒または望ましくない副作用を引き起こす物質誘導体を生じるように、前記物質が化学修飾される可能性がある。

【００５１】

本発明により検出されたＭＤＲ１遺伝子の変異を表１および２に挙げる。当業者に自明のとおり、本明細書において前記に特定したポリヌクレオチドの遺伝子知見を利用して、患者の遺伝子型を正確に信頼性をもって特性決定できる。

【００５２】

有利には、これらの遺伝子知見を考慮すると、イリノテカンまたはその誘導体に基づく療法措置をより効果的に適用できる。その対象の遺伝的性質が分かっているため、それらの物質の望ましくない副作用を避け、有効であるが無害な投与量を個別に計算することがで

きる。さらに、前述によれば、ある薬物が異常な作用を生じる場合、対象の個別の遺伝的性質の知見に基づいて適切な個別療法を計画できる。このテーラード療法は、療法耐性の発生を避けるのにも適するであろう。この耐性は、種々の化学療法薬での癌化学療法における重大な問題の１つであり、この事実は当技術分野で周知である。したがって、前記物質の適量および／または適切な誘導体で対象を個別に治療できるので、本発明の使用は本明細書において前記に述べた物質の療法上望ましい既知の効果に基づく療法適用の改善をもたらす。これにより、望ましくない有害または毒性作用が効果的に避けられる。さらに、それらの物質を薬物療法の開始前に同定して、それらの物質による療法が最も有益であると思われる対象のみを前記物質の適量および／または適切な誘導体で治療できるので、本発明の使用は本明細書において前記に述べた物質の療法上望ましい既知の効果に基づく療法適用の改善をもたらす。これにより、それらの物質による治療に応答しない対象（ノンレスポンダー）の不必要な、有害となる可能性のある治療、並びに最適量を下回る薬物投与による薬物耐性の発現を避けることができる。

【００５３】

本発明の使用の好ましい態様において、第１の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：３４５、４１７または６３６のいずれか１つの核酸配列を有するポリヌクレオチド；

（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６１２または６１８のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；

（ｃ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６、またはＭＤＲ１遺伝子（寄託番号：ＧＩ：１０１２２１３５）の位置８８８８３に対応する位置において置換を有するポリヌクレオチド：

（ｄ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１もしくはＭＤＲ１遺伝子（寄託番号：ＧＩ：１０１２２１３５）の位置８８８８３に対応する位置にＡを、または、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６もしくはＭＤＲ１遺伝子（寄託番号：ＧＩ：１０１２２１３５）の位置８８８８３に対応する位置にＴを有するポリヌクレオチド；

（ｅ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは、ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００または８９３に対応する位置においてアミノ酸置換を含む；および

（ｆ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは、ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００に対応する位置におけるＳｅｒからＡｓｎへの、または位置８９３に対応する位置におけるＡｌａからＳｅｒへのアミノ酸置換を含む。

【００５４】

より好ましくは、第１の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：４１７または６３６の核酸配列を有するポリヌクレオチド；

（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６１８のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；

（ｃ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６、ＭＤＲ１遺伝子（寄託番号：ＧＩ：１０１２２１３５）の位置８８８８３に対応する位置において置換を有するポリヌクレオチド；

（ｄ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６もしくはＭＤＲ１遺伝子（寄託番号：ＧＩ：１０１２２１３５）の位置８８８８３に対応する位置にＴを有するポリヌクレオチド；

（ｅ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは、ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置８９３に

対応する位置においてアミノ酸置換を含む；および
（ｆ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは、ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置８９３に対応する位置におけるＡｌａからＳｅｒへのアミノ酸置換を含む。
【００５５】
最も好ましくは、第１の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：４１７の核酸配列を有するポリヌクレオチド；
（ｂ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６に対応する位置において置換を有するポリヌクレオチド；および
（ｃ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６に対応する位置にＴを有するポリヌクレオチド。
【００５６】
本発明の使用の好ましい態様においては、対象は、下記のものよりなる群から選択されるポリヌクレオチドを含む第２の変異対立遺伝子をもつゲノムを有する：
（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：
【００５７】
【化６】

SEQ ID

NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 および／または 334;

【００５８】
（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６００、６０２および／または６０４のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）多剤耐性タンパク質１（ＭＲＰ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５７９９８、５７８５３、５３２８２および／または３９５０８に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６６７、１３７６４７、１３７７１０、１２４６６７および／または３８６４６に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７２５８、２７１５９、３４２１８、３４２１５、５５４７２および／または３４２０６－３４２０７に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置２１１３３、１４００８、１８０６７、１７９７０および／または１７９００に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置７９、８８および／または２４９に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５および／または２５９に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２５２７７）の位置１５０７２７および／または３３３５１に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２８）の位置１７４に対応する位置におけ

る少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２４８および／または２５８に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１８８４、１６２５、１１６３、３８１、２３３、１８９、４４０および／または１７２０－１７２３に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７および／または４３７／４３８に対応する位置における少なくとも１個のヌクレオチドの挿入；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置５５１５６／５５１５７に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド；

（ｄ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置２１１３３、１４００８および／または１８１９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７２５８および／または３４２１８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置７９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５７９９８および／または５７８５３に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６６７および／または１３７６４７に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２５２７７）の位置１５０７２７および／または３３５５１に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２４８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１８８４、１６２５、２３３および／または１８９に対応する位置にＡを；ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置３９５０８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１７９００、１８０６７および／または１８１９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２８）の位置１７４に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置４４０および／または１１６３に対応する位置にＴを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置８８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７１５９、５５４７２および／または３４２１５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７および／または３８６４６に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５３２８２に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７７１０に対応する位置にＣを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２５８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１に対応する位置にＧを；ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１７９７０に対応する位置におけるＴの欠失を；あるいは、ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置３４２０６－３４２０７に対応する位置におけるＡＴの欠失を；あるいは、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１７２０－１７２３に対応する位置におけるＧＧＴＡの欠失を；ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置におけるＴの挿入および／または４３７／４３８に対応する位置におけるＴＣＣＴＴＣＣの挿入を；ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置５５１５６／５５１５７に対応する位置におけるＴＧＧＧＧＣの挿入を有するポリヌクレオチド；

（ｅ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置２３９に対応する位置におけるＰｈｅからＣｙｓへの置換；または／およびＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置４３３に対応する位置におけるＡｒｇからＳｅｒへの置換；または／およびＭＲＰ１ポリペプチド（寄託番号：

Ｇ２８２８２０６）の位置７２３に対応する位置におけるＡｒｇからＧｌｎへの置換。
【００５９】
前記で行った用語の説明および解釈は、必要に応じて変更を加えて適用され得る。
用語“第２の変異対立遺伝子”は、本明細書において前記に述べた第１の対立遺伝子に対応する第１遺伝子とは異なる第２遺伝子の対立遺伝子に示す。本発明によれば、第２の変異対立遺伝子は前記に特定した１以上のポリヌクレオチドを含むＭＲＰ１遺伝子に対応する。
【００６０】
本発明にしたがって、意外にも、ＭＤＲ１遺伝子に対応する第１の変異対立遺伝子およびＭＲＰ１遺伝子に対応する第２の変異対立遺伝子が対象のゲノム中に合わせて存在すると、その対象のイリノテカンまたはその誘導体の投与に対する薬理学的応答を相乗的に変化させることが見いだされた。したがって、本発明の使用によれば、本明細書に述べられる疾患または障害をより効果的に治療または予防することができ、これによりその治療または予防措置がその対象にとってより好都合になる。さらに、本明細書において前記に述べた物質の投与を含む療法措置の適用可能性を効果的に予測できる。
【００６１】
本発明による好ましい欠失は、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１７９７０および／またはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置３４２０６－３４２０７に対応する位置におけるＴまたはＡＴの欠失であり、好ましい挿入は、ＭＲＰ１遺伝子（寄託番号：ＧＩ：Ｕ０７０５０）の位置４３７／４３８に対応する位置におけるＴＣＣＴＴＣＣの挿入および／またはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置５５１５６／５５１５７に対応する位置におけるＴＧＧＧＧＣの挿入である。
【００６２】
本発明の使用の好ましい態様においては、第２の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：１８１、２０９、２１７、２０５、２７７、２８１、３０１、３２５、２２９、１９３、３１３、２９３または２５３のいずれか１つの核酸配列を有するポリヌクレオチド；
（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６００のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６４７、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５、ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５３２８２、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１、４４０、１６２５、ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置３４２１８、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１８０６７または１７９００に対応する位置における置換；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド；
（ｄ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６４７、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１８０６７または１７９００、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置４４０に対応する位置にＴを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７に対応する位置にＣを；ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５３２８２、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１に対応する位置にＧを；またはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０

２６）の位置３４２１８もしくはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１６２５に対応する位置にＡを；またはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置におけるＴの挿入を有するポリヌクレオチド；
（ｅ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置３２９に対応する位置におけるアミノ酸置換を含む；および
（ｆ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置３２９に対応する位置におけるＰｈｅからＣｙｓへのアミノ酸置換を含む。

【００６３】

より好ましくは、第２の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：２０９、２０５、２７７、２８１、３０１または３２５のいずれか１つの核酸配列を有するポリヌクレオチド；
（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６００のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１に対応する位置における置換；またはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド；
（ｄ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７に対応する位置にＣを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１に対応する位置にＧを；または、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置におけるＴの挿入を有するポリヌクレオチド；
（ｅ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置３２９に対応する位置におけるアミノ酸置換を含む；および
（ｆ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置３２９に対応する位置におけるＰｈｅからＣｙｓへのアミノ酸置換を含む。

【００６４】

本発明の使用の好ましい態様において、対象は下記のものよりなる群から選択されるポリヌクレオチドを含む第３の変異対立遺伝子をもつゲノムを有する：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：１３７、１３８、１４１、１４２、１４５、１４６、１４９および／または１５０のいずれか１つの核酸配列を有するポリヌクレオチド；
（ｂ）シトクロムＰ４５０サブファミリーＩＩＩＡ（ニフェジピンオキシダーゼ）ポリペプチド５（ＣＹＰ３Ａ５）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８および／または９７３６に対応する位置における少なくとも１個のヌクレオチドの置換；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１および／または１４５９２９に対応する位置における少なくとも１個のヌクレオチドの置換を有するポリヌクレオチド；
（ｃ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８に対応する位置にＣ

を；ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１および／または１４５９２９に対応する位置にＧを；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置９７３６に対応する位置にＧを有するポリヌクレオチド。

【００６５】

前記で行った用語の説明および解釈は、必要に応じて変更を加えて適用され得る。

用語“第３の変異対立遺伝子”は、本明細書において前記に述べた第１の対立遺伝子に対応する第１遺伝子および第２の対立遺伝子に対応する第２遺伝子とは異なる第３遺伝子の対立遺伝子を示す。本発明によれば、第３の変異対立遺伝子は前記に特定した１以上のポリヌクレオチドを含むＣＹＰ３Ａ５遺伝子に対応する。

【００６６】

本発明にしたがって、意外にも、ＭＤＲ１遺伝子に対応する第１の変異対立遺伝子、および、所望により、ＭＲＰ１遺伝子に対応する第２の変異対立遺伝子、およびＣＹＰ３Ａ５遺伝子に対応する第３の変異対立遺伝子が、対象のゲノム中に合わせて存在すると、その対象のイリノテカンまたはその誘導体の投与に対する薬理学的応答を相乗的に変化させることが見いだされた。したがって、本発明の使用によれば、本明細書に述べられる疾患または障害をより効果的に治療または予防することができ、これによりその治療または予防措置がその対象にとってより好都合になる。さらに、本明細書において前記に述べた物質の投与を含む療法措置の適用可能性を効果的に予測できる。

【００６７】

本発明の使用の好ましい態様において、第３の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：１３７、１４１、１４５または１４９のいずれか１つの核酸配列を有するポリヌクレオチド；

（ｂ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８もしくは９７３６、またはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１もしくは１４５９２９に対応する位置における置換を有するポリヌクレオチド；

（ｃ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８に対応する位置にＣを；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置９７３６またはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１もしくは１４５９２９に対応する位置にＧを有するポリヌクレオチド。

【００６８】

より好ましくは、第３の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：１３７、１４５および／または１４９のいずれか１つの核酸配列を有するポリヌクレオチド；

（ｂ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８もしくは９７３６、またはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５９２９に対応する位置における置換を有するポリヌクレオチド；

（ｃ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８に対応する位置にＣを；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置９７３６またはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５９２９に対応する位置にＧを有するポリヌクレオチド。

【００６９】

本発明の使用の好ましい態様において、対象は下記のものよりなる群から選択されるポリヌクレオチドを含む第４の変異対立遺伝子をもつゲノムを有する：

（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：
【００７０】
【化７】

SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 および／または 134;

【００７１】
（ｂ）下記のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド：
【００７２】
【化８】

SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 および／または 598;

【００７３】
（ｃ）ウリジン二リン酸グリコシルトランスフェラーゼ１メンバーＡ１（ＵＧＴ１Ａ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５９、１６０、２２６、５３９、５４４、６４０、７０１、８４１、８５５、８９０、９３８、１００６、１００７、１０２０、１０８４、１０８５、１１１４、１１１７、１１３９、１１５８、１１７５－１１７６、１２１６、１２９７、１３２４、１４７１、１４７８、３７２－３７３、５２３－５２５および／または８９２－９０５に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいは、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置４７０／４７１および／または１２２２／１２２３に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド：
（ｄ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置２２６、５３９、７０１、８５５、９３８、１０２０および／または１１１７に対応する位置にＡを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１６０、６４０、８９０、１００６、１０８４、１１３９、１１７６、１３２４および／または１４７８に対応する位置にＴを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５４４、８４１および／または１２１６に対応する位置にＣを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：１８１３０３）の位置５９、１００７、１０８５、１１１４、１１５８、１１７５、１２９７および／または１４７１に対応する位置にＧを；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置３７２－３７３に対応する位置におけるＣＴの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５２３－５２５に対応する位置におけるＴＴＣの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置８９２－９０５に対応する位置におけるＴＡＣＡＴＴＡＡＴＧＣＴＴＣの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置４７０／４７１に対応する位置におけるＴの挿入を；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１２２２／１２２３に対応する位置におけるＧの挿入を有するポリヌクレオチド；
（ｅ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＵＧＴ１Ａ１ポリペプチド（寄託番号：

Ｇ８８５０２３６）の位置１５に対応する位置におけるＬｅｕからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置７１に対応する位置におけるＧｌｙからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１７５に対応する位置におけるＬｅｕからＧｌｎへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１７７に対応する位置におけるＣｙｓからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２０９に対応する位置におけるＡｒｇからＴｒｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２２９に対応する位置におけるＰｒｏからＧｌｎへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２７６に対応する位置におけるＧｌｙからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９２に対応する位置におけるＡｌａからＶａｌへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９３に対応する位置におけるＴｙｒからＴｒｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３０８に対応する位置におけるＧｌｙからＧｌｕへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３３１に対応する位置におけるＧｌｎからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３５７に対応する位置におけるＧｌｎからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３６７に対応する位置におけるＡｒｇからＧｌｙへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３６８に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３８７に対応する位置におけるＰｒｏからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３７５に対応する位置におけるＳｅｒからＰｈｅへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３８１に対応する位置におけるＳｅｒからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４０１に対応する位置におけるＡｌａからＰｒｏへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４２８に対応する位置におけるＬｙｓからＧｌｕへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４８６に対応する位置におけるＴｙｒからＡｓｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４８８に対応する位置におけるＳｅｒからＰｈｅへの置換；

（ｆ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置３７２－３７３に対応する位置におけるＣＴの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１１９に対応する位置におけるアミノ酸Ａｓｐに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置４７０／４７１に対応する位置にＴの挿入を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１５２に対応する位置におけるアミノ酸Ｐｒｏに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置５２３－５２５に対応する位置におけるＴＴＣの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１６８に対応する位置におけるアミノ酸Ｔｈｒに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置８９２－９０５に対応する位置におけるＴＡＣＡＴＴＡＡＴＧＣＴＴＣの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９２に対応する位置におけるアミノ酸Ａｌａに続く１個以上のアミノ酸が置換、付加およ

び／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置１２２２／１２２３に対応する位置におけるＧの挿入を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４０２に対応する位置におけるアミノ酸Ｌｙｓに続く１個以上のアミノ酸が置換、付加および／または欠失するポリヌクレオチド；および

（ｇ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリヌクレオチドは、ＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置４９に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置２８０に対応する位置におけるＣｙｓから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３３１に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３３５に対応する位置におけるＴｒｐから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３５７に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置４３７に対応する位置におけるＬｙｓから終止コドンへのアミノ酸置換を含む。

【００７４】

前記で行った用語の説明および解釈は、必要に応じて変更を加えて適用され得る。用語“第４の変異対立遺伝子”は、本明細書において前記に述べた第１の対立遺伝子に対応する第１遺伝子、第２の対立遺伝子に対応する第２遺伝子および第３の対立遺伝子に対応する第３遺伝子とは異なる第４遺伝子の対立遺伝子を示す。本発明によれば、第４の変異対立遺伝子は前記に特定した１以上のポリヌクレオチドを含むＵＧＴ１Ａ１遺伝子に対応する。

【００７５】

本発明にしたがって、意外にも、ＭＤＲ１遺伝子に対応する第１の変異対立遺伝子、および、所望により、ＭＲＰ１遺伝子に対応する第２の変異対立遺伝子、およびＣＹＰ３Ａ５遺伝子に対応する第３の変異対立遺伝子、およびＵＧＴ１Ａ１遺伝子に対応する第４の変異対立遺伝子が、対象のゲノム中に合わせて存在すると、その対象のイリノテカンまたはその誘導体の投与に対する薬理学的応答を相乗的に変化させることが見いだされた。したがって、本発明の使用によれば、本明細書に述べられる疾患または障害をより効果的に治療または予防することができ、これによりその治療または予防措置がその対象にとってより好都合になる。さらに、本明細書において前記に述べた物質の投与を含む療法措置の適用可能性を効果的に予測できる。

【００７６】

本発明の使用の好ましい態様においては、第４の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：３７、６９または９７のいずれか１つの核酸配列を有するポリヌクレオチド；

（ｂ）ＳＥＱ　ＩＤ　ＮＯ：５５８、５７０または５８４のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；

（ｃ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置８９０、１１１７または１４７１に対応する位置における置換を有するポリヌクレオチド；

（ｄ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１１１７に対応する位置にＡを、位置８９０に対応する位置にＴを、または、位置１４７１に対応する位置にＧを有するポリヌクレオチド；

（ｅ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位

置２９２、３６８または４８６に対応する位置におけるアミノ酸置換を含む；および
（ｆ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置２９２に対応する位置におけるＡｌａからＶａｌへの、位置３６８に対応する位置におけるＡｌａからＴｈｒへの、または位置４８６に対応する位置におけるＴｙｒからＡｓｐへのアミノ酸置換を含む。

【００７７】

より好ましくは、第４の変異対立遺伝子は下記のものよりなる群から選択されるポリヌクレオチドを含む：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：９７のいずれか１つの核酸配列を有するポリヌクレオチド；
（ｂ）ＳＥＱ　ＩＤ　ＮＯ：５８４のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１４７１に対応する位置における置換を有するポリヌクレオチド；
（ｄ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１４７１に対応する位置にＧを有するポリヌクレオチド；
（ｅ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置４８６に対応する位置におけるアミノ酸置換を含む；および
（ｆ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置３６８に対応する位置におけるＡｌａからＴｈｒへの、または位置４８６に対応する位置におけるＴｙｒからＡｓｐへのアミノ酸置換を含む。

【００７８】

本発明にしたがって、意外にも、ＭＤＲ１遺伝子に対応する第１の変異対立遺伝子、および、所望により、ＭＲＰ１遺伝子に対応する第２の変異対立遺伝子、およびＣＹＰ３Ａ５遺伝子に対応する第３の変異対立遺伝子、およびＵＧＴ１Ａ１遺伝子に対応する第４の変異対立遺伝子が、対象のゲノム中に合わせて存在すると、その対象のイリノテカンまたはその誘導体の投与に対する薬理学的応答を相乗的に変化させることが見いだされた。本発明により見いだされたように、イリノテカンまたはその誘導体に基づく薬物の薬物動態および対象の薬理学的応答は、主にＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５およびＵＧＴ１Ａ１遺伝子がコードするポリペプチドにより支配される。したがって、本発明にしたがって適用する療法措置の予測性および／または効力を高めるためには、本明細書に述べられる第１、第２、第３および／または第４の変異対立遺伝子の存在または不存在に関して対象の遺伝子構成を判定しなければならず、その知見に基づいて、療法的に最も有効でありかつ本発明の物質が引き起こす望ましくない毒性または副作用を避ける個別の療法を開発することができる。

【００７９】

本発明はまた、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、および膵癌を治療するための、下記を含む方法に関する：
（ａ）本明細書に述べられるポリヌクレオチドを含む第１、第２、第３および／または第４の変異対立遺伝子の存在または不存在を判定し；そして
（ｂ）対象に療法有効量のイリノテカンを投与すること。

【００８０】

本発明の使用において用いた定義を、必要に応じて変更を加えて上記方法に適用する。さらに、本発明の使用において記載されたすべての態様を、必要に応じて変更を加えて本発明方法に適用できる。さらに本発明方法には、当業者がその知見および本明細書全体に述べられた文献などの先行技術に基づいて過度の負担なしになしうる本発明方法のいかなる

さらなる発展も包含される。

【００８１】

本発明の使用の好ましい態様においては、前記ポリヌクレオチドが含むヌクレオチド欠失、付加および／または置換により、第１、第２または第３の変異対立遺伝子の発現が、対応する野生型対立遺伝子と比較して変化する。

【００８２】

前記のように、本発明の使用において述べられる対立遺伝子は、ＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５および／またはＵＧＴ１Ａ１遺伝子に対応する。遺伝子がアミノ酸配列をコードする構造要素ならびにその遺伝子の発現の調節に関与する調節要素を含むことは、当技術分野で周知である。構造要素はエキソンにより表わされ、これはアミノ酸配列をコードすることができるか、あるいは、アミノ酸配列をコードしないにもかかわらず、たとえばＲＮＡの安定性またはＲＮＡの核輸出を調節することによりＲＮＡ機能に関与するＲＮＡをコードすることができる。

【００８３】

遺伝子の調節要素には、プロモーター要素またはエンハンサー要素を含めることができ、これらは両者とも遺伝子発現の転写制御に関与する。プロモーターが遺伝子の構造要素の上流になければならないことは、当技術分野できわめてよく知られている。しかし、エンハンサー要素のような調節要素は遺伝子座全体に分布することができる。それらの要素は、たとえばイントロン内、すなわち遺伝子のエキソンを分離するゲノムＤＮＡ領域に存在することもできる。プロモーター要素またはエンハンサー要素は、それらのプロモーター要素またはエンハンサー要素を含む遺伝子の調節に関与するポリペプチドを誘引または結合させることができるポリヌクレオチドフラグメントに対応する。たとえば、その遺伝子の調節に関与するポリペプチドにはいわゆる転写因子が含まれる。

【００８４】

前記イントロンはさらに、適正な遺伝子発現に必要な調節要素を含むことができる。イントロンは通常は遺伝子のエキソンと一緒に転写されて、エキソンとイントロンの両配列を含む新生ＲＮＡ転写物になる。イントロンがコードしたＲＮＡ配列は、通常はＲＮＡスプライシングとして知られるプロセスにより除去される。しかし、そのプロセスはＲＮＡ転写物上に調節配列が存在することを要し、これらの調節配列はイントロンがコードすることができる。

【００８５】

さらに、遺伝子の調節要素は、転写の制御ならびに適正なＲＮＡプロセシングおよび／または安定性の制御におけるそれらの機能のほか、遺伝子座の遺伝的安定性の制御にも関与する。それらの要素は、たとえば組換え事象を制御し、あるいは染色体における一定のＤＮＡ構造またはＤＮＡ配列を維持する作用をもつ。

【００８６】

したがって、前記アミノ酸配列をコードする遺伝子の対立遺伝子のエキソンにおいても、前記プロセスに関与する調節領域における場合と同様に、単一ヌクレオチド多型が起きる可能性がある。本発明の使用において述べられるポリヌクレオチドが含む多型は、ＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５および／またはＵＧＴ１Ａ１遺伝子の転写の増強もしくは低下、遺伝子のＲＮＡ転写物の安定化、ならびに一次ＲＮＡ転写物のプロセシングの変化に関する機序により、ＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５および／またはＵＧＴ１Ａ１タンパク質の発現レベルに影響を与える可能性がある。

【００８７】

対応する野生型遺伝子と比較した変異対立遺伝子の発現の変化を判定する方法は当技術分野で周知であり、これには特に本明細書において前記に述べたもの、たとえばＰＣＲをベースとする方法、ＲＦＬＰをベースとする方法、ＤＮＡ配列決定をベースとする方法、ハイブリダイゼーション方法、一本鎖コンホメーション多型（ＳＳＣＰ）、変性濃度勾配ゲル電気泳動（ＤＧＧＥ）、ミスマッチ開裂検出、ヘテロ二重鎖分析、質量分析に基づく方法、ＨＰＬＣをベースとする方法、プライマー延長をベースとする方法、および５’－ヌ

クレアーゼアッセイをベースとする方法が含まれる。野生型および変異対立遺伝子の発現レベルをそれぞれ測定するために上記方法を実施する前に、生物学的材料を含む試料、たとえば単離した細胞または組織を、対象から得る必要があろう。本発明の使用における発現の変化とは、野生型対立遺伝子の発現と変異対立遺伝子の発現が有意に異なることを意味する。有意な違いは、標準的統計学的方法、たとえばスチューデントのｔ－検定、カイ２乗検定、またはマンとウィットニーによるＵ－検定により判定できる。さらに、当業者はこれらのおよび他の当技術分野で既知の統計学的方法を過度の負担なしに個別に採用できる。

【００８８】

本発明の使用のより好ましい態様においては、前記の発現変化は発現の低下または増大である。

本発明において述べられる対立遺伝子の発現が対応する野生型対立遺伝子と比較して増大または低下しているかを判定するためには、周知の方法、たとえばＰＣＲをベースとする方法、ＲＦＬＰをベースとする方法、ＤＮＡ配列決定をベースとする方法、ハイブリダイゼーション法、一本鎖コンホメーション多型（ＳＳＣＰ）、変性剤濃度勾配ゲル電気泳動（ＤＧＧＥ）、不適正塩基対合開裂検出、ヘテロデュプレックス分析、質量分析に基づく方法、ＨＰＬＣをベースとする方法、プライマー延長をベースとする方法、および５’－ヌクレアーゼアッセイをベースとする方法を利用できる。前記のように、本発明の使用において述べられる変異対立遺伝子の発現レベルを測定するためには、細胞または組織を含む試料を対象から得る必要があろう。発現の低下または増大は、これらのアッセイにおける野生型対立遺伝子に対比した変異対立遺伝子の発現レベルの有意な違いにより特徴付けられる。発現低下には、変異対立遺伝子の検出可能な発現がないことも含まれる。

【００８９】

本発明の使用のさらに好ましい態様においては、前記ポリヌクレオチドが含むヌクレオチド欠失、付加および／または置換により、第１、第２、第３および／または第４の変異対立遺伝子によりコードされるポリペプチドの活性が、対応する野生型対立遺伝子によりコードされるポリペプチドと比較して変化する。

【００９０】

前記に述べたように、ＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５および／またはＵＧＴ１Ａ１遺伝子のコーディング領域に対応する本明細書において特定されたポリヌクレオチドを含む変異対立遺伝子は、それらの変異対立遺伝子がコードするポリペプチドのアミノ酸配列に影響を与える。したがって変異ポリペプチドは、それらの対応する野生型ポリペプチドと比較すると、変化した生物学的および／または免疫学的特性を示す。本発明の使用において好ましい変異ポリペプチドは、下記のような生物学的活性の変化を示すものである：すなわち触媒活性の低下、増強または完全な喪失を生じる、酵素機能の変化；あるいは輸送活性の低下、増強または完全な喪失を生じる、輸送機能の変化；あるいは信号伝達経路の活性化の変化またはトランスポーターもしくは酵素の機能阻害の変化を生じる、受容体または他の薬物ターゲットへの結合の変化。野生型および変異ポリペプチドの活性をそれぞれ測定するために上記方法を実施する前に、生物学的材料を含む試料、たとえば単離した細胞または組織を、対象から得る必要があろう。変異ポリペプチドがそれの対応する野生型ポリペプチドと比較して変化した活性または発現レベルをもつかは、当技術分野で周知の標準的方法により判定できる。そのような標準方法には、たとえば下記のものが含まれる：ＥＬＩＳＡをベースとするアッセイ、ＲＩＡをベースとするアッセイ、ＨＰＬＣをベースとするアッセイ、質量分析をベースとするアッセイ、ウェスタンブロット分析、または下記の文献に記載される当技術分野で既知のアッセイ：

【００９１】

【化９】

[Hitzl, *et al.*, 2001, Pharmacogenetics 11:293-8]; Hoffmeyer, 2000 #77; van Helvoort, 1996 #115; Schumacher, 1997 #116; Cordon-Cardo, 1990 #117; Hafkemeyer, 1998 #118] ： MDR1; [Keppler, *et al.*, 1997, Biol Chem 378:787-91, Suzuki, *et al.*, 1994, Adv Prostaglandin Thromboxane Leukot Res 22:83-9, Scheffer, *et al.*, 2000, Cancer Res 60:5269-77, Konig, *et al.*, 1999, Biochim Biophys Acta 1461:377-94, Kool, *et al.*, 1997, Cancer Res 57:3537-47, Bakos, *et al.*, 2000, Mol Pharmacol 57:760-8, Keppler, *et al.*, 1998, Chem Biol Interact 112:153-61, Leier, *et al.*, 2000, Kidney Int 57:1636-42, Evers, *et al.*, 2000, Br J Cancer 83:366-74, Evers, *et al.*, 2000, Br J Cancer 83:375-83] ： MRP1; [Janardan, *et al.*, 1996, Pharmacogenetics 6:379-85, Kivisto, *et al.*, 1996, Br J Clin Pharmacol 42:387-9, Lown, *et al.*, 1994, Drug Metab Dispos 22:947-55, Anttila, *et al.*, 1997, Am J Respir Cell Mol Biol 16:242-9, Tateishi, *et al.*, 1999, Biochem Pharmacol 57:935-9, Gibbs, *et al.*, 1999, Drug Metab Dispos 27:180-7, Maenpaa, *et al.*, 1998, Pharmacogenetics 8:137-55, Haehner, *et al.*, 1996, Mol Pharmacol 50:52-9, Lown, *et al.*, 1994, Drug Metab Dispos 22:947-55] ： CYP3A5; [Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202, Iyer, *et al.*, 1999, Clin Pharmacol Ther 65:576-82, Iolascon, *et al.*, 2000, J Med Genet 37:712-3, Raijmakers, *et al.*, 2000, J Hepatol 33:348-51, von Ahsen, *et al.*, 2000, Clin Chem 46:1939-45, Beutler, *et al.*, 1998, Proc Natl Acad Sci U S A 95:8170-4, Kadakol, *et al.*, 2000, Hum Mutat 16:297-306] ： UGT1A1.

【００９２】
本発明の使用において活性の変化とは、野生型ポリペプチドの活性と変異ポリペプチドの活性に有意な違いがあることを意味する。有意な違いは、本明細書において前記に述べた標準的統計学的方法により判定できる。

【００９３】
最も好ましくは、活性の変化は活性の低下または増強である。発現の増大または低下に関して記載したように、活性の低下または増強は本明細書に述べられるアッセイにおける野生型ポリペプチドに対する変異ポリペプチドの活性の有意な違いにより特徴づけられる。活性低下には、変異対立遺伝子の検出可能な活性がないことも含まれる。

【００９４】
さらに、本発明の使用におけるより好ましい態様においては、対象は動物である。上記のように、本発明の使用における対象には動物が含まれる。本明細書中で用いる用語“動物”には、すべての動物、好ましくは脊椎動物ファミリー、より好ましくは哺乳動物に属する動物が含まれる。さらに、１以上の前記ポリヌクレオチドを動物のゲノムに組み込ませるために遺伝子導入および相同組換えを含めた周知の方法で、動物を遺伝子工学的に処理することもできる。遺伝子工学的に処理した動物を含めたそのような動物を用いて、本明細書に述べられる物質またはその誘導体を基礎とする薬物またはプロドラッグ、好ましくはイリノテカンの薬理作用を調べることができる。

【００９５】
前記において、最も好ましくは、動物はマウスまたはラットである。それらの動物は、本発明の使用において述べられる物質またはその誘導体の薬理学的特性をアッセイするのに特に好適である；詳細はＧｉｏｖａｎｅｌｌａ，ｅｔ ａｌ．，１９９１；Ｃａｎｃｅｒ Ｒｅｓ ５１：３０５２－５；Ｋｕｎｉｍｏｔｏ，ｅｔ ａｌ．，１９８７，Ｃａｎｃｅｒ Ｒｅｓ ４７：５９４４－７；Ｋａｎｅｄａ，ｅｔ ａｌ．，１９９０，Ｃａｎｃ

ｅｒ Ｒｅｓ ５０：１７１５－２０に記載。
【００９６】
好ましくは、上記マウスは機能性シトクロムＰ４５０、ＭＲＰ１またはＭＤＲ１を欠如する。機能性シトクロムＰ４５０、ＭＲＰ１またはＭＤＲ１を欠如するマウスを得る方法は当技術分野で周知である。たとえばそれらのマウスは、下記の文献に記載されるように相同組換えにより作製できる：Ｐ４５０に関して、Ｐｉｎｅａｕ，ｅｔ ａｌ．，１９９８，Ｔｏｘｉｃｏｌ Ｌｅｔｔ １０３：４５９－６４；ＭＲＰ１に関して、Ｒａｐｐａ，ｅｔ ａｌ．，２０００，Ｂｉｏｃｈｅｍｉｓｔｒｙ ３９：３３０４－１０；そしてＭＤＲ１に関して、Ｓｃｈｉｎｋｅｌ，１９９８，Ｉｎｔ Ｊ Ｃｌｉｎ Ｐｈａｒｍａｃｏｌ Ｔｈｅｒ ３６：９－１３；Ｓｃｈｉｎｋｅｌ，ｅｔ ａｌ．，２０００，Ｐｈａｒｍａｃｏｇｅｎｅｔｉｃｓ １０：５８３－９０。
【００９７】
さらに、本発明の使用の別の好ましい態様においては、対象はヒトである。
特に、前記から明らかなとおり本発明はヒトに適用できる。本発明の使用は、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、および膵癌を患う患者を治療し、またはその患者における副作用を阻止するために適用される。前記物質またはその誘導体のヒトにおける薬理作用については十分な記載がある。しかし、慣用的な療法は患者個体の遺伝的性質を考慮していない。人種別集団は異なる遺伝的背景をもち、これも変異対立遺伝子の機能または調節に影響を与え、これにより薬物またはプロドラッグの基礎として本発明において使用する物質または誘導体に対する患者の薬理学的応答を変化させる可能性がある。
【００９８】
以上のことからみて、きわめて慎重に、アフリカ人集団からヒトを選択する；アフリカ人種は、白人種または日本人種（約５０％）と比較してより高い頻度（約８０％）でＭＤＲ１高発現性（high expressor）の対立遺伝子（ＭＤＲ１遺伝子、寄託番号Ｍ２９４４５の位置１３７に対応する位置にヌクレオチドＣ）を示し、したがってイリノテカン毒性を被る可能性がより高い（集団頻度データの出典［Ｃａｓｃｏｒｂｉ，ｅｔ ａｌ．，２００１，Ｊ Ｃｌｉｎ Ｐｈａｒｍａｃｏｌ Ｔｈｅｒ ６９：１６９－７４；Ａｍｅｙａｗ，ｅｔ ａｌ．，２００１，Ｐｈａｒｍａｃｏｇｅｎｅｔｉｃｓ １１：２１７－２１；Ｉｔｏ，ｅｔ ａｌ．，２００１，Ｐｈａｒｍａｃｏｇｅｎｅｔｉｃｓ １１：１７５：８４］）。
【００９９】
以上のことからみて、最も好ましくはヒトはアフリカ人種またはアジア人種である。アジア人集団（１６％）は白人種（３９％）と比較してより低い頻度でＵＧＴ１Ａ１低発現性（lower expressor）の遺伝子型（ＵＧＴ１Ａ１遺伝子、寄託番号ＧＩ：１１１１８７４０の位置１７４９９０－１７４９９３に対応する位置においてホモ接合性野生型）を示し、したがってイリノテカン毒性を被る可能性がより低い。他方、この対立遺伝子はアフリカ人種にはより多くみられる（４３％）。アフリカ人種はさらに別の低発現性の対立遺伝子（ＵＧＴ１Ａ１遺伝子、寄託番号ＧＩ：１１１１８７４０の位置１７４９８９／１７４９９０に対応する位置にＴＡの挿入）をもち、そのホモ接合遺伝子型は７％に起きる。したがって、アフリカ人種はイリノテカン関連の有害事象を生じる可能性がより大きい（集団頻度データの出典［Ｂｅｕｔｌｅｒ，ｅｔ ａｌ．，１９９８，Ｐｒｏｃ Ｎａｔｌ Ａｃａｄ Ｓｃｉ ＵＳＡ ９５：８１７０－４；Ｌａｍｐｅ，ｅｔ ａｌ．，１９９９，Ｐｈａｒｍａｃｏｇｅｎｅｔｉｃｓ ９：３４１－９；Ｈａｌｌ，ｅｔ ａｌ．，１９９９，Ｐｈａｒｍａｃｏｇｅｎｅｔｉｃｓ ９：５９１－９］）。
【０１００】
本発明はまた、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、および膵癌を患う対象に適切な療法を選択するための、下記を含む方法に関する：
（ａ）対象から得た試料中の対象のゲノム中における前記に述べた第１、第２、第３および／または第４の変異対立遺伝子の存在または不存在を判定し；そして

（ｂ）（ａ）において得た結果に基づいてその対象に適切な療法を選択すること。

【０１０１】

前記において行った定義および説明を、必要に応じて変更を加えて上記方法に適用する。本明細書中で用いる用語“適切な療法”は、本発明による物質を選択してその対象に特定量で投与し、その際、その物質および投与量を、本発明の使用において述べられる第１、第２、第３および／または第４の変異対立遺伝子の存在または不存在についての知見に基づいて選択することを意味する。そのような物質およびその物質の投与量は、一方ではそれらが結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、および膵癌の治療または予防に最も有効であり、他方ではそれらが毒性または望ましくない副作用を生じないように選択される。

【０１０２】

前記から明らかなように、適切な療法を選択するための前提条件は、本発明の使用において述べられた第１、第２、第３および／または第４の変異対立遺伝子の存在または不存在についての知見である。したがって本発明方法は、対象から得た試料中における前記の変異対立遺伝子の存在または不存在を判定することを含む。対象から得る試料には、前記の変異対立遺伝子の存在または不存在を判定するのに適した生物学的材料、たとえば単離した細胞または組織が含まれる。本発明方法の変異対立遺伝子の存在または不存在を判定するための方法は、本明細書において前記に述べた方法が含まれる。

【０１０３】

本発明方法により、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、および膵癌を患う対象、好ましくはヒトに適切な療法を効果的に選択できる。これにより、不適正な投薬に基づく患者の不適正な治療、およびそれの結果、たとえば癌療法に対する耐性の発現およびそれに伴う保健費の増大を効果的に避けることができる。さらに、初回投薬の前に高リスク患者を療法から除外でき、および／またはその個体の遺伝的性質に従って薬物療法の開始前に投与量を調整できる。また、遺伝子判定した患者サブポピュレーションに前記トランスポーター遺伝子（たとえばＭＤＲ１）の阻害薬を適用できる。こうして、有害作用を避けることができ、時間および経費のかかる薬物モニタリングに基づいた投与量決定をすることなく速やかに最適薬物レベルに到達できる。これにより疾病の医療費および間接経費を低減することができる（たとえば患者の入院時間の短縮および回数の減少）。

【０１０４】

前記のように本発明は好ましくは、第１のＭＤＲ１の変異対立遺伝子、所望により、第２のＭＲＰ１の変異対立遺伝子、所望により、第３のＣＹＰ３Ａ５の変異対立遺伝子、および、所望により、第４のＵＧＴ１Ａ１の変異対立遺伝子を有するゲノムをもつ対象において、結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、および膵癌を治療するための医薬組成物の調製のための、イリノテカンまたはその誘導体の使用を包含する。しかし、他の組合わせの順位序列も本発明の範囲に含まれる。そのような組合わせの順位序列においては、ＭＲＰ１、ＵＧＴ１Ａ１またはＣＹＰ３Ａ５を第１の変異対立遺伝子として選択し、残りの変異対立遺伝子、すなわち第２、第３および第４の変異対立遺伝子はＭＤＲ１を含めた遺伝子群（ただし、第１の変異対立遺伝子として選択した遺伝子を除いたもの）から選択できる。結論として、第１の変異対立遺伝子はＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ１またはＣＹＰ３Ａ５であってよく、第２の変異対立遺伝子は第１の変異対立遺伝子として選択した遺伝子を除く同じ遺伝子群から選択され、第３の変異対立遺伝子は第１および第２の変異対立遺伝子として選択した遺伝子を除く同じ遺伝子群から選択され、第４の変異対立遺伝子は第１、第２または第３の変異対立遺伝子として選択しなかった遺伝子である。前記において行った定義および説明を、必要に応じて変更を加えてこのような場合に適用する。

【０１０５】

以下の５９の項目も本発明に包含される。前記において行った定義および説明を、必要に応じて変更を加えて、特許請求の範囲を特徴付けるために用いた用語に適用する。

１．癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：
（ａ）患者の遺伝子型をアッセイして、その患者がＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子のうちの２以上のものの変異対立遺伝子を有するかを判定し；そして
（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量のイリノテカンをその患者に投与すること。この量は、ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５およびＵＧＴ１Ａ１遺伝子のうちの２以上のものにおけるそれら患者の対立遺伝子を考慮せずに投与する量と比較して増大または減少される。
【０１０６】
２．ＭＤＲ１遺伝子がそれら２以上の遺伝子の１つである、項目１の方法。
３．それら遺伝子がＭＤＲ１およびＭＲＰ１である、項目１の方法。
４．それら遺伝子がＭＤＲ１およびＣＹＰ３Ａ５である、項目１の方法。
【０１０７】
５．それら遺伝子がＭＤＲ１およびＵＧＴ１Ａ１である、項目１の方法。
６．それら遺伝子がＭＤＲ１、ＭＲＰ１およびＣＹＰ３Ａ５である、項目１の方法。
７．それら遺伝子がＭＤＲ１、ＭＲＰ１およびＵＧＴ１Ａ１である、項目１の方法。
【０１０８】
８．それら遺伝子がＭＤＲ１、ＭＲＰ１およびＣＹＰ３Ａ５である、項目１の方法。
９．それら遺伝子がＭＤＲ１、ＣＹＰ３Ａ５およびＵＧＴ１Ａ１である、項目１の方法。
１０．それら遺伝子がＭＲＰ１およびＵＧＴ１Ａ１である、項目１の方法。
【０１０９】
１１．それら遺伝子がＭＲＰ１およびＣＹＰ３Ａ５である、項目１の方法。
１２．それら遺伝子がＭＲＰ１、ＣＹＰ３Ａ５およびＵＧＴ１Ａ１である、項目１の方法。
１３．それら遺伝子がＭＲＰ１およびＵＧＴ１Ａ１である、項目１の方法。
【０１１０】
１４．それら遺伝子がＣＹＰ３Ａ５およびＵＧＴ１Ａ１である、項目１の方法。
１５．癌が結腸直腸癌、子宮頚癌、胃癌、肺癌、悪性神経膠腫、卵巣癌、または膵癌である、項目１のいずれか１つに記載の方法。
１６．下記の、項目１５の方法：
（ａ）それら１以上の変異対立遺伝子により患者はＭＤＲ１遺伝子生成物の発現量が少なくなり、それにより、毒性を避けるためにその患者へのイリノテカン投与量を減らす；または
（ｂ）それら１以上の変異対立遺伝子により患者はＭＤＲ１遺伝子生成物の発現量が多く、したがって有効性を高めるためにその患者へのイリノテカン投与量を増加する。
【０１１１】
１７．それら変異対立遺伝子がそれら２以上の遺伝子のプロモーター領域にある、項目１６の方法。
１８．それら変異対立遺伝子がそれら２以上の遺伝子のコーディング領域にある、項目１６の方法。
１９．それら２以上の遺伝子それぞれが２以上の変異対立遺伝子を有する、項目１６の方法。
【０１１２】
２０．それら２以上の遺伝子それぞれがそのプロモーター領域に１以上の変異対立遺伝子を有し、そしてそのコーディング領域に１以上の変異対立遺伝子を有する項目１６の方法。
２１．それら２以上の遺伝子それぞれがそのプロモーター領域に１以上の変異対立遺伝子を有するか、またはそのコーディング領域に１以上の変異対立遺伝子を有する、項目１６の方法。

【０１１３】
２２．それら１以上の変異対立遺伝子がそれら２以上の遺伝子のプロモーター領域またはコーディング領域のいずれにもない、項目１６の方法。
２３．ＭＤＲ１がそれら２以上の遺伝子の１つである場合、それら１以上の変異対立遺伝子が下記のものよりなる群から選択されるポリヌクレオチドを含む、項目１６の方法：
（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：
【０１１４】
【化１０】

SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422, 425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482, 485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 および／または 641;

【０１１５】
（ｂ）ＳＥＱ ＩＤ ＮＯ：６０６、６０８、６１０、６１２、６１８、６２０、６２２、６２４および／または６２８のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）多剤耐性１（ＭＤＲ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって、下記の位置に対応する位置において少なくとも１個のヌクレオチドの置換または欠失を有するポリヌクレオチド：
ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の
【０１１６】
【化１１】

位置 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619

【０１１７】
および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の
【０１１８】
【化１２】

位置 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162

【０１１９】
および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１、３０８、
および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１３７、１７６；
（ｄ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８３９４６、７０２００、７０２３７、６５２４１、および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１および／

または、ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４１５２９、１７４９０１、１３９１７７、１４０１１８、１４０５６８、１４０７２７、１３９４７９に対応する位置にＡを；ＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置３０８および／または、ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８４７０１、８３９７３、８４０７４、８４１１９、７８１７０、７０２０４、７０２５３、７０３７１、５０５３７、４３１６２、および／またはＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１３７または１７６、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４５９８４、１７１４６６、１７５０６８、１７５０７４、１３９０６４、１３９２７６、１４０５７６に対応する位置にＴを；ＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４０８３７、１７１４０４、１７１４５６、１７１５１１、１７１５１２、１３９１１９、１４０４９０、１３９６１９、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置４３２６３に対応する位置にＣを；ＭＤＲ１遺伝子（寄託番号：ＡＣ００５０６８）の位置８４０３２、７７８１１、７３２５２、および／またはＭＤＲ１遺伝子（寄託番号：ＡＣ００２４５７）の位置１４１５９０、１７５１４２、１７５１８０、１３９０１５、１４０２１６、１４０５９５に対応する位置にＧを有するポリヌクレオチド；

（ｅ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置２１、１０３、１６８、４００、８９３、９９９、１００１、１１０７および／または１１４１に対応する位置においてアミノ酸置換を含む；

（ｆ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置２１に対応する位置におけるＡｓｎからＡｓｐへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１０３に対応する位置におけるＰｈｅからＬｅｕへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１６８に対応する位置におけるＶａｌからＩｌｅへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００に対応する位置におけるＳｅｒからＡｓｎへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置８９３に対応する位置におけるＡｌａからＳｅｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置９９９に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１００１に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１０７に対応する位置におけるＧｌｎからＰｒｏへの置換；または／およびＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置１１４１に対応する位置におけるＳｅｒからＴｈｒへの置換。

【０１２０】

２４．ポリヌクレオチドが下記のものよりなる群から選択される、項目２３の方法：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：３４５、４１７または６３６のいずれか１つの核酸配列を有するポリヌクレオチド；

（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６１２または６１８のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；

（ｃ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６、またはＭＤＲ１遺伝子（寄託番号：ＧＩ：１０１２２１３５）の位置８８８８３に対応する位置において置換を有するポリヌクレオチド：

（ｄ）ＭＤＲ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４３２）の位置１０１もしくはＭＤＲ１遺伝子（寄託番号：ＧＩ：１０１２２１３５）の位置８８８８３に対応する位置にＡを；または、ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６もしくはＭＤＲ１遺伝子（寄託番号：ＧＩ：１０

１２２１３５）の位置８８８８３に対応する位置にＴを有するポリヌクレオチド；
（ｅ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは、ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００または８９３に対応する位置においてアミノ酸置換を含む；および
（ｆ）ＭＤＲ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは、ＭＤＲ１ポリペプチド（寄託番号：Ｇ２５０６１１８）の位置４００に対応する位置におけるＳｅｒからＡｓｎへの、または位置８９３に対応する位置におけるＡｌａからＳｅｒへのアミノ酸置換を含む。
【０１２１】
２５．ＭＲＰ１がそれら２以上の遺伝子の１つである場合、ＭＲＰ１の１以上の変異対立遺伝子が下記のものよりなる群から選択されるポリヌクレオチドを含む、項目１６の方法：
（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：
【０１２２】
【化１３】

SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 および／または 334;

【０１２３】
（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６００、６０２および／または６０４のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）多剤耐性タンパク質１（ＭＲＰ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５７９９８、５７８５３、５３２８２および／または３９５０８に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６６７、１３７６４７、１３７７１０、１２４６６７および／または３８６４６に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７２５８、２７１５９、３４２１８、３４２１５、５５４７２および／または３４２０６－３４２０７に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置２１１３３、１４００８、１８０６７、１７９７０および／または１７９００に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置７９、８８および／または２４９に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５および／または２５９に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２５２７７）の位置１５０７２７および／または３３３５１に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２８）の位置１７４に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２４８および／または２５８に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１８８４、１６２５、１１６３、３８１、２３３、１８９、４４０および／または１７２０－１７２３に対応する位置における少なくとも１個のヌクレオチドの置

換または欠失；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７および／または４３７／４３８に対応する位置における少なくとも１個のヌクレオチドの挿入；あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置５５１５６／５５１５７に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド；

（ｄ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置２１１３３、１４００８および／または１８１９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７２５８および／または３４２１８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置７９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５７９９８および／または５７８５３に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６６７および／または１３７６４７に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２５２７７）の位置１５０７２７および／または３３５５１に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２４８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１８８４、１６２５、２３３および／または１８９に対応する位置にＡを；ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置３９５０８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１７９００、１８０６７および／または１８１９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２８）の位置１７４に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置４４０および／または１１６３に対応する位置にＴを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置８８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置２７１５９、５５４７２および／または３４２１５に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７および／または３８６４６に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５３２８２に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７７１０に対応する位置にＣを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８２９）の位置２５８に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９に対応する位置、あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１に対応する位置にＧを；ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１７９７０に対応する位置におけるＴの欠失を；あるいは、ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置３４２０６－３４２０７に対応する位置におけるＡＴの欠失を；あるいは、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１７２０－１７２３に対応する位置におけるＧＧＴＡの欠失を；ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置におけるＴの挿入および／または４３７／４３８に対応する位置におけるＴＣＣＴＴＣＣの挿入を；ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置５５１５６／５５１５７に対応する位置におけるＴＧＧＧＧＣの挿入を有するポリヌクレオチド；

（ｅ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置２３９に対応する位置におけるＰｈｅからＣｙｓへの置換；または／およびＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置４３３に対応する位置におけるＡｒｇからＳｅｒへの置換；または／およびＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置７２３に対応する位置におけるＡｒｇからＧｌｎへの置換。

【０１２４】

２６．ポリヌクレオチドが下記のものよりなる群から選択される、項目２５の方法：

（ａ）ＳＥＱ　ＩＤ　ＮＯ：１８１、２０９、２１７、２０５、２７７、２８１、３０１、３２５、２２９、１９３、３１３、２９３または２５３のいずれか１つの核酸配列を有

するポリヌクレオチド；
（ｂ）ＳＥＱ　ＩＤ　ＮＯ：６００のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６４７、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５、ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５３２８２、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１、４４０、１６２５、ＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置３４２１８、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１８０６７または１７９００に対応する位置における置換；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド；
（ｄ）ＭＲＰ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１３７６４７、ＭＲＰ１遺伝子（寄託番号：Ｕ９１３１８）の位置１８０６７、１７９００、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置４４０に対応する位置にＴを；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置９５、ＭＲＰ１遺伝子（寄託番号：ＡＣ０２６４５２）の位置１２４６６７に対応する位置にＣを；ＭＲＰ１遺伝子（寄託番号：ＧＩ：７２０９４５１）の位置５３２８２、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３０）の位置２４９、ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の位置２５９、ＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置３８１に対応する位置にＧを；またはＭＲＰ１遺伝子（寄託番号：ＡＣ００３０２６）の位置３４２１８もしくはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置１６２５に対応する位置にＡを；あるいはＭＲＰ１遺伝子（寄託番号：Ｕ０７０５０）の位置９２６／９２７に対応する位置におけるＴの挿入を有するポリヌクレオチド；
（ｅ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置３２９に対応する位置におけるアミノ酸置換を含む；
（ｆ）ＭＲＰ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＭＲＰ１ポリペプチド（寄託番号：Ｇ２８２８２０６）の位置３２９に対応する位置におけるＰｈｅからＣｙｓへのアミノ酸置換を含む。
【０１２５】
２７．ＣＹＰ３Ａ５がそれら２以上の遺伝子の１つである場合、ＣＹＰ３Ａ５の１以上の変異対立遺伝子が下記のものよりなる群から選択されるポリヌクレオチドを含む、項目１６の方法：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：１３７、１３８、１４１、１４２、１４５、１４６、１４９および／または１５０のいずれか１つの核酸配列を有するポリヌクレオチド；
（ｂ）シトクロムＰ４５０サブファミリーＩＩＩＡ（ニフェジピンオキシダーゼ）ポリペプチド５（ＣＹＰ３Ａ５）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８および／または９７３６に対応する位置における少なくとも１個のヌクレオチドの置換；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１および／または１４５９２９に対応する位置における少なくとも１個のヌクレオチドの置換を有するポリヌクレオチド；
（ｃ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８に対応する位置にＣを；ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１および／または１４５９２９に対応する位置にＧを；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置９７３６に対応する位置にＧを有するポリヌクレオチ

ド。
【０１２６】
２８．ポリヌクレオチドが下記のものよりなる群から選択される、項目２７の方法：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：１３７、１４１、１４５または１４９のいずれか１つの核酸配列を有するポリヌクレオチド；
（ｂ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８もしくは９７３６、またはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１もしくは１４５９２９に対応する位置における置換を有するポリヌクレオチド；
（ｃ）ＣＹＰ３Ａ５遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置４７５１８に対応する位置にＣを；あるいはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１０２８１４５１）の位置９７３６またはＣＹＰ３Ａ５遺伝子（寄託番号：ＧＩ：１１１７７４５２）の位置１４５６０１もしくは１４５９２９に対応する位置にＧを有するポリヌクレオチド。
【０１２７】
２９．ＵＧＴ１Ａ１がそれら２以上の遺伝子の１つである場合、それら１以上の変異対立遺伝子が下記のものよりなる群から選択されるポリヌクレオチドを含む、項目１６の方法：
（ａ）下記のいずれか１つの核酸配列を有するポリヌクレオチド：
【０１２８】
【化１４】

SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 および／または 134;

【０１２９】
（ｂ）下記のいずれか１つのアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド：
【０１３０】
【化１５】

SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 および／または 598;

【０１３１】
（ｃ）ウリジン二リン酸グリコシルトランスフェラーゼ１メンバーＡ１（ＵＧＴ１Ａ１）遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５９、１６０、２２６、５３９、５４４、６４０、７０１、８４１、８５５、８９０、９３８、１００６、１００７、１０２０、１０８４、１０８５、１１１４、１１１７、１１３９、１１５８、１１７５－１１７６、１２１６、１２９７、１３２４、１４７１、１４７８、３７２－３７３、５２３－５２５および／または８９２－９０５に対応する位置における少なくとも１個のヌクレオチドの置換または欠失；あるいは、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置４７０／４７１および／または１２２２／１２２３に対応する位置における少なくとも１個のヌクレオチドの挿入を有するポリヌクレオチド：

（ｄ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置２２６、５３９、７０１、８５５、９３８、１０２０および／または１１１７に対応する位置にＡを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１６０、６４０、８９０、１００６、１０８４、１１３９、１１７６、１３２４および／または１４７８に対応する位置にＴを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５４４、８４１および／または１２１６に対応する位置にＣを；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：１８１３０３）の位置５９、１００７、１０８５、１１１４、１１５８、１１７５、１２９７および／または１４７１に対応する位置にＧを；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置３７２－３７３に対応する位置におけるＣＴの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置５２３－５２５に対応する位置におけるＴＴＣの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置８９２－９０５に対応する位置におけるＴＡＣＡＴＴＡＡＴＧＣＴＴＣの欠失を；ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置４７０／４７１に対応する位置におけるＴの挿入を；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１２２２／１２２３に対応する位置におけるＧの挿入を有するポリヌクレオチド；

（ｅ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドは下記のアミノ酸置換を含む：ＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１５に対応する位置におけるＬｅｕからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置７１に対応する位置におけるＧｌｙからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１７５に対応する位置におけるＬｅｕからＧｌｎへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１７７に対応する位置におけるＣｙｓからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２０９に対応する位置におけるＡｒｇからＴｒｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２２９に対応する位置におけるＰｒｏからＧｌｎへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２７６に対応する位置におけるＧｌｙからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９２に対応する位置におけるＡｌａからＶａｌへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９３に対応する位置におけるＴｙｒからＴｒｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３０８に対応する位置におけるＧｌｙからＧｌｕへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３３１に対応する位置におけるＧｌｎからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３５７に対応する位置におけるＧｌｎからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３６７に対応する位置におけるＡｒｇからＧｌｙへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３６８に対応する位置におけるＡｌａからＴｈｒへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３８７に対応する位置におけるＰｒｏからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３７５に対応する位置におけるＳｅｒからＰｈｅへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置３８１に対応する位置におけるＳｅｒからＡｒｇへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置４０１に対応する位置におけるＡｌａからＰｒｏへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置４２８に対応する位置におけるＬｙｓからＧｌｕへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置４８６に対応する

位置におけるＴｙｒからＡｓｐへの置換；または／およびＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置４８８に対応する位置におけるＳｅｒからＰｈｅへの置換；
（ｆ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置３７２－３７３に対応する位置におけるＣＴの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１１９に対応する位置におけるアミノ酸Ａｓｐに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置４７０／４７１に対応する位置にＴの挿入を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１５２に対応する位置におけるアミノ酸Ｐｒｏに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置５２３－５２５に対応する位置におけるＴＴＣの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置１６８に対応する位置におけるアミノ酸Ｔｈｒに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置８９２－９０５に対応する位置におけるＴＡＣＡＴＴＡＡＴＧＣＴＴＣの欠失を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置２９２に対応する位置におけるアミノ酸Ａｌａに続く１個以上のアミノ酸が置換、付加および／または欠失し；ならびに／あるいはＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３６）の位置１２２２／１２２３に対応する位置におけるＧの挿入を有し、これにより該ポリペプチドにおいてＵＧＴ１Ａ１ポリペプチド（寄託番号：Ｇ８８５０２３６）の位置４０２に対応する位置におけるアミノ酸Ｌｙｓに続く１個以上のアミノ酸が置換、付加および／または欠失するポリヌクレオチド；および
（ｇ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリヌクレオチドはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置４９に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置２８０に対応する位置におけるＣｙｓから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３３１に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３３５に対応する位置におけるＴｒｐから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置３５７に対応する位置におけるＧｌｎから終止コドンへのアミノ酸置換、および／またはＵＧＴ１Ａ１遺伝子（寄託番号：Ｇ８８５０２３６）の位置４３７に対応する位置におけるＬｙｓから終止コドンへのアミノ酸置換を含む。

【０１３２】

３０．ポリヌクレオチドが下記のものよりなる群から選択される、項目２９の方法：
（ａ）ＳＥＱ　ＩＤ　ＮＯ：３７、６９または９７のいずれか１つの核酸配列を有するポリヌクレオチド；
（ｂ）ＳＥＱ　ＩＤ　ＮＯ：５５８、５７０または５８４のアミノ酸配列を有するポリペプチドをコードするポリヌクレオチド；
（ｃ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置８９０、１１１７または１４７１に対応する位置における置換を有するポリヌクレオチド；
（ｄ）ＵＧＴ１Ａ１遺伝子にハイブリダイズしうるポリヌクレオチドであって、ＵＧＴ１Ａ１遺伝子（寄託番号：ＧＩ：８８５０２３５）の位置１１１７に対応する位置にＡを、位置８９０に対応する位置にＴを、または位置１４７１に対応する位置にＧを有するポリヌクレオチド；

（ｅ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置２９２、３６８または４８６に対応する位置におけるアミノ酸置換を含む；
（ｆ）ＵＧＴ１Ａ１ポリペプチドまたはそのフラグメントをコードするポリヌクレオチド：該ポリペプチドはＵＧＴ１Ａ１ポリペプチド（寄託番号：ＧＩ：８８５０２３６）の位置２９２に対応する位置におけるＡｌａからＶａｌへの、位置３６８に対応する位置におけるＡｌａからＴｈｒへの、または位置４８６に対応する位置におけるＴｙｒからＡｓｐへのアミノ酸置換を含む。

【０１３３】

３１．患者がイリノテカンによる治療に対する中毒反応のリスクをもつかを判定する方法であって、ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子を含む２以上の遺伝子の１以上の変異対立遺伝子をその患者が有するかを判定することを含む方法。
３２．さらに、患者に低下された量のイリノテカンを投与することを含む、項目３１の方法。

【０１３４】

３３．癌を患う患者にイリノテカンを投与するのに最適な治療方式を判定するための、下記を含む方法：
（ａ）その患者が、ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有するかを判定し；
（ｂ）２以上の前記遺伝子それぞれの１以上のそのような対立遺伝子を有する患者において、２以上の前記遺伝子におけるその患者の対立遺伝子を考慮せずにイリノテカンを投与する場合その患者におけるピーク量と比較して、その患者におけるイリノテカンのピーク量を低下させるように方式を変更すること。

【０１３５】

３４．ＭＤＲ１遺伝子がそれら２以上の遺伝子の１つである、項目３３の方法。
３５．ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有する患者において癌を治療する方法であって、これら２以上の遺伝子の遺伝子生成物の発現レベルが一般集団のものより低いためイリノテカンに対する高い感受性を示す場合は、その患者に減少された量のイリノテカンを投与することを含む方法。

【０１３６】

３６．ＭＤＲ１遺伝子がそれら２以上の遺伝子の１つである、項目３５の方法。
３７．ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有する患者において癌を治療する方法であって、これら２以上の遺伝子の遺伝子生成物の発現レベルが一般集団のものより高いためイリノテカンに対する耐性または耐性素質を示す場合は、その患者に増加された量のイリノテカンを投与することを含む方法。

【０１３７】

３８．ＭＤＲ１遺伝子がそれら２以上の遺伝子の１つである、項目３７の方法。
３９．患者を１種類以上の阻害薬で治療し、さらに、その際、阻害薬がＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５およびＵＧＴ１Ａ１の阻害薬よりなる群から選択される、項目３７の方法。
４０．それら阻害薬の１つがＭＤＲ１阻害薬である、項目３９の方法。

【０１３８】

４１．ＭＤＲ１阻害薬が下記のものよりなる群から選択される、項目４０の方法：ＧＦ１２０９１８、ＬＹ３３５９７９、ＸＲ９５７６、ＸＲ９０５１、フラボノイド（たとえばアピゲニン（ａｐｉｇｅｎｉｎ）、ゲニスチン（ｇｅｎｉｓｔｉｎ）、ナリンギン（ｎａｒｉｎｇｉｎ）、ケルセチン（ｑｕｅｒｃｅｔｉｎ）、フラボン、フラボノン、フラボピ

リドール）、ベルガモッチン（ｂｅｒｇａｍｏｔｔｉｎ）、クラリスロマイシン、ケトコナゾール（Ｋｅｔｏｃｏｎａｚｏｌｅ）、レセルピン、１，９－ジデオキシフォルスコリン（１，９－ｄｉｄｅｏｘｙｆｏｒｓｋｏｌｉｎ）、アジドピン（Ａｚｉｄｏｐｉｎｅ）、ジメチル－ｂ－シクロデキストリン、イベルメクチン（Ｉｖｅｒｍｅｃｔｉｎ）、ＳＤＺ　ＰＳＣ８３３、ＳＤＺ　２８０－４４６、Ｂ６６９、Ｂ－８５９－３５（Ｒ－鏡像異性体）およびその主代謝産物、ＭＳ－２０９（キノロン誘導体）、ＰＡＫ－１０４ｐ、アミロリド（Ａｍｉｌｏｒｉｄｅ）、アミトリプチリン（Ａｍｙｔｒｉｐｔｙｌｉｎｅ）、アトルバスタチン（Ａｔｏｒｖａｓｔａｔｉｎ）、オーレオバシジン（Ａｕｒｅｏｂａｓｉｄｉｎ）および類似体、フッ化ベリリウム（ＢｅＦｘ）、カルモジュリン阻害薬、クロロキン、クロロプロマジン、クロファジミン（Ｃｌｏｆａｚｉｍｉｎｅ）、クレモフォル（Ｃｒｅｍｏｐｈｏｒ）ＥＬ、ジルチアゼム（Ｄｉｌｔｉａｚｅｍ）、ベラパミル（Ｖｅｒａｐａｍｉｌ）、ニフェジピン（Ｎｉｆｅｄｉｐｉｎｅ）、ベプリジル（Ｂｅｐｒｉｄｉｌ）、ニカルジピン（Ｎｉｃａｒｄｉｐｉｎｅ）、ニグルジピン（Ｎｉｇｕｌｄｉｐｉｎｅ）、ニトレンジピン（Ｎｉｔｒｅｎｄｉｐｉｎｅ）、トリフルオペラジン（Ｔｒｉｆｌｕｏｐｅｒａｚｉｎｅ）、フェロジピン（Ｆｅｌｏｄｉｐｉｎｅ）、バリノマイシン、ジピリダモール（Ｄｉｐｙｒｉｄａｍｏｌ）、エリスロマイシン、フルオロキノロン類：フレロキサシン（Ｆｌｅｒｏｘａｃｉｎ）、イエノキサシン（Ｅｅｎｏｘａｃｉｎ）、グレパフロキサシン（Ｇｒｅｐａｆｌｏｘａｃｉｎ）、レボフロキサシン（Ｌｅｖｏｆｌｏｘａｃｉｎ）、ノルフロキサシン（Ｎｏｒｆｌｏｘａｃｉｎ）、グリベンクラミド（Ｇｌｉｂｅｎｃｌａｍｉｄｅ）類および類似体、グルコネート塩類、グラミシジン（Ｇｒａｍｉｃｉｄｉｎ）、ヒドロコルチゾン、イトラコナゾール（Ｉｔｒａｃｏｎａｚｏｌｅ）、リドカイン、ホスファチジルコリン、プリスチナマイシン（Ｐｒｉｓｔｉｎａｍｙｃｉｎ）Ｉａ、プロパフェノン（Ｐｒｏｐａｆｅｎｏｎｅ）、プロプラノロール（Ｐｒｏｐｒａｎｏｌｏｌ）、タリノロール（Ｔａｌｉｎｏｌｏｌ）、ピリジン類似体、ケルセチン４’－ｂ－グルコシド、キニンおよびキニジン、キナクリン、シンコニン（Ｃｉｎｃｈｏｎｉｎｅ）、リトナビル（Ｒｉｔｏｎａｖｉｒ）、サキナビル（Ｓａｑｕｉｎａｖｉｒ）、ネルフィナビル（Ｎｅｉｆｉｎａｖｉｒ）、タモキシフェン（Ｔａｍｏｘｉｆｅｎ）および代謝産物、タキソイド（四環式タキソピン（ｔａｘｏｐｉｎｅ）Ｃおよび誘導体）、テルフェナジン（Ｔｅｒｆｅｎａｄｉｎｅ）。

【０１３９】

４２．さらに、治療期間中、癌細胞における前記２以上の遺伝子の発現レベルの変化をアッセイすることにより患者をモニターし、これにより前記２以上の遺伝子の発現レベルの増大を、患者に投与するイリノテカンの量の増加により補償することを含む、項目３５の方法。

【０１４０】

４３．ＭＤＲ１遺伝子がそれら２以上の遺伝子の１つである、項目４２の方法。

４４．患者において癌を治療する方法であって、患者に有効量のイリノテカンを内部投与することを含み、その際、患者のＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５およびＵＧＴ１Ａ１を含む遺伝子の遺伝子型に基づいて治療方式を改変する方法。

【０１４１】

４５．癌を患う患者集団を治療するための、下記を含む方法：

（ａ）患者毎に、ＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子をその患者が有するかを判定し；

（ｂ）２以上の前記遺伝子の１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者の２以上の前記遺伝子の対立遺伝子を考慮しない場合の量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【０１４２】

４６．ＭＤＲ１遺伝子がそれら２以上の遺伝子の１つである、項目４５の方法。

４７．癌を患う患者においてイリノテカンに対する感受性を予測する方法であって、その患者がＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される遺伝子を含む２以上の遺伝子それぞれの１以上の変異対立遺伝子を有するかを判定することを含み、そこで、これらの対立遺伝子は癌細胞がこれら２以上の遺伝子のタンパク質を低い量または高い量発現することの指標であり、これにより低発現はイリノテカンに対する感受性が高いことの指標となり、高発現はイリノテカンに対する耐性または耐性素質の指標となる方法。

【０１４３】

４８．さらに、耐性または耐性素質の指標となる遺伝子型を有する患者に、ＭＤＲ１阻害薬、ＭＲＰ１阻害薬、ＣＹＰ３Ａ５阻害薬およびＵＧＴ１Ａ１阻害薬よりなる群から選択される１種類以上の阻害薬を投与することを含む、項目４７の方法。

４９．少なくとも１種類の阻害薬がＭＤＲ１阻害薬である、項目４８の方法。

【０１４４】

５０．ＭＤＲ１阻害薬が下記のものよりなる群から選択される、項目４０の方法：ＧＦ１２０９１８、ＬＹ３３５９７９、ＸＲ９５７６、ＸＲ９０５１、フラボノイド（たとえばアピゲニン、ゲニスチン、ナリンギン、ケルセチン、フラボン、フラボノン、フラボピリドール）、ベルガモッチン、クラリスロマイシン、ケトコナゾール、レセルピン、１，９－ジデオキシフォルスコリン、アジドピン、ジメチル－ｂ－シクロデキストリン、イベルメクチン、ＳＤＺ　ＰＳＣ８３３、ＳＤＺ　２８０－４４６、Ｂ６６９、Ｂ－８５９－３５（Ｒ－鏡像異性体）およびその主代謝産物、ＭＳ－２０９（キノロン誘導体）、ＰＡＫ－１０４ｐ、アミロリド、アミトリプチリン、アトルバスタチン、オーレオバシジンおよび類似体、フッ化ベリリウム（ＢｅＦｘ）、カルモジュリン阻害薬、クロロキン、クロロプロマジン、クロファジミン、クレモフォルＥＬ、ジルチアゼム、ベラパミル、ニフェジピン、ベプリジル、ニカルジピン、ニグルジピン、ニトレンジピン、トリフルオペラジン、フェロジピン、バリノマイシン、ジピリダモール、エリスロマイシン、フルオロキノロン類：フレロキサシン、イエノキサシン、グレパフロキサシン、レボフロキサシン、ノルフロキサシン、グリベンクラミド類および類似体、グルコネート塩類、グラミシジン、ヒドロコルチゾン、イトラコナゾール、リドカイン、ホスファチジルコリン、プリスチナマイシンＩａ、プロパフェノン、プロプラノロール、タリノロール、ピリジン類似体、ケルセチン４’－ｂ－グルコシド、キニンおよびキニジン、キナクリン、シンコニン、リトナビル、サキナビル、ネルフィナビル、タモキシフェンおよび代謝産物、タキソイド（四環式タキソピンＣおよび誘導体）、テルフェナジン。

【０１４５】

５１．治療期間中、耐性または耐性素質の指標となる遺伝子型を有する患者を、癌細胞におけるＭＤＲ１遺伝子生成物の発現レベルの変化をアッセイすることによりモニターし、これにより更新されたイリノテカンに対する感受性の予測値を判定する、項目４７の方法。

【０１４６】

５２．治療期間中、耐性または耐性素質の指標となる遺伝子型を有する患者を、癌細胞におけるＭＲＰ１遺伝子生成物の発現レベルの変化をアッセイすることによりモニターし、これにより更新されたイリノテカンに対する感受性の予測値を判定する、項目４７の方法。

【０１４７】

５３．治療期間中、耐性または耐性素質の指標となる遺伝子型を有する患者を、癌細胞におけるＣＹＰ３Ａ５遺伝子生成物の発現レベルの変化をアッセイすることによりモニターし、これにより更新されたイリノテカンに対する感受性の予測値を判定する、項目４７の方法。

【０１４８】

５４．治療期間中、耐性または耐性素質の指標となる遺伝子型を有する患者を、癌細胞におけるＵＧＴ１Ａ１遺伝子生成物の発現レベルの変化をアッセイすることによりモニター

し、これにより更新されたイリノテカンに対する感受性の予測値を判定する、項目４７の方法。

【０１４９】

５５．治療期間中、耐性または耐性素質の指標となる遺伝子型を有する患者を、癌細胞におけるＭＤＲ１遺伝子、ＭＲＰ１遺伝子、ＣＹＰ３Ａ５遺伝子およびＵＧＴ１Ａ１遺伝子よりなる群から選択される２以上の遺伝子の生成物の発現レベルの変化をアッセイすることによりモニターし、これにより更新されたイリノテカンに対する感受性の予測値を判定する、項目４７の方法。

【０１５０】

５６．癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＭＤＲ１遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者のＭＤＲ１遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【０１５１】

５７．癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＭＲＰ１遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者のＭＲＰ１遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【０１５２】

５８．癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＵＧＴ１Ａ１遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者のＵＧＴ１Ａ１遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【０１５３】

５９．癌を患う患者を治療するためのイリノテカンの使用方法であって、下記を含む方法：

（ａ）その患者が癌組織にＣＹＰ３Ａ５遺伝子の１以上の変異対立遺伝子を有するかを判定し；

（ｂ）１以上のそのような変異対立遺伝子を有する患者において、そのような変異対立遺伝子を有する患者の治療に十分な量であって、患者のＣＹＰ３Ａ５遺伝子における対立遺伝子を考慮せずに投与する量と比較して増大または減少された量のイリノテカンを患者に投与すること。

【０１５４】

本明細書において前記に述べた発現低下には、機能性遺伝子生成物をコードする転写物量が有意に減少することのほか、活性をもたないかまたは活性が有意に低下した遺伝子生成物をコードする転写物量が正常であること、さらには増加することも含まれる。

【０１５５】

“ＭＤＲ１遺伝子における患者の対立遺伝子を考慮せずに投与する量と比較して”とは、

その必要がある患者にその遺伝子型を考慮せずにルーティンに投与する標準量を意味する。そのような一般的な患者集団を、正常な遺伝子型、すなわち野生型の遺伝子型をもつものとみなす。

【０１５６】

さらに本発明は、療法を改善および／または改変する方法であって、ＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ１および／またはＣＹＰ３Ａ５の発現レベル（以下、発現プロフィルという）あるいはＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ１および／またはＣＹＰ３Ａ５タンパク質のタンパク質レベル（以下、タンパク質プロフィルという）あるいはそれらのタンパク質の活性レベル（以下、活性プロフィルという）を判定することを含む方法を包含する。

【０１５７】

本発明の文脈において述べられる用語“発現レベル”は、ハウスキーピング遺伝子、たとえばＰＬＡ２に対する転写物の量と対比したＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５またはＵＧＴ１Ａ１遺伝子の転写物の検出可能な量を意味する。転写物の量は、ノーザン分析、ＲＮＡｓｅ保護アッセイ、ＰＣＲをベースとする方法（Ｔａｑ－Ｍａｎ分析を含む）を含めた標準的分子生物学的方法により測定できる。好ましくは、この測定は後記実施例４および５の記載に従って実施できる。用語“発現プロフィル”は、前述遺伝子のパネルの発現レベルを測定し、この発現レベルを標準試料と比較することを意味する。標準試料としては、それらゲノム中に前述の各遺伝子の野生型対立遺伝子をもつ対象の細胞または組織から転写物を得ることが好ましい。

【０１５８】

用語“タンパク質レベル”は、ハウスキーピング遺伝子、たとえばＰＬＡ２がコードするタンパク質の量と対比したＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５またはＵＧＴ１Ａ１の検出可能な量を意味する。タンパク質の量は、標準的生物学的方法、たとえばウェスタン分析、ＥＬＩＳＡ、ＲＩＡ、または抗体をベースとする当技術分野で既知の他の方法により測定できる。用語“タンパク質プロフィル”は、前述のタンパク質のパネルのタンパク質レベルを測定し、このタンパク質レベルを標準試料と比較されることを意味する。標準試料として、それらゲノム中に各遺伝子の前述の野生型対立遺伝子をもつ対象の細胞または組織からタンパク質を得ることが好ましい。

【０１５９】

用語“活性レベル”は、ＭＤＲ１、ＭＲＰ１、ＣＹＰ３Ａ５またはＵＧＴ１Ａ１の検出可能な生物学的活性であって、その遺伝子の対応する野生型対立遺伝子の活性と対比したものか、または、本発明において開示するこれらの遺伝子の変異対立遺伝子がコードするものの検出可能な量であって、その遺伝子に対応する野生型対立遺伝子がコードするタンパク質の量と対比したものを意味する。前述のタンパク質の生物学的アッセイ法は当技術分野で周知であり、Ｈｉｔｚｌ ｅｔ ａｌ．，２００１，Ｐｈａｒｍａｃｏｇｅｎｅｔｉｃｓ １１：２９３－８；Ｃｕｆｆ ｅｔ ａｌ．，Ｔｏｘｉｃｏｌ Ｌｅｔｔ．，２００１，１２０：４３－９；Ｓｔｅｖｅｎｓ ｅｔ ａｌ．，Ｄｒｕｇ Ｍｅｔａｂ Ｄｉｓｐｏｓ．，２００１，２９：２８９－９５；Ｂａｒｂｉｅｒ ｅｔ ａｌ．，Ｍｏｌ．Ｐｈａｒｍａｃｏｌ．，２００１，５９：６３６－４５；Ｈａｎｉｏｋａ ｅｔ ａｌ．，Ｘｅｎｏｂｉｏｔｉｃａ．２００１，３１：６８７－９９；Ｈａｌｌｏ ｅｔ ａｌ．，Ａｎｔｉｃａｎｃｅｒ Ｒｅｓ．１９９８，１８：２９８１－７に記載されている。標準試料として、それらのゲノム中に各遺伝子の前述の野生型対立遺伝子をもつ対象の細胞または組織からタンパク質を得ることが好ましい。

【０１６０】

前述の各方法は、好ましくは（ｉ）腫瘍療法の特定の段階に患者から腫瘍試料を採取し；そして、（ｉｉ）ＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ１および／またはＣＹＰ３Ａ５について発現プロフィル、タンパク質プロフィルまたは活性プロフィルを測定する工程を含む。それら発現プロフィルに基づいて、臨床医は療法を効果的に適合させることができる。これは特に投与量の調整を含み、ならびに／あるいはＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ１またはＣＹＰ３Ａ５阻害薬の投与を包含する。好ましくは、そのような阻害薬は下記の阻害

薬群から選択される：ＭＤＲ１について：ＧＦ１２０９１８、ＬＹ３３５９７９、ＸＲ９５７６、ＸＲ９０５１、フラボノイド（たとえばアピゲニン、ゲニスチン、ナリンギン、ケルセチン、フラボン、フラボノン、フラボピリドール）、ベルガモッチン、クラリスロマイシン、ケトコナゾール、レセルピン、１，９－ジデオキシフォルスコリン、アジドピン、ジメチル－ｂ－シクロデキストリン、イベルメクチン、ＳＤＺ　ＰＳＣ８３３、ＳＤＺ　２８０－４４６、Ｂ６６９、Ｂ－８５９－３５（Ｒ－鏡像異性体）およびその主代謝産物、ＭＳ－２０９（キノロン誘導体）、ＰＡＫ－１０４ｐ、アミロリド、アミトリプチリン、アトルバスタチン、オーレオバシジンおよび類似体、フッ化ベリリウム（ＢｅＦｘ）、カルモジュリン阻害薬、クロロキン、クロロプロマジン、クロファジミン、クレモフォルＥＬ、ジルチアゼム、ベラパミル、ニフェジピン、ベプリジル、ニカルジピン、ニグルジピン、ニトレンジピン、トリフルオペラジン、フェロジピン、バリノマイシン、ジピリダモール、エリスロマイシン、フルオロキノロン類：フレロキサシン、イエノキサシン、グレパフロキサシン、レボフロキサシン、ノルフロキサシン、グリベンクラミド類および類似体、グルコネート塩類、グラミシジン、ヒドロコルチゾン、イトラコナゾール、リドカイン、ホスファチジルコリン、プリスチナマイシンＩａ、プロパフェノン、プロプラノロール、タリノロール、ピリジン類似体、ケルセチン４’－ｂ－グルコシド、キニンおよびキニジン、キナクリン、シンコニン、リトナビル、サキナビル、ネルフィナビル、タモキシフェンおよび代謝産物、タキソイド（四環式タキソピンＣおよび誘導体）、テルフェナジン；ＭＲＰ１について：ＳＤＺ　ＰＳＣ８３３、ＳＤＺ　２８０－４４６、ＭＫ５７１、ＭＳ－２０９（キノロン誘導体）、ＰＡＫ－１０４ｐ、ベラパミル、ベンズブロマロン（Ｂｅｎｚｂｒｏｍａｒｏｎ）、ジピリダモール、フロセミド（Ｆｕｒｏｓｅｍｉｄｅ）、ガンマ－ＧＳ（ナフチル）システイニル－グリシンジエチルエステル、ゲニステイン（Ｇｅｎｉｓｔｅｉｎ）、キニジン、リファンピシン、ＲＵ　４８６、スルフィンピラゾン（Ｓｕｌｆｉｎｐｙｒａｚｏｎｅ）、三環式イソキサゾール（たとえばＬＹ　４０２９１３）（http://bigfoot.med.unc.edu/watkinsLab/intesinfo.htm、Ｐａｕｌ　Ｗａｔｋｉｎｓ、ノースカロライナ大学）；ＵＧＴ１Ａ１について：β－エストラジオール、４－ヒドロキシエストロン、２－ヒドロキシエストロン、７，８－ベンゾフラボン、ケルセチン、ナリンゲニン（Ｎａｒｉｎｇｅｎｉｎ）、クリシン（Ｃｈｒｙｓｉｎ）、ビリルビン、没食子酸オクチル（Ｂｒｏｕｄｙ　Ｍ（２００１），ＢＤ　Ｇｅｎｔｅｓｔ，米国マサチュセッツ州ウーバン）；ならびにＣＹＰ３Ａ５について：クラリスロマイシン、エリスロマイシン、ジルチアゼム（Ｄｉｌｔｉａｚｅｍ）、ミベフラジル（Ｍｉｂｅｆｒａｄｉｌ）、グレープフーツジュース、シメチジン（Ｃｉｍｅｔｉｄｉｎｅ）、シプロフロキサシン（Ｃｉｐｒｏｆｌｏｘａｃｉｎ）、ノルフロキサシン、フルコナゾール（Ｆｌｕｃｏｎａｚｏｌｅ）、イトラコナゾール、ケトコナゾール、フルボキサミン（Ｆｌｕｖｏｘａｍｉｎｅ）、ノルフルオキセチン（Ｎｏｒｆｌｕｏｘｅｔｉｎｅ）、ネファゾドン（Ｎｅｆａｚｏｄｏｎｅ）、トロレアンドマイシン（Ｔｒｏｌｅａｎｄｏｍｙｃｉｎ）、デラビリジン（Ｄｅｌａｖｉｒｉｄｉｎｅ）、インディナビル（Ｉｎｄｉｎａｖｉｒ）、ネルフィナビル（Ｎｅｌｆｉｎａｖｉｒ）、リトナビル（Ｒｉｔｏｎａｖｉｒ）、サキナビル（Ｓａｑｕｉｎａｖｉｒ）、ミフェプリストン（Ｍｉｆｅｐｒｉｓｔｏｎｅ）、ゲントデン（ｇｅｓｔｏｄｅｎｅ）（http://medicine.iupui.edu/flockhart）。

【０１６１】

本明細書中で用いる阻害薬という用語には、競合阻害薬および非競合阻害薬が含まれる。好ましくは、競合阻害薬はＧＦ１２０９１８、ＬＹ３３５９７９、ＸＲ９５７６、ＸＲ９０５１、フラボノイドなどの基質である。好ましくは、非競合阻害薬はＳＤＺ　ＰＳＣ８３３、ＳＤＺ　２８０－４４６、Ｂ６６９、Ｂ－８５９－３５、ベラパミル、ＭＳ－２０９、ＰＡＫ－１０４ｐなどの基質である。

【０１６２】

最後に、本発明は、本発明の文脈において述べられる薬物に対して患者が耐性を発現したかを判定する方法を包含する。この方法は、（ｉ）腫瘍療法の特定の段階中に患者から腫瘍試料を採取し；そして、（ｉｉ）ＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ１および／またはＣ

ＹＰ３Ａ５の発現レベルを測定する工程を含む。各遺伝子の発現は、実施例４および５の記載または前記に従って測定できる。これら発現プロフィルの評価に基づいて、臨床医は療法をより効果的に適合させることができる。これは特に、投与量の調整を含み、ならびに／あるいは前記に定めたＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ１またはＣＹＰ３Ａ５阻害薬の投与を包含する。

【０１６３】

本明細書に引用した各文献（製造業者の明細、指示などを含む）を参照により本明細書に援用する。

本願中に配列識別番号（ＳＥＱ　ＩＤ　ＮＯ）で述べられる核酸配列およびアミノ酸配列を下記の表１、２、３および４に挙げる。多型性ヌクレオチドの位置については核酸配列中に適切な下記の文字を用いる：Ｒ，ＧまたはＡ；Ｙ，ＴまたはＣ；Ｍ，ＡまたはＣ；Ｋ，ＧまたはＴ；Ｓ，ＧまたはＣ；Ｗ，ＡまたはＴ。

【０１６４】

アミノ酸配列を１文字コードで示す。多型性アミノ酸の位置における文字Ｘは修飾アミノ酸またはそれの対応する野生型アミノ酸を表わす（寄託番号を参照）。

さらに、本明細書中にＧｅｎＢａｎｋ寄託番号の表示により述べられたすべての核酸配列およびアミノ酸配列を以下の図４～２９に示す。

【０１６５】

【表１】

【0166】
【表2】

表1：本発明に述べる核酸配列およびアミノ酸配列

遺伝子	変異SNP	寄託番号	SEQ ID No	配列 フォワード	SEQ ID NO	配列 リバース	SEQ ID NO	配列 フォワード wt>mut	SEQ ID NO	配列 リバース wt>mut
UGT1A1	T>G	59GI:8850235	001	GTCCTGGGCCG GCTGCTGTGT	002	ACACAGCAGCC GGCCCAGGAC	003	GTCCTGGGCCK GCTGCTGTGT	004	ACACAGCAGCM GGCCCAGGAC
UGT1A1	C>T	160GI:8850235	005	GGCCATCCAGT AGCTGCAGCA	006	TGCTGCAGCTA CTGGATGGCC	007	GGCCATCCAGY AGCTGCAGCA	008	TGCTGCAGCTR AGCTGCAGCA
UGT1A1	G>A	226GI:8850235	009	CATCAGAGACA GAGCATTTTA	010	TAAAATGCTCTG TCTCTGATG	011	CATCAGAGACR GAGCATTTTA	012	TAAAATGCTCYG TCTCTGATG
UGT1A1	T>A	539GI:8850235	013	TTGCATGCACA GCCATGCAGC	014	GCTGCATGGCT GTGCATGCAA	015	TTGCATGCACW GCCATGCAGC	016	GCTGCATGGCK GTGCATGCAA
UGT1A1	T>C	544GI:8850235	017	TGCACTGCCAC GCAGCCTGGA	018	TCCAGGCTGCG GTGCATGCAA	019	TGCACTGCCAY GCAGCCTGGA	020	TCCAGGCTGCR GTGCATGCAA
UGT1A1	C>T	640GI:8850235	021	CTTCCTGCAGT GGGTGAAGAA	022	TTCTTCACCCAC TGCAGGAAG	023	CTTCCTGCAGY GGGTGAAGAA	024	TTCTTCACCCRC TGCAGGAAG

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UGT1A1	A>G	1085GI:8850235	061	TGGCTACCCCG	062	CAGATCGTTTC	063	TGGCTACCCCR	064 CAGATCGTTTY
				AAACGATCTG		GGGGTAGCCA		AAACGATCTG	GGGGTAGCCA
UGT1A1	C>G	1114GI:8850235	065	CCCGATGACCG	066	ATAAAGGCACC	067	CCCGATGACCS	068 ATAAAGGCACS
				GTGCCTTTAT		GGTCATCGGG		GTGCCTTTAT	GGTCATCGGG

【０１６８】
【表４】

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UGT1A1	G>A	1117	gi:885023	069	GATGACCCGT**A**	070	GTGATAAAGG**T**	071	GATGACCCGT**R**	072	GTGATAAAGG**Y**
			5		CCTTTATCAC		ACGGGTCATC		CCTTTATCAC		ACGGGTCATC
UGT1A1	C>T	1139	gi:885023	073	CATGCTGGTT**T**	074	AACACCATGG**A**	075	CATGCTGGTT**Y**	076	AACACCATGG**R**
			5		CCATGGTGTT		AACCAGCATG		CCATGGTGTT		AACCAGCATG
UGT1A1	C>G	1158	gi:885023	077	TTTATGAAAG**G**	078	CATTGCATAT**C**	079	TTTATGAAAG**S**	080	CATTGCATAT**S**
			5		TATGCAATG		TTTCATAAA		TATGCAATG		TTTCATAAA
UGT1A1	CC> GT	1175 – 1176	gi:885023	081	AATGGCGTTC**G**	082	TCATCACCAT**AC**	083	AATGGCGTTC**Y**	084	TCATCACCAT**SR**
			5		**T**ATGGTGATGA		GAACGCCATT		ATGGTGATGA		GAACGCCATT
UGT1A1	G>C	1216	gi:885023	085	GATGGACAAT**C**	086	ATGCGCTTTG**G**	087	GATGGACAAT**S**	088	ATGCGCTTTG**S**
			5		CAAAGCGCAT		ATTGTCCATC		CAAAGCGCAT		ATTGTCCATC
UGT1A1	A>G	1297	gi:885023	089	AAATGCTCTA**G**A	090	ATGACTGCTT**C**T	091	AAATGCTCTA**R**A	092	ATGACTGCTT**Y**T
			5		AGCAGTCAT		AGAGCATTT		AGCAGTCAT		AGAGCATTT
UGT1A1	A>T	1324	gi:885023	093	CAAAAGTTAC**T**A	094	ATGTTCTCCT**A**G	095	CAAAAGTTAC**W**	096	ATGTTCTCCT**W**
			5		GGAGAACAT		TAACTTTTG		AGGAGAACAT		GTAACTTTTG
UGT1A1	T>G	1471	gi:885023	097	CTGGTACCAG**G**	098	AAGGAATGGT**C**	099	CTGGTACCAG**K**	100	AAGGAATGGT**M**
			5		ACCATTCCTT		CTGGTACCAG		ACCATTCCTT		CTGGTACCAG
UGT1A1	C>T	1478	gi:885023	101	CAGTACCATT**T**C	102	CACGTCCAAG**A**	103	CAGTACCATT**Y**C	104	CACGTCCAAG**R**

【０１６９】
【表５】

			5		TTGGACGTG	AATGGTACTG	TTGGACGTG	AATGGTACTG		
UGT1A1	*del*CT	372	to	GI:885023	105TAAAAAAGGAC	106AGCATAGCAGT	107 TAAAAAAGGAnC	108 AGCATAGCAGn		
		373		5	TGCTATGCT	CCTTTTTTA	TGCTATGCT	TCCTTTTTTA		
UGT1A1	*del*TT	523 – 525		GI:885023	109GCCCACTGTAT	110CATGCAAGAAT	111 GCCCACTGTAn	112 CATGCAAGAAnT		
	C			5	TCTTGCATG	ACAGTGGGC	TTCTTGCATG	ACAGTGGGC		
UGT1A1	*del*	892 – 905		GI:885023	113ATTTGAAGCCT	114ATGTTCTCCAG	115 ATTTGAAGCCnT	116 ATGTTCTCCAnG		
	TACA			5	GGAGAACAT	GCTTCAAAT	GGAGAACAT	GCTTCAAAT		
	TTA									
	ATGC									
	TTC									
UGT1A1	*ins*T	470/471		GI:885023	129CTGACGGACCC	130AAGGAAGGAAA	131 CTGACGGACCC	132 AAGGAAGGAAA		
				5	TTTTCCTTCCTT	TGGGTCCGTCA	nTTTCCTTCCTT	nGGGTCCGTCA		
						G		G		
UGT1A1	*ins*G	1222/1223		GI:885023	133CAATGCAAAGC	134AGTCTCCATGC	135 CAATGCAAAGC	136 AGTCTCCATGC		
				5	GGCATGGAGAC	CGCTTTGCATT	nGCATGGAGAC	nGCTTTGCATTG		
					T	G	T			
Cyp3A5	T>C	47518		GI:102814	137AAGGACTTCTA	138TAGAAGTCCTT	139 AAGGAYTTCTA	140 TAGAARTCCTT		
				51						
Cyp3A5	T>G	145601		GI:111774	141TGGGCGTGCAA	142TTGCACGGCCCA	143 TGGGCKTGCAA	144 TTGCAMGCCCA		

【０１７０】
【表６】

52

Cyp3A5	A>G	145929	GI:111774 52	145GCCCCGCCTCC C	146GGAGGCGGGG	147 GCCCCRCCTCC	148 GGAGGYGGGG C
Cyp3A5	A>G	9736	GI:102814 51	149CTCACGCTGGG	150CCCAGCGTGAG	151 CTCACRCTGGG	152 CCCAGYGTCTC
MRP1	G>A	21133	U91318	169CCCAAAACACA CACACCCTGC	170GCAGGGTGTGT GTGTTTTGGG	171 CCCAAAACACR CACACCCTGC	172 GCAGGGTGTGY GTGTTTTGGG
MRP1	G>T	57998	GI:720945 1	173ACGCTCAGAGT TTCATGGACT	174AGTCCATGAAA CTCTGAGCGT	175 ACGCTCAGAGK TTCATGGACT	176 AGTCCATGAAM CTCTGAGCGT
MRP1	C>T	137667	AC026452	177GCAGGTGGCCT TGTGCACATT	178AATGTGCACAA GGCCACCTGC	179 GCAGGTGGCCY TGTGCACATT	180 AATGTGCACAR GGCCACCTGC
MRP1	C>T	137647	AC026452	181TTGCCGTCTAT GTGACCATTG	182CAATGGTCACA TAGACGGCAA	183 TTGCCGTCTAY GTGACCATTG	184 CAATGGTCACR TAGACGGCAA
MRP1	G>A	27258	AC003026	185GATTCTCTCCAA GAAAACATC	186GATGTTTTCTTG GAGAGAATC	187 GATTCTCTCCRA GAAAACATC	188 GATGTTTTCTYG GAGAGAATC
MRP1	G>A	14008	U91318	189CTGGGAAGTCA TCCCTGACCC	190GGGTCAGGGAT GACTTCCCAG	191 CTGGGAAGTCR TCCCTGACCC	192 GGGTCAGGGAY GACTTCCCAG
MRP1	C>T	18067	U91318	193CCACGGCAGCT GTCCACAA	194CCAGGTCCACA CCAGGTCCACA	195 CCACGGCAGCY CCAGGTCCACA	196 CCAGGTCCACR CCAGGTCCACR

【０１７１】
【表７】

| | | |

				TGGCCGGGTG	GTGAGTGCAC	TGGCCGGGTG	GTGAGTGCAC
MRP1	G>C 34215	AC003026	233	CATGTGCACTC	234CCGGCCACGTG	235 CATGTGCACTS	236 CCGGCCACGTS
				ACGTGGCCGG	AGTGCACATG	ACGTGGCCGG	AGTGCACATG
MRP1	G>A 39508	GI:720945	237	GTTTCGTTGTA	238TCCCACCCCCT	239 GTTTCGTTGTR	240 TCCCACCCCCY
		1		GGGGGTGGGA	ACAACGAAAC	GGGGGTGGGA	ACAACGAAAC
MRP1	T>C 55472	AC003026	241	TGTCTAATTACA	242ATCCATTTCTGT	243 TGTCTAATTAYA	244 ATCCATTTCTRT
				GAAATGGAT	AATTAGACA	GAAATGGAT	AATTAGACA
MRP1	G>A 150727	AC025277	245	CCATGTCAGCA	246ACCTGTGTCAT	247 CCATGTCAGCR	248 ACCTGTGTCAY
				TGACACAGGT	GCTGACATGG	TGACACAGGT	GCTGACATGG
MRP1	delT 17970	U91318	249	CTGGTTTTTTCT	250TGACCGGAAGA	251 CTGGTTTTTTnC	252 TGACCGGAAGn
				TCCGGTCA	AAAAACCAG	TTCCGGTCA	AAAAAACCAG
MRP1	C>T 17900	U91318	253	TGTCTCCTTTTG	254TGGGAGAAGCA	255 TGTCTCCTTTYG	256 TGGGAGAAGCR
				CTTCTCCCA	AAGGAGACA	CTTCTCCCA	AAGGAGACA
MRP1	G>A 18195	U91318	257	CACTGGCACAA	258CTAGAGGCCAT	259 CACTGGCACAR	260 CTAGAGGCCAY
				TGGCCTCTAG	TGTGCCAGTG	TGGCCTCTAG	TGTGCCAGTG
MRP1	G>A 33551	AC025277	261	TGTGACCACAA	262ACACACTCATT	263 TGTGACCACAR	264 ACACACTCATYT
				ATGAGTGTGT	GTGGTCACA	ATGAGTGTGT	GTGGTCACA
MRP1	C>T 174	AF022828	265	CCAGGCCCCCT	266CCTGAGGTCTA	267 CCAGGCCCCCY	268 CCTGAGGTCTR

【０１７３】
【表９】

			AGACCTCAGG	GGGGGCCTGG		AGACCTCAGG		GGGGGCCTGG					
MRP1	C>A 248	AF022829	269 CCTTTCCACTAC	270 GAGGCCACAGT	271	CCTTTCCACTM	272	GAGGCCACAGK					
			TGTGGCCTC	AGTGGAAAGG		CTGTGGCCTC		AGTGGAAAGG					
MRP1	C>G 258	AF022829	273 CCTGTGGCCTG	274 ATCCTGGATTC	275	CCTGTGGCCTS	276	ATCCTGGATTSA					
			AATCCAGGAT	AGGCCACAGG		AATCCAGGAT		GGCCACAGG					
MRP1	A>G 259	AF022831	277 AAGGTAGGGGG	278 TGGCACAGCGC	279	AAGGTAGGGGR	280	TGGCACAGCGY					
			CGCTGTGCCA	CCCCTACCTT		CGCTGTGCCA		CCCCTACCTT					
MRP1	T>C 124667	AC026452	281 GCGTGCCCAGC	282 AAACCCCCAGGG	283	GCGTGCCCAGY	284	AAACCCCCAGGR					
			CCTGGGGTTT	CTGGGCACGC		CCTGGGGTTT		CTGGGCACGC					
MRP1	G>A 1884	U07050	285 AGCCTTGGAGA	286 CACCCCAGATT	287	AGCCTTGGAGR	288	CACCCCAGATY					
			ATCTGGGGTG	CTCCAAGGCT		ATCTGGGGTG		CTCCAAGGCT					
MRP1	G>C 38646	AC026452	289 CCTTAAACAGC	290 CTTTTCAAATGC	291	CCTTAAACAGSA	292	CTTTTCAAATSC					
			ATTTGAAAAG	TGTTTAAGG		TTTGAAAAG		TGTTTAAGG					
MRP1	C>A 1625	U07050	293 GGGAATCACTA	294 CAGAGAGGTTT	295	GGGAATCACTM	296	CAGAGAGGTTK					
			AACCTCTCTG	AGTGATTCCC		AACCTCTCTG		AGTGATTCCC					
MRP1	C>T 1163	U07050	297 TGTGATCGGCT	298 AGCCGAGGCGA	299	TGTGATCGGCY	300	AGCCGAGGCGR					
			CGCCTCGGCT	GCCGATCACA		CGCCTCGGCT		GCCGATCACA					
MRP1	A>G 381	U07050	301 TGGGGGACCCG	302 TTTATTGGCCC	303	TGGGGGACCCR	304	TTTATTGGCCY					

【０１７４】
【表１０】

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MDR1	A>G	77811	AC005068	373	GGCTTGAAGGT	374	ATTCTTACACCT	375	GGCTTGAAGRT	376	ATTCTTACAYCT
					GTAAGAAT		TCAAGCC		GTAAGAAT		TCAAGCC
MDR1	T>A	78170	AC005068	377	TATTCCTTTACA	378	CAAAAATTTGTA	379	TATTCCTTTACW	380	ACAAAAATTWG
					AATTTTTG		AAGGAATA		AATTTTTG		TAAAGGAAT
MDR1	A>G	73252	AC005068	381	ACTTTGTCTGAT	382	GCAGGAGATCA	383	ACTTTGTCTRAT	384	GCAGGAGATYA
					CTCCTGC		GACAAAGT		CTCCTGC		GACAAAGT
MDR1	G>A	141529	AC002457	385	CTTCAGGTCGG	386	CAAGATCCATTC	387	CTTCAGGTCGG	388	CAAGATCCATY
					AATGGATCTTG		CGACCTGA		RATGGATCTTG		CCGACCTGAAG
MDR1	A>G	141590	AC002457	389	AAACTGAACGA	390	TACCTTTTATCG	391	AACTGAACRAT	392	TACCTTTTATYG
					TAAAAGGTA		TTCAGTTTAA		AAAAGGTA		TTCAGTTTAA
MDR1	>T	70200	AC005068	393	TTCTCCTTATGG	394	CTAACACCCAT	395	TTCTCCTTAYGG	396	CTAACACCCRT
					GTGTTAG		AAGGAGAA		GTGTTAG		AAGGAGAA
MDR1	C>A	70204	AC005068	397	AATTTTCTCATT	398	CACCCGTAATG	399	AATTTTCTCMTT	400	CACCCGTAAKG
					ACGGGTG		AGAAAATT		ACGGGTG		AGAAAATT
MDR1	C>T	70237	AC005068	401	TTAATTGGCTAT	402	GTCCAAAATAG	403	TTAATTGGCYAT	404	GTCCAAAATRG
					TTTGGAC		CCAATTAA		TTTGGAC		CCAATTAA
MDR1	G>A	70253	AC005068	405	TCTACTGGTATT	406	TAAGACAAATAC	407	TCTACTGGTRTT	408	TAAGACAAAYAC
					TGTCTTA		CAGTAGA		TGTCTTA		CAGTAGA

【０１７７】
【表１３】

MDR1	C>A	70371	AC005068	409	AATCATTTTATG	410	TGTGGCACATA	411	AATCATTTTMTG	412	TGTGGCACAKA
					TGCCACA		AAATGATT		TGCCACA		AAATGATT
MDR1	C>T	137	M29445	413	GAACATTGCTTA	414	GTCTCCATAAG	415	GAACATTGCYTA	416	GTCTCCATARG
					TGGAGAC		CAATGTTC		TGGAGAC		CAATGTTC
MDR1	C>T	176	M29445	417	GAAGAGATTGT	418	CCCTCACAATC	419	GAAGAGATYGT	420	CCCTCACRATC
					GAGGG		TCTTC		GAGGGC		TCTTC
MDR1	A>C	43263	AC005068	421	TGAATGTTCCG	422	CGGAGCCACGG	423	TGAATGTTCMG	424	CGGAGCCACKG
					TGGCTCCG		AACATTCA		TGGCTCCG		AACATTCA
MDR1	T>A	43162	AC005068	425	CGGGTGGTGAC	426	CTTCCTGTGTCA	427	CGGGTGGTGW	428	CTTCCTGTGWC
					ACAGGAAG		CCACCCG		CACAGGAAG		ACCACCCG
MDR1	C>T	145984	AC002457	429	AAAATACTTTGG	430	CAAATTTCCAAA	431	AAAATACTTYGG	432	CAAATTTCCRAA
					AAATTTG		GTATTTT		AAATTTG		GTATTTT
MDR1	T>C	171404	AC002457	433	ATCATTAAACGA	434	ACTCATTTCGTT	435	ATCATTAAAYGA	436	ACTCATTTCRTT
					AATGAGT		TAATGAT		AATGAGT		TAATGAT
MDR1	G>C	171456	AC002457	437	GACTAAAGACA	438	CATTTATGTGTC	439	GACTAAAGASA	440	CATTTATGTSTC
					CATAAATG		TTTAGTC		CATAAATG		TTTAGTC
MDR1	G>T	171466	AC002457	441	GACATAAATGTT	442	AAACAAACATAA	443	AGACATAAATG	444	AAACAAACATA
					ATGTTTGTTT		CATTTATGTCT		KTATGTTTGT		MCATTTATGTC

【０１７８】
【表１４】

MDR1	T>C	171511	AC002457	445	GATACAGGGCT CTTCATGA	446	TCATGAAGAGC CCTGTATC	447	GATACAGGGYT CTTCATGA	448	TCATGAAGARC CCTGTATC
MDR1	T>C	171512	AC002457	449	GATACAGGGTC CTTCATGAAT	450	ATTCATGAAGG ACCCTGTATC	451	GATACAGGGTY CTTCATGAAT	452	ATTCATGAAGR ACCCTGTATC
MDR1	G>A	174901	AC002457	453	GTGCACGATAT TGGGGAGC	454	GCTCCCCCAATA TCGTGCAC	455	GTGCACGATRT TGGGGAGC	456	GCTCCCCCAAYA TCGTGCAC
MDR1	C>T	175068	AC002457	457	TAAGCAGCAAT AATGTCGTGT	458	ACACGACATTAT TGCTGCTTA	459	TAAGCAGCAAY AATGTCGTGT	460	ACACGACATTRT TGCTGCTTA
MDR1	C>T	175074	AC002457	461	CAACAATGTTGT GTGCATC	462	GATGCACACAA CATTGTTG	463	CAACAATGTYGT GTGCATC	464	GATGCACACRA CATTGTTG
MDR1	A>G	175142	AC002457	465	CATTAAATGGA GGACTGGG	466	CCCAGTCCTCC ATTTAATG	467	CATTAAATGRAG GACTGGG	468	CCCAGTCCTYC ATTTAATG
MDR1	A>G	175180	AC002457	469	TCCTCTGAGGA TGTGCAGT	470	ACTGCACATCC TCAGAGGA	471	TCCTCTGAGRA TGTGCAGT	472	ACTGCACATYCT CAGAGGA
MDR1	A>G	139015	AC002457	473	AACTTACTTGTA TCTTTGA	474	TCAAAGATACAA GTAAGTT	475	AACTTACTTRTA TCTTTGA	476	TCAAAGATAYAA GTAAGTT
MDR1	A>T	139064	AC002457	477	AGAAATAGTTTA ATCAACA	478	TGTTGATTAAAC TATTTCT	479	AGAAATAGTWT AATCAACA	480	TGTTGATTAWA CTATTTCT

【０１７９】
【表１５】

MDR1	T>C 139119	AC002457	481	TAGGGAGGGCT	482	TGGCCTTAAGC	483	TAGGGAGGGYT	484	TGGCCTTAARC
				TAAGGCCA		CCTCCCTA		TAAGGCCA		CCTCCCTA
MDR1	G>A 139177	AC002457	485	GAAAGGTGAAA	486	TTGCTTTATTTC	487	GAAAGGTGARA	488	TTGCTTTATYTC
				TAAAGCAA		ACCTTTC		TAAAGCAA		ACCTTTC
MDR1	C>T 139276	AC002457	489	CATTTACCCTAG	490	GGTCCATCTAG	491	CATTTACCCYAG	492	GGTCCATCTRG
				ATGGACC		GGTAAATG		ATGGACC		GGTAAATG
MDR1	G>A 140118	AC002457	493	ATATGGAAGAA	494	TTGTAATTTTCT	495	ATATGGAAGRA	496	TTGTAATTTYCT
				AATTACAA		TCCATAT		AATTACAA		TCCATAT
MDR1	A>G 140216	AC002457	497	AACACGGGCGT	498	TCAGATCAACG	499	AACACGGGCRT	500	TCAGATCAAYG
				TGATCTGA		CCCGTGTT		TGATCTGA		CCCGTGTT
MDR1	T>C 140490	AC002457	501	TGTATTAAACGC	502	GGGATTCGCGT	503	TGTATTAAAYGC	504	GGGATTCGCRT
				GAATCCC		TTAATACA		GAATCCC		TTAATACA
MDR1	G>A 140568	AC002457	505	TTGAAAGACAT	506	ATGTAGACATG	507	TTGAAAGACRT	508	ATGTAGACAYG
				GTCTACAT		TCTTTCAA		GTCTACAT		TCTTTCAA
MDR1	A>T 140576	AC002457	509	CGTGTCTACTTA	510	TTCAACTTAAGT	511	CGTGTCTACWT	512	TTCAACTTAWG
				AGTTGAA		AGACACG		AAGTTGAA		TAGACACG
MDR1	A>G 140595	AC002457	513	ATGTCCCCAGT	514	GCTGAATCACT	515	ATGTCCCCART	516	GCTGAATCAYT
				GATTCAGC		GGGGACAT		GATTCAGC		GGGGACAT

【０１８０】
【表１６】

MDR1	G>A	140727	AC002457	517	CCGGGCCGGAA	518	ATGACTGCTTC	519	CCGGGCCGGRA	520	ATGACTGCTYC
					GCAGTCAT		CGGCCCGG		GCAGTCAT		CGGCCCGG
MDR1	G>A	139479	AC002457	521	GAGGCGGGCA	522	CTCGTGATCTG	523	GAGGCGGGCR	524	CTCGTGATCYG
					GATCACGAG		CCCGCCTC		GATCACGAG		CCCGCCTC
MDR1	T>C	139619	AC002457	525	GGAGAATGGCG	526	CGGGTTCACGC	527	GGAGAATGGYG	528	CGGGTTCACRC
					TGAACCCG		CATTCTCC		TGAACCCG		CATTCTCC
MDR1	G>T	65241	AC005068	636	ACTAGAAGGTT	637	ACCTTCCCAGA	638	ACTAGAAGGTK	639	ACCTTCCCAGM
					CTGGGAAGGT		ACCTTCTAGT		CTGGGAAGGT		ACCTTCTAGT
MDR1	G>A	50537	AC005068	640	TCCTGACTATAC	641	TTGGCTTTGGT	642	TCCTGACTATRC	643	TTGGCTTTGGY
					CAAAGCCAA		ATAGTCAGGA		CAAAGCCAA		ATAGTCAGGA
TOP1	1334	13341845	Gi:112252	529	ACTTTTCCGTTG	530	TTGCCGCGGCA	531	ACTTTTCCGTKG	532	TTGCCGCGGCM
	G>T		59		CCGCGGCAACT		ACGGAAAAGTT		CCGCGGCAACT		ACGGAAAAGTT
							C				C
TOP1	1845	1845	Gi:112252	533	CTCGGGAAGGG	534	TCTGATGGAGC	535	CTCGGGAAGGR	536	TCTGATGGAGY
	A>G		59		CTCCATCAGA		CCTTCCCGAG		CTCCATCAGA		CCTTCCCGAG

【０１８１】
【表１７】

表２：本発明に述べる核酸配列およびアミノ酸配列

遺伝子	AS 変異	タンパク質 Acc No	SEQ ID NO	タンパク質	SEQ ID N=	タンパク質 wt>mut
UGT1A1	L15R	G8850236	538	PLVLGRLLCVL	539	PLVLGXLLCVL
UGT1A1	G71R	G8850236	540	LYIRDRAFYTL	541	LYIRDXAFYTL
UGT1A1	D119Dframeshift	G8850236	542	KKIKKDCYAFC	543	KKIKKDX
UGT1A1	P152Pframeshift	G8850236	544	VMLTDPFPSLQ	545	VMLTDPX
UGT1A1	F170del	G8850236	546	LSLPTVFLHAL	547	LSLPTVFX
UGT1A1	L175Q	G8850236	548	FFLHAQPCSLE	549	FFLHAXPCSLE
UGT1A1	C177R	G8850236	550	LHALPRSLEFE	551	LHALPXSLEFE
UGT1A1	R209W	G8850236	552	MTFLQWVKNML	553	MTFLQXVKNML
UGT1A1	P229Q	G8850236	554	DVVYSQYATLA	555	DVVYSXYATLA
UGT1A1	G276R	G8850236	556	NMVFVRGINCL	557	NMVFVXGINCL
UGT1A1	A292V	G8850236	558	SQEFEVYINAS	559	SQEFEXYINAS

【０１８２】
【表１８】

UGT1A1	Y293Wframeshift	G8850236	560	QEFEAWRTWN	561	QEFEAXINASG	
UGT1A1	G308E	G8850236	562	VVFSLESMVSE	563	VVFSLXSMVSE	
UGT1A1	Q331R	G8850236	564	LGKIPRTVLWR	565	LGKIPXTVLWR	
UGT1A1	Q357R	G8850236	566	VKWLPRNDLLG	567	VKWLPXNDLLG	
UGT1A1	R367G	G8850236	568	GHPMTGAFITH	569	GHPMTXAFITH	
UGT1A1	A368T	G8850236	570	HPMTRTFITHA	571	HPMTRXFITHA	
UGT1A1	P387R	G8850236	572	ICNGVRMVMMP	573	ICNGVXMVMMP	
UGT1A1	S375F	G8850236	574	ITHAGFHGVYE	575	ITHAGXHGVYE	
UGT1A1	S381R	G8850236	576	HGVYERICNGV	577	HGVYEXICNGV	
UGT1A1	A401P	G8850236	578	DQMDNPKRMET	579	DQMDNXKRMET	
UGT1A1	R403Rframeshift	G8850236	580	MDNAKRHGD.	581	MDNAKX	
UGT1A1	K428E	G8850236	582	LENALEAVIND	583	LENALXAVIND	
UGT1A1	Y486D	G8850236	584	LTWYQDHSLDV	585	LTWYQXHSLDV	
UGT1A1	S488F	G8850236	586	WYQYHFLDVIG	587	WYQYHXLDVIG	

【０１８３】
【表１９】

UGT1A1	Q49stop	G8850236	588	LGAIQ;	589	LGAIQ;
UGT1A1	C280stop	G8850236	590	VGGIN;	591	VGGIN;
UGT1A1	Q331stop	G8850236	592	LGKIP;	593	LGKIP;
UGT1A1	W335stop	G8850236	594	PQTVL;	595	PQTVL;
UGT1A1	Q357stop	G8850236	596	VKWLP;	597	VKWLP;
UGT1A1	K437stop	G8850236	598	NDKSY;	599	NDKSY;
MRP1	F329C	G2828206	600	YFLMSCFFKAI	601	YFLMSXFFKAI
MRP1	R433S	G2828206	602	SVDAQSFMDLA	603	SVDAQXFMDLA
MRP1	R723Q	G2828206	604	QNDSLQENILF	605	QNDSLXENILF
MDR1	N21D	G2506118	606	FFKLNDKSEKD	607	FFKLNXKSEKD
MDR1	F103L	G2506118	608	INDTGLFMNLE	609	INDTGXFMNLE
MDR1	V168I	G2506118	610	FDVHDIGELNT	611	FDVHDXGELNT
MDR1	S400N	G2506118	612	RNVHFNYPSRK	613	RNVHFXYPSRK
MDR1	G412G	G2506118	614	VKILKGLNLKV	615	VKILKXLNLKV

【０１８４】
【表２０】

MDR1	T436T		G2506118	616	CGKSTTVQLMQ	617	CGKSTXVQLMQ
MDR1	A893S		G2506118	618	KELEGSGKIAT	619	KELEGXGKIAT
MDR1	A999T		G2506118	620	FAPDYTKAKIS	621	FAPDYXKAKIS
MDR1	A1001T		G2506118	622	PDYAKTKISAA	623	PDYAKXKISAA
MDR1	Q1107P		G2506118	624	KRLNVPWLRAH	625	KRLNVXWLRAH
MDR1	A1132A		G2506118	626	IAENIAYGDNS	627	IAENIXYGDNS
MDR1	S1141T		G2506118	628	NSRVVTQEEIV	629	NSRVVXQEEIV
MDR1	I1145I		G2506118	630	VSQEEIVRAAK	631	VSQEEXVRAAK
TOP1	G363C		G12644118	632	PGLFRCRGNHP	633	PGLFRXRGNHP
TOP1	D533G		G12644118	634	DFLGKGSIRYY	635	DFLGKXSIRYY

Acc No：寄託番号

del：欠失

ins：挿入

frameshift：フレームシフト変異

stop：終止コドン

【０１８５】

【表２１】

表３：本発明に述べる選択された核酸配列

遺伝子	変異	SNP	Genbank Acc No	SEQ ID NO
UGT1A1	C>T	890	GI:8850235	037
UGT1A1	G>A	1117	GI:8850235	069
UGT1A1	T>G	1471	GI:8850235	097
Cyp3A5	T>C	47518	GI:10281451	137
Cyp3A5	T>G	145601	GI:11177452	141
Cyp3A5	A>G	145929	GI:11177452	145
Cyp3A5	A>G	9736	GI:10281451	149
MRP1	C>T	137647	AC026452	181
MRP1	T>C	95	AF022831	209
MRP1	C>G	53282	GI:7209451	217
MRP1	T>G	249	AF022830	205
MRP1	A>G	259	AF022831	277
MRP1	T>C	124667	AC026452	281
MRP1	A>G	381	U07050	301
MRP1	*ins*T	926/927	U07050	325
MRP1	G>A	34218	AC003026	229
MRP1	C>T	18067	U91318	193
MRP1	C>T	440	U07050	313
MRP1	C>A	1625	U07050	293
MRP1	C>T	17900	U91318	253
MDR1	G>A	101	M29432	345
MDR1	C>T	176	M29445	417
MDR1	G>T	88883	GI:10122135	636

【０１８６】
【表２２】
表４：本発明に述べる選択されたアミノ酸配列

遺伝子	AA 変異	タンパク質 Genbank No	SEQ ID NO
UGT1A1	A292V	G8850236	558
UGT1A1	A368T	G8850236	570
UGT1A1	Y486D	G8850236	584
MRP1	F329C	G2828206	600
MDR1	S400N	G2506118	612
MDR1	A893S	G2506118	618

【０１８７】
以下の生物学的実施例を参照して本発明を説明する。これらは説明のためのものにすぎず、本発明の範囲の限定と解すべきではない。
【実施例１】
【０１８８】
ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６に対応する位置におけるＣからＴへの置換が表現型に与える影響
ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６に対応する位置におけるＣから

Ｔへの単一ヌクレオチド置換（ＭＤＲ１エキソン２６　ＳＮＰ　Ｃ３４３５Ｔともいう）が腸のＰ－糖タンパク質（ＰＧＰ）の発現に与える影響を調べるために、２１人からの生検材料および十二指腸の腸細胞標本を、Ｄｒ．Ｍａｒｇａｒｅｔｅ　Ｆｉｓｃｈｅｒ－Ｂｏｓｃｈ－Ｉｎｓｔｉｔｕｔｅ　ｆｏｒ　Ｃｌｉｎｉｃａｌ　Ｐｈａｒｍａｃｏｌｏｇｙ（シュツットガルト）において、定量免疫組織化学的方法およびウェスタンブロット法により調べた。結果を図１に示す。Ｔ対立遺伝子（ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６に対応する位置にＴをもつ）のホモ接合性保持者は、Ｃ対立遺伝子（ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の位置１７６に対応する位置にＣをもつ）のホモ接合性保持者と比較して有意に高いＰＧＰレベルを示した。ヘテロ接合性遺伝子型をもつ個体は中間レベルのＰＧＰ発現を示した。

【０１８９】

さらに、ＭＤＲ１遺伝子型が腸のジゴキシンの取込み関連薬物動態に与える影響を、大学メディカルセンター、Ｃｈａｒｉｔｅ、ベルリンにおける臨床試験で調べた。ジゴキシン経口投与後の１４人の健康なボランティアにおいて、定常状態での最大血中ジゴキシン濃度（Ｃｍａｘ）は、ＭＤＲ１　３４３５Ｃ＞Ｔ遺伝子型と相関していた。図２は、Ｔ対立遺伝子についてホモ接合性であるボランティアはＣ／Ｃ遺伝子型のボランティアより統計学的に有意に低いジゴキシン濃度を示し（ｐ＝０．００６，マン－ウィットニーのＵ検定）、この多型性がジゴキシンの薬物動態に影響を与えることを示す。

【実施例２】

【０１９０】

ＭＲＰ１多型とＭＲＰ１発現の相関性およびＭＲＰ１基質を用いた療法に際しての副作用

ＭＲＰ１遺伝子における機能性多型は輸送活性に影響を与え、これが結果的にＭＲＰ１基質薬物の血漿中濃度および／または細胞内濃度を調節する。そのような薬物の濃度が上昇すると副作用が生じる可能性があり、これに対し濃度が低下すると療法量以下の薬物濃度になり、療法が失敗する可能性がある。ＭＲＰ１多型は、ＭＲＰ１基質薬物で治療した患者における薬物関連有害作用および療法効果の発生と相関性があった。患者－対照研究において、シスプラチン関連の腎毒性を患う患者群ならびに抗癌薬により起きた腎毒性および肝毒性を患う患者群と、健康な対照群の間で、ＭＲＰ１　ＳＮＰの頻度分布を比較した。さらに、分かっているＭＲＰ１　ｍＲＮＡレベルをもつ試料をＭＲＰ１遺伝子型についてスクリーニングした。抗癌薬治療に際して起きた腎毒性および肝毒性を示す患者群における結果を、１つのＭＲＰ１　ＳＮＰについて次表に挙げる。

【０１９１】

【表２３】

SNP	群	対立遺伝子頻度 [%]			遺伝子型頻度 [%]		
		G対立遺伝子	A対立遺伝子	*G/A	*A/A	*A/A 予測 [2]	
150727G>A[1]	対照	66.7	33.3	50	8.3	10.9	
	症例	50.0	50.0	14.3	42.9	25.0	

【０１９２】

[1]　寄託番号ＡＣ０２５２７７による；

[2]　ハーディー－ワインバーグに従って計算。

対照試料と異なり、薬物関連の腎および肝副作用を伴う患者において、Ａ対立遺伝子（ＭＲＰ１遺伝子、寄託番号ＡＣ０２５２７７の位置１５０７２７に従う位置におけるＧからＡへの置換）が健康な対照と比較して統計学的に有意に過剰発現（overpresent）しており（ｐ＝０．０４４，カイ２乗検定）、したがってこれらの副作用は予測可能であった。

【０１９３】

さらに、リファンピシン投与の前と後におけるＭＲＰ１遺伝子型とｍＲＮＡ発現の関連性を、２種類のＭＲＰ１　ＳＮＰ、すなわち９５Ｔ＞Ｃ（ＳＥＱ　ＩＤ　ＮＯ：２０９、２１０、２１１および２１２；ＭＲＰ１遺伝子、寄託番号ＡＦ０２２８３１の位置９５に対応する位置におけるＴからＣへのヌクレオチド置換）、および２５９Ａ＞Ｇ（ＳＥＱ　ＩＤ　ＮＯ：２７７、２７８、２７９および２８０；ＭＲＰ１遺伝子、寄託番号ＡＦ０２２８３１の位置２５９に対応する位置におけるＡからＧへのヌクレオチド置換）について検出した。これらのＳＮＰは連携して１つの対立遺伝子を形成する。図３に示すように、２つの独立した実験（リファンピシン誘導したものと誘導しないもの）において、この変異対立遺伝子（ＭＲＰ１ｍｕｔ；ＭＲＰ１遺伝子、寄託番号ＡＦ０２２８３１の位置９５のＣおよび位置２５９のＧ）は統計学的に有意にＭＲＰ１　ｍＲＮＡの発現低下と相関し、野生型対立遺伝子（ＭＲＰ１ｗｔ；ＭＲＰ１遺伝子、寄託番号ＡＦ０２２８３１の位置９５のＴおよび位置２５９のＡ）はＭＲＰ１　ｍＲＮＡの発現増大と相関する。

【０１９４】

ＭＲＰ１　ｍＲＮＡ含量の相異はＭＲＰ１遺伝子型関連の個体差に基づくものであり、これらのＳＮＰの分析は、ＭＲＰ１発現レベルについて、およびＭＲＰ１基質薬物の療法結果および有害作用を予測するために、診断的および予後診断的に有用性が高いものである。

【実施例３】

【０１９５】

投与量の計算

イリノテカンの療法効果および有害作用は、親化合物および活性代謝産物（たとえばＳＮ－３８）の血漿中濃度および細胞内濃度、ＣＹＰ３Ａ５－およびＵＧＴ１Ａ１－関連の代謝により制御されるプロセス、ならびにＭＲＰ１－およびＭＤＲ１－関連の輸送プロセスに依存する。

【０１９６】

【化１６】

[Atsumi, *et al.*, 1991, Xenobiotica 21:1159-69, Iyer, *et al.*, 1998, J Clin Invest 101:847-54, Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202, Santos, *et al.*, 2000, Clin Cancer Res 6:2012-20, Kuhn, 1998, Oncology (Huntingt) 12:39-42, Chen, *et al.*, 1999, Mol Pharmacol 55:921-8, Chu, *et al.*, 1997, Cancer Res 57:1934-8, Chu, *et al.*, 1997, J Pharmacol Exp Ther 281:304-14; Chu, *et al.*, 1998, Cancer Res 58:5137-43, Chu, *et al.*, 1999, Drug Metab Dispos 27:440-1, Chu, *et al.*, 1999, J Pharmacol Exp Ther 288:735-41, Mattern, *et al.*, 1993, Oncol Res 5:467-74, Hoki, *et al.*, 1997, Cancer Chemother Pharmacol 40:433-8, Sugiyama, *et al.*, 1998, Cancer Chemother Pharmacol 42:S44-9].

【０１９７】

たとえば、ＭＲＰ１はグルクロノシルトランスフェラーゼと密接に関連して細胞性解毒系の一部として作用し、グルクロン酸抱合体、たとえばＳＮ－３８Ｇを輸送することが知られている［Ｋｏｅｎｉｇ，ｅｔ　ａｌ．，１９９９，Ｂｉｏｃｈｉｍ　Ｂｉｏｐｈｙｓ　Ａｃｔａ　１４６１：３７７－３９４；Ｋｅｒｂ　ｅｔ　ａｌ．，２００１，Ｐｈａｒｍａｃｏｇｅｎｏｍｉｃｓ　２：５１－６４］。たとえばＳＮ－３８Ｇが細胞から胆汁中へ輸出される程度は、それの形成速度に大きな影響を与える。ＳＮ－３８が効果的に解毒されるためには、ＵＧＴ１Ａ１による抱合およびグルクロン酸抱合体による輸出の両プロセスが必要である。

【０１９８】

ＣＹＰ３Ａ５遺伝子（寄託番号ＧＩ：１０２８１４５１）の４７５１８Ｔ＞Ｃ（ＳＥＱ

ＩＤ ＮＯ：１３７、１３８、１３９および１４０）および９７３６Ａ＞Ｇ（ＳＥＱ ＩＤ ＮＯ：１４９、１５０、１５１、１５２）ヌクレオチド置換、ならびにＣＹＰ３Ａ５遺伝子（寄託番号ＧＩ：１１１７７４５２）の１４５６０１Ｔ＞Ｇ（ＳＥＱ ＩＤ ＮＯ：１４１、１４２、１４３、１４４）および１４５９２９Ａ＞Ｇ（ＳＥＱ ＩＤ ＮＯ：１４５、１４６、１４７および１４８）ヌクレオチド置換は、高ＣＹＰ３Ａ５発現関連の対立遺伝子を形成し、したがって高いイリノテカン代謝不活性化と関連がある。この対立遺伝子をもつ個体は高度メタボライザー（ＥＭ）であり、したがってリマインダー（reminder）の低度メタボライザー（ＰＭ）と対照的にイリノテカン毒性を被る可能性が低い。１つの高発現関連の対立遺伝子および１つの低発現関連の対立遺伝子をもつ者は、中間メタボライザー（ＩＭ）とみなされる。

【０１９９】

ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の１７６Ｃ＞Ｔヌクレオチド置換（ＳＥＱ ＩＤ ＮＯ：２１７、２１８、２１９および２２０）は、低ＰＧＰ発現関連の低薬物排出と関連する；ＭＲＰ１遺伝子（寄託番号：ＡＦ０２２８３１）の９５Ｔ＞Ｃ（ＳＥＱ ＩＤ ＮＯ：２０９、２１０、２１１および２１２）および２５９Ａ＞Ｇ（ＳＥＱ ＩＤ ＮＯ：２７７、２７８、２７９および２８０）ヌクレオチド置換は、低ｍＲＮＡ発現と関連する；ＭＲＰ１遺伝子（寄託番号：Ｍ２９４４５）の１５０７２７Ｇ＞Ａヌクレオチド置換（ＳＥＱ ＩＤ ＮＯ：２１７、２１８、２１９および２２０）は、低ＰＧＰ発現関連の低薬物排出と関連する；ＭＲＰ１遺伝子（寄託番号：ＡＣ０２５２７７）の１５０７２７Ｇ＞Ａヌクレオチド置換（ＳＥＱ ＩＤ ＮＯ：２１７、２１８、２１９および２２０）は、有害作用と関連する。したがって、低いトランスポーター発現関連の対立遺伝子をもつ個体は、細胞から有害化合物を排除する能力が低い。輸送および代謝の両方が、遺伝子－用量依存性に影響を受ける。各輸送タンパク質の低発現関連の対立遺伝子の数に従って、個体は、高度輸送能（ＥＴ）、中間輸送能（ＩＴ）または低度輸送能（ＰＴ）のいずれかの遺伝子を有するものに分類できる。

【０２００】

イリノテカンによる治療を開始する前に遺伝子検査を行うことにより、患者のＭＤＲ１関連およびＭＲＰ１関連の輸送能を推定できる。個体が有害作用を受けるリスクは、ＰＭおよび／またはＰＴ対立遺伝子の数に依存する。ＣＹＰ３Ａ５およびＵＧＴ１Ａ１のＰＭ関連対立遺伝子、ならびにＭＤＲ１およびＭＲＰ１のＰＴ関連対立遺伝子をもつ個体は、イリノテカン毒性を被るリスクが最も高い。

【０２０１】

この知見に基づいて、Ｂｒｏｃｋｍｏｅｌｌｅｒら（２０００，Ｐｈａｒｍａｃｏｇｅｎｏｍｉｃｓ １：１２５）がＣＹＰ２Ｄ６、ＣＹＰ２Ｃ９およびＣＹＰ２Ｃ１９の基質薬物について示したように、１回目の投与前に初回投与量を調整できる。

【０２０２】

投与量調整は、評点方式により達成できる。ＰＭ関連またはＰＴ関連対立遺伝子それぞれについて、一定の評点を割り当てる。たとえば評点２をＵＧＴ１Ａ１のＰＭ対立遺伝子２２６Ａ（ＳＥＱ ＩＤ ＮＯ：９、１０、１１、１２、５４０、５４１）および７０１Ａ（ＳＥＱ ＩＤ ＮＯ：２５、２６、２７、２８、５５４、５５５）に割り当て、評点１をＣＹＰ３Ａ５のＰＭ関連対立遺伝子（４７５２３Ｔ プラス ３５６４９Ａ プラス １４５６０１Ｔ プラス １４５９２９Ａ、４７５２３Ｔ プラス ３５６４９Ｇ プラス １４５６０１Ｇ プラス １４５９２９Ｇ、および４７５２３Ｃ プラス ３５６４９Ａ プラス １４５６０１Ｔ プラス １４５９２９Ａ）、ＭＤＲ１低発現対立遺伝子１７６Ｔ（ＳＥＱ ＩＤ ＮＯ：４１７、４１８、４１９および４２０）、ＭＲＰ１低発現対立遺伝子１５０７２７Ａ（ＳＥＱ ＩＤ ＮＯ：２１７、２１８、２１９および２２０）および２５９Ｇ（ＳＥＱ ＩＤ ＮＯ：２７７、２７８、２７９および２８０）、ＭＲＰ１ １５０７２７Ａ対立遺伝子（ＳＥＱ ＩＤ ＮＯ：２１７、２１８、２１９および２２０）に割り当てる。遺伝子型判定の後、評点を要約し、その合計に従ってイリノテカン投与量を調整する。各１評点が１０％の投与量減少に相当する。すなわち、評点１は

１０％の投与量減少、評点２は２０％の投与量減少、評点３は３０％の投与量減少などとなる。

【実施例４】

【０２０３】

培養条件および生物学的アッセイ

ヒト上皮性子宮頚癌細胞系ＫＢ　３－１および２つのサブクローン（ＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５））、ならびに膀胱癌細胞系ＲＴ１１２およびサブクローン（ＲＴ１１２（ＭＤＲ１$^{+}$、ＵＧＴ１Ａ１））を、ダルベッコの改変イーグル培地（ＤＭＥＭ）、すなわち３．７ｇ／ｌのＮａＨＣＯ$_3$、４．５ｇ／ｌのＤ－グルコース、１．０２８ｇ／ｌのＮ－アセチル－Ｌ－アラニル－Ｌ－グルタミンを含有し、１０％ウシ胎仔、１ｍＭのピルビン酸ナトリウムおよび１％の非必須アミノ酸を補充した培地で培養した。ヒト大腸癌細胞系ＬＳ１７４Ｔを、ダルベッコの改変イーグル培地（ＤＭＥＭ）、すなわちＬ－グルタミン、塩酸ピリドキシンおよび２５ｍＭのヘペス緩衝液を含有するが、フェノールレッドを含有せず、１０％ウシ胎仔、１ｍＭのピルビン酸ナトリウムおよび１％の非必須アミノ酸を補充した培地で培養した。すべての細胞を３７℃、５％ＣＯ$_2$で加湿雰囲気でインキュベートした。

【０２０４】

薬物

イリノテカン（ＣＰＴ－１１）およびその活性代謝産物ＳＮ－３８はファルマシアから提供された。原液を調製するために、これらの物質をメタノールに溶解して、ＣＰＴ－１１については１０ｍｇ／ｍｌ、ＳＮ－３８については１ｍｇ／ｍｌとし、遮光下で４℃に保存した。より低濃度の希釈液をＰＢＳおよび細胞培地中に調製した。Ｒ－ベラパミルをシグマから入手し、ＤＭＳＯに溶解して５０ｍｇ／ｍｌとし、さらにＰＢＳ中に希釈した。

【０２０５】

細胞の薬物処理

細胞を処理の２４時間前に９６ウェル培養プレートに接種した。増殖速度の差を考慮して、ＫＢ　３－１およびＲＴ１１２細胞を７００個／ウェル、ＲＴ１１２（ＭＤＲ１$^{+}$、ＵＧＴ１Ａ１）細胞を１０００個／ウェル、ＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）細胞を１２００個／ウェルで接種した。ＬＳ１７４Ｔ細胞は１．０×１０^{4}個／ウェルで接種された。調製したばかりの系列希釈液で培地中で細胞を処理した：ＣＰＴ－１１については０、０．５、１、２．５、５、７．５、１０、２５、５０、７５、１００および２００μｇ／ｍｌ、ＳＮ－３８については０、０．１、０．２５、０．５、１、５、１０、２５、５０、７５、１００および２００ｎｇ／ｍｌ。４つのウェルを同一の薬物希釈液で処理した。細胞を３７℃、加湿５％ＣＯ$_2$雰囲気で３日間インキュベートした。

ＭＤＲ１阻害実験のために、Ｒ－ベラパミルを１０μｇ／ｍｌの最終濃度となるように各薬物希釈液の２つのウェルに添加した。

【０２０６】

細胞毒性アッセイ

市販のＭＴＳアッセイ系（Ｐｒｏｍｅｇａ、米国マディソン）を用い、製造業者の指示に従って、増殖阻害および細胞死を測定した。薬物添加後３日目に、２０μｌの混合ＭＴＳ／ＰＭＳ溶液を９６ウェル培養プレートの各ウェルに添加した。プレートを３７℃、加湿５％ＣＯ$_2$雰囲気で少なくとも４５分間インキュベートし、４９２ｎｍで吸光度を測定した。各プレートの非処理対照細胞の吸光度値を１００％増殖と設定し、残りの薬物処理細胞の増殖を計算するのに用いた。培養プレート上の非処理細胞を、影響を受けていない増殖および生存についての対照として用いた。

細胞増殖の５０％阻害作用を示す薬物濃度をＩＣ$_{50}$と定めた。

【０２０７】

ＲＮＡの調製およびｃＤＮＡの合成

これらの実験に用いた各細胞バッチから、細胞溶解物からオリゴ－ｄＴ磁性ビーズ（μＭ

ＡＣＳ　ｍＲＮＡ単離キット；Ｍｉｌｔｅｎｙｉ　Ｂｉｏｔｅｃｈ）によって製造業者の指示に従ってメッセンジャーＲＮＡを単離した。各細胞系のｍＲＮＡ　２５０ｎｇを、Ｓｕｐｅｒｓｃｒｉｐｔ　ＩＩ逆転写酵素（Ｇｉｂｃｏ　ＢＲＬ）による２０μｌのｃＤＮＡ合成反応に用いた。このｃＤＮＡの希釈液を、転写特異的増幅反応の鋳型として用いた。

【０２０８】

ＰＣＲプライマーおよび反応条件

０．５単位のＴａｑポリメラーゼ（Ｑｕｉａｇｅｎ）、２００μＭのヌクレオチドミックス、５μｌのｃＤＮＡ鋳型希釈液、および０．２μＭの遺伝子特異的プライマー（表５に示す）を含む２５μｌの反応にＰＣＲを設定した。すべての反応を同一の増幅条件で、サイクル数のみを変更して（表）実施した；９４℃で２分間の予備変性、次いで増幅のために：９４℃で４５秒間の変性、６２℃で４５秒間のアニーリング、および７２℃で４５秒間の延長。ただし、より長い延長を必要としたＵＧＴ１Ａ１は２分間。

【０２０９】

【表２４】

表５：遺伝子特異的プライマーの配列およびＰＣＲ反応条件

Ｆ：mRNA配列に対するフォワードプライマー；Ｒ：リバースプライマー

遺伝子	プライマー配列(5'-3')	cDNA 希釈度	サイクル数
MDR1	F: TGCCTTCATCGAGTCACTGCC R: TCACTGGCGCTTTGTTCCAGC	1:100	26
MRP1	F: TCTCCAAGGAGCTGGACACA R: CGTGGTGACCTGCAATGAGT	1:10	30
UGT1A	F: GATGATGCCCTTGTTTGGTG R: TGTTTTCAAGTTTGGAAATGACTAGGG	1:100	30
UGT1A1	F: AACCTCTGGCAGGAGCAAAGG R: TGTTTTCAAGTTTGGAAATGACTAGGG	1:10	34
CYP3A4	F: TCAGCCTGGTGCTCCTCTATCTAT R: AAGCCCTTATGGTAGGACAAAATATTT	1:10	34
CYP3A5	F: TTGTTGGGAAATGTTTTGTCCTATC R: ACAGGGAGTTGACCTTCATACGTT	1:10	34
PLA2 (ハウスキーピング遺伝子)	F: GCTGGTTCAGAAGGCCAAAC R: GGGCCAGACCCAGTCTGATA	1:100	26

【実施例５】

【０２１０】

イリノテカン代謝に関与する遺伝子の発現

メッセンジャーＲＮＡを、ヒト膀胱細胞系ＲＴ１１２およびサブクローンＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）、ヒト上皮性子宮頚癌細胞系ＫＢ　３－１ならびに２つのサブクローンＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３

Ａ５）、ならびに大腸癌細胞系ＬＳ１７４Ｔ（ＡＴＣＣ　ＣＬ－１８８）から単離した。これらのｍＲＮＡをｃＤＮＡに逆転写し、鋳型として転写物特異的増幅反応に用いて、イリノテカンの輸送および代謝に関与する遺伝子（ＭＤＲ１、ＭＲＰ１、ＵＧＴ１Ａ、ＵＧＴ１Ａ１、ＣＹＰ３Ａ４、ＣＹＰ３Ａ５）の発現レベルを測定した。ハウスキーピング遺伝子であるホスホリパーゼＡ２（ＰＬＡ２）の増幅を、これらの反応において比較できるｃＤＮＡ量のための対照として用いた。

【０２１１】

図２９の増幅反応は、癌細胞系ＲＴ１１２、ＫＢ　３－１およびＬＳ１７４Ｔはそれぞれ ＭＤＲ１の発現が全くないか、またはきわめて低いことを示す。ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）はＲＴ１１２のサブクローンであり、Ｓｅｅｍａｎｎら（Ｕｒｏｌ　Ｒｅｓ　１９９５；２２：３５３－３６０）の記載に従って細胞毒性薬物に対する耐性のため選択され、ＭＤＲ１発現が中等度に増大していることを特色とする。薬物耐性サブクローンＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）は、同様に元のＫＢ　３－１細胞系からＭＤＲ１基質への曝露により得られた。これらのサブクローンはＭＤＲ１発現が高度に増大していることを特色とする。それらは元のＫＢ　３－１細胞より＞２０倍多い転写物を示し、これはＭＤＲ１活性がきわめて高いことに関係する。ＭＲＰ１はすべての細胞系で同レベルに発現する。ＵＧＴ１Ａ酵素の転写物はＲＴ１１２、ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）およびＬＳ１７４Ｔ細胞にのみ存在する。ＵＧＴ１Ａ１はＲＴ１１２においてはごく弱く発現し、ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）においてはより強く発現し、ＬＳ１７４Ｔ細胞においては最も高い発現を示す。ＣＹＰ３Ａ４は、ＬＳ１７４Ｔにおいてきわめて少量検出されたにすぎない。ＲＴ１１２細胞、ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）およびＬＳ１７４Ｔは、ＣＹＰ３Ａ５の機能的に不活性なスプライス変異体と機能的に活性な転写物のヘテロ接合性発現を示す。これに対し、ＫＢ　３－１およびＫＢ　３－１（ＭＤＲ１$^{+++}$）細胞は活性ＣＹＰ３Ａ５転写物のみをもち、ＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）は活性ＣＹＰ３Ａ５転写物の最も高い発現を示した。これは、後者が最も高いＣＹＰ３Ａ５活性をもつことに関係する。

【実施例６】

【０２１２】

ＭＤＲ１活性およびＣＹＰ３Ａ５活性がないかまたは低い大腸癌細胞系その他の表皮性癌細胞系はＣＰＴ－１１およびＳＮ－３８に対して感受性である

大腸癌細胞系ＬＳ１７４Ｔ、子宮頚癌細胞系ＫＢ　３－１および膀胱癌細胞系ＲＴ１１２を、処理の２４時間前に９６ウェル培養プレートに接種した。４ウェルの各細胞系をＣＰＴ－１１およびＳＮ－３８の系列希釈液と共にインキュベートし、前記と同様に分析した。図３０は、ＣＰＴ－１１およびＳＮ－３８で処理すると３種類すべての表皮性癌細胞系が増殖を停止して死滅することを示す。ＣＰＴ－１１に関して５０％阻害を生じる濃度（IC_{50}）は、ＬＳ１７４Ｔ細胞については１．５μｇ／ｍｌ、ＲＴ１１２細胞については２．５μｇ／ｍｌ、ＫＢ　３－１細胞については５μｇ／ｍｌである。ＣＰＴ－１１の活性代謝産物ＳＮ－３８は10^{3}倍低い濃度で同程度の増殖阻害および細胞死を引き起こすので、ＣＰＴ－１１より１０００倍高い効力を示す。ＳＮ－３８のIC_{50}は、ＬＳ１７４Ｔ細胞については５ｎｇ／ｍｌ、ＲＴ１１２細胞については４ｎｇ／ｍｌ、ＫＢ　３－１細胞については２５ｎｇ／ｍｌである。

【０２１３】

これらの結果は、異なる組織に由来するにもかかわらず３種類すべての表皮性癌細胞系がＣＰＴ－１１およびＳＮ－３８処理に対して同様に感受性であることを示す。これは、ＭＤＲ１を全くまたは発現しないかまたは低いレベルでのみ発現する癌細胞（図２９）はＣＰＴ－１１およびＳＮ－３８で効果的に殺せることも示す（図３０）。

【実施例７】

【０２１４】

ＭＤＲ１活性はＣＰＴ－１１およびＳＮ－３８に対する癌細胞の耐性と相関する

ＫＢ　３－１、ならびにＭＤＲ１を強く発現するそのサブクローンＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）を、処理の２４時間前に９６ウェル培養プレートに接種した。４ウェルの各細胞系をＣＰＴ－１１およびＳＮ－３８の系列希釈液と共にインキュベートし、前記と同様に処理した。ＭＤＲ１高発現体であるＫＢ　３－１サブクローン（ＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５））（図２９）の阻害曲線（図３１）は、ＭＤＲ１低発現体であるＫＢ　３－１細胞系（ＫＢ３－１）と比較して、ＣＰＴ－１１およびＳＮ－３８に対して有意に高い耐性を示す。ＣＰＴ－１１に対するIC_{50}は、ＫＢ　３－１細胞における５μｇ／ｍｌから、ＫＢ　３－１（ＭＤＲ１$^{+++}$）細胞における８５μｇ／ｍｌおよびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）細胞における２００μｇ／ｍｌへと、１７～４０倍増大する。ＳＮ－３８に対するIC_{50}は、ＫＢ　３－１細胞における２５ｎｇ／ｍｌから、ＫＢ　３－１（ＭＤＲ１$^{+++}$）細胞における２００ｎｇ／ｍｌおよびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）細胞における＞２００ｎｇ／ｍｌへと、少なくとも８倍増大する。

【０２１５】

ＣＰＴ－１１およびＳＮ－３８はＭＤＲ１の基質であり、したがって細胞からＭＤＲ１活性により排除される。ＭＤＲ１の発現レベルは、ＣＰＴ－１１およびＳＮ－３８に対する腫瘍細胞の感受性と逆相関する。それに伴い、高ＭＤＲ１発現性表現型をもつ細胞を殺すには、はるかに高い濃度のＣＰＴ－１１が必要である。

【実施例８】

【０２１６】

ＵＧＴ１Ａ１活性はＣＰＴ－１１に対してではなくＳＮ－３８に対する感受性と相関する

ＣＰＴ－１１およびＳＮ－３８感受性を、ＲＴ１１２細胞とそのサブクローンＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）の間で比較した。４ウェルの各細胞系をＣＰＴ－１１およびＳＮ－３８の系列希釈液と共にインキュベートし、前記と同様に処理した。図３２に示すように、ＣＰＴ－１１に対する感受性の差はわずかにすぎない。ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）細胞のＣＰＴ－１１　IC_{50}である４μｇ／ｍｌは、ＲＴ１１２細胞（２．５μｇ／ｍｌのIC_{50}）と比較して２倍高い。ＭＤＲ１を発現しないＲＴ１１２と対照的に、ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）細胞は中間量のＭＤＲ１を発現する。これにより、ＣＰＴ－１１感受性がわずかではあるが有意に増大することを説明できる。ＳＮ－３８で処理した後は、ＲＴ１１２細胞（４ｎｇ／ｍｌのIC_{50}）とＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）細胞（７５ｎｇ／ｍｌのIC_{50}）の間にはるかに強い相異がある（図３２Ｂ）。ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）細胞系がもつこの１９倍高い耐性は、ＲＴ１１２細胞の場合より高いレベルでＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）細胞に発現するＵＧＴ１Ａ１（図２９）の追加解毒効果により説明できる。ＳＮ－３８と対照的にＣＰＴ－１１はＵＧＴにより代謝されない。したがって、ＣＰＴ－１１関連毒性はＵＧＴ１Ａ１発現により影響されず、ＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）細胞におけるＵＧＴの耐性増強能はＳＮ－３８投与によってのみ検出される。

【実施例９】

【０２１７】

ＭＤＲ１の阻害は、ＭＤＲ１高発現性の癌細胞においてＣＰＴ－１１およびＳＮ－３８に対する増感作用をもつが、低発現性の癌細胞においてはその作用をもたない

特異的阻害薬Ｒ－ベラパミルによりＭＤＲ１機能を遮断した後、ＣＰＴ－１１およびＳＮ－３８に対するＫＢ　３－１細胞およびそのサブクローンＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）の感受性を評価した。４ウェルの各細胞系をＣＰＴ－１１およびＳＮ－３８の系列希釈液と共にインキュベートし、前記と同様に分析した。２ウェルをさらにＭＤＲ１阻害薬Ｒ－ベラパミルで処理した。図３３は、Ｒ－ベラパミルの添加がＭＤＲ１低発現体であるＫＢ　３－１細胞のＣＰＴ－１１およびＳＮ－３８感受性にはわずかな影響を与えるにすぎないことを示す（ＣＰＴ－１１およびＳＮ－３８のIC_{50}は、Ｒ－ベラパミルを用いない場合の５μｇ／ｍｌおよび２５

ｎｇ／ｍｌに対して、Ｒ－ベラパミルを用いた場合はそれぞれ４．５μｇ／ｍｌおよび１５ｎｇ／ｍｌ）。これと対照的に、ＭＤＲ１発現性の細胞ＫＢ　３－１（ＭＤＲ１$^{+++}$）およびＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）のＣＰＴ－１１およびＳＮ－３８に対する感受性は、Ｒ－ベラパミルでＭＤＲ１輸送機能を阻害した後には８倍および１０倍高かった。ＣＰＴ－１１に対しては、ＫＢ３－１（ＭＤＲ１$^{+++}$）細胞のIC_{50}がＲ－ベラパミルを添加しない場合の８５μｇ／ｍｌから添加した場合の１０μｇ／ｍｌに低下し、ＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）細胞においてはＲ－ベラパミルを添加しない場合の２００ｎｇ／ｍｌから添加した場合の２５ｎｇ／ｍｌに低下した。ＳＮ－３８処理に際してのＭＤＲ１阻害作用はこれらのＭＤＲ１高発現細胞においてさらに強く、Ｒ－ベラパミルがＭＤＲ１の輸送を完全に遮断してＫＢ　３－１細胞と同様に感受性になる。

【０２１８】

これらの結果は、ＭＤＲ１活性がＣＰＴ－１１およびＳＮ－３８に対する癌細胞の耐性と関連すること、ならびにＭＤＲ１の阻害が細胞を増感させ、これによりそれらの細胞がより低い薬物濃度でより効果的に死滅することを証明する。

【実施例１０】

【０２１９】

ＣＹＰ３Ａ５活性はＣＰＴ－１１に対する耐性に影響を与える

ＫＢ　３－１（ＭＤＲ１$^{+++}$）細胞とＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）細胞は、それらのＣＹＰ３Ａ５量が異なる（図２９）。４ウェルの各細胞系をＣＰＴ－１１およびＳＮ－３８の系列希釈液と共にインキュベートし、前記と同様に分析した。２ウェルをさらにＭＤＲ１阻害薬Ｒ－ベラパミルで処理した。

【０２２０】

ＭＤＲ１活性はＣＰＴ－１１およびＳＮ－３８に対する細胞感受性の主決定因子であるので、過剰の特異的ＭＤＲ１阻害薬Ｒ－ベラパミルを用いてこれらのＭＤＲ１高発現細胞系におけるＭＤＲ１活性を完全に遮断し、ＣＹＰ３Ａ５がＭＤＲ１の影響なしにＣＰＴ－１１およびＳＮ－３８感受性に与える影響を分析した。

【０２２１】

高ＣＹＰ３Ａ５発現細胞系ＫＢ　３－１（ＭＤＲ１$^{+++}$、ＣＹＰ３Ａ５）はＣＰＴ－１１に対して２５μｇ／ｍｌのIC_{50}をもち、１０μｇ／ｍｌのIC_{50}を示すＫＢ　３－１（ＭＤＲ１$^{+++}$）より２．５倍耐性が大きい（図３４）。ＳＮ－３８に対する感受性に関しては、これら２細胞系間に差がみられない。

【０２２２】

これらの実験は、ＣＹＰ３Ａ５発現がＳＮ－３８と対照的にＣＰＴ－１１耐性に有意の影響を与えることを証明する。ＣＹＰ３Ａ５活性がＳＮ－３８毒性に影響を与えなかったという事実により、ＣＹＰ３Ａ５の作用がさらに確認される。ＣＰＴ－１１はＣＹＰ３Ａ５により代謝されるが、ＳＮ－３８は代謝されないからである。

【実施例１１】

【０２２３】

ＭＤＲ１遺伝子型判定は、遺伝子型に基づく薬物耐性の予測およびモニタリングによりイリノテカンの療法効果を改善する

イリノテカンの療法効果および有害作用は、親化合物および活性代謝産物（たとえばＳＮ－３８）の血漿中濃度および腫瘍細胞内濃度に依存する。ＭＤＲ１遺伝子は、膜を通るイリノテカンのＰＧＰ依存性透過を制御し［Ｌｕｏ　ｅｔ　ａｌ．，Ｄｒｕｇ　Ｍｅｔａｂ　Ｄｉｓｐｏｓ　２００２，３０：７６３－７７０；Ｊａｎｓｅｎ　ｅｔ　ａｌ．，Ｂｒ　Ｊ　Ｃａｎｃｅｒ　１９９８，７７：３５９－６５；Ｃｈｕ　ｅｔ　ａｌ．，Ｊ　Ｐｈａｒｍａｃｏｌ　Ｅｘｐ　Ｔｈｅｒ　１９９９，２８８，７３５－４１；Ｓｕｇｌｙａｍａ　ｅｔ　ａｌ．，Ｃａｎｃｅｒ　Ｃｈｅｍｏｔｈｅｒ　Ｐｈａｒｍａｃｏｌ　１９９８，４２，Ｓｕｐｐｌ：Ｓ４４－９］、したがってそれの全身利用能および細胞内蓄積に対する重要な決定因子である。ＭＤＲ１遺伝子（寄託番号：Ｍ２９４４５）の１７６Ｃ＞Ｔ

ヌクレオチド置換（ＳＥＱ　ＩＤ　ＮＯ：２１７、２１８、２１９および２２０）は、低ＰＧＰ発現関連の低薬物排出と関連し、この置換をもつ患者は下記の２つの理由でよりイリノテカン治療に応答しやすい：１）腸細胞内のＰＧＰ量がより少ないので、より多量のイリノテカンが腸バリヤーを越えて体内へ進入でき、このためより多量のイリノテカンがそれの作用部位である腫瘍へ到達する；２）腫瘍細胞膜中のＰＧＰ量がより少ないので、より多量のイリノテカンが腫瘍細胞内へ透過してその細胞毒性を展開する可能性がある。現在採用されている標準用量のイリノテカンは、大部分の細胞を化学療法の初期サイクル以内にきわめて効果的に殺し、生存する薬物耐性腫瘍細胞はきわめてわずかにすぎず、有害事象は耐容できる。薬物耐性機序とは別に、これらの患者において、もはやイリノテカン療法に応答しない薬物耐性腫瘍を発現するには生存細胞数が少なすぎる。

【０２２４】

高発現性ＭＤＲ１遺伝子型（ＭＤＲ１遺伝子、寄託番号：Ｍ２９４４５の位置１７６におけるヌクレオチドＣ）をもつ患者は、イリノテカン治療に対する応答性がより低いと思われる。十分に効果的に腫瘍細胞を殺すには、薬物耐性腫瘍の発現を阻止するために、より高い投与量が必要であろう。しかし、イリノテカン投与量の増加は、耐容できない有害事象（たとえば下痢、好中球減少症または血栓性合併症）の発生のため制限される。あるいは、イリノテカン治療の効力はＰＧＰ阻害薬の添加によって改善できる。ＰＧＰ阻害薬はＭＤＲ１高発現患者においてＰＧＰ機能を効果的に遮断し、これによりイリノテカンが腫瘍細胞内に濃縮され、ＭＤＲ１低発現患者の場合と同様に有効にその毒性を及ぼすことができる。その結果、遺伝子型においてＭＤＲ１の高発現性である患者が表現型においてはＭＤＲ１低発現患者に類似することとなる。

【０２２５】

ＭＤＲ１遺伝子の低発現性または高発現性の対立遺伝子の数に従って、個体を高度（ＥＴ、２つの高発現性対立遺伝子）、中間（ＩＴ、１つの高発現性対立遺伝子、１つの低発現性対立遺伝子）また低度（ＰＴ、２つの低発現性対立遺伝子）輸送能をもつと分類できる。イリノテカンによる治療の開始前に遺伝子試験を行うことにより、患者をＥＴ、ＩＴまたはＰＴとして分類し、患者のＭＤＲ１関連の輸送能を予測することができる。個体が不十分な抗癌治療を受けるリスクは、ＭＤＲ１高発現性対立遺伝子の数に伴って高まる。ＥＴ遺伝子型をもつ個体はイリノテカンに対する不十分な応答を生じるリスクが最も高く、薬物耐性腫瘍が発現するリスクが最も高い。ＥＴ患者は、イリノテカンに加えてＰＧＰ阻害薬により治療し、有害事象および化学療法関連の薬物耐性の発現をより厳密にモニターすべきである。さらに、薬物耐性腫瘍が発現するリスクが高いこれらの患者は、化学療法の各サイクル間で腫瘍生検を行い、それに伴って腫瘍細胞を薬物耐性に関して個別にプロファイリングすることが特に有益である。

【図面の簡単な説明】

【０２２６】

【図１】２１人のボランティアにおいてウェスタンブロット分析により測定したエキソン２６　ＳＮＰと腸ＭＤＲ１発現の相関を示す。ボックスプロットは、ＭＤＲ１遺伝子（ＧｅｎＢａｎｋ寄託番号Ｍ２９４４５）の位置１７６に対応する位置におけるＭＤＲ１　３４３５Ｃ＞Ｔ遺伝子型に従ってクラスターしたＭＤＲ１発現の分布を示す。このＴ対立遺伝子はＰ－糖タンパク質の発現低下と関連していた。

【図２】定常状態のピーク血漿ジゴキシン濃度を調べる臨床試験に参加した１４人の健康なボランティアにおけるＭＤＲ１　３４３５Ｃ＞Ｔ遺伝子型とジゴキシン取込みの相関を示す［Ｊｏｈｎｅ　ｅｔ　ａｌ．，１９９９，Ｃｌｉｎ．Ｐｈａｒｍａｃｏｌ．Ｔｈｅｒ　６６：３３８－３４５］。ＴおよびＣ対立遺伝子に関してそれぞれホモ接合性である２群間で、最大ジゴキシン濃度は統計学的に有意差があった（ｐ＝０．００６，マン－ウィットニーのＵ検定）。

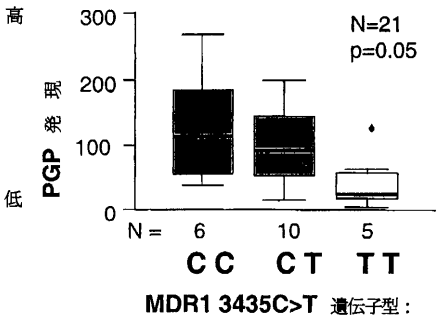
【図３】２つの独立した実験に属する健康なボランティアからリファンピシン投与の前と後に得た十二指腸生検材料中における、遺伝子型（ｗｔ／ｗｔ：１；ｗｔ／ｍｕｔおよびｍｕｔ／ｍｕｔ：２）とＭＲＰ１　ｍＲＮＡ含量の相関を表わす。リファンピシン投与は

ＭＲＰ１　ｍＲＮＡ発現に影響を与えなかった（ｐ＜０．００１，対ｔ－検定）。ＭＲＰ１遺伝子型とＭＲＰ１　ｍＲＮＡレベルの強い関連傾向が検出された（ｐ＝０．０８６，クルスカル－ウォリス検定）。
【図４】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図５】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図６】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図７】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図８】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図９】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図１０】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
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【図１３】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図１４】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図１５】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図１６】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図１７】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図１８】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
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【図２０】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
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【図２２】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図２３】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図２４】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
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【図２６】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図２７】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図２８】本明細書に述べられた核酸配列およびアミノ酸配列を示す。
【図２９】癌細胞系におけるイリノテカン代謝関連遺伝子の発現プロフィルを示す。この半定量ＲＴ－ＰＣＲは、アンプリコンの右側に示した遺伝子に関する転写物の量を示す。ＰＣＲ生成物をアガロース電気泳動により分析し、臭化エチジウムで染色した。各フラグメントサイズを左側に塩基対（ｂｐ）で示す。
【図３０】上皮癌細胞系ＬＳ１７４Ｔ（結腸）、ＫＢ　３－１（子宮頚）およびＲＴ１１２（膀胱）について、ＣＰＴ－１１（Ａ）およびＳＮ－３８（Ｂ）に関する増殖阻害曲線を示す。ＣＰＴ－１１の濃度は０～２００μｇ／ｍｌ、ＳＮ－３８の濃度は０～２００ｎｇ／ｍｌであった。細胞を３日間処理した。各濃度についてのデータは少なくとも３つのウェルの平均値である。
【図３１】上皮性子宮頚癌細胞系ＫＢ　３－１、ならびに高い量のＭＤＲ１を発現する２つのサブクローン、ＫＢ　３－１（ＭＤＲ１）およびＫＢ　３－１（ＭＤＲ１、ＣＹＰ３Ａ５）について、ＣＰＴ－１１（Ａ）およびＳＮ－３８（Ｂ）に関する増殖阻害曲線を示す。ＣＰＴ－１１の濃度は０～２００μｇ／ｍｌ、ＳＮ－３８の濃度は０～２００ｎｇ／ｍｌであった。細胞を３日間処理した。各濃度についてのデータは少なくとも３つのウェルの平均値および標準偏差である。
【図３２】膀胱癌細胞系ＲＴ１１２、ならびに、ＭＤＲ１および高い量のＵＧＴ１Ａ１を発現するそのサブクローンＲＴ１１２（ＭＤＲ１、ＵＧＴ１Ａ１）について、ＣＰＴ－１１（Ａ）およびＳＮ－３８（Ｂ）に関する増殖阻害曲線を示す。ＣＰＴ－１１の濃度は０～２００μｇ／ｍｌ、ＳＮ－３８の濃度は０～２００ｎｇ／ｍｌであった。細胞を３日間処理した。各濃度についてのデータは少なくとも３つのウェルの平均値および標準偏差である。
【図３３】Ｒ－ベラパミルによりＭＤＲ１を阻害した状態でのＣＰＴ－１１（Ａ）および

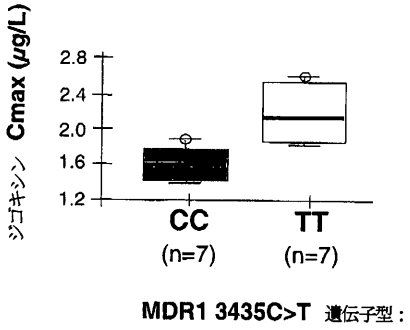
ＳＮ－３８（Ｂ）に関する増殖阻害曲線を示す。上皮性子宮頚癌細胞系ＫＢ　３－１、ならびに高い量のＭＤＲ１を発現する２つのサブクローンＫＢ　３－１（ＭＤＲ１）およびＫＢ　３－１（ＭＤＲ１、ＣＹＰ３Ａ５）を、Ｒ－ベラパミルによるｍｄｒ１の阻害が薬物感受性に与える影響について調べた。ＣＰＴ－１１の濃度は０～２００μｇ／ｍｌ、ＳＮ－３８の濃度は０～２００ｎｇ／ｍｌであり、Ｒ－ベラパミルを最終濃度１０μｇ／ｍｌになるように添加した（＋Ｖ）。細胞を３日間処理した。各濃度についてのデータは２つのウェルの平均値である。

【図３４】Ｒ－ベラパミルによりＭＤＲ１を阻害した状態でのＣＰＴ－１１（Ａ）およびＳＮ－３８（Ｂ）に関する増殖阻害曲線を示す。薬物耐性に対するＭＤＲ１の影響を回避するために、細胞をＲ－ベラパミルで並行処理した。それらのＣＹＰ３Ａ５発現が異なるＫＢ　３－１（ＭＤＲ１）およびＫＢ　３－１（ＭＤＲ１、ＣＹＰ３Ａ５）を、ＭＤＲ１阻害後の残留耐性について調べた。ＣＰＴ－１１の濃度は０～２００μｇ／ｍｌ、ＳＮ－３８の濃度は０～２００ｎｇ／ｍｌであり、Ｒ－ベラパミルを最終濃度１０μｇ／ｍｌになるように添加した（＋Ｖ）。細胞を３日間処理した。各濃度についてのデータは２つのウェルの平均値である。

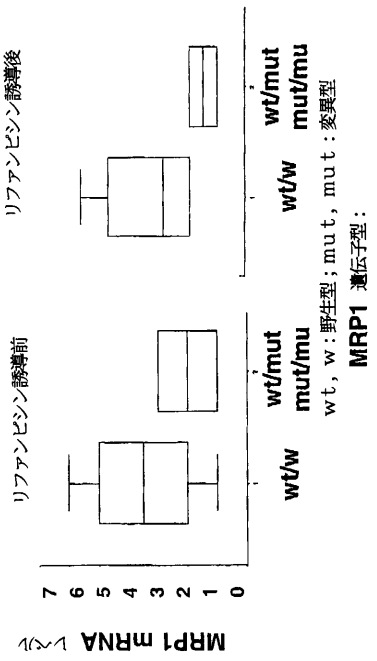
【図１】



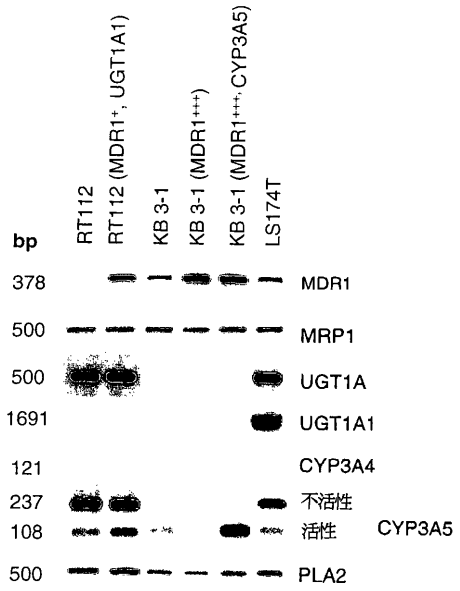
【図２】



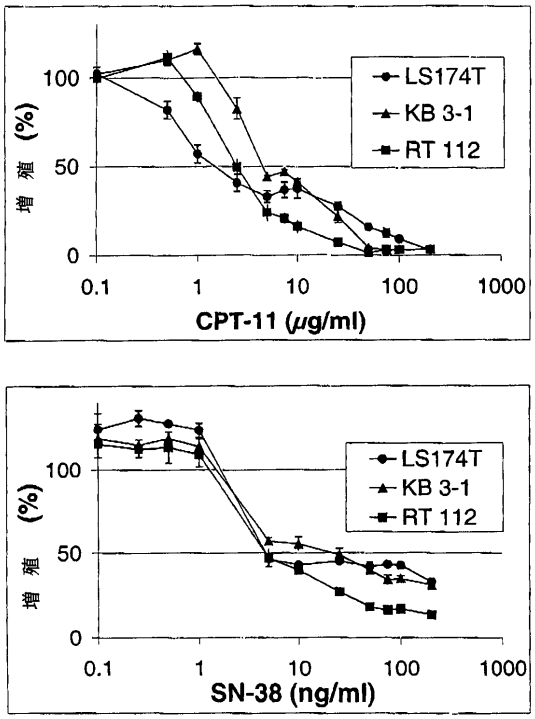
【図３】



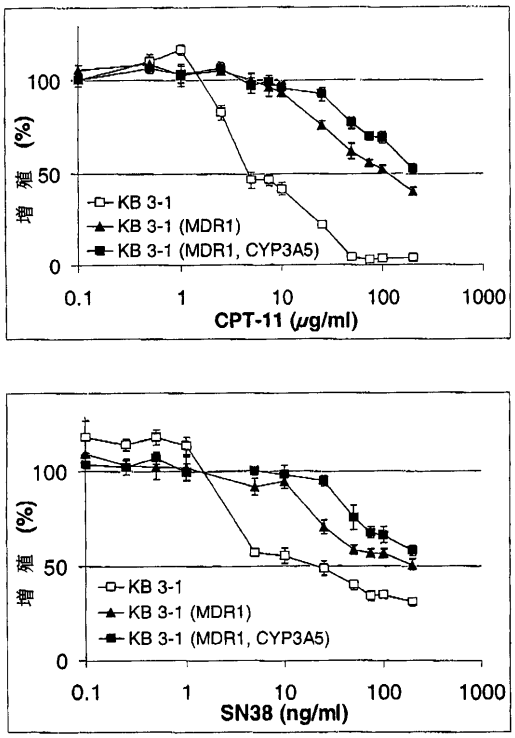
【図２９】



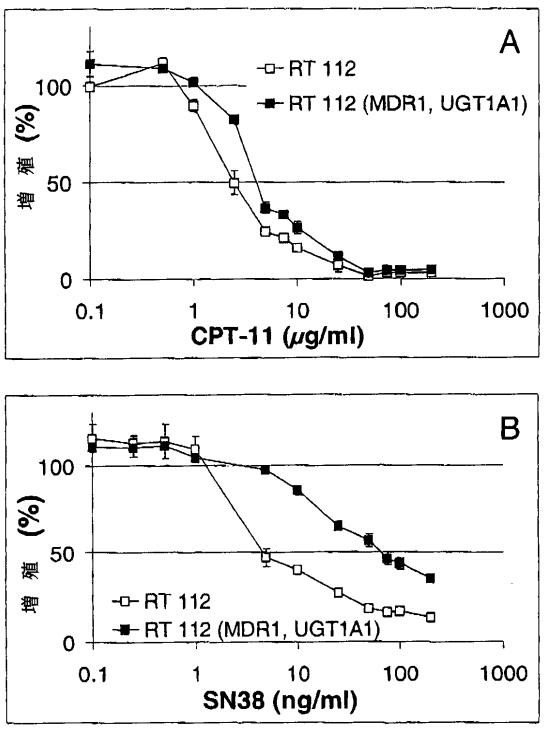
【図３０】



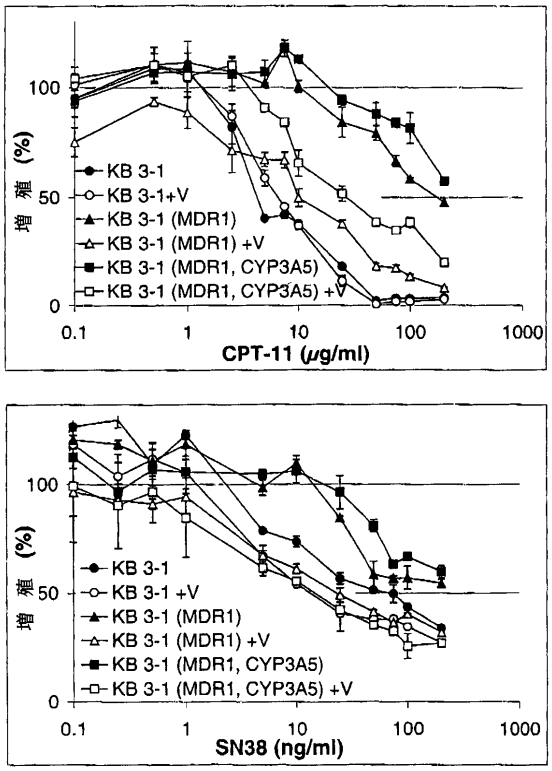
【図３１】



【図３２】

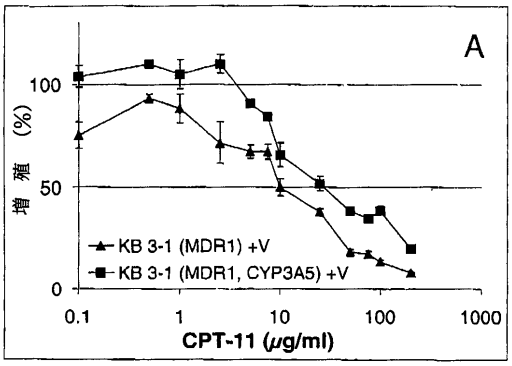


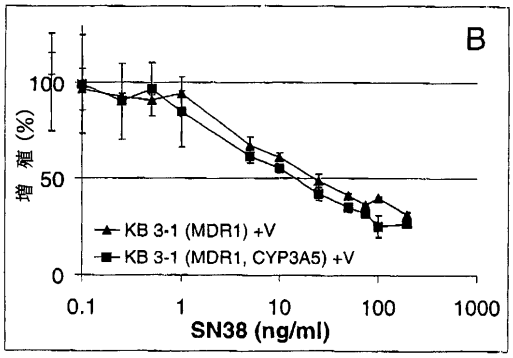
【図３３】


増殖 (%)
100
50
0
KB 3-1
KB 3-1+V
KB 3-1 (MDR1)
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5)
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
CPT-11 (μg/ml)

増殖 (%)
100
50
0
KB 3-1
KB 3-1 +V
KB 3-1 (MDR1)
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5)
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
SN38 (ng/ml)

【図３４】


A
増殖 (%)
100
50
0
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
CPT-11 (μg/ml)


B
増殖 (%)
100
50
0
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
SN38 (ng/ml)

【国際公開パンフレット】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number
WO 03/013537 A2

(51) International Patent Classification⁷: A61K 31/4745, A61P 35/00

(21) International Application Number: PCT/EP02/08218

(22) International Filing Date: 23 July 2002 (23.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01117608.8 23 July 2001 (23.07.2001) EP
02011710.7 24 May 2002 (24.05.2002) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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WO 03/013537 A2

(54) Title: MEANS AND METHODS FOR IMPROVED TREATMENT OF CANCER

(57) Abstract: The present invention relates to the use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a patient having a genotype with a first, a second, a third, and/or a fourth variant allele which comprises a polynucleotide in accordance with the present invention. Preferably, a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of a first, a second, a third and/or a fourth variant allele compared to the corresponding wild type allele or an altered activity of the polypeptide encoded by the variant allele compared to the polypeptide encoded by the corresponding wild type allele. Finally, the present invention relates to a method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer.

Means and methods for improved treatment of cancer

The present invention relates to the use of camptothecin drugs, such as irinotecan (CPT-11) or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a patient having a genotype with a first, a second, a third, and/or a fourth variant allele which comprises a polynucleotide in accordance with the present invention. Preferably, a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first, second, third, and/or fourth variant allele compared to the corresponding wild type allele or an altered activity of the polypeptide encoded by the variant allele compared to the polypeptide encoded by the corresponding wild type allele. Finally, the present invention relates to a method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer or pancreatic cancer.

Irinotecan is a semisynthetic analog of the cytotoxic alkaloid camptothecin (CPT), which is obtained from the oriental tree, Camptotheca acuminata Camptothecins demonstrate anti-neoplastic activities by inhibiting specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks [D'Arpa, *et al.*, 1989, Biochim Biophys Acta 989:163-77, Horwitz, *et al.*, 1973, Cancer Res 33:2834-6]. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks [Kawato, *et al.*, 1991, Cancer Res 51:4187-91]. Irinotecan serves as a water-soluble prodrug of the lipophilic metabolite SN-38 (7-ethyl-10-hydroxycamptothecin) which is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and

the dipiperidino side chain [Tsuji, *et al.*, 1991, J Pharmacobiodyn 14:341-9]. Carboxylesterase-2 is the primary enzyme involved in this hydrolysis at at pharmacological concentrations [Humerickhouse, *et al.*, 2000, Cancer Res 60:1189-92]. Topoisomerase inhibition and irinotecan-related single strand breaks are caused primarily by SN-38 [Kawato, *et al.*, 1991, Cancer Res 51:4187-91]. Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types [Furuta, *et al.*, 1988, Gan To Kagaku Ryoho 15:2757-60, Giovanella, *et al.*, 1989, Science 246:1046-8, Giovanella, *et al.*, 1991, Cancer Res 51:3052-5, Hawkins, 1992, Oncology (Huntingt) 6:17-23, Kunimoto, *et al.*, 1987, Cancer Res 47:5944-7].

Irinotecan is also oxidized by CYP3A4 and CYP3A5 [Haaz, *et al.*, 1998, Drug Metab Dispos 26:769-74, Kuhn, 1998, Oncology (Huntingt) 12:39-42, Santos, *et al.*, 2000, Clin Cancer Res 6:2012-20, Rivory, *et al.*, 1996, Cancer Res 56:3689-94]. The major elimination pathway of SN-38 is conjugation with glucuronic acid to form the corresponding glucuronide (SN-38G) [Atsumi, *et al.*, 1991, Xenobiotica 21:1159-69.]. SN-38G is reported to be deconjugated by the intestinal microflora to form SN-38 [Kaneda, *et al.*, 1990, Cancer Res 50:1715-20]. Glucuronidation of SN-38 is mediated by UGT1A1 and UGT1A7 [Lyer, *et al.*, 1998, J Clin Invest 101:847-54, Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202]. Mass balance studies have demonstrated that 64% of the total dose is excreted in the feces, confirming the important role of biliary excretion [Slatter, *et al.*, 2000, Drug Metab Dispos 28:423-33]. Studies suggest that the multidrug rsistance protein 1 (MRP1) is a major transporter of irinotecan and its metabolites [Kuhn, 1998, Oncology (Huntingt) 12:39-42, Chen, *et al.*, 1999, Mol Pharmacol 55:921-8, Chu, *et al.*, 1997, Cancer Res 57:1934-8, Chu, *et al.*, 1997, J Pharmacol Exp Ther 281:304-14] and facilitate their biliary excretion, where they cause side effects, although P-glycoprotein also participates in irinotecan excretion [Chu, *et al.*, 1998, Cancer Res 58:5137-43, Chu, *et al.*, 1999, Drug Metab Dispos 27:440-1, Chu, *et al.*, 1999, J Pharmacol Exp Ther 288:735-41, Mattern, *et al.*, 1993, Oncol Res 5:467-74, Hoki, *et al.*, 1997, Cancer Chemother Pharmacol 40:433-8, Sugiyama, *et al.*, 1998, Cancer Chemother Pharmacol 42:S44-9].

Cellular resistance to camptothecins and thus, therapeutic response of irinotecan has been related to intracellular carboxylesterase activity and cleavage activity of topoisomerase I [van Ark-Otte, *et al.*, 1998, Br J Cancer 77:2171-6, Guichard, *et al.*, 1999, Br J Cancer 80:364-70].

The use of such camptothecin drugs, e.g. irinotecan, is limited by clearly dose-dependent myelosuppression and gastrointestinal toxicities, including nausea, vomiting, abdominal pain, and diarrhea which side effects can prove fatal. The major dose-limiting toxicity of irinotecan therapy is diarrhea, which occurs in up to 88% of patients and which depends on intestinal SN-38 accumulation [van Ark-Otte, *et al.*, 1998, Br J Cancer 77:2171-6, Guichard, *et al.*, 1999, Br J Cancer 80:364-70, Araki, *et al.*, 1993, Jpn J Cancer Res 84:697-702] secondary to the biliary excretion of SN-38, the extent of which is determined by SN-38 glucuronidation [Gupta, *et al.*, 1994, Cancer Res 54:3723-5, Gupta, *et al.*, 1997, J Clin Oncol 15:1502-10]. Myelosuppression has been correlated with the area under the concentration-time curve of both irinotecan and SN-38 [Sasaki, *et al.*, 1995, Jpn J Cancer Res 86:101-10].

Despite the approval of irinotecan for patients with metastatic colorectal cancer refractory to 5-fluorouracil therapy in 1997, the therapeutic benefit remains questionable. Recently two large clinical trials on colorectal cancer involving more than 2000 patients had to be canceled by the National Institute of Cancer (NCI) due to an almost 3-times increase of irinotecan toxicity-related mortality within the first 60 days of treatment. Causes of death were diarrhea- and vomiting-related dehydratation and neutropenia-related sepsis [2001, arznei-telegramm 32:58]. Although irinotecan was proven to be effective against then cancer itself, not all patients could benefit from longterm survival due to short term toxicity. Thus, it is highly desirable to identify those patients who will most likely suffer from irinotecan toxicity.

Currently, patients are treated according to most treatment schedules with a standard dose of initially 60 to 125 mg/m^2 irinotecan in combination with other anti-neoplastic drugs administered several courses of 3 to 4 weekly dosings, and subsequent doses are adjusted in 25 to 50 mg/m^2 increments based upon individual patient tolerance to treatment. Treatment may be delayed 1 to 2 weeks to

allow for recovery from irinotecan-related toxicity and if the patient has not recovered, therapy has to be discontinued. Provided intolerable toxicity does not develop, treatment with additional courses are continued indefinitely as long as the patient continues to experience clinical benefit. Response rates varies depending from tumor type from less than 10 % to almost 90 %. However, it takes at least 6 to 8 weeks to evaluate therapeutic response and to consider alternatives. Thus, finding the right dosage for the patient is tedious, time-consuming and takes the risk of lifethreatening adverse effects. Patients might be unnecessarily put to this risk who do not benefit from treatment and additionally, worthwhile time is wasted before these patients receive their suitable treatment.

Furthermore, as observed for many chemotherapeutic agents, the risk to develop cellular resistances against therapy is increased upon suboptimal exposure of cells to chemotherapeutic agents, such as irinotecan.

Pharmacokinetic modulation with inhibitors of biliary excretion (*e. g.,* MRP and P-glycoprotein) and inducers of UGT1A1 have been suggested as a tool to reduce camptothecin-related toxicity [Gupta, *et al.*, 1996, Cancer Res 56:1309-14, Gupta, *et al.,* 1997, Cancer Chemother Pharmacol 39:440-4]. Although preliminary data of a clinical study of irinotecan in combination with cyclosporine A, and phenobarbital show some promising results in respect to limit camptothecin-related diarrhea [Ratain, 2000, Clin Cancer Res 6:3393-4], cotreatment with drugs such as cyclosporine A, and phenobarbital takes the additional risk of adverse events and drug interactions.

Large interpatient variability exist for both SN-38 and SN-38G pharmacokinetics [Canal, *et al.*, 1996, J Clin Oncol 14:2688-95], which is likely to be due to interpatient differences in the metabolism pathways of irinotecan [Rivory, *et al.*, 1997, Clin Cancer Res 3:1261-6]. Furthermore, severe irinotecan toxicity has been reported in patients with Gilbert syndrome [Wasserman, *et al.*, 1997, Ann Oncol 8:1049-51]. Consequently, a genetic predisposition to the metabolism of irinotecan, that patients with low UGT1A1 activity are at increased risk for irinotecan toxicity has been suggested [Iyer, *et al.*, 1998, J Clin Invest 101:847-54, Ando, *et al.*, 1998, Ann Oncol 9:845-7]. A common polymorphism in the UGT1A1 promoter [Monaghan, *et al.*, 1996, Lancet 347:578-81] has been correlated with *in vitro*

glucuronidation of SN-38 [Iyer, *et al.*, 1999, Clin Pharmacol Ther 65:576-82], and its possible clinical use has been suggested from a case control study [Ando, *et al.*, 2000, Cancer Res 60:6921-6]. However, irinotecan-related toxicity was predicted by UGT1A1 genotype only in the minority of affected patients (< 15 %).

In conclusion, it would be highly desirable to significantly improve therapeutic efficacy and safety of camptothecin-based therapies and to avoid therapy-caused fatalities, to avoid unnecessary development of resistances, and to reduce adverse events- and therapeutic delay-related hospitalization costs. However, no accepted mechanism for reducing irinotecan toxicity or to improve therapeutic efficacy are currently available.

Thus, the technical problem underlying the present invention is to provide improved means and methods for the efficient treatment of colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer, whereby the aforementioned undesirable side effects are to be avoided.
The technical problem underlying the present invention is solved by the embodiments characterized in the claims.

Accordingly, the present invention relates to the use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating cancer, especially, colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genome with a first variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422, 425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482,

485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 and/or 641;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 606, 608, 610, 612, 618, 620, 622, 624, and/or 628;

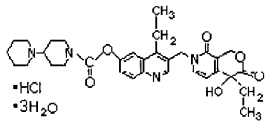
(c) a polynucleotide capable of hybridizing to a Multidrug Resistance 1 (MDR1) gene, wherein said polynucleotide is having at a position corresponding to positions 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619 of the MDR1 gene (Accession No: AC002457) and/or 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162 of the MDR1 gene (Accession No: AC005068) and/or 101, 308 of the MDR1 gene (Accession No: M29432) and/or 137, 176 of the MDR1 gene (Accession No: M29445), a substitution or deletion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having at a position corresponding to position 83946, 70200, 70237, 65241 of the MDR1 gene (Accession No: AC005068) and/or 101 of the MDR1 gene (Accession No: M29432) and/or 141529, 174901, 139177, 140118, 140568, 140727, 139479 of the MDR1 gene (Accession No: AC002457) an A, at a position corresponding to position 308 of the MDR1 gene (Accession No: M29432) and/or 84701, 83973, 84074, 84119, 78170, 70204, 70253, 70371, 50537, 43162 of the MDR1 gene (Accession No: AC005068) and/or 137 or 176 of the MDR1 gene (Accession No: M29445) and/or 145984, 171466, 175068, 175074, 139064, 139276, 140576 of the MDR1 gene (Accession No: AC002457) a T, at a position corresponding to position 140837, 171404, 171456, 171511, 171512, 139119, 140490, 139619 of the MDR1 gene (Accession No: AC002457) and/or 43263 of the MDR1 gene (Accession No: AC005068) a C, at a position corresponding to position 84032, 77811, 73252 of the MDR1 gene (Accession No: AC005068) and/or 141590, 175142, 175180, 139015, 140216, 140595 of the MDR1 gene (Accession No: AC002457) a G;

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to positions 21, 103, 168, 400, 893, 999, 1001, 1107, and/or 1141 of the MDR1 polypeptide (Accession No: G2506118);

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118).

The term "irinotecan or a derivative thereof" as used in accordance with the present invention preferably refers to a substance which is characterized by the general structural formula



$C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$

further described in US patents US05106742, US05340817, US05364858, US05401747, US05468754, US05559235 and US05663177. Moreover, also comprised by the term "irinotecan or a derivative thereof" are analogues and derivatives of camptothecin. The types and ranges of camptothecin analogues available are well known to those of skill in the art and described in numerous texts, e.g. [Hawkins, 1992, Oncology (Huntingt) 6:17-23, Burris, *et al.*, 1994, Hematol Oncol Clin North Am 8:333-55, Slichenmyer, *et al.*, 1993, J Natl Cancer Inst 85:271-91, Slichenmyer, *et al.*, 1994, Cancer Chemother Pharmacol 34:S53-7]. Specific examples of active camptothecin analogues are hexacyclic camptothecin analogues, 9-nitro-camptothecin, camptothecin analogues with 20S configuration with 9- or 10-substituted amino, halogen, or hydroxyl groups, seven-substituted water-soluble camptothecins, 9-substituted camptothecins, E-ring-modified camptothecins such as (RS)-20-deoxyamino-7-ethyl-10-methoxycamptothecin, and 10-substituted camptothecin analogues [Emerson, *et al.*, 1995, Cancer Res 55:603-9, Ejima, *et al.*, 1992, Chem Pharm Bull (Tokyo) 40:683-8, Sugimori, *et al.*, 1994, J Med Chem 37:3033-9, Wall, *et al.*, 1993, J Med Chem 36:2689-700, Wani, *et al.*, 1980, J Med Chem 23:554-60, Kingsbury, *et al.*, 1991, J Med Chem 34:98-107]. Various other camptothecin analogues with similar therapeutic activity are described [Hawkins, 1992, Oncology (Huntingt) 6:17-23, Burris and Fields, 1994, Hematol Oncol Clin North Am 8:333-55, Slichenmyer, *et al.*, 1993, J Natl Cancer Inst 85:271-91, Slichenmyer, *et al.*, 1994, Cancer Chemother Pharmacol 34:S53-7]. Suitable methods for synthezising camptothecin analogues are described [Emerson, *et al.*, 1995, Cancer Res 55:603-9, Ejima, *et al.*, 1992, Chem Pharm Bull (Tokyo) 40:683-8, Sugimori, *et al.*, 1994, J Med Chem 37:3033-9, Wall, *et al.*, 1993, J Med Chem 36:2689-700, Wani, *et al.*, 1980, J Med Chem 23:554-60, Kingsbury, *et al.*, 1991, J Med Chem 34:98-107, Sugasawa, *et al.*, 1976, J Med Chem 19:675-9].

Said substances are known to be therapeutically useful as described, e.g., in colorectal cancer, non-small cell and small cell lung cancer, oesophageal cancer, renal cell carcinoma, ovarian cancer, breast cancer, pancreatic cancer, squamous cell cancer, leukemias and lymphomas [Kawato, *et al.*, 1991, Cancer Res 51:4187-91, Furuta, *et al.*, 1988, Gan To Kagaku Ryoho 15:2757-60, Hawkins, 1992, Oncology (Huntingt) 6:17-23, Slichenmyer, *et al.*, 1993, J Natl Cancer Inst 85:271-

91, Slichenmyer, *et al.*, 1994, Cancer Chemother Pharmacol 34:S53-7, Tsuruo, *et al.*, 1988, Cancer Chemother Pharmacol 21:71-4, Wiseman, *et al.*, 1996, Drugs 52:606-23, Gottlieb, *et al.*, 1970, Cancer Chemother Rep 54:461-70, Negoro, *et al.*, 1991, J Natl Cancer Inst 83:1164-8, Rowinsky, *et al.*, 1994, Cancer Res 54:427-36]. Also encompassed by the use of the present invention are derivatives of those substances which are obtainable by way of any chemical modification, wherein said derivatives are equally well therapeutically suited for the use of the present invention. To determine whether a derivative of the substances of the invention is equally well therapeutically suited for the use of the invention biological assays well known in the art can be performed. Such assays are described , e.g., in [Kawato, *et al.*, 1991, Cancer Res 51:4187-91, Furuta, *et al.*, 1988, Gan To Kagaku Ryoho 15:2757-60, Giovanella, *et al.*, 1989, Science 246:1046-8, Giovanella, *et al.*, 1991, Cancer Res 51:3052-5, Kunimoto, *et al.*, 1987, Cancer Res 47:5944-7, Mattern, *et al.*, 1993, Oncol Res 5:467-74, Tsuruo, *et al.*, 1988, Cancer Chemother Pharmacol 21:71-4, Burris, *et al.*, 1992, J Natl Cancer Inst 84:1816-20, Friedman, *et al.*, 1994, Cancer Chemother Pharmacol 34:171-4].

It is contemplated that any of the compounds described in the above publications may be used in this invention.

It has been show that irinotecan is particularly well suited for the treatment of colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer. Thus, most preferably the substance used according to the present invention is irinotecan.

The term "pharmaceutical composition" as used herein comprises the substances of the present invention and optionally one or more pharmaceutically acceptable carrier. The substances of the present invention may be formulated as pharmaceutically acceptable salts. Acceptable salts comprise acetate, methylester, HCl, sulfate, chloride and the like. The pharmaceutical compositions can be conveniently administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The substances may be administered in conventional dosage forms prepared by combining the drugs with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating and

compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are phosphate buffered saline solution, syrup, oil such as peanut oil and olive oil, water, emulsions, various types of wetting agents, sterile solutions and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax. The substance according to the present invention can be administered in various manners to achieve the desired effect. Said substance can be administered either alone or in the formulated as pharmaceutical preparations to the subject being treated either orally, topically, parenterally or by inhalation. Moreover, the substance can be administered in combination with other substances either in a common pharmaceutical composition or as separated pharmaceutical compositions.

The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like. A therapeutically effective dose refers to that amount of the substance according to the invention which ameliorate the symptoms or condition. Therapeutic efficacy and toxicity of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50.

The dosage regimen will be determined by the attending physician and other clinical factors; preferably in accordance with any one of the above described

methods. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Progress can be monitored by periodic assessment.

A typical dose can be, for example, in the range of 5 to 100 mg however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. Generally, the regimen as a regular administration of the pharmaceutical composition should be in the range of 1 μg to 10 mg units per day. If the regimen is a continuous infusion, it should also be in the range of 1 μg to 10 mg units per kilogram of body weight per minute, respectively. Progress can be monitored by periodic assessment. However, depending on the subject and the mode of administration, the quantity of substance administration may vary over a wide range to provide from about 1 mg per m^2 body surface to about 500 mg per m^2 body surface, usually 20 to 200 mg per m^2 body surface.

The pharmaceutical compositions and formulations referred to herein are administered at least once in accordance with the use of the present invention. However, the said pharmaceutical compositions and formulations may be administered more than one time, for example once weekly every other week up to a non-limited number of weeks.

Specific formulations of the substance according to the invention are prepared in a manner well known in the pharmaceutical art and usually comprise at least one active substance referred to herein above in admixture or otherwise associated with a pharmaceutically acceptable carrier or diluent thereof. For making those formulations the active substance(s) will usually be mixed with a carrier or diluted by a diluent, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other suitable containers or vehicles. A carrier may be solid, semisolid, gel-based or liquid material which serves as a vehicle, excipient or medium for the active ingredients. Said suitable carriers comprise those mentioned above and others well known in the art, see, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania. The formulations can be adopted to the mode of administration comprising the forms of tablets, capsules, suppositories, solutions, suspensions or the like.

The dosing recommendations will be indicated in product labeling by allowing the prescriber to anticipate dose adjustments depending on the considered patient group, with information that avoids prescribing the wrong drug to the wrong patients at the wrong dose.

The term "treating" or "preventing" means alleviation of the diseases symptoms i.e., regression of symptoms or inhibited progression of such symptoms, in subjects or disease populations which have been treated. Said alleviation of the diseases can be monitored by the degree of the clinical symptoms (e.g., tumor size) accompanied with the disease. While the invention may not be effective in 100% of patients treated, it is effective in treating a statistically significant (p value less than 0.05) number of patients. Whether said number of subjects is significant can be determined by statistical tests such as the Student´s t-test, the chi^2-test, the U-test according to Mann and Whitney, the Kruskal-Wallis-test (H-Test), Jonckheere-Terpstra-test or the Wilcoxon-test.

The present invention also encompasses all embodiments described in connection with pharmaceutical compositions in US patents US05106742, US05340817, US05364858, US05401747, US05468754, US05559235 and US05663177.

The terms "colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer" comprise diseases and dysregulations related to cancer. Preferred diseases encompassed by the use of the present invention are colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer. Said diseases and dysregulations are well known in the art and the accompanied symptoms are described, e.g., in standard text books such as Stedman.

The term "subject" as used in the sense of the present invention comprises animals, preferably those specified herein after, and humans.

The term "first variant allele" as used herein refers to a polynucleotide comprising one or more of the polynucleotides described herein below corresponding to a MDR1 gene. Each individual subject carries at least two alleles of the MDR1 gene, wherein said alleles are distinguishable or identical. In accordance with the use of the present invention a variant allele comprises at least one or more of the

polynucleotides specified herein below. Said polynucleotides may have a synergistic influence on the regulation or function of the first variant allele. Preferably, a variant allele in accordance with the use of the present invention comprises at least two of the polynucleotides specified herein.

In the context of the present invention the term "polynucleotides" or "polypeptides" refers to different variants of a polynucleotide or a polypeptide specified in accordance with the uses of the present invention. Said variants comprise a reference or wild type sequence of the polynucleotides or polypeptides specified herein as well as variants which differ therefrom in structure or composition. Reference or wild type sequences for the polynucleotides are Genbank accession No: GI:8850235, GI:11118740, GI:10281451, GI:11177452, GI:10281451, GI:6706037, U91318, GI:7209451, AC026452, AC003026, U91318, AF022830, GI:7209451, AC026452, AC003026, AC025277, AF022828, AF022829, AF022831, U07050, AC003026, AC002457, AC005068, M29432, M29445, and GI:11225259 or Accession No (Pid No): G8850236, G2828206, G2506118, and G12644118 for polypeptides. The differences in structure or composition usually occur by way of nucleotide or amino acid substitution(s), addition(s) and/or deletion(s).

Preferably, said nucleotide substitution(s), addition(s) or deletion(s) referred to in accordance with the use of the present invention result(s) in one or more changes of the corresponding amino acid(s) of the polypeptides. The variant polynucleotides also comprise fragments of said polynucleotides or polypeptides. The polynucleotides or polypeptides as well as the aforementioned fragments thereof are characterized as being associated with a MDR1 dysfunction or dysregulation comprising, e.g., insufficient and/or altered drug uptake.

The present invention also encompasses all embodiments described in connection with polynucleotides in WO9957322, WO0109183 or US5786344.

The term "hybridizing" as used herein refers to polynucleotides which are capable of hybridizing to the above polynucleotides or parts thereof which are associated with a MDR1 dysfunction or dysregulation. Thus, said hybridizing polynucleotides are also associated with said dysfunctions and dysregulations. Preferably, said polynucleotides capable of hybridizing to the aforementioned polynucleotides or parts thereof which are associated with MDR1 dysfunctions or dysregulations are at

least 70%, at least 80%, at least 95% or at least 100% identical to the polynucleotides or parts thereof which are associated with MDR1 dysfunctions or dysregulations. Therefore, said polynucleotides may be useful as probes in Northern or Southern Blot analysis of RNA or DNA preparations, respectively, or can be used as oligonucleotide primers in PCR analysis dependent on their respective size. Also comprised in accordance with the use of the invention are hybridizing polynucleotides which are useful for analyzing DNA-Protein interactions via, e.g., electrophoretic mobility shift analysis (EMSA). Preferably, said hybridizing polynucleotides comprise at least 10, more preferably at least 15 nucleotides in length while a hybridizing polynucleotide to be used as a probe preferably comprises at least 100, more preferably at least 200, or most preferably at least 500 nucleotides in length.

It is well known in the art how to perform hybridization experiments with nucleic acid molecules, i.e. the person skilled in the art knows what hybridization conditions s/he has to use in accordance with the present invention. Such hybridization conditions are referred to in standard text books, such as Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory (1989) N.Y. Preferred in accordance with the use of the present inventions are polynucleotides which are capable of hybridizing to the above polynucleotides or parts thereof which are associated with a MDR1 dysfunction or dysregulation under stringent hybridization conditions, i.e. which do not cross hybridize to unrelated polynucleotides such as polynucleotides encoding a polypeptide different from the MDR1 polypeptides of the invention.

Moreover, methods for determining whether a subject comprises a polynucleotide referred to herein above are well known in the art. To carry out said methods, it might be necessary to take a sample comprising biological material, such as isolated cells or tissue, from said subject. Further, the methods known in the art could comprise for example, PCR based techniques, RFLP-based techniques, DNA sequencing-based techniques, hybridization techniques, Single strand conformational polymorphism (SSCP), denaturating gradient gel electrophoresis (DGGE), mismatch cleavage detection, heteroduplex analysis, techniques based on mass spectroscopy, HPLC-based techniques, primer extension-based techniques, and 5'-nuclease assay-based techniques. A preferred and convenient method to be used in order to determine the presence or absence of one or more of the above

specified polynucleotides is to isolate blood cells from a subject and to perform a PCR based assay on genomic DNA isolated from those blood cells, whereby the PCR is used to determine whether said polynucleotides specified herein above or parts thereof are present or absent. Said method is described in more detail below and in the Examples.

The term "corresponding" as used herein means that a position is not only determined by the number of the preceding nucleotides and amino acids, respectively. The position of a given nucleotide or amino acid in accordance with the use of the present invention which may be deleted, substituted or comprise one or more additional nucleotide(s) may vary due to deletions or additional nucleotides or amino acids elsewhere in the gene or the polypeptide. Thus, under a "corresponding position" in accordance with the present invention it is to be understood that nucleotides or amino acids may differ in the indicated number but may still have similar neighboring nucleotides or amino acids. Said nucleotides or amino acids which may be exchanged, deleted or comprise additional nucleotides or amino acids are also comprised by the term "corresponding position". Said nucleotides or amino acids may for instance together with their neighbors form sequences which may be involved in the regulation of gene expression, stability of the corresponding RNA or RNA editing, as well as encode functional domains or motifs of the protein of the invention.

By, e.g., "position 17970 to 17970" it is meant that said polynucleotide comprises one or more deleted nucleotides which are deleted between positions 17970 and position 17970 of the corresponding wild type version of said polynucleotide. The same applies mutatis mutandis to all other position numbers referred to in the above embodiment which are drafted in the same format.

By, e.g., "position 1222/1223" it is meant that said polynucleotide comprises one or more additional nucleotide(s) which are inserted between positions 1222 and position 1223 of the corresponding wild type version of said polynucleotide. The same applies mutatis mutandis to all other position numbers referred to in the above embodiment which are drafted in the same format, i.e. two consecutive position numbers separated by a slash (/).

In accordance with the present invention, the mode and population distribution of genetic variations in the MDR1 gene - the different alleles of the MDR1 gene - have been analyzed by sequence analysis of relevant regions of the human said gene from many different individuals. It is a well known fact that genomic DNA of individuals, which harbor the individual genetic makeup of all genes, including the MDR1 gene, can easily be purified from individual blood samples. These individual DNA samples are then used for the analysis of the sequence composition of the alleles of the MDR1 gene that are present in the individual which provided the blood sample. The sequence analysis was carried out by PCR amplification of relevant regions of said genes, subsequent purification of the PCR products, followed by automated DNA sequencing with established methods (e.g. ABI dyeterminator cycle sequencing).
One important parameter that has to be considered in the attempt to determine the individual genotypes and identify novel variants of the MDR1 gene by direct DNA-sequencing of PCR-products from human blood genomic DNA is the fact that each human harbors (usually, with very few abnormal exceptions) two gene copies of each autosomal gene (diploidy). Because of that, great care has to be taken in the evaluation of the sequences to be able to identify unambiguously not only homozygous sequence variations but also heterozygous variations. The details of the different steps in the identification and characterization of the polymorphisms in the MDR1 gene (homozygous and heterozygous) are described in the Examples below.

Over the past 20 years, genetic heterogeneity has been increasingly recognized as a significant source of variation in drug response. Many scientific communications (Meyer, Ann. Rev. Pharmacol. Toxicol. 37 (1997), 269-296 and West, J. Clin. Pharmacol. 37 (1997), 635-648) have clearly shown that some drugs work better in some patients than in others or may even be highly toxic and that such variations in patients' responses to drugs can be correlated to a molecular basis. This "pharmacogenomic" concept spots correlations between responses to drugs and genetic profiles of patient's (Marshall, Nature Biotechnology, 15 (1997), 954-957; Marshall, Nature Biotechnology, 15 (1997), 1249-1252). In this context of population variability with regard to drug therapy, pharmacogenomics has been proposed as a tool useful in the identification and selection of patients which can

respond to a particular drug without side effects. This identification/selection can be based upon molecular diagnosis of genetic polymorphisms by genotyping DNA from leukocytes in the blood of a patient, for example, and characterization of disease (Bertz, Clin. Pharmacokinet. 32 (1997), 210-256; Engel, J. Chromatogra. B. Biomed. Appl. 678 (1996), 93-103). For the founders of health care, such as health maintenance organizations in the US and government public health services in many European countries, this pharmacogenomics approach can represent a way of both improving health care and reducing costs related to health care caused by the development of unnecessary drugs, by ineffective drugs and by side effects due to drug administration.

The mutations in the variant genes of the invention sometimes result in amino acid deletion(s), insertion(s) and in particular in substitution(s) either alone or in combination. It is of course also possible to genetically engineer such mutations in wild type genes or other mutant forms. Methods for introducing such modifications in the DNA sequence of said genes are well known to the person skilled in the art; see, e.g., Sambrook, Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory (1989) N.Y.

For the investigation of the nature of the alterations in the amino acid sequence of the polypeptides of the invention may be used such as BRASMOL that are obtainable from the Internet. Furthermore, folding simulations and computer redesign of structural motifs can be performed using other appropriate computer programs (Olszewski, Proteins 25 (1996), 286-299; Hoffman, Comput. Appl. Biosci. 11 (1995), 675-679). Computers can be used for the conformational and energetic analysis of detailed protein models (Monge, J. Mol. Biol. 247 (1995), 995-1012; Renouf, Adv. Exp. Med. Biol. 376 (1995), 37-45). These analysis can be used for the identification of the influence of a particular mutation on metabolism, binding, inhibition, mediating of therapeutic action and/or transport of drugs. Moreover, based on the knowledge of the altered structure of the polypeptides which are encoded by the polynucleotides specified in the use of the present invention derivatives of the substances referred to above can be designed and synthesized which can be more efficiently metabolized, modified, transported, eliminated, and/or binded. Thereby, drugs or pro-drugs can be designed on the basis of the substances referred to herein which are more efficient in therapy of colorectal

cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genotype characterized by the presence of one or more polynucleotides of the invention.

Usually, said amino acid deletion, addition or substitution in the amino acid sequence of the protein encoded by the polynucleotide referred to in accordance with the use of the present invention is due to one or more nucleotide substitution, insertion or deletion, or any combinations thereof. Preferably said nucleotide substitution, insertion or deletion may result in an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118). The polypeptides encoded by the polynucleotides referred to in accordance with the use described herein have altered biological properties due to the mutations referred to in accordance with the present invention. Examples for said altered properties are stability of the polypeptides or amount of the polypeptides which may be effected resulting in, e.g. an altered drug metabolism or an altered transport of drugs or an altered substrate specificity or an altered catalytic activity characterized by, e.g. insufficiencies in drug metabolism or a complete loss of the capability to metabolize drugs or an enhanced capacity to metabolize drugs or an altered transport activity characterized by, e.g., insufficiencies in drug transport or a complete loss of the capability of transporting drugs or an altered substrate binding characterized by, e.g. an altered drug action or an altered inhibition or induction of transport or an altered binding to receptors or other target molecules characterized by, e.g. an altered activation of signal

transduction pathways or an altered protein or enzyme function. These altered properties result in an impaired pharmacological response to the substances referred to above of the subject to be treated in accordance with the use of the present invention. Moreover, due to said altered properties of the polypeptides encoded by the variant alleles specified herein the substances may be chemically modified in a way resulting in derivatives of the substances which are harmful or toxic for the subject or which cause undesirable side effects.

The mutations in the MDR1 gene detected in accordance with the present invention are listed in Tables 1 and 2. As is evident to the person skilled in the art, the genetic knowledge of the polynucleotides specified herein above can be used to exactly and reliably characterize the genotype of a patient.

Advantageously, therapeutical measures which are based on irinotecan or a derivative thereof can be more efficiently applied when taking into consideration said genetic knowledge. Undesirable side effects of said substances can be avoided and an effective but not harmful dosage can be calculated individually due the knowledge of the genetic makeup of the subject. Moreover in accordance with the foregoing, in cases where a given drug causes an unusual effect, a suitable individual therapy can be designed based on the knowledge of the individual genetic makeup of a subject. This tailored therapy will also be suitable to avoid the occurance of therapy resistances. Said resistances are one major problem in cancer chemotherapy with various chemotherapeutic agents, this fact being well known in the art. The use of the present invention, therefore, provides an improvement of the therapeutic applications which are based on the known therapeutically desirable effects of the substances referred to herein above since it is possible to individually treat the subject with an appropriate dosage and/or an appropriate derivative of said substances. Thereby, undesirable, harmful or toxic effects are efficiently avoided. Furthermore, the use of the present invention provides an improvement of the therapeutic applications which are based on the known therapeutically desirable effects of the substances referred to herein above since it is possible to identify those subject prior to onset of drug therapy and treat only those subjects with an appropriate dosage and/or an appropriate derivative of said substances who are most likely to benefit from therapy with said substances. Thereby, the unnecessary and potentially harmful treatment of those subjects who do not respond to the treatment with said substances (nonresponders), as well as

the development of drug resistances due to suboptimal drug dosing can be avoided.

In a preferred embodiment of the use of the present invention said first variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 345, 417 or 636:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 612 or 618;

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432), 176 of the MDR1 gene (Accession No: M29445), or 88883 of the MDR1 gene (Accession No: GI:10122135);

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having an A at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432) or 88883 of the MDR1 gene (Accession No: GI:10122135), or a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) or 88883 of the MDR1 gene (Accession No: GI:10122135);

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 400 or 893 of the MDR1 polypeptide (Accession No: G2506118); and

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Ser to Asn at a position corresponding to position 400 or Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118).

More preferably, said first variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of SEQ ID NO: 417 or 636;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 618;

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445), 88883 of the MDR1 gene (Accession No: GI:10122135);

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) or 88883 of the MDR1 gene (Accession No: GI:10122135);

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118); and

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118).

Most preferably, said first variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of SEQ ID NO: 417;

(b) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445); and

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445).

In a preferred embodiment of the use of the present invention said subject having a genome with a second variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 and/or 334;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 600, 602 and/or 604;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance Protein 1 (MRP1) gene, wherein said polynucleotide is having at a position corresponding to positions 57998, 57853, 53282, and/or 39508 of the MRP1 gene (Accession No: GI:7209451), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 137667, 137647, 137710, 124667, and/or 38646 of the MRP1 gene (Accession No: AC026452), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 27258, 27159, 34218, 34215, 55472, and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 21133, 14008, 18067, 17970, and/or 17900 of the MRP1 gene (Accession No: U91318), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 79, 88, and/or 249 of the MRP1 gene (Accession No: AF022830), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 95 and/or 259 of the MRP1 gene (Accession No: AF022831), a substitution or deletion

of at least one nucleotide or at a position corresponding to positions 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277), a substitution or deletion of at least one nucleotide or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 248 and/or 258 of the MRP1 gene (Accession No: AF022829), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 1884, 1625, 1163, 381, 233, 189, 440, and/or 1720 to 1723 of the MRP1 gene (Accession No: U07050), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 926/927 and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of at least one nucleotide or at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having at a position corresponding to position 21133, 14008 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 27258 and/or 34218 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 79 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 57998, and/or 57853 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137667 and/or 137647 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277) or at a position corresponding to position 248 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 1884, 1625, 233, and/or 189 of the MRP1 gene (Accession No: U07050) an A, at a position corresponding to position 39508 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 17900, 18067 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828) or at a position corresponding to position 440 and/or 1163 of the MRP1 gene (Accession No: U07050) a T, at a position corresponding to position 88 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 95 of the MRP1 gene

(Accession No: AF022831) or at a position corresponding to position 27159, 55472 and/or 34215 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 124667 and/or 38646 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137710 of the MRP1 gene (Accession No: AC026452) a C, at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 258 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 259 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 381 of the MRP1 gene (Accession No: U07050) a G, at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) a deletion of a T or at a position corresponding to position 34206 to 34207 of the MRP1 gene (Accession No: AC003026) a deletion of a AT or at a position corresponding to position 1720 to 1723 of the MRP1 gene (Accession No: U07050) a deletion of GGTA, at a position corresponding to position 926/927 a insertion of a T and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of a TCCTTCC, at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of TGGGGC;

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 239 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Ser at a position corresponding to position 433 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Gln at a position corresponding to position 723 of the MRP1 polypeptide (Accession No: G2828206).

The explanations and interpretations of the terms made above can be applied mutatis mutandis.

The term "second variant allele" refers to an allele of a second gene being different from said first gene corresponding to said first allele described herein above.

According to the present invention said second variant allele corresponds to a MRP1 gene comprising one or more of the polynucleotides specified above.
In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and a second variant allele corresponding to the MRP1 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. Hence, in accordance with the use of the present invention the diseases and disorders referred to herein can be more efficiently treated or prevented whereby said therapies or preventive measures are more convenient for the subject. Moreover, the applicability of therapeutic measures comprising administration of the substances referred to herein above can be efficiently predicted.

Preferred deletions in accordance with the invention are a T or AT deletion at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), preferred insertion is a TCCTTCC at a position corresponding to position 437/438 of the MRP1 gene (Accession No: GI: U07050) and/or a TGGGGC insertion at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026).

In a preferred embodiment of the use of the present invention said second variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 181, 209, 217, 205, 277, 281, 301, 325, 229, 193, 313, 293 or 253:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 600;

(c) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 95 of the MRP1 gene (Accession No: AF022831), 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene

(Accession No: AC026452), 381, 440,1625 of the MRP1 gene (Accession No: U07050), 34218 of the MRP1 gene (Accession No: AC003026), 18067 or 17900 of the MRP1 gene (Accession No: U91318) or an insertion of at least one nucleotide at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a T at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 18067 or 17900 of the MRP1 gene (Accession No: U91318), 440 of the MRP1 gene (Accession No: U07050), a C at a position corresponding toposition 95 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), a G at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 381 of the MRP1 gene (Accession No: U07050), or an A at a position corresponding to position 34218 of the MRP1 gene (Accession No: AC003026) or 1625 of the MRP1 gene (Accession No: U07050) or an insertion of a T at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206); and

(f) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206).

More preferably, said second variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 209, 205, 277, 281, 301 or 325;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 600;

(c) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), 381 of the MRP1 gene (Accession No: U07050), or an insertion of at least one nucleotide at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a C at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), a G at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 381 of the MRP1 gene (Accession No: U07050), or an insertion of a T at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206); and

(f) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206).

In a preferred embodiment of the use of the present invention said subject having a genome with a third variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 137, 138, 141, 142, 145, 146, 149 and/or 150;

(b) a polynucleotide capable of hybridizing to a Cytochrome P450, subfamily IIIA (nifedipene oxidase), polypeptide 5 (CYP3A5) gene, wherein said polynucleotide is having at a position corresponding to positions 47518 and/or 9736 of the CYP3A5 gene (Accession No: GI:10281451), a substitution of at least one nucleotide or at a position corresponding to positions 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452), a substitution of at least one nucleotide;

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) a C, at a position corresponding to position 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452) a G or at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451) a G.

The explanations and interpretations of the terms made above can be applied mutatis mutandis.

The term " third variant allele" refers to an allele of a third gene being different from said first gene corresponding to said first allele and said second gene corresponding to said second allele described herein above. According to the present invention said third variant allele corresponds to a CYP3A5 gene comprising one or more of the polynucleotides specified above.

In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and optionally a second variant allele corresponding to the MRP1 gene and a third variant allele corresponding to the CYP3A5 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. Hence, in accordance with the use of the present invention the diseases and disorders referred to herein can be more efficiently treated or prevented whereby said therapies or preventive measures are more convenient for the subject. Moreover, the applicability of therapeutic measures comprising administration of the substances referred to herein above can be efficiently predicted.

In a preferred embodiment of the use of the present invention said third variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 137, 141, 145 or 149:

(b) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 47518 or 9736 of the CYP3A5 gene (Accession No: GI:10281451) or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452);

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a C at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) or a G at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451), or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452).

More preferably, said third variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 137, 145 and/or 149;

(b) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 47518 or 9736 of the CYP3A5 gene (Accession No: GI:10281451) or 145929 of the CYP3A5 gene (Accession No: GI:11177452);

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a C at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) or a G at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451), or 145929 of the CYP3A5 gene (Accession No: GI:11177452).

In a preferred embodiment of the use of the present invention said subject having a genome with a fourth variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 and/or 134;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 and/or 598;

(c) a polynucleotide capable of hybridizing to a Uridine Diphosphate Glycosyltransferase1 Member A1 (UGT1A1) gene, wherein said polynucleotide is having at a position corresponding to positions 59, 160, 226, 539, 544, 640, 701, 841, 855, 890, 938, 1006, 1007, 1020, 1084, 1085, 1114, 1117, 1139, 1158, 1175 to 1176, 1216, 1297, 1324, 1471, 1478, 372 to 373, 523 to 525, and/or 892 to 905 of the UGT1A1 gene (Accession No. GI:8850235), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 470/471, and/or 1222/1223 of the UGT1A1 gene (Accession No. GI:8850235) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having at a position corresponding to position 226, 539, 701, 855, 938, 1020, and/or 1117 of the UGT1A1 gene (Accession No: GI:8850235) an A, at a position corresponding to position 160, 640, 890, 1006, 1084, 1139, 1176, 1324, and/or 1478 of the UGT1A1 gene (Accession No: GI: 8850235) a T, at a position corresponding to position 544, 841, and/or 1216 of the UGT1A1 gene (Accession No: GI: 8850235) a C, at a position corresponding to position 59, 1007, 1085, 1114, 1158, 1175, 1297, and/or 1471 of the UGT1A1 gene (Accession No: GI:181303) a G, and/or at

a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TTC, at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TACATTAATGCTTC, at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a T, and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a G;

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Leu to Arg at a position corresponding to position 15 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 71 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Leu to Gln at a position corresponding to position 175 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Cys to Arg at a position corresponding to position 177 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Trp at a position corresponding to position 209 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Gln at a position corresponding to position 229 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 276 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Val at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Trp at a position corresponding to position 293 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Glu at a position corresponding to position 308 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 331 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 357 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Gly at a position corresponding to position 367 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Thr at a position corresponding to position 368 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Arg at a position corresponding to position 387 of

the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 375 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Arg at a position corresponding to position 381 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Pro at a position corresponding to position 401 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Lys to Glu at a position corresponding to position 428 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 488 of the UGT1A1 polypeptide (Accession No: G8850236);

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide is having at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, whereby in said polypeptide one or more amino acids following amino acid Asp at a position corresponding to position 119 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a T, whereby in said polypeptide one or more amino acids following amino acid Pro at a position corresponding to position 152 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TTC, whereby in said polypeptide one or more amino acids following amino acid Thr at a position corresponding to position 168 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TACATTAATGCTTC, whereby in said polypeptide one or more amino acids following amino acid Ala at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a G, whereby in said polypeptide one or more

amino acids following amino acid Lys at a position corresponding to position 402 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted; and

(g) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide comprises an amino acid substitution of Gln to a stop codon at a position corresponding to position 49 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Cys to a stop codon at a position corresponding to position 280 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 331 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Trp to a stop codon at a position corresponding to position 335 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 357 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Lys to a stop codon at a position corresponding to position 437 of the UGT1A1 gene (Accession No: G8850236).

The explanations and interpretations of the terms made above can be applied mutatis mutandis.

The term "fourth variant allele" refers to an allele of a fourth gene being different from said first gene corresponding to said first allele and said second gene corresponding to said second allele and said third gene corresponding to said third allele described herein above. According to the present invention said fourth variant allele corresponds to a UGT1A1 gene comprising one or more of the polynucleotides specified above.

In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and optionally a second variant allele corresponding to the MRP1 gene and a third variant allele corresponding to the CYP3A5 gene and a fourth variant allele corresponding to the UGT1A1 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. Hence, in accordance with the use of the present invention the

diseases and disorders referred to herein can be more efficiently treated or prevented whereby said therapies or preventive measures are more convenient for the subject. Moreover, the applicability of therapeutic measures comprising administration of the substances referred to herein above can be efficiently predicted.

In a preferred embodiment of the use of the present invention said fourth variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 37, 69 or 97;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 558, 570 or 584;

(c) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 890, 1117 or 1471 of the UGT1A1 gene (Accession No: GI: 8850235);

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having an A at a position corresponding to position 1117, a T at a position corresponding to position 890 or a G at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI:8850235);

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 292, 368 or 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236); and

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises amino acid substitution of Ala to Val at a position corresponding to position 292, Ala to Thr at aposition corresponding to position 368 or Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236).

More preferably, said fourth variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 97;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 584;

(c) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI: 8850235);

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a G at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI:8850235);

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236); and

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises amino acid substitution of Ala to Thr at a position corresponding to position 368 or Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236).

In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and optionally a second variant allele corresponding to the MRP1 gene and a third variant allele corresponding to the CYP3A5 gene and a fourth variant allele corresponding to the UGT1A1 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. As has been found in accordance with he present invention, the pharmacokinetics of a drug which is based on irinotecan or a derivative thereof and the pharmacological response of a subject is mainly governed by the polypeptides

encoded by the MDR1, MRP1, CYP3A5 and UGT1A1 genes. Therefore, in order to increase the predictability and/or efficiency of therapeutic measures applied in accordance with the present invention, the genetic constitution of a subject as regards the present or absence of the first, second, third, and/or variant alleles referred to herein has to be determined and based on that knowledge an individual therapy can be developed which is therapeutically most effective and which avoids toxic or undesirable side effects caused by the substances according to the invention.

The present invention also relates to a method of treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer comprising:

(a) determining the presence or absence of a first, a second, a third and/or a fourth variant allele comprising a polynucleotide referred to herein; and

(b) administering to a subject a therapeutically effective dosage of irinotecan.

The definitions used in accordance with the use of the present invention apply mutatis mutandis to the above method. Further, all embodiments described in accordance with the use of the present invention can be applied mutatis mutandis to the method of the present invention. Moreover, also encompassed by the method of the present invention are any further developments of said method which the person skilled in the art can make without undue burden based on its knowledge and the prior art, such as those documents referred to throughout this specification.

In a preferred embodiment of the use of the present invention a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first, second or third variant allele compared to the corresponding wild type allele.

As discussed above, the alleles referred to in accordance with the use of the present invention correspond to the MDR1, MRP1, CYP3A5 and/or UGT1A1 gene. It is well known in the art that genes comprise structural elements which encode an amino acid sequence as well as regulatory elements which are involved in the regulation of the expression of said genes. Structural elements are represented by

exons which may either encode an amino acid sequence or which may code for RNA which is not encoding an amino acid sequence but is nevertheless involved in RNA function, e.g. by regulating the stability of the RNA or the nuclear export of the RNA.

Regulatory elements of a gene may comprise promoter elements or enhancer elements both of which could be involved in transcriptional control of gene expression. It is very well known in the art that a promoter is to be found upstream of the structural elements of a gene. Regulatory elements such as enhancer elements, however, can be found distributed over the entire locus of a gene. Said elements could reside, e.g., in introns, regions of genomic DNA which separate the exons of a gene. Promoter or enhancer elements correspond to polynucleotide fragments which are capable of attracting or binding polypeptides involved in the regulation of the gene comprising said promoter or enhancer elements. For example, polypeptides involved in regulation of said gene comprise the so called transcription factors.

Said introns may comprise further regulatory elements which are required for proper gene expression. Introns are usually transcribed together with the exons of a gene resulting in a nascent RNA transcript which contains both, exon and intron sequences. The intron encoded RNA sequences are usually removed by a process known as RNA splicing. However, said process also requires regulatory sequences present on a RNA transcript said regulatory sequences may be encoded by the introns.

In addition, besides their function in transcriptional control and control of proper RNA processing and/or stability, regulatory elements of a gene could be also involved in the control of genetic stability of a gene locus. Said elements control, e.g., recombination events or serve to maintain a certain structure of the DNA or the arrangement of DNA in a chromosome.

Therefore, single nucleotide polymorphisms can occur in exons of an allele of a gene which encode an amino acid sequence as discussed supra as well as in regulatory regions which are involved in the above discussed process. The polymorphisms comprised by the polynucleotides referred to in accordance with the use of the present invention can influence the expression level of MDR1, MRP1,

CYP3A5, and/or UGT1A1 protein via mechanisms involving enhanced or reduced transcription of the MDR1, MRP1, CYP3A5 and/or UGT1A1 gene, stabilization of the gene's RNA transcripts and alteration of the processing of the primary RNA transcripts.

Methods for the determination of an altered expression of a variant allele when compared to its wild type counterpart are well known in the art and comprise inter alia those referred to herein above, e.g., PCR based techniques, RFLP-based techniques, DNA sequencing-based techniques, hybridization techniques, Single strand conformational polymorphism (SSCP), denaturating gradient gel electrophoresis (DGGE), mismatch cleavage detection, heteroduplex analysis, techniques based on mass spectroscopy, HPLC-based techniques, primer extension-based techniques, and 5'-nuclease assay-based techniques. It might be necessary to obtain a sample comprising biological material, such as isolated cells or tissue from the subject prior to perform said methods for determination of the expression levels of the wild type and the variant alleles, respectively. An altered expression in accordance with the use of the present invention means that the expression of the wild type allele differs significantly from the expression of the variant allele. A significant difference can be determined by standard statistical methods, such as Student´s t-test, chi^2-test or the U-test according to Mann and Whitney. Moreover, the person skilled in the art can adopt these and other statistical method known in the art individually without an undue burden.

In a more preferred embodiment of the use of the invention said altered expression is decreased or increased expression.

To determine whether the expression of an allele referred to in accordance to the present invention is increased or decreased in comparison to the corresponding wild type allele well known methods such as PCR based techniques, RFLP-based techniques, DNA sequencing-based techniques, hybridization techniques, Single strand conformational polymorphism (SSCP), denaturating gradient gel electrophoresis (DGGE), mismatch cleavage detection, heteroduplex analysis, techniques based on mass spectroscopy, HPLC-based techniques, primer extension-based techniques, and 5'-nuclease assay-based techniques can be applied. As discussed above, it might be necessary to obtain a sample comprising cells or tissue from the subject in order to determine the expression level of the

variant allele referred to in the use of the invention. A decrease or increase of the expression is characterized by a significant difference in the expression level of the variant versus the wild type allele in those assays. Also encompassed by decreased expression is the absence detectable expression of a variant allele.

In a furthermore preferred embodiment of the use of the present invention a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered activity of the polypeptide encoded by the first, second, third, and/or fourth variant allele compared to the polypeptide encoded by the corresponding wild type allele.

As discussed supra, the variant alleles comprising those polynucleotides specified herein which correspond to coding regions of the MDR1, MRP1, CYP3A5 and/or UGT1A1 gene effect the amino acid sequences of the polypeptides encoded by said variant alleles. The variant polypeptides, therefore, exhibit altered biological and/or immunological properties when compared to their corresponding wild type counterpart. Preferred variant polypeptides in accordance with the use of the invention are those, which exhibit an altered biological activity, i.e. altered enzymatic function resulting in reduced, enhanced or complete loss of catalytic activity or altered transport function resulting in reduced, enhanced or complete loss of transport activity or altered binding to receptors or other drug targets resulting in altered activation of signal transduction pathways or altered inhibition of transporter or enzyme function. It might be necessary to obtain a sample comprising biological material such as isolated cells or tissue from the subject prior to perform said methods for determination of the activities of the wild type and the variant polypeptides, respectively. Whether a variant polypeptide has an altered activity or level of expression compared to its wild type corresponding counterpart can be determined by standard techniques well known in the art. Such standard techniques may comprise, e.g., ELISA based assays, RIA based assays, HPLC-based assays, mass spectroscopy-based assays, western blot analysis or assays which are known in the art and described in [Hitzl, *et al.*, 2001, Pharmacogenetics 11:293-8]; Hoffmeyer, 2000 #77; van Helvoort, 1996 #115; Schumacher, 1997 #116; Cordon-Cardo, 1990 #117; Hafkemeyer, 1998 #118] for MDR1, [Keppler, *et al.*, 1997, Biol Chem 378:787-91, Suzuki, *et al.*, 1994, Adv Prostaglandin Thromboxane Leukot Res 22:83-9, Scheffer, *et al.*, 2000, Cancer Res 60:5269-77,

Konig, *et al.*, 1999, Biochim Biophys Acta 1461:377-94, Kool, *et al.*, 1997, Cancer Res 57:3537-47, Bakos, *et al.*, 2000, Mol Pharmacol 57:760-8, Keppler, *et al.*, 1998, Chem Biol Interact 112:153-61, Leier, *et al.*, 2000, Kidney Int 57:1636-42, Evers, *et al.*, 2000, Br J Cancer 83:366-74, Evers, *et al.*, 2000, Br J Cancer 83:375-83] for MRP1, [Janardan, *et al.*, 1996, Pharmacogenetics 6:379-85, Kivisto, *et al.*, 1996, Br J Clin Pharmacol 42:387-9, Lown, *et al.*, 1994, Drug Metab Dispos 22:947-55, Anttila, *et al.*, 1997, Am J Respir Cell Mol Biol 16:242-9, Tateishi, *et al.*, 1999, Biochem Pharmacol 57:935-9, Gibbs, *et al.*, 1999, Drug Metab Dispos 27:180-7, Maenpaa, *et al.*, 1998, Pharmacogenetics 8:137-55, Haehner, *et al.*, 1996, Mol Pharmacol 50:52-9, Lown, *et al.*, 1994, Drug Metab Dispos 22:947-55] for CYP3A5, [Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202, Iyer, *et al.*, 1999, Clin Pharmacol Ther 65:576-82, Iolascon, *et al.*, 2000, J Med Genet 37:712-3, Raijmakers, *et al.*, 2000, J Hepatol 33:348-51, von Ahsen, *et al.*, 2000, Clin Chem 46:1939-45, Beutler, *et al.*, 1998, Proc Natl Acad Sci U S A 95:8170-4, Kadakol, *et al.*, 2000, Hum Mutat 16:297-306] for UGT1A1.

An altered activity in accordance with the use of the present invention means that the activity of the wild type polypeptide differs significantly from the variant polypeptide. A significant difference can be determined by standard statistical methods referred to herein above.

Most preferably, said altered activity is decreased or increased activity.
As discussed for the increase or decrease of expression, a decrease or increase of the activities is characterized by a significant difference in the activity of the variant versus the wild type polypeptide in the assays referred to herein. Also encompassed by decreased activity is the absence detectable activity of a variant allele.

Moreover, in a further preferred embodiment of the use of the present invention said subject is an animal.
As described supra, the subject in accordance with the use of the present invention encompasses animals. The term "animal" as used herein encompasses all animals, preferably animals belonging to the vertebrate family, more preferably mammals. Moreover, the animals can be genetically engineered by well known techniques

comprising transgenesis and homologous recombination in order to incorporate one or more of the polynucleotides referred to supra into the genome of said animals. Said animals comprising the genetically engineered animals can be used to study the pharmacological effects of drugs or pro-drugs which are based on the substances or derivatives thereof referred to herein, preferably irinotecan.

In accordance with the foregoing, most preferably, said animal is a mouse or rat.
Said animals are particularly well suited for assaying the pharmacological properties of the substances or derivatives referred to in accordance with the use of the present invention as described in detail in Giovanella, *et al.*, 1991, Cancer Res 51:3052-5, Kunimoto, *et al.*, 1987, Cancer Res 47:5944-7, Kaneda, *et al.*, 1990, Cancer Res 50:1715-20.
Preferably, said mouse is lacking functional cytochrome P450, MRP1, or MDR1. It is well known in the art how said mice lacking functional cytochrome P450, MRP1 or MDR1 can be obtained. For instance said mice might be generated by homologous recombination as described for cytochrome P450 in Pineau, *et al.*, 1998, Toxicol Lett 103:459-64, MRP1 in Rappa, *et al.*, 2000, Biochemistry 39:3304-10, and MDR1 in Schinkel, 1998, Int J Clin Pharmacol Ther 36:9-13, Schinkel, *et al.*, 2000, Pharmacogenetics 10:583-90.

Moreover, in another preferred embodiment of the use of the present invention said subject is a human.
In particular, the present invention is applicable to humans as is evident from the above. The use of the present invention is to be applied in order to treat or prevent side effects in patients which suffer from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer. The pharmacological effects of the above substances or derivatives thereof are well described in humans. However, the conventional therapies do not take into account the individual genetic makeup of the patient. Ethnical populations have different genetic backgrounds, which can also influence the function or regulation of a variant allele and thereby alter the pharmacological response of a patient to a substance or derivative used as a basis for a drug or pro-drug in accordance with the invention.

In light of the foregoing, most carefully, said human is selected from the African population who shows compared to Caucasians or Japanese (approx. 50 %) a higher frequency (approx. 80%) of the MDR1 high expressor allele (nucleotide C at a position corresponding to position 137 of the MDR1 gene Acc. No. M29445) and are therefore more likely to suffer from irinotecan toxicity. (population frequency data are from [Cascorbi, *et al.*, 2001, Clin Pharmacol Ther 69:169-74, Ameyaw, *et al.*, 2001, Pharmacogenetics 11:217-21, Ito, *et al.*, 2001, Pharmacogenetics 11:175-84].

In light of the foregoing, most preferably, said human is African or Asian.
The Asian population (16 %) who shows compared to Caucasians (39 %) a lower frequency of the UGT1A1 low expressor genotype (homozygously wildtype at positions corresponding to positions 174990 to 174993 of the UGT1A1 gene Acc. No. GI:11118740) and is therefore less likely to suffer from irinotecan toxicity. On the other hand, this allele is more common in Africans (43 %) who have additionally another low expressor allele (insertion of TA at positions corresponding to positions 174989/174990 of the UGT1A1 gene Acc. No. GI:11118740) the homozygous genotype of which occurs in 7 %. Africans are therefore more susceptible to irinotecan-related adverse events (population frequency data are from [Beutler, *et al.*, 1998, Proc Natl Acad Sci U S A 95:8170-4, Lampe, *et al.*, 1999, Pharmacogenetics 9:341-9, Hall, *et al.*, 1999, Pharmacogenetics 9:591-9]).

The present invention also relates to a method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer, wherein said method comprises:

(a) determining the presence or absence of a first, second, third and/or fourth variant allele referred to above in the genome of a subject in a sample obtained from said subject; and

(b) selecting a suitable therapy for said subject based on the results obtained in (a).

The definitions and explanations of the terms made above apply mutatis mutandis to the above method.

The term "suitable therapy" as used herein means that a substance according to the invention is selected and said substance being administered in a certain dosage to a subject, wherein said substance and said dosage are selected based on the knowledge of the presence or absence of a first, second, third and/or fourth variant allele referred to in accordance with the use of the invention. Said substance and said dosage of the substance are selected in a way that on one hand they are most effective in treating or preventing colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer on the other hand they do not cause toxic or undesirable side effects.
As is evident from the above, a prerequisite for selecting a suitable therapy is the knowledge of the presence or absence of a first, second, third, and/or fourth variant allele referred to in accordance with the use of the invention. Therefore, the method of the present invention encompasses the determination of the presence or absence of said variant alleles in a sample which has been obtained from said subject. The sample which is obtained by the subject comprises biological material which is suitable for the determination of the presence or absence of said variant alleles, such as isolated cells or tissue. Methods for the determination of the presence or absence of the variant alleles of the method of the invention comprise those methods referred to herein above.

Thanks to the method of the present invention, it is possible to efficiently select a suitable therapy for a subject, preferably a human, suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer Thereby, mistreatment of patients based on wrong medications and the results thereof, such as development of resistance towards cancer therapy, and subsequent increased costs in health care, can be efficiently avoided. Furthermore, patients that are at high risk can be excluded from therapy prior to the first dose and/or dosage can be adjusted according to the individual's genetic makeup prior to the onset of drug therapy. Also, inhibitors for the mentioned transporter genes (e.g. MDR1) can be applied in genetically defined patient subpopulations. Thus, adverse effects can be avoided and the optimal drug level can be reached faster without time-consuming and expensive drug monitoring-

based dose finding. This can reduce costs of medical treatment and indirect costs of disease (e.g. shorter time and less frequent hospitalization of patients).
As described supra, the present invention preferably encompasses the use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genome with a first variant allele of MDR1, optionally a second allele of MRP1, optionally a third variant allele of CYP3A5 and optionally a fourth variant allele of UGT1A1. However, other combinations of rank orders are also within the scope of the present invention. In said combinations of rank orders MRP1, UGT1A1 or CYP3A5 may be chosen as the first variant allele, while the remaining variant alleles, i.e. the second, the third and the fourth variant allele may be chosen from the group of genes including MDR1 but lacking the gene chosen as the first variant allele. In conclusion, the first variant allele may be MDR1, MRP1, UGT1A1 or CYP3A5, the second variant allele is selected from the same group of genes excluding the gene chosen as the first variant allele, the third variant allele is selected from the same group of genes excluding the gene chosen as the first and second variant allele and the fourth variant allele is the gene which has not selected as first, second or third variant allele. The explanations and definitions made before apply mutatis mutandis in such cases.

The following 59 items are also encompassed by the present invention. The definitions and explanations made supra apply mutatis mutandis to the terms used to characterize the claims.

1. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) assaying the genotype of the patient to determine if the patient has variant alleles of two or more of the MDR1 gene, the MRP1 gene, the CYP3A5 gene, and the UGT1A1 gene; and
(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in

the two or more of the MDR1 gene, the MRP1 gene, the CYP3A5 gene, and the UGT1A1 gene.

2. The method of item 1 wherein the MDR1 gene is one of the two or more genes.

3. The method of item 1 wherein the genes are MDR1 and MRP1.

4. The method of item 1 wherein the genes are MDR1 and CYP3A5.

5. The method of item 1 wherein the genes are MDR1 and UGT1A1.

6. The method of item 1 wherein the genes are MDR1, MRP1 and CYP3A5.

7. The method of item 1 wherein the genes are MDR1, MRP1, and UGT1A1.

8. The method of item 1 wherein the genes are MDR1, MRP1, and CYP3A5.

9. The method of item 1 wherein the genes are MDR1, CYP3A5, and UGT1A1.

10. The method of item 1 wherein the genes are MRP1 and UGT1A1.

11. The method of item 1 wherein the genes are MRP1 and CYP3A5.

12. The method of item 1 wherein the genes are MRP1, CYP3A5 and UGT1A1.

13. The method of item 1 wherein the genes are MRP1 and UGT1A1.

14. The method of item 1 wherein the genes are CYP3A5 and UGT1A1.

15. The method of any one of items 1 wherein the cancer is colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, or pancreatic cancer.

16. The method of item 15 in which:

(a) the one or more variant alleles result in the patient expressing low amounts of the MDR1 gene product, whereby the amount of irinotecan administered to the patient is decreased to avoid toxicity; or

(b) the one or more variant alleles result in the patient expressing high amounts of the MDR1 gene product, whereby the amount of irinotecan administered to the patient is increased to enhance efficacy.

17. The method of item 16 wherein the variant alleles are in the promoter regions of the two or more genes.

18. The method of item 16 wherein the variant alleles are in the coding regions of the two or more genes.

19. The method of item 16 wherein each of the two or more genes has two or more variant alleles.

20. The method of item 16 wherein each of the two or more genes has one or more variant alleles in the promoter region and one or more variant alleles in the coding region.

21. The method of item 16 wherein each of the two or more genes has one or more variant alleles in the promoter region or one or more variant alleles in the coding region.

22. The method of item 16 wherein the one or more variant alleles are not in either the promoter region or the coding region of the two or more genes.

23. The method of item 16 wherein when MDR1 is one of the two or more genes the one or more variant alleles comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422,

425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482, 485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 and/or 641;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 606, 608, 610, 612, 618, 620, 622, 624, and/or 628;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance 1 (MDR1) gene, wherein said polynucleotide is having at a position corresponding to positions 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619 of the MDR1 gene (Accession No: AC002457) and/or 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162 of the MDR1 gene (Accession No: AC005068) and/or 101, 308 of the MDR1 gene (Accession No: M29432) and/or 137, 176 of the MDR1 gene (Accession No: M29445), a substitution or deletion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having at a position corresponding to position 83946, 70200, 70237, 65241 of the MDR1 gene (Accession No: AC005068) and/or 101 of the MDR1 gene (Accession No: M29432) and/or 141529, 174901, 139177, 140118, 140568, 140727, 139479 of the MDR1 gene (Accession No: AC002457) an A, at a position corresponding to position 308 of the MDR1 gene (Accession No: M29432) and/or 84701, 83973, 84074, 84119, 78170, 70204, 70253, 70371, 50537, 43162 of the MDR1 gene (Accession No: AC005068) and/or 137 or 176 of the MDR1 gene (Accession No: M29445) and/or 145984, 171466, 175068, 175074, 139064, 139276, 140576 of the MDR1 gene (Accession No: AC002457) a T, at a position corresponding to position 140837, 171404, 171456, 171511, 171512, 139119, 140490, 139619 of the MDR1 gene (Accession No: AC002457) and/or 43263 of the MDR1 gene (Accession No: AC005068) a C, at a position corresponding to position 84032, 77811, 73252 of the MDR1 gene

(Accession No: AC005068) and/or 141590, 175142, 175180, 139015, 140216, 140595 of the MDR1 gene (Accession No: AC002457) a G;

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to positions 21, 103, 168, 400, 893, 999, 1001, 1107, and/or 1141 of the MDR1 polypeptide (Accession No: G2506118);

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118).

24. The method of item 23 wherein when the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 345, 417 or 636:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 612 or 618;

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432), 176 of the MDR1 gene

(Accession No: M29445), or 88883 of the MDR1 gene (Accession No: GI:10122135);

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having an A at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432) or 88883 of the MDR1 gene (Accession No: GI:10122135), or a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) or 88883 of the MDR1 gene (Accession No: GI:10122135);

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 400 or 893 of the MDR1 polypeptide (Accession No: G2506118); and

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Ser to Asn at a position corresponding to position 400 or Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118).

25. The method of item 16 wherein when MRP1 is one of the two or more genes the one or more variant alleles of MRP1 comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 and/or 334;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 600, 602 and/or 604;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance Protein 1 (MRP1) gene, wherein said polynucleotide is having at a position corresponding to positions 57998, 57853, 53282, and/or 39508 of the MRP1 gene (Accession No: GI:7209451), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 137667, 137647, 137710, 124667, and/or 38646 of the MRP1 gene (Accession No: AC026452), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 27258, 27159, 34218, 34215, 55472, and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 21133, 14008, 18067, 17970, and/or 17900 of the MRP1 gene (Accession No: U91318), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 79, 88, and/or 249 of the MRP1 gene (Accession No: AF022830), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 95 and/or 259 of the MRP1 gene (Accession No: AF022831), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277), a substitution or deletion of at least one nucleotide or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 248 and/or 258 of the MRP1 gene (Accession No: AF022829), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 1884, 1625, 1163, 381, 233, 189, 440, and/or 1720 to 1723 of the MRP1 gene (Accession No: U07050), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 926/927 and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of at least one nucleotide or at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having at a position corresponding to position 21133, 14008 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 27258 and/or 34218 of the MRP1 gene (Accession

No: AC003026) or at a position corresponding to position 79 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 57998, and/or 57853 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137667 and/or 137647 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277) or at a position corresponding to position 248 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 1884, 1625, 233, and/or 189 of the MRP1 gene (Accession No: U07050) an A, at a position corresponding to position 39508 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 17900, 18067 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828) or at a position corresponding to position 440 and/or 1163 of the MRP1 gene (Accession No: U07050) a T, at a position corresponding to position 88 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 27159, 55472 and/or 34215 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 124667 and/or 38646 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137710 of the MRP1 gene (Accession No: AC026452) a C, at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 258 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 259 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 381 of the MRP1 gene (Accession No: U07050) a G, at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) a deletion of a T or at a position corresponding to position 34206 to 34207 of the MRP1 gene (Accession No: AC003026) a deletion of a AT or at a position corresponding to position 1720 to 1723 of the MRP1 gene (Accession No: U07050) a deletion of GGTA, at a position corresponding to position 926/927 a insertion of a T and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of a TCCTTCC, at a

position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of TGGGGC;

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 239 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Ser at a position corresponding to position 433 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Gln at a position corresponding to position 723 of the MRP1 polypeptide (Accession No: G2828206).

26. The method of item 25 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 181, 209, 217, 205, 277, 281, 301, 325, 229, 193, 313, 293 or 253:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 600;

(c) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 95 of the MRP1 gene (Accession No: AF022831), 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), 381, 440,1625 of the MRP1 gene (Accession No: U07050), 34218 of the MRP1 gene (Accession No: AC003026), 18067 or 17900 of the MRP1 gene (Accession No: U91318) or an insertion of at least one nucleotide at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a T at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 18067 or 17900 of the MRP1 gene (Accession No: U91318), 440 of the MRP1 gene (Accession No: U07050), a C at a position corresponding toposition 95 of the MRP1 gene

(Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), a G at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 381 of the MRP1 gene (Accession No: U07050), or an A at a position corresponding to position 34218 of the MRP1 gene (Accession No: AC003026) or 1625 of the MRP1 gene (Accession No: U07050) or an insertion of a T at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206); and

(f) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206).

27. The method of item16 wherein when CYP3A5 is one of the two or more genes the one or more variant alleles of CYP3A5 comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 137, 138, 141, 142, 145, 146, 149 and/or 150;

(b) a polynucleotide capable of hybridizing to a Cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 5 (CYP3A5) gene, wherein said polynucleotide is having at a position corresponding to positions 47518 and/or 9736 of the CYP3A5 gene (Accession No: GI:10281451), a substitution of at least one nucleotide or at a position corresponding to positions 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452), a substitution of at least one nucleotide;

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having at a position corresponding to position 47518 of the

CYP3A5 gene (Accession No: GI:10281451) a C, at a position corresponding to position 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452) a G or at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451) a G.

28. The method of item 27 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 137, 141, 145 or 149:

(b) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 47518 or 9736 of the CYP3A5 gene (Accession No: GI:10281451) or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452);

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a C at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) or a G at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451), or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452).

29. The method of item 16 wherein when UGT1A1 is one of the two or more genes the one or more variant alleles comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 and/or 134;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556,

558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 and/or 598;

(c) a polynucleotide capable of hybridizing to a Uridine Diphosphate Glycosyltransferase1 Member A1 (UGT1A1) gene, wherein said polynucleotide is having at a position corresponding to positions 59, 160, 226, 539, 544, 640, 701, 841, 855, 890, 938, 1006, 1007, 1020, 1084, 1085, 1114, 1117, 1139, 1158, 1175 to 1176, 1216, 1297, 1324, 1471, 1478, 372 to 373, 523 to 525, and/or 892 to 905 of the UGT1A1 gene (Accession No. GI:8850235), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 470/471, and/or 1222/1223 of the UGT1A1 gene (Accession No. GI:8850235) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having at a position corresponding to position 226, 539, 701, 855, 938, 1020, and/or 1117 of the UGT1A1 gene (Accession No: GI:8850235) an A, at a position corresponding to position 160, 640, 890, 1006, 1084, 1139, 1176, 1324, and/or 1478 of the UGT1A1 gene (Accession No: GI: 8850235) a T, at a position corresponding to position 544, 841, and/or 1216 of the UGT1A1 gene (Accession No: GI: 8850235) a C, at a position corresponding to position 59, 1007, 1085, 1114, 1158, 1175, 1297, and/or 1471 of the UGT1A1 gene (Accession No: GI:181303) a G, and/or at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TTC, at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TACATTAATGCTTC, at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a T, and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a G;

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Leu to Arg

at a position corresponding to position 15 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 71 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Leu to Gln at a position corresponding to position 175 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Cys to Arg at a position corresponding to position 177 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Trp at a position corresponding to position 209 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Gln at a position corresponding to position 229 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 276 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Val at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Trp at a position corresponding to position 293 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Glu at a position corresponding to position 308 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 331 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 357 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Gly at a position corresponding to position 367 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Thr at a position corresponding to position 368 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Arg at a position corresponding to position 387 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 375 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Arg at a position corresponding to position 381 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Pro at a position corresponding to position 401 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Lys to Glu at a position corresponding to position 428 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 488 of the UGT1A1 polypeptide (Accession No: G8850236);

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide is having at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, whereby in said polypeptide one or more amino acids following amino acid Asp at a position corresponding to position 119 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a T, whereby in said polypeptide one or more amino acids following amino acid Pro at a position corresponding to position 152 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TTC, whereby in said polypeptide one or more amino acids following amino acid Thr at a position corresponding to position 168 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TACATTAATGCTTC, whereby in said polypeptide one or more amino acids following amino acid Ala at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a G, whereby in said polypeptide one or more amino acids following amino acid Lys at a position corresponding to position 402 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted; and

(g) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide comprises an amino acid substitution of Gln to a stop codon at a position corresponding to position 49 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Cys to a stop codon at a position corresponding to position 280 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 331 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Trp to a stop

codon at a position corresponding to position 335 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 357 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Lys to a stop codon at a position corresponding to position 437 of the UGT1A1 gene (Accession No: G8850236).

30. The method of item 29 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 37, 69 or 97;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 558, 570 or 584;

(c) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 890, 1117 or 1471 of the UGT1A1 gene (Accession No: GI: 8850235);

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having an A at a position corresponding to position 1117, a T at a position corresponding to position 890 or a G at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI:8850235);

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 292, 368 or 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236); and

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises amino acid substitution of Ala to Val at a position corresponding to position 292, Ala to Thr at aposition corresponding to position 368 or Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236).

31. A method for determining whether a patient is at risk for a toxic reaction to treatment with irinotecan which comprises determining if the patient has one or more variant alleles of two or more genes, wherein the genes comprise an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene.

32. The method of item 31 which further comprises administering to the patient reduced amounts of irinotecan.

33. A method for determining the optimum treatment regimen for administering irinotecan to a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;
(b) in a patient having one or more such alleles of each of the two or more genes, altering the regimen to reduce peak amounts of irinotecan in the patient in comparison to the peak amount in the patient when irinotecan is administered without regard to the patient's alleles in the two or more genes.

34. The method of item 33 wherein MDR1 is one of the two or more genes.

35. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two or more genes are lower than in the general population and so indicates high sensitivity to irinotecan, the method comprises administering to the patient a decreased amount of irinotecan.

36. The method of item 35 wherein MDR1 is one of the two or more genes.

37. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two

or more genes are higher than in the general population and so indicates resistance or predisposition to resistance to irinotecan, the method comprises administering to the patient an increased amount of irinotecan.

38. The method of item 37 wherein MDR1 is one of the two or more genes.

39. The method of item 37 wherein the patients are treated with one or more inhibitors, further wherein the inhibitors are selected from the group consisting of an inhibitor of MDR1, MRP1, CYP3A5, and UGT1A1.

40. The method of item 39 wherein one of the inhibitors is an MDR1 inhibitor.

41. The method of item 40 wherein the MDR1 inhibitor is selected from the group consisting of: GF120918, LY335979, XR 9576, XR 9051, flavonoids (e.g. apigenin, genistin, naringin, quercetin, flavone, flavonone, flavopiridol), bergamottin, Clarithromycin, Ketoconazole, Reserpine, 1,9-dideoxyforskolin, Azidopine, Dimethyl-b-cyclodextrin, Ivermectin, SDZ PSC 833, SDZ 280-446, B669, B-859-35 (R-enantiomere) and its major metabolite, MS-209 (quinolone derivative), PAK-104p, Amiloride, Amytriptyline, Atorvastatin, Aureobasidin & analogues, Berrylium fluoride (BeFx), Calmodulin inhibitors, Chloroquine, Chloropromazine, Clofazimine, Cremophor EL, Diltiazem, Verapamil, Nifedipine, Bepridil, Nicardipine, Niguldipine, Nitrendipine, Trifluoperazine, Felodipine, Valinomycin, Dipyridamole, Erythromycine, Fluoroquinolones: Fleroxacin, Eenoxacin, Grepafloxacin, Levofloxacin, Norfloxacine, Glibenclamides & analogues, Gluconate salts, Gramicidin, Hydrocortisone, Itraconazole, Lidocaine, Phosphatidyl-choline, Pristinamycin Ia, Propafenone, Propranolol, Talinolol, Pyridine analogue, Quercetin 4'-b-glucoside, Quinine & quinidine, Quinacrine, Cinchonine, Ritonavir , Saquinavir, Nelfinavir, Tamoxifen and metabolites, Taxoid (Tetracyclic taxopine C & derivatives), Terfenadine.

42. The method of item 35 which further comprises monitoring the patient during treatment by assaying for changes in expression levels of the two or more genes in the cancerous cells whereby an increase in the expression level of

the two or more genes is compensated for by an increase in the amount of irinotecan administered to the patient.

43. The method of item 42 wherein MDR1 is one of the two or more genes.

44. A method of treating cancer in a patient which comprises internally administering to the patient an effective amount of irinotecan, wherein the treatment regimen is modified based upon the patient's genotype of genes comprising MDR1, MRP1, CYP3A5, and UGT1A1.

45. A method of treating a population of patients suffering from cancer which comprises:

(a) determining, on a patient by patient basis, if the patient has one or more variant alleles of each of two or more genes comprising an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;

(b) in a patient having one or more of such variant alleles of the two or more genes, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount without regard to the patient's alleles of the two or more genes.

46. The method of item 45 wherein MDR1 is one of the two or more genes.

47. A method for predicting sensitivity to irinotecan in a patient suffering from cancer which comprises determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, which alleles indicate that the cancerous cells express low or high amounts of the proteins of the two or more genes, whereby low expression indicates high sensitivity to irinotecan and high expression indicates resistance or predisposition to resistance to irinotecan.

48. The method of item 47 which further comprises administering to patients that have a genotype that indicates resistance or predisposition to resistance one

or more inhibitors selected from the group consisting of an MDR1 inhibitor, an MRP1 inhibitor, a CYP3A5 inhibitor, and a UGT1A1 inhibitor.

49. The method of item 48 wherein at least one inhibitor is an MDR1 inhibitor.

50. The method of item 49 wherein the MDR1 inhibitor is selected from the group consisting of: GF120918, LY335979, XR 9576, XR 9051, flavonoids (e.g. apigenin, genistin, naringin, quercetin, flavone, flavonone, flavopiridol), bergamottin, Clarithromycin, Ketoconazole, Reserpine, 1,9-dideoxyforskolin, Azidopine, Dimethyl-b-cyclodextrin, Ivermectin, SDZ PSC 833, SDZ 280-446, B669, B-859-35 (R-enantiomere) and its major metabolite, MS-209 (quinolone derivative), PAK-104p, Amiloride, Amytriptyline, Atorvastatin, Aureobasidin & analogues, Berrylium fluoride (BeFx), Calmodulin inhibitors, Chloroquine, Chloropromazine, Clofazimine, Cremophor EL, Diltiazem, Verapamil, Nifedipine, Bepridil, Nicardipine, Niguldipine, Nitrendipine, Trifluoperazine, Felodipine, Valinomycin, Dipyridamole, Erythromycine, Fluoroquinolones: Fleroxacin, Eenoxacin, Grepafloxacin, Levofloxacin, Norfloxacine, Glibenclamides & analogues, Gluconate salts, Gramicidin, Hydrocortisone, Itraconazole, Lidocaine, Phosphatidyl-choline, Pristinamycin Ia, Propafenone, Propranolol, Talinolol, Pyridine analogue, Quercetin 4'-b-glucoside, Quinine & quinidine, Quinacrine, Cinchonine, Ritonavir , Saquinavir, Nelfinavir, Tamoxifen and metabolites, Taxoid (Tetracyclic taxopine C & derivatives), Terfenadine.

51. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the MDR1 gene product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

52. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the MRP1 gene

product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

53. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the CYP3A5 gene product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

54. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the UGT1A1 gene product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

55. The method of item 47 wherein patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of two or more of the gene products selected from the group consisting of the MDR1 gene, the MRP1 gene, the CYP3A5 gene, and the UGT1A1 gene in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

56. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MDR1 gene in the cancerous tissue;
(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MDR1 gene.

57. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MRP1 gene in the cancerous tissue;
(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MRP1 gene.

58. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the UGT1A1 gene in the cancerous tissue;
(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the UGT1A1 gene.

59. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the CYP3A5 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the CYP3A5 gene.

The decreased expression as referred to herein above includes in addition to a significantly decreased amount of transcripts encoding a functional gene product also a normal or even elevated amount of transcripts encoding a gene product which has no activity or a significantly decreased activity.

By "in comparison to the amount that is administered without regard to the patient's alleles in the MDR1 gene" a standard dose is meant which is routinely administered to patients in need thereof without regarding the genotype. Such a general

population of patients is considered as having the normal genotype, i.e. wildtype genotype.

Further, the present invention encompasses a method for improving and/or modifying a therapy comprising determining the expression levels of MDR1, MRP1, UGT1A1, and/or CYP3A5, hereinafter referred to as expression profile or the protein level of the MDR1, MRP1, UGT1A1, and/or CYP3A5 proteins, hereinafter referred to as the protein profile, or the activity level of the said proteins, hereinafter referred to as the activity profile.

The term "expression level" as referred to in the context of the present invention means the detectable amount of transcripts of the MDR1, MRP1, CYP3A5 or UGT1A1 genes relative to the amount of transcripts for a housekeeping gene, such as PLA2. The amount of transcripts can be determined by standard molecular biology techniques including Northern analysis, RNAse protection assays, PCR based techniques encompassing Taq-Man analysis. Preferably, the determination can be carried out as described in the accompanied Examples 4 and 5. The term "expression profile" means that the expression level of a panel of the aforementioned genes is determined and the expression levels are compared to a reference standard. As a reference standard, preferably transcripts are obtained from cells or tissues of a subject having the aforementioned wildtype alleles of the respective genes in their genomes.
The term "protein level" refers to the detectable amount of MDR1, MRP1, CYP3A5 or UGT1A1 relative to the amount of a protein encoded by a housekeeping gene, such as PLA2. The amount of proteins can be determined by standard biochemical techniques, such as Western analysis, ELISA, RIA or other antibody based techniques known in the art. The term "protein profile" means that the protein level of a panel of the aforementioned proteins is determined and the protein levels are compared to a reference standard. As a reference standard, preferably proteins are obtained from cells or tissues of a subject having the aforementioned wildtype alleles of the respective genes in their genomes.

The term "activity level" means the detectable biological activity of MDR1, MRP1, CYP3A5 or UGT1A1 relative to the activity or amount of a encoded by the allellic variants of these genes as disclosed in the present invention relative to the activity of the protein encoded by the corresponding wild-type allele of the gene. Biological assays for the aforementioned proteins are well known in the art and described in Hitzl *et al.*, 2001, Pharmacogenetics 11:293-8, Cuff *et al.*, Toxicol Lett., 2001,

120:43-9, Stevens *et al.*, Drug Metab Dispos., 2001, 29:289-95, Barbier *et al.*, Mol Pharmacol., 2001, 59:636-45, Hanioka *et al.*, Xenobiotica. 2001, 31:687-99, Hallo *et al.*, Anticancer Res. 1998, 18:2981-7. As a reference standard, preferably proteins are obtained from cells or tissues of a subject having the aforementioned wildtype alleles of the respective genes in their genomes.

The aforementioned methods, preferably, comprise the steps (i) obtaining a tumor sample from a patient during specific stages of a tumor therapy; and (ii) determining the expression profile, protein profile or activity profile for MDR1, MRP1, UGT1A1, and/or CYP3A5. Based on the expression profiles a clinician can efficiently adapt the therapy. This comprises inter alia dosage adjustment and/or including administration of an MDR1, MRP1, UGT1A1 or CYP3A5 inhibitor. Preferably, said inhibitor is selected from the following group of inhibitors: for MDR1: GF120918, LY335979, XR 9576, XR 9051, flavonoids (e.g. apigenin, genistin, naringin, quercetin, flavone, flavonone, flavopiridol), bergamottin, Clarithromycin, Ketoconazole, Reserpine, 1,9-dideoxyforskolin, Azidopine, Dimethyl-b-cyclodextrin, Ivermectin, SDZ PSC 833, SDZ 280-446, B669, B-859-35 (R-enantiomere) and its major metabolite, MS-209 (quinolone derivative), PAK-104p, Amiloride, Amytriptyline, Atorvastatin, Aureobasidin & analogues, Berrylium fluoride (BeFx), Calmodulin inhibitors, Chloroquine, Chloropromazine, Clofazimine, Cremophor EL, Diltiazem, Verapamil, Nifedipine, Bepridil, Nicardipine, Niguldipine, Nitrendipine, Trifluoperazine, Felodipine, Valinomycin, Dipyridamole, Erythromycine, Fluoroquinolones: Fleroxacin, Eenoxacin, Grepafloxacin, Levofloxacin, Norfloxacine, Glibenclamides & analogues, Gluconate salts, Gramicidin, Hydrocortisone, Itraconazole, Lidocaine, Phosphatidyl-choline, Pristinamycin Ia, Propafenone, Propranolol, Talinolol, Pyridine analogue, Quercetin 4'-b-glucoside, Quinine & quinidine, Quinacrine, Cinchonine, Ritonavir , Saquinavir, Nelfinavir, Tamoxifen and metabolites, Taxoid (Tetracyclic taxopine C & derivatives), Terfenadine, for MRP1: SDZ-PSC 833, SDZ 280-446, MK571, MS209 (quinolone derivative), PAK-104p, Verapamil, Benzbromarone, Dipyridamole, Furosemide, Gamma-GS(naphtyl)cysteinyl-glycine diethyl ester, Genistein, Quinidine, Rifampicin, RU 486, Sulfinpyrazone, tricyclic isoxazole (e.g. LY 402913) (http://bigfoot.med.unc.edu/watkinsLab/intesinfo.htm, Paul Watkins, University of North Carolina); for UGT1A1: ß-estradiol, 4-hydroxyestrone, 2-hydroxyestrone, 7,8-Benzoflavone, Quercetin, Naringenin, Chrysin, Bilirubin, Octylgallate (Broudy M

(2001), BD Gentest, Woburn MA, USA); and for CYP3A5: Clarithromycin, Erythromycin, Diltiazem, Mibefradil, grapefuit juice, Cimetidine, Ciprofloxacin, Norfloxacin, Fluconazole, Itraconazole, Ketoconazole, Fluvoxamine, Norfluoxetine, Nefazodone, Troleandomycin, Delaviridine, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Mifepristone, gestodene (http://medicine.iupui.edu/flockhart).
The term inhibitor as used herein encompasses competitive and non-competitive inhibitors. Preferably competitive inhibitors are substrates such as (GF120918, LY335979, XR 9576, XR 9051, flavonoids). Preferably non-competitive inhibitors are substrates such as (SDZ PSC 833, SDZ 280-446, B669, B-859-35, Verapamil, MS-209, PAK-104p).

Finally, the present invention encompasses a method for determining whether a patient has developed a resistance against the drugs referred to in the context of the present invention. Said method comprising the steps of (i) obtaining a tumor sample from a patient during specific stages of a tumor therapy; and (ii) determining the expression levels of MDR1, MRP1, UGT1A1, and/or CYP3A5. The expression of the respective genes can be determined as described in Examples 4 and 5 or as described above. Based on the evaluation of said expression profile, a clinician can more efficiently adapt the therapy. This comprises inter alia dosage adjustment and/or including administration of an MDR1, MRP1, UGT1A1 or CYP3A5 inhibitor as defined supra.

Each of the documents cited herein (including any manufacturer's specifications, instructions, etc.) are hereby incorporated by reference.

The nucleic acid and amino acid sequences referred to in this application by sequence identification numbers (SEQ ID NOs.) are listed in the following Tables 1 2, 3 and 4. For positions of polymorphic nucleotides, the following substitute letters are used in the nucleic acid sequences: R, G or A; Y, T or C; M, A or C; K, G or T; S, G or C; W, A or T.

Amino acid sequences are shown in the one letter code. The letter X at polymorphic amino acid positions represents the modified amino acid or its corresponding wild type amino acid (see accession numbers).

Moreover, all nucleic acid and amino acid sequences referred to herein by making reference to GenBank accession numbers are shown in Figures 4 to 29 below.

Table 1: The nucleic acid and amino acid sequences referred to in this application

Gene	Variation	SNP Acc.no.	SEQ ID No	Sequence forward	SEQ ID NO	Sequence reverse	SEQ ID NO	Sequence wt>mut forward	SEQ ID NO	Sequence wt>mut reverse
UGT1A1	T>G	59Gi:8850235	001	GTCCTGGGCC**G**	002	ACACAGCAGC**C**	003	GTCCTGGGCC**K**	004	ACACAGCAGC**M**
				GCTGCTGTGT		GGCCCAGGAC		GCTGCTGTGT		GGCCCAGGAC
UGT1A1	C>T	160Gi:8850235	005	GGCCATCCAG**T**	006	TGCTGCAGCT**A**	007	GGCCATCCAG**Y**	008	TGCTGCAGCT**R**
				AGCTGCAGCA		CTGGATGGCC		AGCTGCAGCA		AGCTGCAGCA
UGT1A1	G>A	226Gi:8850235	009	CATCAGAGAC**A**	010	TAAAATGCTC**T**G	011	CATCAGAGAC**R**	012	TAAAATGCTC**Y**G
				GAGCATTTTA		TCTCTGATG		GAGCATTTTA		TCTCTGATG
UGT1A1	T>A	539Gi:8850235	013	TTGCATGCAC**A**	014	GCTGCATGGC**T**	015	TTGCATGCAC**W**	016	GCTGCATGGC**K**
				GCCATGCAGC		GTGCATGCAA		GCCATGCAGC		GTGCATGCAA
UGT1A1	T>C	544Gi:8850235	017	TGCACTGCCA**C**	018	TCCAGGCTGC**G**	019	TGCACTGCCA**Y**	020	TCCAGGCTGC**R**
				GCAGCCTGGA		GTGCATGCAA		GCAGCCTGGA		GTGCATGCAA
UGT1A1	C>T	640Gi:8850235	021	CTTCCTGCAG**T**	022	TTCTTCACCC**A**C	023	CTTCCTGCAG**Y**	024	TTCTTCACCC**R**C
				GGGTGAAGAA		TGCAGGAAG		GGGTGAAGAA		TGCAGGAAG

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UGT1A1	A>G	1085GI:8850235	061	TGGCTACCCC**G**	062	CAGATCGTTT**C**	063	TGGCTACCCC**R**	064	CAGATCGTTT**Y**
				AAACGATCTG		GGGGTAGCCA		AAACGATCTG		GGGGTAGCCA
UGT1A1	C>G	1114GI:8850235	065	CCCGATGACC**G**	066	ATAAAGGCAC**C**	067	CCCGATGACC**S**	068	ATAAAGGCAC**S**
				GTGCCTTTAT		GGTCATCGGG		GTGCCTTTAT		GGTCATCGGG

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UGT1A1	G>A	1117	GI:885023	069	GATGACCCGT**A**	070	GTGATAAAGG**T**	071	GATGACCCGT**R**	072	GTGATAAAGG**Y**
			5		CCTTTATCAC		ACGGGTCATC		CCTTTATCAC		ACGGGTCATC
UGT1A1	C>T	1139	GI:885023	073	CATGCTGGTT**T**	074	AACACCATGG**A**	075	CATGCTGGTT**Y**	076	AACACCATGG**R**
			5		CCATGGTGTT		AACCAGCATG		CCATGGTGTT		AACCAGCATG
UGT1A1	C>G	1158	GI:885023	077	TTTATGAAAG**G**	078	CATTGCATAT**C**	079	TTTATGAAAG**S**	080	CATTGCATAT**S**
			5		TATGCAATG		TTTCATAAA		TATGCAATG		TTTCATAAA
UGT1A1	CC> GT	1175 to 1176	GI:885023	081	AATGGCGTTC**G**	082	TCATCACCAT**AC**	083	AATGGCGTTC**Y**	084	TCATCACCAT**SR**
			5		**T**ATGGTGATGA		GAACGCCATT		ATGGTGATGA		GAACGCCATT
UGT1A1	G>C	1216	GI:885023	085	GATGGACAAT**C**	086	ATGCGCTTTG**G**	087	GATGGACAAT**S**	088	ATGCGCTTTG**S**
			5		CAAAGCGCAT		ATTGTCCATC		CAAAGCGCAT		ATTGTCCATC
UGT1A1	A>G	1297	GI:885023	089	AAATGCTCTA**G**	090	ATGACTGCTT**C**	091	AAATGCTCTA**R**	092	ATGACTGCTT**Y**
			5		AGCAGTCAT		AGAGCATTT		AGCAGTCAT		AGAGCATTT
UGT1A1	A>T	1324	GI:885023	093	CAAAAGTTAC**T**	094	ATGTTCTCCT**A**	095	CAAAAGTTAC**W**	096	ATGTTCTCCT**W**
			5		GGAGAACAT		TAACTTTTG		AGGAGAACAT		GTAACTTTTG
UGT1A1	T>G	1471	GI:885023	097	CTGGTACCAG**G**	098	AAGGAATGGT**C**	099	CTGGTACCAG**K**	100	AAGGAATGGT**M**
			5		ACCATTCCTT		CTGGTACCAG		ACCATTCCTT		CTGGTACCAG
UGT1A1	C>T	1478	GI:885023	101	CAGTACCATT**T**	102	CACGTCCAAG**A**	103	CAGTACCATT**Y**	104	CACGTCCAAG**R**

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			5		TTGGACGTG	AATGGTACTG		TTGGACGTG		AATGGTACTG		
UGT1A1	*del*CT	372 to	Gi:885023	105	TAAAAAAGG**AC**	106	AGCATAGCA**GT**	107	TAAAAAAGGA**n**C	108	AGCATAGCAG**n**
		373	5		TGCTATGCT		CCTTTTTTA		TGCTATGCT		TCCTTTTTTA
UGT1A1	*del*TT	523 to 525	Gi:885023	109	GCCCACTGT**AT**	110	CATGCAAGA**AT**	111	GCCCACTGTA**n**	112	CATGCAAGAA**n**T
	C		5		TCTTGCATG		ACAGTGGGC		TTCTTGCATG		ACAGTGGGC
UGT1A1	*del*	892 to 905	Gi:885023	113	ATTTGAAGC**CT**	114	ATGTTCTCC**AG**	115	ATTTGAAGCC**n**T	116	ATGTTCTCCA**n**G
			5		GGAGAACAT		GCTTCAAAT		GGAGAACAT		GCTTCAAAT
	TACA										
	TTA										
	ATGC										
	TTC										
UGT1A1	*ins*T	470/471	Gi:885023	129	CTGACGGACC**C**	130	AAGGAAGGAA**A**	131	CTGACGGACCC	132	AAGGAAGGAAA
			5		**TT**TCCTTCCTT		**TG**GGTCCGTCA		**n**TTTCCTTCCTT		**n**GGGTCCGTCA
							G				G
UGT1A1	*ins*G	1222/1223	Gi:885023	133	CAATGCAAAG**C**	134	AGTCTCCATG**C**	135	CAATGCAAAGC	136	AGTCTCCATGC
			5		**GG**CATGGAGAC		**CG**CTTTGCATT		**n**GCATGGAGAC		**n**GCTTTGCATTG
					T		G		T		
Cyp3A5	T>C	47518	Gi:102814	137	AAGGA**C**TTCTA	138	TAGAA**G**TCCTT	139	AAGGA**Y**TTCTA	140	TAGAA**R**TCCTT
			51								
Cyp3A5	T>G	145601	Gi:111774	141	TGGGC**G**TGCAA	142	TTGCA**C**GCCCA	143	TGGGC**K**TGCAA	144	TTGCA**M**GCCCA

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				52							
Cyp3A5	A>G	145929	Gi:111774	52	145GCCCCGCCTCC	146GGAGGCGGGG C	147 GCCCCRCCTCC	148 GGAGGYGGGG C			
Cyp3A5	A>G	9736	Gi:102814	51	149CTCACGCTGGG	150CCCAGCGTGAG	151 CTCACRCTGGG	152 CCCAGYGTCTC			
MRP1	G>A	21133	U91318		169CCCAAAACACA	170GCAGGGTGTGT	171 CCCAAAACACR CACACCCTGC	172 GCAGGGTGTGY GTGTTTTGGG			
MRP1	G>T	57998	Gi:720945	1	173ACGCTCAGAGT	174AGTCCATGAAA	175 ACGCTCAGAGK TTCATGGACT	176 AGTCCATGAAM CTCTGAGCGT			
MRP1	C>T	137667	AC026452		177GCAGGTGGCCT	178AATGTGCACAA	179 GCAGGTGGCCY TGTGCACATT	180 AATGTGCACAR GGCCACCTGC			
MRP1	C>T	137647	AC026452		181TTGCCGTCTAT	182CAATGGTCACA	183 TTGCCGTCTAY GTGACCATTG	184 CAATGGTCACR TAGACGGCAA			
MRP1	G>A	27258	AC003026		185GATTCTCTCCA	186GATGTTTTCTT	187 GATTCTCTCCR GAAAACATC	188 GATGTTTTCTY GAGAGAATC			
MRP1	G>A	14008	U91318		189CTGGGAAGTCA	190GGGTCAGGGAT	191 CTGGGAAGTCR TCCCTGACCC	192 GGGTCAGGGAY GACTTCCCAG			
MRP1	C>T	18067	U91318		193CCACGGCAGCT	194CCAGGTCCACA	195 CCACGGCAGCY	196 CCAGGTCCACR			

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				GTGGACCTGG	GCTGCCGTGG	GTGGACCTGG	GCTGCCGTGG						
MRP1	G>A	79	AF022830	197 CCAGGCAGCCA[A/T] 198 CAACCTTCAC[T/Y]		199 CCAGGCAGCC[A/R]		200 CAACCTTCAC[T/Y]					
				GTGAAGGTTG	GGCTGCCTGG	GTGAAGGTTG	GGCTGCCTGG						
MRP1	T>C	88	AF022830	201 CGGTGAAGGT[C/T] 202 AGGAGTACAC[G/R]		203 CGGTGAAGGT[T/Y]		204 AGGAGTACAC[G/R]					
				GTGTACTCCT	ACCTTCACCG	GTGTACTCCT	ACCTTCACCG						
MRP1	T>G	249	AF022830	205 CTCATGAGCT[G] 206 CTTGAAGAAG[C/T]		207 CTCATGAGCT[K]		208 CTTGAAGAAG[M]					
				CTTCTTCAAG	AGCTCATGAG	CTTCTTCAAG	AGCTCATGAG						
MRP1	T>C	95	AF022831	209 AGTTCGTGAA[C/T] 210 CCTTCGTGTC[G/R]		211 AGTTCGTGAA[T/Y]		212 CCTTCGTGTC[G/R]					
				GACACGAAGG	TTCACGAACT	GACACGAAGG	TTCACGAACT						
MRP1	C>T	57853	GI:720945	213 GGCAGTGGGC[T/Y] 214 CCACTCCCTC[A/R]		215 GGCAGTGGGC[T/Y]		216 CCACTCCCTC[A/R]					
			1	GAGGGAGTGG	GCCCACTGCC	GAGGGAGTGG	GCCCACTGCC						
MRP1	C>G	53282	GI:720945	217 GCCAGTTGGA[G/S] 218 CCCCAAGTGA[C/S]		219 GCCAGTTGGA[S]		220 CCCCAAGTGA[S]					
			1	TCACTTGGGG	TCCAACTGGC	TCACTTGGGG	TCCAACTGGC						
MRP1	A>G	137710	AC026452	221 ACTCTCACTC[G] 222 TGCTGTGCCC[C/Y]		223 ACTCTCACTC[R]		224 TGCTGTGCCC[Y]					
				GGGCACAGCA	GAGTGAGAGT	GGGCACAGCA	GAGTGAGAGT						
MRP1	G>C	27159	AC003026	225 TCGTTGATCA[C/G] 226 ACAGACAGAT[G]		227 TCGTTGATCA[S]		228 ACAGACAGAT[S]					
				TCTGTCTGT	TGATCAACGA	TCTGTCTGT	TGATCAACGA						
MRP1	G>A	34218	AC003026	229 GTGCACTCAC[A] 230 CACCCGGCCA[T]		231 GTGCACTCAC[R]		232 CACCCGGCCA[Y]					

				TGGCCGGGTG	GTGAGTGCAC	TGGCCGGGTG	GTGAGTGCAC						
MRP1	G>C	34215	AC003026	233CATGTGCACT[C/G]	234CCGGCCACGT[G/S]	235 CATGTGCACT[S]	236 CCGGCCACGT[S]						
				ACGTGGCCGG	AGTGCACATG	ACGTGGCCGG	AGTGCACATG						
MRP1	G>A	39508	GI:720945	237GTTTCGTTGT[A]	238TCCCACCCCC[T]	239 GTTTCGTTGT[R]	240 TCCCACCCCC[Y]						
			1	GGGGGTGGGA	ACAACGAAAC	GGGGGTGGGA	ACAACGAAAC						
MRP1	T>C	55472	AC003026	241TGTCTAATTA[C/A]	242ATCCATTTCT[G/T]	243 TGTCTAATTA[Y/A]	244 ATCCATTTCT[R/T]						
				GAAATGGAT	AATTAGACA	GAAATGGAT	AATTAGACA						
MRP1	G>A	150727	AC025277	245CCATGTCAGC[A]	246ACCTGTGTCA[T]	247 CCATGTCAGC[R]	248 ACCTGTGTCA[Y]						
				TGACACAGGT	GCTGACATGG	TGACACAGGT	GCTGACATGG						
MRP1	*del*T	17970	U91318	249CTGGTTTTTT[C/T]	250TGACCGGAAG[A/A]	251 CTGGTTTTTT[nC]	252 TGACCGGAAG[n]						
				TCCGGTCA	AAAAACCAG	TTCCGGTCA	AAAAAAACCAG						
MRP1	C>T	17900	U91318	253TGTCTCCTTT[T/G]	254TGGGAGAAGC[A/A]	255 TGTCTCCTTT[Y/G]	256 TGGGAGAAGC[R]						
				CTTCTCCCA	AAAGGAGACA	CTTCTCCCA	AAAGGAGACA						
MRP1	G>A	18195	U91318	257CACTGGCACA[A]	258CTAGAGGCCA[T]	259 CACTGGCACA[R]	260 CTAGAGGCCA[Y]						
				TGGCCTCTAG	TGTGCCAGTG	TGGCCTCTAG	TGTGCCAGTG						
MRP1	G>A	33551	AC025277	261TGTGACCACA[A]	262ACACACTCAT[T/T]	263 TGTGACCACA[R]	264 ACACACTCAT[Y/T]						
				ATGAGTGTGT	GTGGTCACA	ATGAGTGTGT	GTGGTCACA						
MRP1	C>T	174	AF022828	265CCAGGCCCCC[T]	266CCTGAGGTCT[A]	267 CCAGGCCCCC[Y]	268 CCTGAGGTCT[R]						

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				AGACCTCAGG	GGGGGCCTGG	AGACCTCAGG	GGGGGCCTGG						
MRP1	C>A	248	AF022829	269CCTTTCCACT**A/C**270GAGGCCACAG**T/I**		271 CCTTTCCACT**M**		272 GAGGCCACAG**K**					
				TGTGGCCTC	AGTGGAAAGG	CTGTGGCCTC	AGTGGAAAGG						
MRP1	C>G	258	AF022829	273CCTGTGGCCT**G**	274ATCCTGGATT**C**	275 CCTGTGGCCT**S**		276 ATCCTGGATT**S/A**					
				AATCCAGGAT	AGGCCACAGG	AATCCAGGAT	GGCCACAGG						
MRP1	A>G	259	AF022831	277AAGGTAGGGG**G**	278TGGCACAGCG**C**	279 AAGGTAGGGG**R**		280 TGGCACAGCG**Y**					
				CGCTGTGCCA	CCCCTACCTT	CGCTGTGCCA	CCCCTACCTT						
MRP1	T>C	124667	AC026452	281GCGTGCCCAG**C**	282AAACCCCAGG**G**	283 GCGTGCCCAG**Y**		284 AAACCCCAGG**R**					
				CCTGGGGTTT	CTGGGCACGC	CCTGGGGTTT	CTGGGCACGC						
MRP1	G>A	1884	U07050	285AGCCTTGGAG**A**	286CACCCCAGAT**I**	287 AGCCTTGGAG**R**		288 CACCCCAGAT**Y**					
				ATCTGGGGTG	CTCCAAGGCT	ATCTGGGGTG	CTCCAAGGCT						
MRP1	G>C	38646	AC026452	289CCTTAAACAG**C**	290CTTTTCAAAT**G/C**	291 CCTTAAACAG**S**		292 CTTTTCAAAT**S/C**					
				ATTTGAAAAG	TGTTTAAGG	TTTGAAAAG	TGTTTAAGG						
MRP1	C>A	1625	U07050	293GGGAATCACT**A**	294CAGAGAGGTT**T/T**	295 GGGAATCACT**M**		296 CAGAGAGGTT**K**					
				AACCTCTCTG	AGTGATTCCC	AACCTCTCTG	AGTGATTCCC						
MRP1	C>T	1163	U07050	297TGTGATCGGC**T/I**	298AGCCGAGGCG**A**	299 TGTGATCGGC**Y**		300 AGCCGAGGCG**R**					
				CGCCTCGGCT	GCCGATCACA	CGCCTCGGCT	GCCGATCACA						
MRP1	A>G	381	U07050	301TGGGGGACCC**G**	302TTTATTGGCC**C**	303 TGGGGGACCC**R**		304 TTTATTGGCC**Y**					

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					GGCCAATAAA	GGGTCCCCCA		GGCCAATAAA		GGGTCCCCCA			
MRP1	G>A	233	U07050	305	AAGAGTAGCA**A**	306	CAAGATAAAA**T**T	307	AAGAGTAGCA**R**	308	CAAGATAAAA**YT**		
					TTTTATCTTG		GCTACTCTT		TTTTATCTTG		GCTACTCTT		
MRP1	C>A	189	U07050	309	AAAAAAATCC**A**A	310	TTTTTGGATT**T**G	311	AAAAAAATCC**M**	312	TTTTTGGATT**K**G		
					ATCCAAAAA		GATTTTTTT		AATCCAAAAA		GATTTTTTT		
MRP1	C>T	440	U07050	313	CTCCTTCCCT**T**G	314	AGGACCTAGC**A**	315	CTCCTTCCCT**Y**	316	AGGACCTAGC**R**		
					CTAGGTCCT		AGGGAAGGAG		GCTAGGTCCT		AGGGAAGGAG		
MRP1	*del*AT	34206 to 34207	AC003026	317	AGTCTCACAC**G**	318	GTGAGTGCA**C**G	319	AGTCTCACAC**n**	320	GTGAGTGCAC**n**		
					TGCACTCAC		TGTGAGACT		GTGCACTCAC		GTGTGAGACT		
MRP1	*del*GG	1720 to 1723	U07050	321	ACTCCAGGC**A**G	322	GAACGGAGC**C**T	323	ACTCCAGGCA**n**	324	GAACGGAGCC**n**		
		TA			GCTCCGTTC		GCCTGGAGT		GGCTCCGTTC		TGCCTGGAGT		
MRP1	*ins*T	926/ 927	U07050	325	TTAATTTTTTT**T**T	326	AAATAATAA**T**AA	327	TTAATTTTTTTT**n**	328	AAATAATAAT**n**A		
					ATTATTATTT		AAAAAAATTAA		ATTATTATTT		AAAAAAATTAA		
MRP1	*ins*TC	437/ 438	U07050	329	TTCCTCCTTC**C**T	330	ACCTAGCGA**GG**	331	TTCCTCCTTCC**n**	332	ACCTAGCGAG**A**		
	CTTC				**CCTTCCC**TCGC		**GAAGGAG**GAAG		CTCGCTAGGT		GGAAGGAGGAA		
	C				TAGGT		GAGGAA						
MRP1	*ins*TG	55156/	AC003026	333	GGGGCTGGGG	334	CACGCACCCG**A**	335	GGGGCTGGGG	336	CACGCACCCG**n**		
	GGG				**CTGGGGCT**GGG		**CCCCGA**CCCAG		C**n**TGGGTGCGT		ACCCAGCCCC		
	C	55157			TGCGTG		CCCC		G				

MDR1	T>C	140837	AC002457	337	GCTCATTCGAG	338	AGAGCCGCTGC	339	CTCATTCGAGY	340	AGAGCCGCTRC
					CAGCGGCTCT		TCGAATGAG		AGCGGCTCTT		TCGAATGAG
MDR1	G>A	84701	AC005068	341	AAAATTGCTATC	342	AGATAGTGATA	343	AAAATTGCTRTC	344	AGATAGTGAYA
					ACTATCT		GCAATTTT		ACTATCT		GCAATTTT
MDR1	G>A	101	M29432	345	TTCACTTCAATT	346	ATGGGTAATTG	347	TCACTTCARTTA	348	GATGGGTAAYT
					ACCCATC		AAGTGAA		CCCATC		GAAGTGAA
MDR1	C>T	308	M29432	349	CTTGAAGGGTC	350	TCAGGTTCAGA	351	TCTTGAAGGGY	352	TCAGGTTCAGR
					TGAACCTGA		CCCTTCAAGA		CTGAACCTG		CCCTTCAAGA
MDR1	C>T	83946	AC005068	353	TCAGCAGTTAC	354	TGCAATGTAACT	355	CAGCAGTYACA	356	TGCAATGTRAC
					ATTGCA		GCTGA		TTGCAC		TGCTGA
MDR1	G>A	83973	AC005068	357	GACCCATGCAA	358	GGTCTAGCTTG	359	GACCCATGCRA	360	GGTCTAGCTYG
					GCTAGACC		CATGGGTC		GCTAGACC		CATGGGTC
MDR1	A>G	84032	AC005068	361	GAGCACAACGG	362	CAGCTGGACCG	363	GAGCACAACRG	364	CAGCTGGACYG
					TCCAGCTG		TTGTGCTC		TCCAGCTG		TTGTGCTC
MDR1	G>A	84074	AC005068	365	TGGGCAGACAG	366	CAGGGCCACTG	367	TGGGCAGACRG	368	CAGGGCCACYG
					TGGCCCTG		TCTGCCCA		TGGCCCTG		TCTGCCCA
MDR1	G>A	84119	AC005068	369	CTCGTCCTGAT	370	CAAGATCTATCA	371	CTCGTCCTGRT	372	CAAGATCTAYCA
					AGATCTTG		GGACGAG		AGATCTTG		GGACGAG

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MDR1	T>C	171511	AC002457	445	GATACAGGGCT	446	TCATGAAGAGC	447	GATACAGGGYT	448	TCATGAAGARC
					CTTCATGA		CCTGTATC		CTTCATGA		CCTGTATC
MDR1	T>C	171512	AC002457	449	GATACAGGGTC	450	ATTCATGAAGG	451	GATACAGGGTY	452	ATTCATGAAGR
					CTTCATGAAT		ACCCTGTATC		CTTCATGAAT		ACCCTGTATC
MDR1	G>A	174901	AC002457	453	GTGCACGATAT	454	GCTCCCCAATA	455	GTGCACGATRT	456	GCTCCCCAAYA
					TGGGGAGC		TCGTGCAC		TGGGGAGC		TCGTGCAC
MDR1	C>T	175068	AC002457	457	TAAGCAGCAAT	458	ACACGACATTA	459	TAAGCAGCAAY	460	ACACGACATTR
					AATGTCGTGT		TGCTGCTTA		AATGTCGTGT		TGCTGCTTA
MDR1	C>T	175074	AC002457	461	CAACAATGTTGT	462	GATGCACACAA	463	CAACAATGTYGT	464	GATGCACACRA
					GTGCATC		CATTGTTG		GTGCATC		CATTGTTG
MDR1	A>G	175142	AC002457	465	CATTAAATGGA	466	CCCAGTCCTCC	467	CATTAAATGRAG	468	CCCAGTCCTYC
					GGACTGGG		ATTTAATG		GACTGGG		ATTTAATG
MDR1	A>G	175180	AC002457	469	TCCTCTGAGGA	470	ACTGCACATCC	471	TCCTCTGAGRA	472	ACTGCACATYCT
					TGTGCAGT		TCAGAGGA		TGTGCAGT		CAGAGGA
MDR1	A>G	139015	AC002457	473	AACTTACTTGTA	474	TCAAAGATACAA	475	AACTTACTTRTA	476	TCAAAGATAYAA
					TCTTTGA		GTAAGTT		TCTTTGA		GTAAGTT
MDR1	A>T	139064	AC002457	477	AGAAATAGTTTA	478	TGTTGATTAAAC	479	AGAAATAGTWT	480	TGTTGATTAWA
					ATCAACA		TATTTCT		AATCAACA		CTATTTCT

MDR1	T>C	139119	AC002457	481	TAGGGAGAGGGCT TAAGGCCA	482	TGGCCTTAAGC CCTCCCTA	483	TAGGGAGGGYT TAAGGCCA	484	TGGCCTTAARC CCTCCCTA
MDR1	G>A	139177	AC002457	485	GAAAGGTGAAA TAAAGCAA	486	TTGCTTTATTTC ACCTTTC	487	GAAAGGTGARA TAAAGCAA	488	TTGCTTTATYTC ACCTTTC
MDR1	C>T	139276	AC002457	489	CATTTACCCTAG ATGGACC	490	GGTCCATCTAG GGTAAATG	491	CATTTACCCYAG ATGGACC	492	GGTCCATCTRG GGTAAATG
MDR1	G>A	140118	AC002457	493	ATATGGAAGAA AATTACAA	494	TTGTAATTTTCT TCCATAT	495	ATATGGAAGRA AATTACAA	496	TTGTAATTTYCT TCCATAT
MDR1	A>G	140216	AC002457	497	AACACGGGCGT TGATCTGA	498	TCAGATCAACG CCCGTGTT	499	AACACGGGCRT TGATCTGA	500	TCAGATCAAYG CCCGTGTT
MDR1	T>C	140490	AC002457	501	TGTATTAAACGC GAATCCC	502	GGGATTCGCGT TTAATACA	503	TGTATTAAAYGC GAATCCC	504	GGGATTCGCRT TTAATACA
MDR1	G>A	140568	AC002457	505	TTGAAAGACAT GTCTACAT	506	ATGTAGACATG TCTTTCAA	507	TTGAAAGACRT GTCTACAT	508	ATGTAGACAYG TCTTTCAA
MDR1	A>T	140576	AC002457	509	CGTGTCTACTTA AGTTGAA	510	TTCAACTTAAGT AGACACG	511	CGTGTCTACWT AAGTTGAA	512	TTCAACTTAWG TAGACACG
MDR1	A>G	140595	AC002457	513	ATGTCCCCAGT GATTCAGC	514	GCTGAATCACT GGGGACAT	515	ATGTCCCCART GATTCAGC	516	GCTGAATCAYT GGGGACAT

MDR1	G>A	140727	AC002457	517	CCGGGCCGGA**A**	518	ATGACTGCTT**C**	519	CCGGGCCGG**R**A	520	ATGACTGCT**Y**C
					GCAGTCAT		CGGCCCGG		GCAGTCAT		CGGCCCGG
MDR1	G>A	139479	AC002457	521	GAGGCGGGC**A**	522	CTCGTGATC**T**G	523	GAGGCGGGC**R**	524	CTCGTGATC**Y**G
					GATCACGAG		CCCGCCTC		GATCACGAG		CCCGCCTC
MDR1	T>C	139619	AC002457	525	GGAGAATGG**C**G	526	CGGGTTCAC**G**C	527	GGAGAATGG**Y**G	528	CGGGTTCAC**R**C
					TGAACCCG		CATTCTCC		TGAACCCG		CATTCTCC
MDR1	G>T	65241	AC005068	636	ACTAGAAGGT**T**	637	ACCTTCCCAG**A**	638	ACTAGAAGGT**K**	639	ACCTTCCCAG**M**
					CTGGGAAGGT		ACCTTCTAGT		CTGGGAAGGT		ACCTTCTAGT
MDR1	G>A	50537	AC005068	640	TCCTGACTAT**A**C	641	TTGGCTTTGG**T**	642	TCCTGACTAT**R**C	643	TTGGCTTTGG**Y**
					CAAAGCCAA		ATAGTCAGGA		CAAAGCCAA		ATAGTCAGGA
TOP1	1334	13341845	GI:112252	529	ACTTTTCCGT**T**G	530	TTGCCGCGGC**A**	531	ACTTTTCCGT**K**G	532	TTGCCGCGGC**M**
	G>T		59		CCGCGGCAACT		ACGGAAAAGTT		CCGCGGCAACT		ACGGAAAAGTT
							C				C
TOP1	1845	1845	GI:112252	533	CTCGGGAAGG**G**G	534	TCTGATGGAG**C**	535	CTCGGGAAGG**R**G	536	TCTGATGGAG**Y**
	A>G		59		CTCCATCAGA		CCTTCCCGAG		CTCCATCAGA		CCTTCCCGAG

Table 2: The nucleic acid and amino acid sequences referred to in this application

Gene	AS change	Protein Acc No	SEQ ID NO	Protein	SEQ ID N=	Protein wt>mut
UGT1A1	L15R	G8850236	538	PLVLG**R**LLCVL	539	PLVLG**X**LLCVL
UGT1A1	G71R	G8850236	540	LYIRD**R**AFYTL	541	LYIRD**X**AFYTL
UGT1A1	D119Dframeshift	G8850236	542	KKIKK**DCYAFC**	543	KKIKK**DX**
UGT1A1	P152Pframeshift	G8850236	544	VMLTDPF**PSLQ**	545	VMLTD**PX**
UGT1A1	F170del	G8850236	546	LSLPTV**FLHAL**	547	LSLPTV**FX**
UGT1A1	L175Q	G8850236	548	FFLHA**Q**PCSLE	549	FFLHA**X**PCSLE
UGT1A1	C177R	G8850236	550	LHALP**R**SLEFE	551	LHALP**X**SLEFE
UGT1A1	R209W	G8850236	552	MTFLQ**W**VKNML	553	MTFLQ**X**VKNML
UGT1A1	P229Q	G8850236	554	DVVYS**Q**YATLA	555	DVVYS**X**YATLA
UGT1A1	G276R	G8850236	556	NMVFV**R**GINCL	557	NMVFV**X**GINCL
UGT1A1	A292V	G8850236	558	SQEFE**V**YINAS	559	SQEFE**X**YINAS

UGT1A1	Y293Wframeshift	G8850236	560	QEFEA**W**RTWN	561	QEFEA**X**INASG
UGT1A1	G308E	G8850236	562	VVFSL**E**SMVSE	563	VVFSL**X**SMVSE
UGT1A1	Q331R	G8850236	564	LGKIP**R**TVLWR	565	LGKIP**X**TVLWR
UGT1A1	Q357R	G8850236	566	VKWLP**R**NDLLG	567	VKWLP**X**NDLLG
UGT1A1	R367G	G8850236	568	GHPMT**G**AFITH	569	GHPMT**X**AFITH
UGT1A1	A368T	G8850236	570	HPMTR**T**FITHA	571	HPMTR**X**FITHA
UGT1A1	P387R	G8850236	572	ICNGV**R**MVMMP	573	ICNGV**X**MVMMP
UGT1A1	S375F	G8850236	574	ITHAG**F**HGVYE	575	ITHAG**X**HGVYE
UGT1A1	S381R	G8850236	576	HGVYE**R**ICNGV	577	HGVYE**X**ICNGV
UGT1A1	A401P	G8850236	578	DQMDN**P**KRMET	579	DQMDN**X**KRMET
UGT1A1	R403Rframeshift	G8850236	580	MDNAK**RHGD.**	581	MDNAK**X**
UGT1A1	K428E	G8850236	582	LENAL**E**AVIND	583	LENAL**X**AVIND
UGT1A1	Y486D	G8850236	584	LTWYQ**D**HSLDV	585	LTWYQ**X**HSLDV
UGT1A1	S488F	G8850236	586	WYQYH**F**LDVIG	587	WYQYH**X**LDVIG

UGT1A1	Q49stop	G8850236	588	LGAIQ*		589	LGAIQ*		
UGT1A1	C280stop	G8850236	590	VGGIN*		591	VGGIN*		
UGT1A1	Q331stop	G8850236	592	LGKIP*		593	LGKIP*		
UGT1A1	W335stop	G8850236	594	PQTVL*		595	PQTVL*		
UGT1A1	Q357stop	G8850236	596	VKWLP*		597	VKWLP*		
UGT1A1	K437stop	G8850236	598	NDKSY*		599	NDKSY*		
MRP1	F329C	G2828206	600	YFLMSCFFKAI		601	YFLMSXFFKAI		
MRP1	R433S	G2828206	602	SVDAQSFMDLA		603	SVDAQXFMDLA		
MRP1	R723Q	G2828206	604	QNDSLQENILF		605	QNDSLXENILF		
MDR1	N21D	G2506118	606	FFKLNDKSEKD		607	FFKLNXKSEKD		
MDR1	F103L	G2506118	608	INDTGLFMNLE		609	INDTGXFMNLE		
MDR1	V168I	G2506118	610	FDVHDIGELNT		611	FDVHDXGELNT		
MDR1	S400N	G2506118	612	RNVHFNYPSRK		613	RNVHFXYPSRK		
MDR1	G412G	G2506118	614	VKILKGLNLKV		615	VKILKXLNLKV		

MDR1	T436T	G2506118	616	CGKSTTVQLMQ	617	CGKSTXVQLMQ
MDR1	A893S	G2506118	618	KELEGSGKIAT	619	KELEGXGKIAT
MDR1	A999T	G2506118	620	FAPDYTKAKIS	621	FAPDYXKAKIS
MDR1	A1001T	G2506118	622	PDYAKTKISAA	623	PDYAKXKISAA
MDR1	Q1107P	G2506118	624	KRLNVPWLRAH	625	KRLNVXWLRAH
MDR1	A1132A	G2506118	626	IAENIAYGDNS	627	IAENIXYGDNS
MDR1	S1141T	G2506118	628	NSRVVTQEEIV	629	NSRVVXQEEIV
MDR1	I1145I	G2506118	630	VSQEEIVRAAK	631	VSQEEXVRAAK
TOP1	G363C	G12644118	632	PGLFRCRGNHP	633	PGLFRXRGNHP
TOP1	D533G	G12644118	634	DFLGKGSIRYY	635	DFLGKXSIRYY

Table 3: Selected nucleic acid sequences referred to in this application

Gene	Variation	SNP	Genbank Accession No	SEQ ID NO
UGT1A1	C>T	890	GI:8850235	037
UGT1A1	G>A	1117	GI:8850235	069
UGT1A1	T>G	1471	GI:8850235	097
Cyp3A5	T>C	47518	GI:10281451	137
Cyp3A5	T>G	145601	GI:11177452	141
Cyp3A5	A>G	145929	GI:11177452	145
Cyp3A5	A>G	9736	GI:10281451	149
MRP1	C>T	137647	AC026452	181
MRP1	T>C	95	AF022831	209
MRP1	C>G	53282	GI:7209451	217
MRP1	T>G	249	AF022830	205
MRP1	A>G	259	AF022831	277
MRP1	T>C	124667	AC026452	281
MRP1	A>G	381	U07050	301
MRP1	*ins*T	926/927	U07050	325
MRP1	G>A	34218	AC003026	229
MRP1	C>T	18067	U91318	193
MRP1	C>T	440	U07050	313
MRP1	C>A	1625	U07050	293
MRP1	C>T	17900	U91318	253
MDR1	G>A	101	M29432	345
MDR1	C>T	176	M29445	417
MDR1	G>T	88883	GI:10122135	636

Table 4 Selected amino acid sequences referred to in this application

Gene	AA change	Protein Genbank No	SEQ ID NO
UGT1A1	A292V	G8850236	558
UGT1A1	A368T	G8850236	570
UGT1A1	Y486D	G8850236	584
MRP1	F329C	G2828206	600
MDR1	S400N	G2506118	612
MDR1	A893S	G2506118	618

The figure show:

Figure 1 shows the correlation of the exon 26 SNP with inestinal MDR1 expression in 21 volunteres determined by Western blot analyses. The box plot shows the distribution of MDR1 expression clustered according to the MDR1 3435C>T genotype at position corresponding to position 176 of the MDR1 gene (GenBank Acc. No. M29445). The T allele was associated with a lower expression of p-glycoprotein.

Figure 2 shows the correlation of MDR1 3435C>T genotype and digoxin uptake in 14 healthy volunteers who participated in a clinical study that addresses peak plama levels of digoxin at steady state [Johne et al., 1999, Clin. Pharmacol. Ther 66:338-345]. Maximum digoxin levels were statistically significantly different (p=0.006, Mann Whitney U test) between the two groups which were homozygous for the T and C allele, respectively.

Figure 3 represent the correlation of the genotype (wt/wt: 1; wt/mut and mut/mut:2) with MRP1 mRNA content in duodenal biopsies from healthy volunteers derived from two independent experiments, before and after application of rifampicin. Treatment with rifampicin had no effect on MRP1 mRNA expression ($p<0.001$, paired t-test). A strong trend of an association of MRP1 genotype with MRP1 mRNA levels was detected (p=0.086, Kruskal-Wallis test).

Figures 4 to 28 show the nucleic acid and amino acid sequences referred to herein.

Figure 29 shows the expression profile of genes relevant to Irinotecan metabolism in carcinoma cell lines. This semiquantitativ RT-PCR shows amounts of transcripts for the genes indicated right to the amplicons. PCR products were analyzed by agarose electrophoresis, stained with ethidium bromid. The respective fragment sizes are indicated on the left in basepaires (bp).

Figure 30 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with epithelial carcinoma cell lines LS174T (colon), KB 3-1 (cervix) and RT112 (bladder). Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200

ng/ml. Cells were treated for three days. The data for each concentration are mean values of at least three wells.

Figure 31 growth inhibition curves for CPT-11 (A) and SN-38 (B) with a epithelial cervix carcinoma cell line KB 3-1 and two subclones expressing high amounts of MDR1, KB 3-1 (MDR1) and KB 3-1 (MDR1, CYP3A5). Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml. Cells were treated for three days. The data for each concentration are mean values and standard deviation of at least three wells.

Figure 32 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with the bladdercancer cell line RT112 and and its subclones RT112 (MDR1, UGT1A1) expressing MDR1 and higher amounts of UGT1A1. Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml. Cells were treated for three days. The data for each concentration are mean values and standard deviation of at least three wells.

Figure 33 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with inhibition of MDR1 by R-Verapamil. The epithelial cervix carcinoma cell line KB 3-1 and the two subclones KB 3-1 (MDR1) and KB 3-1 (MDR1, CYP3A5), with high MDR1 expression, were tested for the influence of MDR1 inhibition by R-Verapamil on drug sensitivity. Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml and R-Verapamil was added to 10 μg/ml final concentration(+V). Cells were treated for three days. The data for each concentration are mean values of two wells.

Figure 34 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with inhibition of MDR1 by R-Verapamil. To circumvent the MDR1 effect on drug resistance cells were treated in parallel with R-Verapamil. The KB 3-1 (MDR1) and KB 3-1 (MDR1, CYP3A5), which differ in their CYP3A5 expression, were tested for remaining resistance after inhibition of MDR1. Concentrations of CPT-11 ranged

from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml and R-Verapamil was added to 10 μg/ml final concentration(+V). Cells were treated for three days. The data for each concentration are mean values of two wells.

The present invention is illustrated by reference to the following biological Examples which are merely illustrative and are not to be constructed as a limitation of the scope of the present invention.

Example 1: Phenotypically impact of the C to T substitution at position corresponding to position 176 of the MDR1 gene (Acc. No. M29445).

To investigate the influence of the single nucleotide C to T substitution at position corresponding to position 176 of the MDR1 gene (Acc. No. M29445) also referred to as MDR1 exon 26 SNP C3435T on intestinal P-glycoprotein (PGP) expression, samples from biopsies and duodenal enterocyte preparations from 21 were investigated at the Dr. Margarete Fischer-Bosch-Institute for Clinical Pharmacology in Stuttgart by quantitative immunohistochemistry and Western blots. The results are shown in Figure 1. Homozygous carriers of the T allele (having at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) a T) demonstrated significantly higher PGP levels compared to homozygous carriers of the C allele (having at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) a C). Individuals with heterozygous genotype showed an intermediate level of PGP expression.

Furthermore, the influence of the MDR1 genotype on intestinal uptake-related pharmacokinetics of digoxin was investigated in a clinical study at the University Medical Center, Charite in Berlin. Maximal digoxin blood levels (Cmax) at steady state were correlated with the MDR1 3435C>T genotype 14 healthy volunteers after oral application of digoxin. Figure 2 shows, volunteers homozygous for the T allele show statistically significantly lower digoxin levels than volunteers with a C/C genotype. (p=0.006, Mann Whitney U test) and reflects the impact of this polymorphism on digoxin pharmacokinetics.

Example 2: Correlation of MRP1 polymorphisms with MRP1 expression and side effects during therapy with MRP1 substrates

Functional polymorphisms in the MRP1 gene affect the transport activity which in consequence modulates plasma levels and/or intracellular concentrations of MRP1 substrate drugs. Increased levels of such drugs can lead to side effects whereas decreased levels may result in subtherapeutical drug levels and therapy failure. MRP1 polymorphisms were correlated with the occurence of drug-related adverse effects and therapeutic efficacy in patients treated with MRP1 substrate drugs. In a case-control study, the frequency distribution of MRP1 SNPs was compared between a group of patients who suffered from cisplatin-related nephrotoxicity and a group of patients with nephro- and hepatotoxicities caused from anti-cancer drugs with a group of healthy controls. Furthermore, samples of known MRP1 mRNA levels were screened for MRP1 genotype. The results in the group of patients demonstrating nephro- and hepatotoxicity during anti-cancer treatment, are listed in the following table for one MRP1 SNP:

SNP	group	Allele frequency [%]		Genotype frequency [%]		
		G allele	A allele	*G/A	*A/A	*A/A expected[2]
150727G>A[1]	Controls	66.7	33.3	50	8.3	10.9
	Cases	50.0	50.0	14.3	42.9	25.0

[1]according to Acc. No. AC025277

[2] calculated according to Hardy-Weinberg

In contrast to control samples, the A allele (substitution of G to A at position according to position 150727 of the MRP1 gene, Acc. No. AC025277) was statistically significantly overrepresented in patients suffering from drug-related kidney- and liver side effects compared to healthy controls ($p=0.044$, Chi^2 test) and was thus predictive for these side effects.

Furthermore, an association of MRP1 genotype with mRNA expression before and after rifampicin application was detected for two MRP1 SNP's, 95T>C (SEQ ID NOs. 209, 210, 211, and 212, nucleotide substitution of T to C at a position corresponding to position 95 of the MRP1 gene, Acc. No. AF022831) and 259A>G (SEQ ID NOs. 277, 278, 279, and 280, nucleotide substitution of A to G at a position corresponding to position 259 of the MRP1 gene, Acc. No. AF022831). These SNPs are linked and form one allele. The mutant allele (MRP1mut, C at position 95 and G at position 259 of the MRP1 gene, Acc. No. AF022831) is statistically significantly correlated with decreased MRP1 mRNA expression and the wildtype allele (MRP1wt, T at position 95 and A at position 259 of the MRP1 gene, Acc. No. AF022831) with increased MRP1 expression in two independent experiments (with and without rifampicin induction), as illustrated in figure 3.

The differences in the MRP1 mRNA content are based on MRP1 genotype-related interindividual differences and the analysis of these SNP's is of high diagnostic and prognostic value for MRP1 expression levels and to predict the therapeutic outcome and adverse effects of MRP1 substrate drugs.

Example 3: Dosage calculation

Therapeutic efficacy ans adverse effects of irinotecan depend on plasma levels and intracellular concentrations of the parent compound and the active metabolites (e.g. SN-38), processes which are controlled by CYP3A5- and UGT1A1-related metabolism and MRP1- and MDR1-related transport processes [Atsumi, *et al.*, 1991, Xenobiotica 21:1159-69, Iyer, *et al.*, 1998, J Clin Invest 101:847-54, Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202, Santos, *et al.*, 2000, Clin Cancer Res 6:2012-20, Kuhn, 1998, Oncology (Huntingt) 12:39-42, Chen, *et al.*, 1999, Mol Pharmacol 55:921-8, Chu, *et al.*, 1997, Cancer Res 57:1934-8, Chu, *et al.*, 1997, J Pharmacol Exp Ther 281:304-14; Chu, *et al.*, 1998, Cancer Res 58:5137-43, Chu, *et al.*, 1999, Drug Metab Dispos 27:440-1, Chu, *et al.*, 1999, J Pharmacol Exp Ther 288:735-41, Mattern, *et al.*, 1993, Oncol Res 5:467-74, Hoki, *et al.*, 1997, Cancer Chemother Pharmacol 40:433-8, Sugiyama, *et al.*, 1998, Cancer Chemother Pharmacol 42:S44-9]. For example, MRP1 works in close connection with glucuronosyltransferases as part of the cellular detoxification system and is known to transport glucuronosyl conjugates such as SN-38G [König

et al., 1999, Biochim Biophys Acta 1461:377-394, Kerb et al., 2001, Pharmacogenomics 2:51-64]. For example, the extend to which SN-38G is exported from the cell into bile greatly influences the rate of its formation. For an efficient detoxification of SN-38 both processes are necessary, conjugation by UGT1A1 and export of the glucuronide.

The 47518T>C (SEQ ID NOs.137, 138, 139, and 140) and 9736A>G (SEQ ID NOs. 149, 150, 151, 152) nucleotide substitutions of the CYP3A5 gene (Acc. No. GI:10281451), and the 145601T>G (SEQ ID NOs. 141, 142, 143, 144) and 145929A>G (SEQ ID NOs. 145, 146, 147, and 148) nucleotide substitutions of the CYP3A5 gene (Acc. No. GI:11177452) form an high CYP3A5 expression-related allele and are therefore associated with a higher metabolic inactivation of irinotecan. Individuals with this allele are extensive metabolizers (EMs) and are therefore in contrast the reminder poor metabolizers (PMs) less likely to suffer from irinotecan toxicity. Those with one high expressor and one low expressor-related allele are regarded as intermediate metabolizers (IMs).

The 176C>T nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MDR1 gene (Accession No: M29445) is associated with low PGP expression-related low drug efflux, and the 95T>C (SEQ ID NOs. 209, 210, 211, and 212) and the 259A>G (SEQ ID NOs. 277, 278, 279, and 280) nucleotide substitutions of the MRP1 gene (Acc. No. AF022831) are associated with low mRNA expression and the 150727G>A nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MRP1 gene (Accession No: M29445) is associated with low PGP expression-related low drug efflux and the 150727G>A nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MRP1 gene (Accession No: AC025277) is associated with adverse effects. Individuals carrying low transporter expression-related alleles are therefore less capable to clear cells from toxic compounds. Both, transport and metabolism are affected in a gene-dose dependant manner. According to the number of low expression-related alleles of the respective transport protein, individuals can be classified as having either extensive (ET), intermediate (IT) or poor transporter capacity (PT) of the respective gene.

By genetic testing prior to onset of treatment with irinotecan, the MDR1- and MRP1-related transport capacity of the patients can be predicted. The individual risk to adverse effects depends on the number of PM and/or PT alleles Individuals with

PM-related alleles of CYP3A5 and UGT1A1 and PT-related alleles of MDR1 and MRP1 are at the highest risk to suffer from irinotecan toxicity.

Based on this knowledge, the initial dose can be adjusted prior to the first dose as shown by Brockmöller et al. (2000, Pharmacogenomics 1:125) for substrate drugs of CYP2D6, CYP2C9, and CYP2C19.

Dose adjustment can be achieved using a scoring system. For each PM- or PT-related allele a certain score is assigned e.g. a score of 2 is assigned to UGT1A1 PM alleles 226A, (SEQ ID NOs 9, 10, 11, 12, 540, 541) and 701A (SEQ ID NOs. 25, 26, 27, 28, 554, 555), and a score of 1 is assigned to the CYP3A5 PM-related alleles (47523T plus 35649A plus 145601T plus 145929A, 47523T plus 35649G plus 145601G plus 145929G, and 47523C plus 35649A plus 145601T plus 145929A), to the MDR1 low expression allele 176T (SEQ ID NOs.: 417, 418, 419, and 420), to the MRP1 low expression alleles 150727A (SEQ ID NOs. 217, 218, 219, and 220) and 259G (SEQ ID NOs. 277, 278, 279, and 280), to the MRP1 150727A allele (SEQ ID NOs. 217, 218, 219, and 220). After genotyping the scores are summarized and irinotecan dosage is adjusted according to the sum. Each single score corresponds to a dose reduction of 10%, i.e. a score of one corresponds to a 10% dose reduction, a score of two to 20%, a score of 3 to 30%, etc.

Example 4: Culture conditions and biological assays

The human epithelial cervical cancer cell line KB 3-1 with two subclones (KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5)) and the bladder cancer cell line RT112, also with subclone (RT112 ($MDR1^{+}$, UGT1A1)), were cultured in Dulbecco's Modified Eagle Medium (DMEM) including 3.7 g/l $NaHCO_3$, 4.5 g/l D-Glucose, 1.028 g/l N-Acetyl-L-Alanyl-L-glutamine and supplemented with 10% fetal bovine, 1 mM Na-pyruvate and 1% non-essential amino acids. The human colon cancer cell line LS174T was cultured in Dulbecco's modified Eagle medium containing L-glutamine, pyridoxine hydrochloride and 25 mM Hepes buffer without phenol red, supplemented with 10% fetal bovine, 1 mM Na-pyruvate and 1% non-essential amino acids. All cells were incubated at 37°C with 5% CO_2 in a humidified atmosphere.

Drugs

Irinotecan (CPT-11) and its active metabolite SN-38 were provided by Pharmacia. For preparation of stock solutions the substances were dissolved in methanol, 10 mg/ml for CPT-11 and 1 mg/ml for SN-38 and stored at 4°C protected from light. Lower concentrated dilutions were prepared in PBS and cell culture medium. R-Verapamil was applied from SIGMA, dissolved in DMSO to 50 mg/ml and further diluted in PBS.

Treatment of cells with drugs

Cells were seeded in 96-well culture plates 24 h prior to treatment. With respect to differential growth rates KB 3-1 and RT112 cells were seeded at 700 cells/well, RT112 ($MDR1^{+}$, UGT1A1) at 1000 cells/well and KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) at 1200 cells/well. LS174T were seeded at 1.0×10^4 cells/well. Cells were treated with freshly prepared serial dilutions in culture medium, 0, 0.5, 1, 2.5, 5, 7.5, 10, 25, 50, 75, 100 and 200 μg/ml for CPT-11, and 0, 0.1, 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 and 200 ng/ml for SN-38. Four well were treated with the same drug dilution. Cells were incubated for 3 days at 37°C in a humidified 5% CO_2 atmosphere.

For MDR1 inhibition experiments R-Verapamil was added to 10 μg/ml final concentration in two wells of each drug dilution.

Cytotoxicity assay

A commercially available MTS assay system (Promega, Madison, USA) was used to determine growth inhibition and cell death according to the instructions of the manufacturer. Three days after adding the drugs, 20 μl of the combined MTS/PMS solution was added to each well of the 96-well culture plate. The plate was incubated for at least 45 min at 37°C in a humidified 5% CO_2 atmosphere and the absorbance at 492 nm was measured. The absorbance values of untreated control cells on each plate were set as 100% growth and used to calculate the remaining growth of drug treated cells. Untreated cells on the culture plates served as controls for unaffected growth and survival.

The drug concentration effecting a 50% inhibition of cell growth was defined as the IC_{50}.

RNA preparation and cDNA synthesis

From each cell batch used in these experiments messenger RNA was isolated from cell lysates by oligo-dT magnet beads (μMACS mRNA Isolation Kit; Miltenyi Biotech) following the instructions of the manufacturer. 250 ng mRNA of each cell line was applied in a 20 μl cDNA synthesis reaction with Superscript II reverse transcriptase (Gibco BRL). Dilutions of this cDNAs served as template in transcript specific amplification reactions.

PCR primers and reaction conditions

PCRs were set up in 25 μl reactions with 0.5 units Taq Polymerase (Qiagen), 200 μM nucleotide mix, 5 μl cDNA template dilution and 0.2 μM gene specific primers, as indicated in Table 5. All reactions were run under the same amplification conditions, differing only in number of cycles (table), 2 min pre-denaturation at 94°C, than for amplification: 45 sec denaturation at 94°C, 45 sec annealing at 62°C and 45 sec elongation at 72°C, except for UGT1A1 which needed longer elongation of 2 min.

Table 5: Sequences of gene specific primers and conditions for PCR reactions. F: forward primer; R: reverse primer for mRNA sequences.

Gene	Primer sequence (5'-3')	cDNA dilution	cycle number
MDR1	F: TGCCTTCATCGAGTCACTGCC R: TCACTGGCGCTTTGTTCCAGC	1:100	26
MRP1	F: TCTCCAAGGAGCTGGACACA R: CGTGGTGACCTGCAATGAGT	1:10	30
UGT1A	F: GATGATGCCCTTGTTTGGTG	1:100	30

	R: TGTTTTCAAGTTTGGAAATGACTAGGG		
UGT1A1	F: AACCTCTGGCAGGAGCAAAGG R: TGTTTTCAAGTTTGGAAATGACTAGGG	1:10	34
CYP3A4	F: TCAGCCTGGTGCTCCTCTATCTAT R: AAGCCCTTATGGTAGGACAAAATATTT	1:10	34
CYP3A5	F: TTGTTGGGAAATGTTTTGTCCTATC R: ACAGGGAGTTGACCTTCATACGTT	1:10	34
PLA2 (house keeping gene)	F: GCTGGTTCAGAAGGCCAAAC R: GGGCCAGACCCAGTCTGATA	1:100	26

Example 5: Expression of genes involved in irinotecan metabolism

Messenger RNA was isolated from the human bladder cancer cell line RT112, its subclone RT112 (MDR1, UGT1A1), the human epithelial cervical cancer cell line KB 3-1 and two subclones KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5), and the colon carcinoma cell line LS174T (ATCC CL-188). These mRNAs were reverse transcribed into cDNA and applied as templates in transcript-specific amplification reactions to determine the expression levels of genes involved in irinotecan transport and metabolism (MDR1, MRP1, UGT1A, UGT1A1, CYP3A4, CYP3A5). Amplification of the house keeping gene phospholipase A2 (PLA2) was used as a control for comparable cDNA amounts in the reactions.

The amplification reactions in figure 29 show that the carcinoma cell lines RT112, KB 3-1, and LS174T have no or very low expression of MDR1, respectively. RT112 (MDR1, UGT1A1) is a subclone of RT112, which was selected for resistance to cytotoxic drugs as described in Seemann et al. (Urol Res 1995; 22:353-360), and is characterised by a moderately increased MDR1 expression. The drug resistant subclones KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) were derived similarly from the original KB 3-1 cell line by exposure to MDR1 substrates. These subclones are characterized by highly increased MDR1 expression. They show >20-times more transcripts than the original KB 3-1 cells, implicating a very high

MDR1 activity. MRP1 is expressed at the same level in all cell lines. Transcripts of UGT1A enzymes are present only in RT112, RT112 (MDR1, UGT1A1), and LS174T cells. UGT1A1 is only weakly expressed in RT112, stronger expressed in RT112 (MDR1, UGT1A1) and shows highest expression in LS174T cells. CYP3A4 was solely detected in very small amounts in LS174T. RT112 cells, RT112 (MDR1, UGT1A1), and LS174T show a heterozygous expression of the functionally inactive splice variant and the functionally active transcript of CYP3A5. In contrast, KB 3-1 and KB 3-1 ($MDR1^{+++}$) cells have only the active CYP3A5 transcript and the KB 3-1 ($MDR1^{+++}$, CYP3A5) showed the highest expression of the active CYP3A5 transcript, implicating that the latter have the highest CYP3A5 activity.

Example 6: Colon and other epidermal cancer cell lines with no or low MDR1 and CYP3A5 activity are sensitive to CPT-11 and SN-38.

The colon cancer cell line LS174T, the cervical cancer cell line KB 3-1 and the bladder cancer cell line RT112 were seeded in 96-well culture plates 24 h prior to treatment. Four wells of each cell line were incubated with serial dilutions of CPT-11 and SN-38 and analysed as described above. Figure 30 shows that all three epidermal cancer cell lines stop proliferation and die upon treatment with CPT-11 and SN-38. The concentrations resulting in 50% inhibition (IC_{50}) for CPT-11 are 1.5 μg/ml for LS174T, 2.5 μg/ml for RT112 and 5 μg/ml for KB 3-1 cells. The active metabolite of CPT-11, SN-38 shows a 1000-fold higher efficacy than CPT-11, since 10^3-times lower concentrations cause the same degree of growth inhibition and cell death. The IC_{50} of SN-38 is 5 ng/ml for LS174T cells, 4 ng/ml for RT112 cells and 25 ng/ml for KB 3-1 cells.

These results show that all three epidermal cancer cell lines although derived from different tissues are similarly sensitive to CPT-11 and SN-38 treatment. This also indicates that cancer cells expressing no or only low levels of MDR1 (Figure 29) can be efficiently killed by CPT-11 and SN-38 (Figure 30).

Example 7: MDR1 activity correlates with resistance of cancer cells toward CPT-11 and SN-38

Cells of KB 3-1 and its strongly MDR1 expressing subclones KB 3-1 ($MDR1^{+++}$) and the KB 3-1 ($MDR1^{+++}$, CYP3A5) were seeded in 96-well culture 24 h prior to treatment. Four wells of each cell line were incubated with serial dilutions of CPT-11 and SN-38 and treated as described above. The inhibition curves (Figure 31) of the MDR1 high expresser KB 3-1 subclones (KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5)) (Figure 29) demonstrate a significant higher resistance to CPT-11 and SN-38 compared to the MDR1 low expresser KB 3-1 cell line (KB 3-1). The IC_{50} for CPT-11 increases 17 to 40 fold from 5 μg/ml in KB 3-1 to 85 μg/ml in KB 3-1 ($MDR1^{+++}$) and 200 μg/ml in KB 3-1 ($MDR1^{+++}$, CYP3A5) cells. The IC_{50} for SN-38 increases at least 8 times from 25 ng/ml in KB 3-1 to 200 ng/ml in KB 3-1 ($MDR1^{+++}$) and >200 ng/ml in KB 3-1($MDR1^{+++}$, CYP3A5).

CPT-11 and SN-38 are substrates of MDR1, and are therefore removed from the cells by MDR1 activity. The MDR1 expression level correlates inversely with the sensitivity of tumor cells towards CPT-11 and SN-38. Subsequently, the killing of cells with high MDR1 expresser phenotype requires much higher concentrations of CPT-11.

Example 8: UGT1A1 activity correlates with sensitivity towards SN-38 and not towards CPT-11

CPT-11 and SN-38 sensitivity was compared between RT112 cells and its subclone RT112 (MDR1, UGT1A1). Four wells of each cell line were incubated with serial dilutions of CPT-11 and SN-38 and treated as described above.
The difference in sensitivity against CPT-11 is only small as shown in Figure 32A. The IC_{50} of RT112(MDR1, UGT1A1) cells of 4 μg/ml CPT-11 is two-times higher compared to RT112 cells (IC_{50} of 2.5 μg/ml). In contrast to RT112 cells which express no MDR1, RT112 MDR1, UGT1A1) cells express an intermediate amount of MDR1 which can explain the small though significant increase of CPT-11

sensitivity. A much stronger difference exists between RT112 (IC_{50} of 4 ng/ml) and RT112 (MDR1, UGT1A1) cells (IC_{50} of 75 ng/ml) after treatment with SN-38 (Figure 32B). This 19-fold higher resistance of the RT112 (MDR1, UGT1A1) cell line can be explained by the additional detoxifying effect of UGT1A1 which is expressed at a higher level in RT112 (MDR1, UGT1A1) than in RT112 cells (Figure 29). In contrast to SN-38, CPT-11 is not metabolized by UGTs. Therefore, CPT-11-related toxicity is not affected by UGT1A1 expression and the resistance-enhancing capabilitiy of UGTs in RT112(MDR1, UGT1A1) cells is only detected by application of SN-38.

Example 9: MDR1 inhibition serves as sensitizer towards CPT-11 and SN-38 in MDR1 high expressing but not low expressing cancer cells.

The sensitivity of KB 3-1 cells and its subclones KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) against CPT-11 and SN-38 was assessed after blocking MDR1 function using the specific inhibitor R-Verapamil. Four wells of each cell line were incubated with serial dilutions of CPT-11, SN-38 and analysed as described above. Two wells were additionally treated with the MDR1 inhibitor R-Verapamil. Figure 33 shows that addition of R-Verapamil has only marginal effects on the CPT-11 and SN-38 sensitivity of MDR1 low expresser KB 3-1 cells (CPT-11 and SN-38 IC50s of 5 μg/ml and 25 ng/ml without R-Verapamil versus 4.5 μg/ml and 15 ng/m with R-Verapamil, respectively). In contrast, the sensitivity of the MDR1 expressing cells KB 3-1($MDR1^{+++}$) and KB 3-1($MDR1^{+++}$, CYP3A5) towards CPT-11 and SN-38 was 8-fold and 10-fold higher after inhibition of MDR1 transport function with R-Verapamil. The IC_{50} of KB 3-1($MDR1^{+++}$) cells for CPT-11 decreased from 85 μg/ml without to 10 μg/ml with R-Verapamil and from 200 μg/ml without to 25 μg/ml with R-Verapamil in KB 3-1 ($MDR1^{+++}$, CYP3A5) cells. The effect of MDR1 inhibition during SN-38 treatment is even stronger in these MDR1 high expresser cells, R-Verapamil blocked the MDR1 transport completely and they become as sensitive as KB 3-1 cells.

These results demonstrate that the MDR1 activity is relevant for resistance of cancer cells to CPT-11 and SN-38 and that inhibition of MDR1 sensitises the cells, so that they are more efficiently killed at lower drug concentrations.

Example 10: CYP3A5 activity influences resistance to CPT-11

KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) cells which differ by their amounts of CYP3A5 (Figure 29). Four wells of each cell line were incubated with serial dilutions of CPT-11, SN-38 and analyzed as described above. Two wells were additionally treated with the MDR1 inhibitor R-Verapamil.

Because MDR1 activity is a major determinant of cellular sensitivity toward CPT11 and SN-38, the MDR1 activity in these MDR1 high expresser cell lines was completely blocked using an excess of the specific MDR1 inhibitor R-Verapamil to analyze the impact of CYP3A5 on CPT-11 and SN-38 sensitivity without interference of MDR1.

The high CYP3A5 expresser cell line KB 3-1 ($MDR1^{+++}$, CYP3A5) is with an IC_{50} of 25 μg/ml 2.5-times more resistant to CPT-11 than KB 3-1 ($MDR1^{+++}$) showing an IC_{50} of 10 μg/ml (Figure 34). No difference between these two cell lines can be observed regarding their sensitivity towards SN-38.

These experiments demonstrate a significant impact of CYP3A5 expression on the resistance to CPT-11 in contrast to SN-38. The fact that CYP3A5 activity had no influence on SN-38 toxicity further confirms the CYP3A5 effect, because CPT-11 but not SN-38 is metabolized by CYP3A5.

Example 11: MDR1 genotyping improves therapeutic efficacy of irinotecan by genotype-based prediction and monitoring of drug resistance.

Therapeutic efficacy and adverse effects of irinotecan depend on plasma levels and on intracellular tumor concentrations of the parent compound and the active metabolites (e.g. SN-38). The MDR1 gene controls the PGP-dependent penetration of irinotecan across membranes [Luo et al., Drug Metab Dispos 2002, 30:763-770; Jansen et al., Br J Cancer 1998, 77:359-65 Chu et al., J Pharmacol Exp Ther 1999; 288, 735-41; Sugiyama et al., Cancer Chemother Pharmacol 1998, 42 Suppl:S44-9] and is therefore an important determinant for its systemic availability and intracellular accumulation. The 176C>T nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MDR1 gene (Accession No: M29445) is associated with low PGP expression-related low drug efflux and patient carrying this substitution are

more likely to respond to irinotecan treatment for two reasons: 1) Due to the lower amount of PGP in enterocytes more irinotecan can enter the body across the intestinal barrier causing more irinotecan to reach its site of action, the tumor. 2) Due to the lower amount of PGP in the tumor cell membranes more irinotecan can penetrate into the tumor cells to deploy its cytotoxic effects. The currently used standard dose of irinotecan kills highly effective most tumor cells within the first cycles of chemotherapy with only very few surviving drug-resistant tumor cells and tolerable adverse events. Independently from the mechanisms of drug resistance, in these patients, the number of surviving cells is to small to develop into a drug-resistant tumor which does not respond any longer to irinotecan therapy.

Patients with the high expresser MDR1 genotype (nucleotide C at position 176 of the MDR1 gene, Accession No: M29445) are less likely to respond to irinotecan treatment. Higher doses would be necessary to achieve a sufficiently efficient killing of tumor cells in order to prevent the development of a drug-resistant tumor. However, elevation of irinotecan dosage is limited due to the occurrence of intolerable adverse events (e.g. diarrhea, neutropenia, or thromboembolic complications). Alternatively, efficacy of irinotecan treatment can be improved by addition of a PGP inhibitor. A PGP inhibitor blocks efficiently the PGP function in MDR1 high expresser patients in such a way as to enable irinotecan to concentrate in the tumor cells for exerting its cytotoxicity as effective as in MDR1 low expresser patients. Consequently, genotypically MDR1 high expresser patients become phenotypically comparable to MDR1 low expressers.

According to the number of low or high expresser alleles of the MDR1 gene, individuals can be classified as having either extensive (ET, two high expresser alleles), intermediate (IT, one high expresser, one low expresser allele) or poor transport capacity (PT, two low expresser alleles). By genetic testing prior to onset of treatment with irinotecan, patients can be classified as ET, IT, or PT and the MDR1-related transport capacity of the patients can be predicted. The individual risk of an insufficient anticancer treatment increases with the number of MDR1 high expresser alleles. Individuals with ET genotype are at the highest risk to suffer from insufficient response to irinotecan and are at the highest risk to develop a drug resistant tumor. ET patients should be treated with a PGP-inhibitor in addition to irinotecan and more closely monitored for adverse events and for the development of chemotherapy-related drug-resistance. Furthermore, these patients, who are at

high risk for developing a drug-resistant tumor, can particularly benefit from taking a tumor biopsy between each cycle of chemotherapy with subsequent individual profiling of tumor cells for drug resistance.

Claims

1. Use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genome with a first variant allele which comprises a polynucleotide selected from the group consisting of:

   (a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422, 425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482, 485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 and/or 641;

   (b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 606, 608, 610, 612, 618, 620, 622, 624, and/or 628;

   (c) a polynucleotide capable of hybridizing to a Multidrug Resistance 1 (MDR1) gene, wherein said polynucleotide is having at a position corresponding to positions 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619 of the MDR1 gene (Accession No: AC002457) and/or 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162 of the MDR1 gene (Accession No: AC005068) and/or 101, 308 of the MDR1 gene (Accession No: M29432) and/or 137, 176 of the MDR1 gene (Accession No: M29445), a substitution or deletion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having at a position corresponding to position 83946, 70200, 70237, 65241 of the MDR1 gene (Accession No: AC005068) and/or 101 of the MDR1 gene (Accession No: M29432) and/or 141529, 174901, 139177, 140118, 140568, 140727, 139479 of the MDR1 gene (Accession No: AC002457) an A, at a position corresponding to position 308 of the MDR1 gene (Accession No: M29432) and/or 84701, 83973, 84074, 84119, 78170, 70204, 70253, 70371, 50537, 43162 of the MDR1 gene (Accession No: AC005068) and/or 137 or 176 of the MDR1 gene (Accession No: M29445) and/or 145984, 171466, 175068, 175074, 139064, 139276, 140576 of the MDR1 gene (Accession No: AC002457) a T, at a position corresponding to position 140837, 171404, 171456, 171511, 171512, 139119, 140490, 139619 of the MDR1 gene (Accession No: AC002457) and/or 43263 of the MDR1 gene (Accession No: AC005068) a C, at a position corresponding to position 84032, 77811, 73252 of the MDR1 gene (Accession No: AC005068) and/or 141590, 175142, 175180, 139015, 140216, 140595 of the MDR1 gene (Accession No: AC002457) a G;

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to positions 21, 103, 168, 400, 893, 999, 1001, 1107, and/or 1141 of the MDR1 polypeptide (Accession No: G2506118);

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a

position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118).

2. The use of claim 1, wherein said subject having a genome with a second variant allele comprising a polynuncleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 and/or 334;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 600, 602 and/or 604;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance Protein 1 (MRP1) gene, wherein said polynucleotide is having at a position corresponding to positions 57998, 57853, 53282, and/or 39508 of the MRP1 gene (Accession No: GI:7209451), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 137667, 137647, 137710, 124667, and/or 38646 of the MRP1 gene (Accession No: AC026452), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 27258, 27159, 34218, 34215, 55472, and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 21133, 14008, 18067, 17970, and/or 17900 of the MRP1 gene (Accession No: U91318), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 79, 88, and/or 249 of the MRP1 gene (Accession No:

AF022830), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 95 and/or 259 of the MRP1 gene (Accession No: AF022831), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277), a substitution or deletion of at least one nucleotide or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 248 and/or 258 of the MRP1 gene (Accession No: AF022829), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 1884, 1625, 1163, 381, 233, 189, 440, and/or 1720 to 1723 of the MRP1 gene (Accession No: U07050), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 926/927 and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of at least one nucleotide or at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having at a position corresponding to position 21133, 14008 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 27258 and/or 34218 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 79 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 57998, and/or 57853 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137667 and/or 137647 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277) or at a position corresponding to position 248 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 1884, 1625, 233, and/or 189 of the MRP1 gene (Accession No: U07050) an A, at a position corresponding to position 39508 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 17900, 18067 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to

position 174 of the MRP1 gene (Accession No: AF022828) or at a position corresponding to position 440 and/or 1163 of the MRP1 gene (Accession No: U07050) a T, at a position corresponding to position 88 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 27159, 55472 and/or 34215 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 124667 and/or 38646 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137710 of the MRP1 gene (Accession No: AC026452) a C, at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 258 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 259 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 381 of the MRP1 gene (Accession No: U07050) a G, at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) a deletion of a T or at a position corresponding to position 34206 to 34207 of the MRP1 gene (Accession No: AC003026) a deletion of a AT or at a position corresponding to position 1720 to 1723 of the MRP1 gene (Accession No: U07050) a deletion of GGTA, at a position corresponding to position 926/927 a insertion of a T and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of a TCCTTCC, at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of TGGGGC;

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 239 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Ser at a position corresponding to position 433 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Gln at a position corresponding to position 723 of the MRP1 polypeptide (Accession No: G2828206).

3. The use of claim 1 or 2, wherein said subject having a genome with a third variant allele comprising a polynuncleotide selected from the group consisting of:

   (a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 137, 138, 141, 142, 145, 146, 149 and/or 150;

   (b) a polynucleotide capable of hybridizing to a Cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 5 (CYP3A5) gene, wherein said polynucleotide is having at a position corresponding to positions 47518 and/or 9736 of the CYP3A5 gene (Accession No: GI:10281451), a substitution of at least one nucleotide or at a position corresponding to positions 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452), a substitution of at least one nucleotide;

   (c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) a C, at a position corresponding to position 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452) a G or at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451) a G.

4. The use of any one of claims 1 to 3, wherein said subject having a genome with a fourth variant allele comprising a polynuncleotide selected from the group consisting of:

   (a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 and/or 134;

   (b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 and/or 598;

(a) a polynucleotide capable of hybridizing to a Uridine Diphosphate Glycosyltransferase1 Member A1 (UGT1A1) gene, wherein said polynucleotide is having at a position corresponding to positions 59, 160, 226, 539, 544, 640, 701, 841, 855, 890, 938, 1006, 1007, 1020, 1084, 1085, 1114, 1117, 1139, 1158, 1175 to 1176, 1216, 1297, 1324, 1471, 1478, 372 to 373, 523 to 525, and/or 892 to 905 of the UGT1A1 gene (Accession No. GI:8850235), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 470/471, and/or 1222/1223 of the UGT1A1 gene (Accession No. GI:8850235) a insertion of at least one nucleotide;

(b) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having at a position corresponding to position 226, 539, 701, 855, 938, 1020, and/or 1117 of the UGT1A1 gene (Accession No: GI:8850235) an A, at a position corresponding to position 160, 640, 890, 1006, 1084, 1139, 1176, 1324, and/or 1478 of the UGT1A1 gene (Accession No: GI: 8850235) a T, at a position corresponding to position 544, 841, and/or 1216 of the UGT1A1 gene (Accession No: GI: 8850235) a C, at a position corresponding to position 59, 1007, 1085, 1114, 1158, 1175, 1297, and/or 1471 of the UGT1A1 gene (Accession No: GI:181303) a G, and/or at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TTC, at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TACATTAATGCTTC, at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a T, and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a G;

(c) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Leu to Arg at a position corresponding to position 15 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position

corresponding to position 71 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Leu to Gln at a position corresponding to position 175 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Cys to Arg at a position corresponding to position 177 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Trp at a position corresponding to position 209 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Gln at a position corresponding to position 229 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 276 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Val at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Trp at a position corresponding to position 293 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Glu at a position corresponding to position 308 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 331 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 357 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Gly at a position corresponding to position 367 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Thr at a position corresponding to position 368 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Arg at a position corresponding to position 387 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 375 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Arg at a position corresponding to position 381 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Pro at a position corresponding to position 401 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Lys to Glu at a position corresponding to position 428 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 488 of the UGT1A1 polypeptide (Accession No: G8850236);

(d) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide is having at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, whereby in said polypeptide one or more amino acids following amino acid Asp at a position corresponding to position 119 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a T, whereby in said polypeptide one or more amino acids following amino acid Pro at a position corresponding to position 152 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TTC, whereby in said polypeptide one or more amino acids following amino acid Thr at a position corresponding to position 168 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TACATTAATGCTTC, whereby in said polypeptide one or more amino acids following amino acid Ala at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a G, whereby in said polypeptide one or more amino acids following amino acid Lys at a position corresponding to position 402 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted; and

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide comprises an amino acid substitution of Gln to a stop codon at a position corresponding to position 49 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Cys to a stop codon at a position corresponding to position 280 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position

331 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Trp to a stop codon at a position corresponding to position 335 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 357 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Lys to a stop codon at a position corresponding to position 437 of the UGT1A1 gene (Accession No: G8850236).

5. The use of any one of claims 1 to 4, wherein a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first, second, third and/or fourth variant allele compared to the corresponding wild type alleles.

6. The use of claim 5, wherein said altered expression is decreased or increased expression.

7. The use of any one of claims 1 to 7, wherein a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered activity of the polypeptide encoded by the first, second, third and/or variant allele compared to the polypeptide encoded by the corresponding wild type allele.

8. The use of claim 6, wherein said altered activity is decreased or increased activity.

9. The use of any one of claims 1 to 8, wherein said subject is an animal.

10. The use of any one of claims 9, wherein said subject is a mouse.

11. The use of any one of claims 1 to 8, wherein said subject is a human.

12. The use of claim 11, wherein said human is African or Asian.

13. A method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer, wherein said method comprises:

(a) determining the presence or absence of a first, second, third and/or fourth, variant allele as specified in any one of claims 1 to 4 in the genome of a subject in a sample obtained from said subject; and

(b) selecting a suitable therapy for said subject based on the results obtained in (a).

14. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) assaying the genotype of the patient to determine if the patient has one or more variant alleles of each of two or more genes, wherein the two or more genes comprise genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene; and

(b) in a patient having such variant alleles of the two or more genes, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the two or more of the genes.

15. A method for determining whether a patient is at risk for a toxic reaction to treatment with irinotecan which comprises determining if the patient has one or more variant alleles of two or more genes, wherein the genes comprise an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene.

16. A method for determining the optimum treatment regimen for administering irinotecan to a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;

(b) in a patient having one or more such alleles of each of the two or more genes, altering the regimen to reduce peak amounts of irinotecan in the patient in comparison to the peak amount in the patient when irinotecan is administered without regard to the patient's alleles in the two or more genes.

17. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two or more genes are lower than in the general population and so indicates high sensitivity to irinotecan, the method comprises administering to the patient a decreased amount of irinotecan.

18. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two or more genes are higher than in the general population and so indicates resistance or predisposition to resistance to irinotecan, the method comprises administering to the patient an increased amount of irinotecan.

19. A method of treating cancer in a patient which comprises internally administering to the patient an effective amount of irinotecan, wherein the treatment regimen is modified based upon the patient's genotype of genes comprising MDR1, MRP1, CYP3A5, and UGT1A1.

20. A method of treating a population of patients suffering from cancer which comprises:

(a) determining, on a patient by patient basis, if the patient has one or more variant alleles of each of two or more genes comprising an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;
(b) in a patient having one or more of such variant alleles of the two or more genes, administering to the patient an amount of irinotecan which is

sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount without regard to the patient's alleles of the two or more genes.

21. A method for predicting sensitivity to irinotecan in a patient suffering from cancer which comprises determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, which alleles indicate that the cancerous cells express low or high amounts of the proteins of the two or more genes, whereby low expression indicates high sensitivity to irinotecan and high expression indicates resistance or predisposition to resistance to irinotecan.

22. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MDR1 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MDR1 gene.

23. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MRP1 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MRP1 gene.

24. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the UGT1A1 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the UGT1A1 gene.

25. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the CYP3A5 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the CYP3A5 gene.

Figure 1

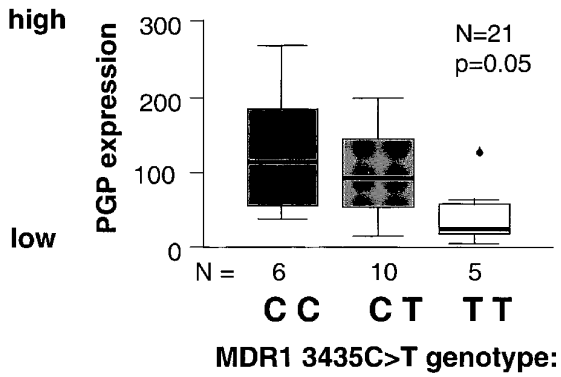
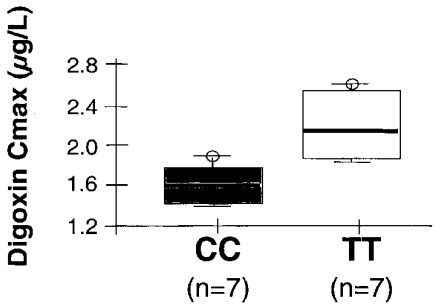

high
low
PGP expression
300
200
100
0
N=21
p=0.05
N = 6 10 5
C C C T T T
MDR1 3435C>T genotype:

Figure 2


Digoxin Cmax (µg/L)
2.8
2.4
2.0
1.6
1.2
CC
(n=7)
TT
(n=7)
MDR1 3435C>T genotype:

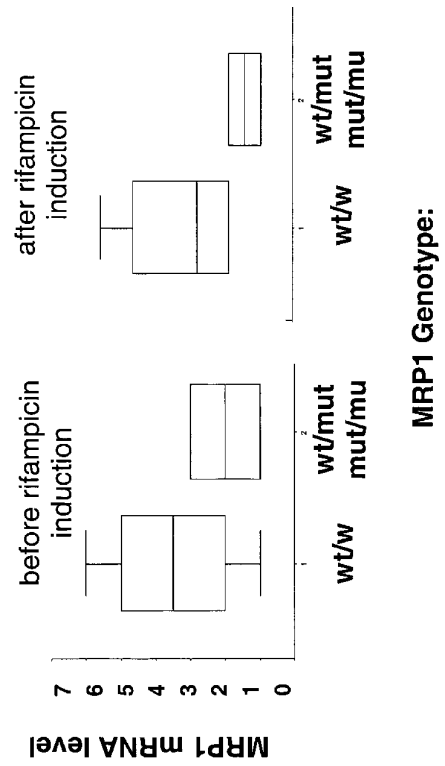

MRP1 mRNA level
7
6
5
4
3
2
1
0
before rifampicin induction
after rifampicin induction
wt/w
wt/mut
mut/mu
MRP1 Genotype:

Figure 3

Figure 29

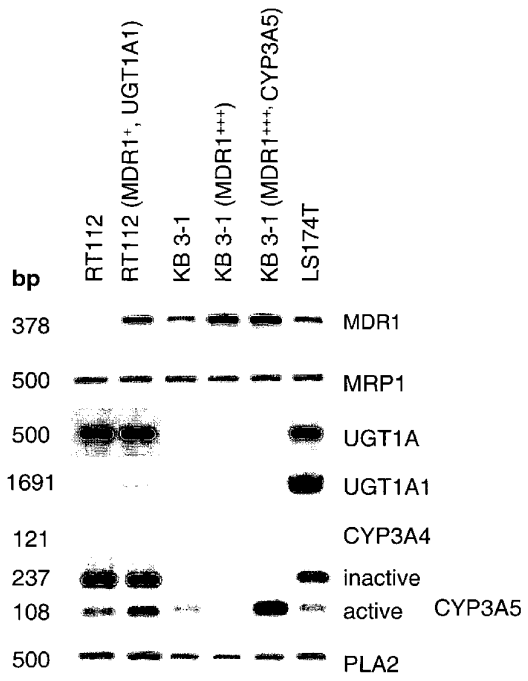
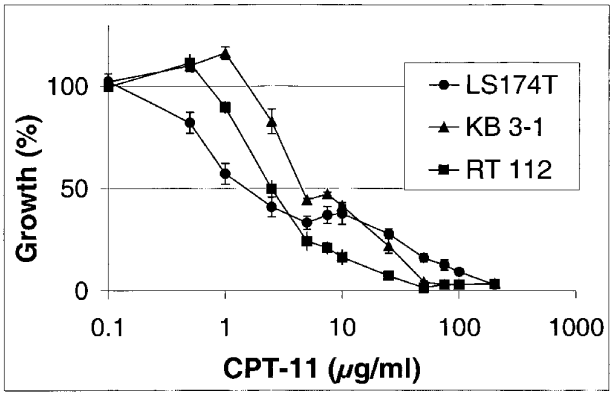

RT112
RT112 (MDR1+, UGT1A1)
KB 3-1
KB 3-1 (MDR1+++)
KB 3-1 (MDR1+++, CYP3A5)
LS174T
bp
378
MDR1
500
MRP1
500
UGT1A
1691
UGT1A1
121
CYP3A4
237
inactive
108
active
CYP3A5
500
PLA2

Figure 30


100
50
0
Growth (%)
0.1
1
10
100
1000
CPT-11 (μg/ml)
LS174T
KB 3-1
RT 112

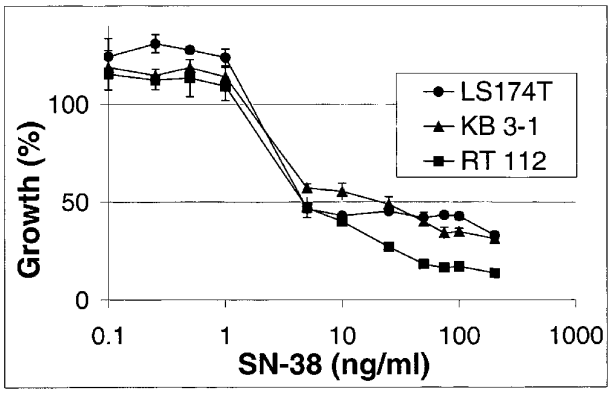
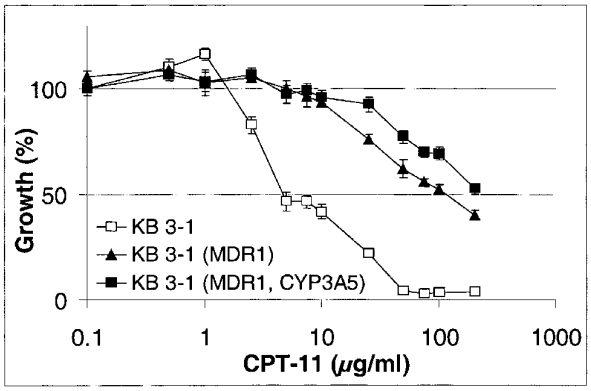

100
50
0
Growth (%)
0.1
1
10
100
1000
SN-38 (ng/ml)
LS174T
KB 3-1
RT 112

Figure 31


100
50
0
Growth (%)
KB 3-1
KB 3-1 (MDR1)
KB 3-1 (MDR1, CYP3A5)
0.1
1
10
100
1000
CPT-11 (μg/ml)

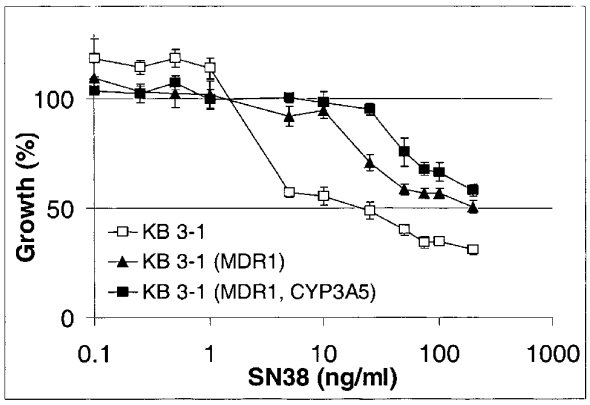

100
50
0
Growth (%)
KB 3-1
KB 3-1 (MDR1)
KB 3-1 (MDR1, CYP3A5)
0.1
1
10
100
1000
SN38 (ng/ml)

Figure 32

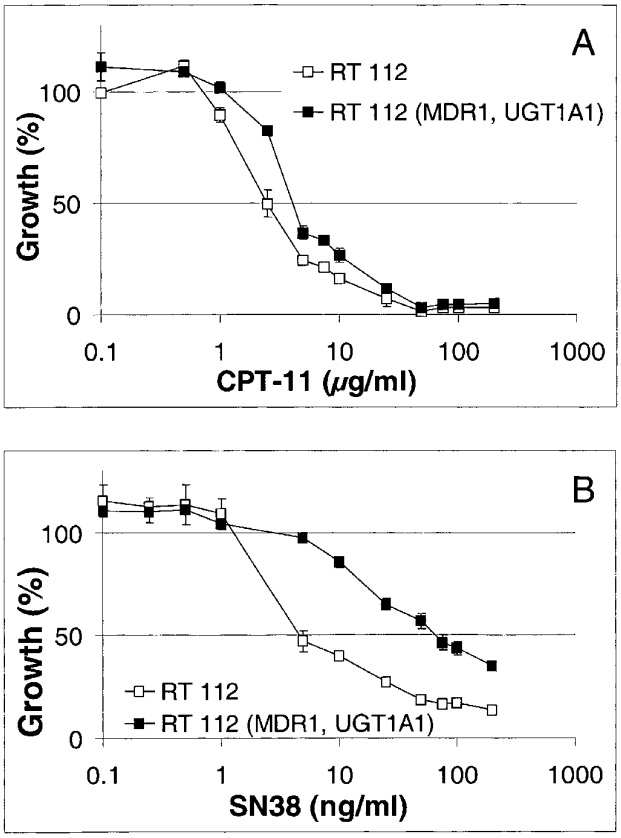
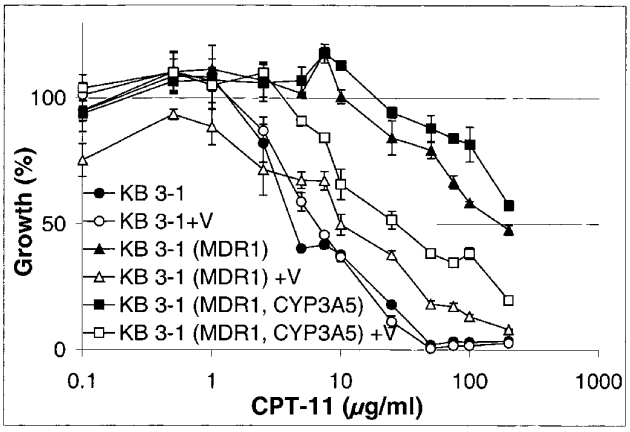

A
RT 112
RT 112 (MDR1, UGT1A1)
Growth (%)
100
50
0
0.1
1
10
100
1000
CPT-11 (μg/ml)
B
Growth (%)
100
50
0
RT 112
RT 112 (MDR1, UGT1A1)
0.1
1
10
100
1000
SN38 (ng/ml)

Figure 33


100
50
0
Growth (%)
KB 3-1
KB 3-1+V
KB 3-1 (MDR1)
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5)
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
CPT-11 (μg/ml)

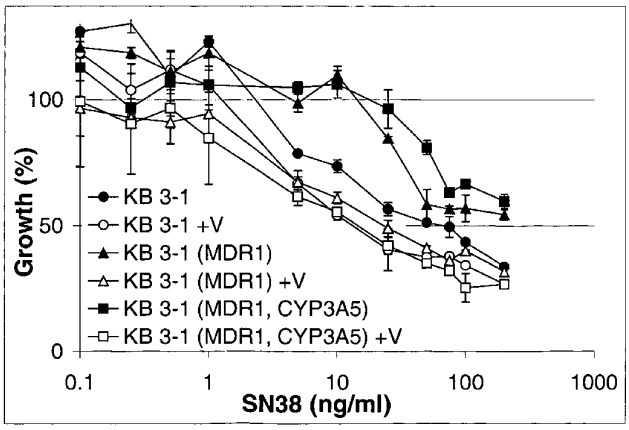
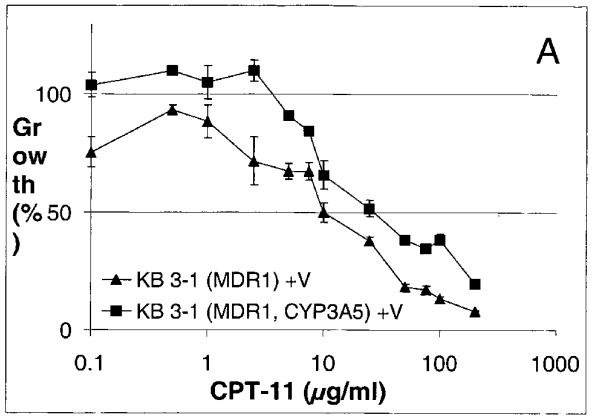
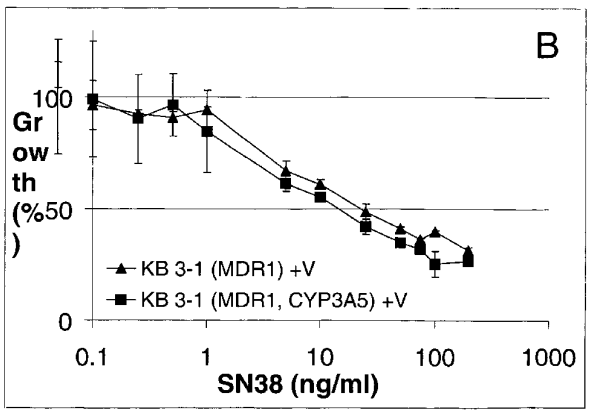

100
50
0
Growth (%)
KB 3-1
KB 3-1 +V
KB 3-1 (MDR1)
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5)
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
SN38 (ng/ml)

Figure 34


A
100
Gr
ow
th
(%
)
50
0
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
CPT-11 (μg/ml)


B
100
Gr
ow
th
(%50
)
0
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
SN38 (ng/ml)

【国際公開パンフレット（コレクトバージョン）】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number
WO 03/013537 A3

(51) International Patent Classification⁷: A61K 31/4745, A61P 35/00

(21) International Application Number: PCT/EP02/08218

(22) International Filing Date: 23 July 2002 (23.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01117608.8 23 July 2001 (23.07.2001) EP
02011710.7 24 May 2002 (24.05.2002) EP

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report

(88) Date of publication of the international search report:
25 September 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/013537 A3

(54) Title: IRINOTECAN FOR TREATMENT OF CANCER

(57) Abstract: The present invention relates to the use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a patient having a genotype with a first, a second, a third, and/or a fourth variant allele which comprises a polynucleotide in accordance with the present invention. Preferably, a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of a first, a second, a third and/or a fourth variant allele compared to the corresponding wild type allele or an altered activity of the polypeptide encoded by the variant allele compared to the polypeptide encoded by the corresponding wild type allele. Finally, the present invention relates to a method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer.

【国際公開パンフレット（コレクトバージョン）】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2003 (20.02.2003)

PCT

(10) International Publication Number
WO 2003/013537 A3

(51) International Patent Classification[7]: A61K 31/4745, A61P 35/00

(21) International Application Number: PCT/EP2002/008218

(22) International Filing Date: 23 July 2002 (23.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01117608.8 23 July 2001 (23.07.2001) EP
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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

(88) Date of publication of the international search report: 25 September 2003

(48) Date of publication of this corrected version: 29 April 2004

(15) Information about Correction: see PCT Gazette No. 18/2004 of 29 April 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2003/013537 A3

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(57) Abstract: The present invention relates to the use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a patient having a genotype with a first, a second, a third, and/or a fourth variant allele which comprises a polynucleotide in accordance with the present invention. Preferably, a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of a first, a second, a third and/or a fourth variant allele compared to the corresponding wild type allele or an altered activity of the polypeptide encoded by the variant allele compared to the polypeptide encoded by the corresponding wild type allele. Finally, the present invention relates to a method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer.

IRINOTECAN FOR TREATMENT OF CANCER

The present invention relates to the use of camptothecin drugs, such as irinotecan (CPT-11) or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a patient having a genotype with a first, a second, a third, and/or a fourth variant allele which comprises a polynucleotide in accordance with the present invention. Preferably, a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first, second, third, and/or fourth variant allele compared to the corresponding wild type allele or an altered activity of the polypeptide encoded by the variant allele compared to the polypeptide encoded by the corresponding wild type allele. Finally, the present invention relates to a method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer or pancreatic cancer.

Irinotecan is a semisynthetic analog of the cytotoxic alkaloid camptothecin (CPT), which is obtained from the oriental tree, Camptotheca acuminata Camptothecins demonstrate anti-neoplastic activities by inhibiting specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks [D'Arpa, *et al.*, 1989, Biochim Biophys Acta 989:163-77, Horwitz, *et al.*, 1973, Cancer Res 33:2834-6]. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks [Kawato, *et al.*, 1991, Cancer Res 51:4187-91]. Irinotecan serves as a water-soluble prodrug of the lipophilic metabolite SN-38 (7-ethyl-10-hydroxycamptothecin) which is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and

the dipiperidino side chain [Tsuji, *et al.*, 1991, J Pharmacobiodyn 14:341-9]. Carboxylesterase-2 is the primary enzyme involved in this hydrolysis at at pharmacological concentrations [Humerickhouse, *et al.*, 2000, Cancer Res 60:1189-92]. Topoisomerase inhibition and irinotecan-related single strand breaks are caused primarily by SN-38 [Kawato, *et al.*, 1991, Cancer Res 51:4187-91]. Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types [Furuta, *et al.*, 1988, Gan To Kagaku Ryoho 15:2757-60, Giovanella, *et al.*, 1989, Science 246:1046-8, Giovanella, *et al.*, 1991, Cancer Res 51:3052-5, Hawkins, 1992, Oncology (Huntingt) 6:17-23, Kunimoto, *et al.*, 1987, Cancer Res 47:5944-7].

Irinotecan is also oxidized by CYP3A4 and CYP3A5 [Haaz, *et al.*, 1998, Drug Metab Dispos 26:769-74, Kuhn, 1998, Oncology (Huntingt) 12:39-42, Santos, *et al.*, 2000, Clin Cancer Res 6:2012-20, Rivory, *et al.*, 1996, Cancer Res 56:3689-94]. The major elimination pathway of SN-38 is conjugation with glucuronic acid to form the corresponding glucuronide (SN-38G) [Atsumi, *et al.*, 1991, Xenobiotica 21:1159-69.]. SN-38G is reported to be deconjugated by the intestinal microflora to form SN-38 [Kaneda, *et al.*, 1990, Cancer Res 50:1715-20]. Glucuronidation of SN-38 is mediated by UGT1A1 and UGT1A7 [Lyer, *et al.*, 1998, J Clin Invest 101:847-54, Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202]. Mass balance studies have demonstrated that 64% of the total dose is excreted in the feces, confirming the important role of biliary excretion [Slatter, *et al.*, 2000, Drug Metab Dispos 28:423-33]. Studies suggest that the multidrug rsistance protein 1 (MRP1) is a major transporter of irinotecan and its metabolites [Kuhn, 1998, Oncology (Huntingt) 12:39-42, Chen, *et al.*, 1999, Mol Pharmacol 55:921-8, Chu, *et al.*, 1997, Cancer Res 57:1934-8, Chu, *et al.*, 1997, J Pharmacol Exp Ther 281:304-14] and facilitate their biliary excretion, where they cause side effects, although P-glycoprotein also participates in irinotecan excretion [Chu, *et al.*, 1998, Cancer Res 58:5137-43, Chu, *et al.*, 1999, Drug Metab Dispos 27:440-1, Chu, *et al.*, 1999, J Pharmacol Exp Ther 288:735-41, Mattern, *et al.*, 1993, Oncol Res 5:467-74, Hoki, *et al.*, 1997, Cancer Chemother Pharmacol 40:433-8, Sugiyama, *et al.*, 1998, Cancer Chemother Pharmacol 42:S44-9].

Cellular resistance to camptothecins and thus, therapeutic response of irinotecan has been related to intracellular carboxylesterase activity and cleavage activity of topoisomerase I [van Ark-Otte, *et al.*, 1998, Br J Cancer 77:2171-6, Guichard, *et al.*, 1999, Br J Cancer 80:364-70].

The use of such camptothecin drugs, e.g. irinotecan, is limited by clearly dose-dependent myelosuppression and gastrointestinal toxicities, including nausea, vomiting, abdominal pain, and diarrhea which side effects can prove fatal. The major dose-limiting toxicity of irinotecan therapy is diarrhea, which occurs in up to 88% of patients and which depends on intestinal SN-38 accumulation [van Ark-Otte, *et al.*, 1998, Br J Cancer 77:2171-6, Guichard, *et al.*, 1999, Br J Cancer 80:364-70, Araki, *et al.*, 1993, Jpn J Cancer Res 84:697-702] secondary to the biliary excretion of SN-38, the extent of which is determined by SN-38 glucuronidation [Gupta, *et al.*, 1994, Cancer Res 54:3723-5, Gupta, *et al.*, 1997, J Clin Oncol 15:1502-10]. Myelosuppression has been correlated with the area under the concentration-time curve of both irinotecan and SN-38 [Sasaki, *et al.*, 1995, Jpn J Cancer Res 86:101-10].

Despite the approval of irinotecan for patients with metastatic colorectal cancer refractory to 5-fluorouracil therapy in 1997, the therapeutic benefit remains questionable. Recently two large clinical trials on colorectal cancer involving more than 2000 patients had to be canceled by the National Institute of Cancer (NCI) due to an almost 3-times increase of irinotecan toxicity-related mortality within the first 60 days of treatment. Causes of death were diarrhea- and vomiting-related dehydratation and neutropenia-related sepsis [2001, arznei-telegramm 32:58]. Although irinotecan was proven to be effective against then cancer itself, not all patients could benefit from longterm survival due to short term toxicity. Thus, it is highly desirable to identify those patients who will most likely suffer from irinotecan toxicity.

Currently, patients are treated according to most treatment schedules with a standard dose of initially 60 to 125 mg/m^2 irinotecan in combination with other anti-neoplastic drugs administered several courses of 3 to 4 weekly dosings, and subsequent doses are adjusted in 25 to 50 mg/m^2 increments based upon individual patient tolerance to treatment. Treatment may be delayed 1 to 2 weeks to

allow for recovery from irinotecan-related toxicity and if the patient has not recovered, therapy has to be discontinued. Provided intolerable toxicity does not develop, treatment with additional courses are continued indefinitely as long as the patient continues to experience clinical benefit. Response rates varies depending from tumor type from less than 10 % to almost 90 %. However, it takes at least 6 to 8 weeks to evaluate therapeutic response and to consider alternatives. Thus, finding the right dosage for the patient is tedious, time-consuming and takes the risk of lifethreatening adverse effects. Patients might be unnecessarily put to this risk who do not benefit from treatment and additionally, worthwhile time is wasted before these patients receive their suitable treatment.

Furthermore, as observed for many chemotherapeutic agents, the risk to develop cellular resistances against therapy is increased upon suboptimal exposure of cells to chemotherapeutic agents, such as irinotecan.

Pharmacokinetic modulation with inhibitors of biliary excretion (*e. g.,* MRP and P-glycoprotein) and inducers of UGT1A1 have been suggested as a tool to reduce camptothecin-related toxicity [Gupta, *et al.*, 1996, Cancer Res 56:1309-14, Gupta, *et al.*, 1997, Cancer Chemother Pharmacol 39:440-4]. Although preliminary data of a clinical study of irinotecan in combination with cyclosporine A, and phenobarbital show some promising results in respect to limit camptothecin-related diarrhea [Ratain, 2000, Clin Cancer Res 6:3393-4], cotreatment with drugs such as cyclosporine A, and phenobarbital takes the additional risk of adverse events and drug interactions.

Large interpatient variability exist for both SN-38 and SN-38G pharmacokinetics [Canal, *et al.*, 1996, J Clin Oncol 14:2688-95], which is likely to be due to interpatient differences in the metabolism pathways of irinotecan [Rivory, *et al.*, 1997, Clin Cancer Res 3:1261-6]. Furthermore, severe irinotecan toxicity has been reported in patients with Gilbert syndrome [Wasserman, *et al.*, 1997, Ann Oncol 8:1049-51]. Consequently, a genetic predisposition to the metabolism of irinotecan, that patients with low UGT1A1 activity are at increased risk for irinotecan toxicity has been suggested [Iyer, *et al.*, 1998, J Clin Invest 101:847-54, Ando, *et al.*, 1998, Ann Oncol 9:845-7]. A common polymorphism in the UGT1A1 promoter [Monaghan, *et al.*, 1996, Lancet 347:578-81] has been correlated with *in vitro*

glucuronidation of SN-38 [Iyer, *et al.*, 1999, Clin Pharmacol Ther 65:576-82], and its possible clinical use has been suggested from a case control study [Ando, *et al.*, 2000, Cancer Res 60:6921-6]. However, irinotecan-related toxicity was predicted by UGT1A1 genotype only in the minority of affected patients (< 15 %).

In conclusion, it would be highly desirable to significantly improve therapeutic efficacy and safety of camptothecin-based therapies and to avoid therapy-caused fatalities, to avoid unnecessary development of resistances, and to reduce adverse events- and therapeutic delay-related hospitalization costs. However, no accepted mechanism for reducing irinotecan toxicity or to improve therapeutic efficacy are currently available.

Thus, the technical problem underlying the present invention is to provide improved means and methods for the efficient treatment of colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer, whereby the aforementioned undesirable side effects are to be avoided.
The technical problem underlying the present invention is solved by the embodiments characterized in the claims.

Accordingly, the present invention relates to the use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating cancer, especially, colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genome with a first variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422, 425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482,

485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 and/or 641;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 606, 608, 610, 612, 618, 620, 622, 624, and/or 628;

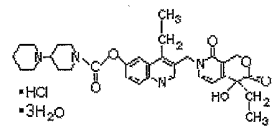
(c) a polynucleotide capable of hybridizing to a Multidrug Resistance 1 (MDR1) gene, wherein said polynucleotide is having at a position corresponding to positions 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619 of the MDR1 gene (Accession No: AC002457) and/or 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162 of the MDR1 gene (Accession No: AC005068) and/or 101, 308 of the MDR1 gene (Accession No: M29432) and/or 137, 176 of the MDR1 gene (Accession No: M29445), a substitution or deletion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having at a position corresponding to position 83946, 70200, 70237, 65241 of the MDR1 gene (Accession No: AC005068) and/or 101 of the MDR1 gene (Accession No: M29432) and/or 141529, 174901, 139177, 140118, 140568, 140727, 139479 of the MDR1 gene (Accession No: AC002457) an A, at a position corresponding to position 308 of the MDR1 gene (Accession No: M29432) and/or 84701, 83973, 84074, 84119, 78170, 70204, 70253, 70371, 50537, 43162 of the MDR1 gene (Accession No: AC005068) and/or 137 or 176 of the MDR1 gene (Accession No: M29445) and/or 145984, 171466, 175068, 175074, 139064, 139276, 140576 of the MDR1 gene (Accession No: AC002457) a T, at a position corresponding to position 140837, 171404, 171456, 171511, 171512, 139119, 140490, 139619 of the MDR1 gene (Accession No: AC002457) and/or 43263 of the MDR1 gene (Accession No: AC005068) a C, at a position corresponding to position 84032, 77811, 73252 of the MDR1 gene (Accession No: AC005068) and/or 141590, 175142, 175180, 139015, 140216, 140595 of the MDR1 gene (Accession No: AC002457) a G;

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to positions 21, 103, 168, 400, 893, 999, 1001, 1107, and/or 1141 of the MDR1 polypeptide (Accession No: G2506118);

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118).

The term "irinotecan or a derivative thereof" as used in accordance with the present invention preferably refers to a substance which is characterized by the general structural formula



$C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$

further described in US patents US05106742, US05340817, US05364858, US05401747, US05468754, US05559235 and US05663177. Moreover, also comprised by the term "irinotecan or a derivative thereof" are analogues and derivatives of camptothecin. The types and ranges of camptothecin analogues available are well known to those of skill in the art and described in numerous texts, e.g. [Hawkins, 1992, Oncology (Huntingt) 6:17-23, Burris, *et al.*, 1994, Hematol Oncol Clin North Am 8:333-55, Slichenmyer, *et al.*, 1993, J Natl Cancer Inst 85:271-91, Slichenmyer, *et al.*, 1994, Cancer Chemother Pharmacol 34:S53-7]. Specific examples of active camptothecin analogues are hexacyclic camptothecin analogues, 9-nitro-camptothecin, camptothecin analogues with 20S configuration with 9- or 10-substituted amino, halogen, or hydroxyl groups, seven-substituted water-soluble camptothecins, 9-substituted camptothecins, E-ring-modified camptothecins such as (RS)-20-deoxyamino-7-ethyl-10-methoxycamptothecin, and 10-substituted camptothecin analogues [Emerson, *et al.*, 1995, Cancer Res 55:603-9, Ejima, *et al.*, 1992, Chem Pharm Bull (Tokyo) 40:683-8, Sugimori, *et al.*, 1994, J Med Chem 37:3033-9, Wall, *et al.*, 1993, J Med Chem 36:2689-700, Wani, *et al.*, 1980, J Med Chem 23:554-60, Kingsbury, *et al.*, 1991, J Med Chem 34:98-107]. Various other camptothecin analogues with similar therapeutic activity are described [Hawkins, 1992, Oncology (Huntingt) 6:17-23, Burris and Fields, 1994, Hematol Oncol Clin North Am 8:333-55, Slichenmyer, *et al.*, 1993, J Natl Cancer Inst 85:271-91, Slichenmyer, *et al.*, 1994, Cancer Chemother Pharmacol 34:S53-7]. Suitable methods for synthezising camptothecin analogues are described [Emerson, *et al.*, 1995, Cancer Res 55:603-9, Ejima, *et al.*, 1992, Chem Pharm Bull (Tokyo) 40:683-8, Sugimori, *et al.*, 1994, J Med Chem 37:3033-9, Wall, *et al.*, 1993, J Med Chem 36:2689-700, Wani, *et al.*, 1980, J Med Chem 23:554-60, Kingsbury, *et al.*, 1991, J Med Chem 34:98-107, Sugasawa, *et al.*, 1976, J Med Chem 19:675-9].

Said substances are known to be therapeutically useful as described, e.g., in colorectal cancer, non-small cell and small cell lung cancer, oesophageal cancer, renal cell carcinoma, ovarian cancer, breast cancer, pancreatic cancer, squamous cell cancer, leukemias and lymphomas [Kawato, *et al.*, 1991, Cancer Res 51:4187-91, Furuta, *et al.*, 1988, Gan To Kagaku Ryoho 15:2757-60, Hawkins, 1992, Oncology (Huntingt) 6:17-23, Slichenmyer, *et al.*, 1993, J Natl Cancer Inst 85:271-

91, Slichenmyer, *et al.*, 1994, Cancer Chemother Pharmacol 34:S53-7, Tsuruo, *et al.*, 1988, Cancer Chemother Pharmacol 21:71-4, Wiseman, *et al.*, 1996, Drugs 52:606-23, Gottlieb, *et al.*, 1970, Cancer Chemother Rep 54:461-70, Negoro, *et al.*, 1991, J Natl Cancer Inst 83:1164-8, Rowinsky, *et al.*, 1994, Cancer Res 54:427-36]. Also encompassed by the use of the present invention are derivatives of those substances which are obtainable by way of any chemical modification, wherein said derivatives are equally well therapeutically suited for the use of the present invention. To determine whether a derivative of the substances of the invention is equally well therapeutically suited for the use of the invention biological assays well known in the art can be performed. Such assays are described , e.g., in [Kawato, *et al.*, 1991, Cancer Res 51:4187-91, Furuta, *et al.*, 1988, Gan To Kagaku Ryoho 15:2757-60, Giovanella, *et al.*, 1989, Science 246:1046-8, Giovanella, *et al.*, 1991, Cancer Res 51:3052-5, Kunimoto, *et al.*, 1987, Cancer Res 47:5944-7, Mattern, *et al.*, 1993, Oncol Res 5:467-74, Tsuruo, *et al.*, 1988, Cancer Chemother Pharmacol 21:71-4, Burris, *et al.*, 1992, J Natl Cancer Inst 84:1816-20, Friedman, *et al.*, 1994, Cancer Chemother Pharmacol 34:171-4].

It is contemplated that any of the compounds described in the above publications may be used in this invention.

It has been show that irinotecan is particularly well suited for the treatment of colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer. Thus, most preferably the substance used according to the present invention is irinotecan.

The term "pharmaceutical composition" as used herein comprises the substances of the present invention and optionally one or more pharmaceutically acceptable carrier. The substances of the present invention may be formulated as pharmaceutically acceptable salts. Acceptable salts comprise acetate, methylester, HCl, sulfate, chloride and the like. The pharmaceutical compositions can be conveniently administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The substances may be administered in conventional dosage forms prepared by combining the drugs with standard pharmaceutical carriers according to conventional procedures. These procedures may involve mixing, granulating and

compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are phosphate buffered saline solution, syrup, oil such as peanut oil and olive oil, water, emulsions, various types of wetting agents, sterile solutions and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax. The substance according to the present invention can be administered in various manners to achieve the desired effect. Said substance can be administered either alone or in the formulated as pharmaceutical preparations to the subject being treated either orally, topically, parenterally or by inhalation. Moreover, the substance can be administered in combination with other substances either in a common pharmaceutical composition or as separated pharmaceutical compositions.

The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like. A therapeutically effective dose refers to that amount of the substance according to the invention which ameliorate the symptoms or condition. Therapeutic efficacy and toxicity of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., ED50 (the dose therapeutically effective in 50% of the population) and LD50 (the dose lethal to 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index, and it can be expressed as the ratio, LD50/ED50.

The dosage regimen will be determined by the attending physician and other clinical factors; preferably in accordance with any one of the above described

methods. As is well known in the medical arts, dosages for any one patient depends upon many factors, including the patient's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Progress can be monitored by periodic assessment.

A typical dose can be, for example, in the range of 5 to 100 mg however, doses below or above this exemplary range are envisioned, especially considering the aforementioned factors. Generally, the regimen as a regular administration of the pharmaceutical composition should be in the range of 1 μg to 10 mg units per day. If the regimen is a continuous infusion, it should also be in the range of 1 μg to 10 mg units per kilogram of body weight per minute, respectively. Progress can be monitored by periodic assessment. However, depending on the subject and the mode of administration, the quantity of substance administration may vary over a wide range to provide from about 1 mg per m^2 body surface to about 500 mg per m^2 body surface, usually 20 to 200 mg per m^2 body surface.

The pharmaceutical compositions and formulations referred to herein are administered at least once in accordance with the use of the present invention. However, the said pharmaceutical compositions and formulations may be administered more than one time, for example once weekly every other week up to a non-limited number of weeks.

Specific formulations of the substance according to the invention are prepared in a manner well known in the pharmaceutical art and usually comprise at least one active substance referred to herein above in admixture or otherwise associated with a pharmaceutically acceptable carrier or diluent thereof. For making those formulations the active substance(s) will usually be mixed with a carrier or diluted by a diluent, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other suitable containers or vehicles. A carrier may be solid, semisolid, gel-based or liquid material which serves as a vehicle, excipient or medium for the active ingredients. Said suitable carriers comprise those mentioned above and others well known in the art, see, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania. The formulations can be adopted to the mode of administration comprising the forms of tablets, capsules, suppositories, solutions, suspensions or the like.

The dosing recommendations will be indicated in product labeling by allowing the prescriber to anticipate dose adjustments depending on the considered patient group, with information that avoids prescribing the wrong drug to the wrong patients at the wrong dose.

The term "treating" or "preventing" means alleviation of the diseases symptoms i.e., regression of symptoms or inhibited progression of such symptoms, in subjects or disease populations which have been treated. Said alleviation of the diseases can be monitored by the degree of the clinical symptoms (e.g., tumor size) accompanied with the disease. While the invention may not be effective in 100% of patients treated, it is effective in treating a statistically significant (p value less than 0.05) number of patients. Whether said number of subjects is significant can be determined by statistical tests such as the Student's t-test, the chi^2-test, the U-test according to Mann and Whitney, the Kruskal-Wallis-test (H-Test), Jonckheere-Terpstra-test or the Wilcoxon-test.

The present invention also encompasses all embodiments described in connection with pharmaceutical compositions in US patents US05106742, US05340817, US05364858, US05401747, US05468754, US05559235 and US05663177.

The terms "colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer" comprise diseases and dysregulations related to cancer. Preferred diseases encompassed by the use of the present invention are colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer. Said diseases and dysregulations are well known in the art and the accompanied symptoms are described, e.g., in standard text books such as Stedman.

The term "subject" as used in the sense of the present invention comprises animals, preferably those specified herein after, and humans.

The term "first variant allele" as used herein refers to a polynucleotide comprising one or more of the polynucleotides described herein below corresponding to a MDR1 gene. Each individual subject carries at least two alleles of the MDR1 gene, wherein said alleles are distinguishable or identical. In accordance with the use of the present invention a variant allele comprises at least one or more of the

polynucleotides specified herein below. Said polynucleotides may have a synergistic influence on the regulation or function of the first variant allele. Preferably, a variant allele in accordance with the use of the present invention comprises at least two of the polynucleotides specified herein.

In the context of the present invention the term "polynucleotides" or "polypeptides" refers to different variants of a polynucleotide or a polypeptide specified in accordance with the uses of the present invention. Said variants comprise a reference or wild type sequence of the polynucleotides or polypeptides specified herein as well as variants which differ therefrom in structure or composition. Reference or wild type sequences for the polynucleotides are Genbank accession No: GI:8850235, GI:11118740, GI:10281451, GI:11177452, GI:10281451, GI:6706037, U91318, GI:7209451, AC026452, AC003026, U91318, AF022830, GI:7209451, AC026452, AC003026, AC025277, AF022828, AF022829, AF022831, U07050, AC003026, AC002457, AC005068, M29432, M29445, and GI:11225259 or Accession No (Pid No): G8850236, G2828206, G2506118, and G12644118 for polypeptides. The differences in structure or composition usually occur by way of nucleotide or amino acid substitution(s), addition(s) and/or deletion(s).

Preferably, said nucleotide substitution(s), addition(s) or deletion(s) referred to in accordance with the use of the present invention result(s) in one or more changes of the corresponding amino acid(s) of the polypeptides. The variant polynucleotides also comprise fragments of said polynucleotides or polypeptides. The polynucleotides or polypeptides as well as the aforementioned fragments thereof are characterized as being associated with a MDR1 dysfunction or dysregulation comprising, e.g., insufficient and/or altered drug uptake.

The present invention also encompasses all embodiments described in connection with polynucleotides in WO9957322, WO0109183 or US5786344.

The term "hybridizing" as used herein refers to polynucleotides which are capable of hybridizing to the above polynucleotides or parts thereof which are associated with a MDR1 dysfunction or dysregulation. Thus, said hybridizing polynucleotides are also associated with said dysfunctions and dysregulations. Preferably, said polynucleotides capable of hybridizing to the aforementioned polynucleotides or parts thereof which are associated with MDR1 dysfunctions or dysregulations are at

least 70%, at least 80%, at least 95% or at least 100% identical to the polynucleotides or parts thereof which are associated with MDR1 dysfunctions or dysregulations. Therefore, said polynucleotides may be useful as probes in Northern or Southern Blot analysis of RNA or DNA preparations, respectively, or can be used as oligonucleotide primers in PCR analysis dependent on their respective size. Also comprised in accordance with the use of the invention are hybridizing polynucleotides which are useful for analyzing DNA-Protein interactions via, e.g., electrophoretic mobility shift analysis (EMSA). Preferably, said hybridizing polynucleotides comprise at least 10, more preferably at least 15 nucleotides in length while a hybridizing polynucleotide to be used as a probe preferably comprises at least 100, more preferably at least 200, or most preferably at least 500 nucleotides in length.

It is well known in the art how to perform hybridization experiments with nucleic acid molecules, i.e. the person skilled in the art knows what hybridization conditions s/he has to use in accordance with the present invention. Such hybridization conditions are referred to in standard text books, such as Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory (1989) N.Y. Preferred in accordance with the use of the present inventions are polynucleotides which are capable of hybridizing to the above polynucleotides or parts thereof which are associated with a MDR1 dysfunction or dysregulation under stringent hybridization conditions, i.e. which do not cross hybridize to unrelated polynucleotides such as polynucleotides encoding a polypeptide different from the MDR1 polypeptides of the invention.

Moreover, methods for determining whether a subject comprises a polynucleotide referred to herein above are well known in the art. To carry out said methods, it might be necessary to take a sample comprising biological material, such as isolated cells or tissue, from said subject. Further, the methods known in the art could comprise for example, PCR based techniques, RFLP-based techniques, DNA sequencing-based techniques, hybridization techniques, Single strand conformational polymorphism (SSCP), denaturating gradient gel electrophoresis (DGGE), mismatch cleavage detection, heteroduplex analysis, techniques based on mass spectroscopy, HPLC-based techniques, primer extension-based techniques, and 5'-nuclease assay-based techniques. A preferred and convenient method to be used in order to determine the presence or absence of one or more of the above

specified polynucleotides is to isolate blood cells from a subject and to perform a PCR based assay on genomic DNA isolated from those blood cells, whereby the PCR is used to determine whether said polynucleotides specified herein above or parts thereof are present or absent. Said method is described in more detail below and in the Examples.

The term "corresponding" as used herein means that a position is not only determined by the number of the preceding nucleotides and amino acids, respectively. The position of a given nucleotide or amino acid in accordance with the use of the present invention which may be deleted, substituted or comprise one or more additional nucleotide(s) may vary due to deletions or additional nucleotides or amino acids elsewhere in the gene or the polypeptide. Thus, under a "corresponding position" in accordance with the present invention it is to be understood that nucleotides or amino acids may differ in the indicated number but may still have similar neighboring nucleotides or amino acids. Said nucleotides or amino acids which may be exchanged, deleted or comprise additional nucleotides or amino acids are also comprised by the term "corresponding position". Said nucleotides or amino acids may for instance together with their neighbors form sequences which may be involved in the regulation of gene expression, stability of the corresponding RNA or RNA editing, as well as encode functional domains or motifs of the protein of the invention.

By, e.g., "position 17970 to 17970" it is meant that said polynucleotide comprises one or more deleted nucleotides which are deleted between positions 17970 and position 17970 of the corresponding wild type version of said polynucleotide. The same applies mutatis mutandis to all other position numbers referred to in the above embodiment which are drafted in the same format.

By, e.g., "position 1222/1223" it is meant that said polynucleotide comprises one or more additional nucleotide(s) which are inserted between positions 1222 and position 1223 of the corresponding wild type version of said polynucleotide. The same applies mutatis mutandis to all other position numbers referred to in the above embodiment which are drafted in the same format, i.e. two consecutive position numbers separated by a slash (/).

In accordance with the present invention, the mode and population distribution of genetic variations in the MDR1 gene - the different alleles of the MDR1 gene - have been analyzed by sequence analysis of relevant regions of the human said gene from many different individuals. It is a well known fact that genomic DNA of individuals, which harbor the individual genetic makeup of all genes, including the MDR1 gene, can easily be purified from individual blood samples. These individual DNA samples are then used for the analysis of the sequence composition of the alleles of the MDR1 gene that are present in the individual which provided the blood sample. The sequence analysis was carried out by PCR amplification of relevant regions of said genes, subsequent purification of the PCR products, followed by automated DNA sequencing with established methods (e.g. ABI dyeterminator cycle sequencing).

One important parameter that has to be considered in the attempt to determine the individual genotypes and identify novel variants of the MDR1 gene by direct DNA-sequencing of PCR-products from human blood genomic DNA is the fact that each human harbors (usually, with very few abnormal exceptions) two gene copies of each autosomal gene (diploidy). Because of that, great care has to be taken in the evaluation of the sequences to be able to identify unambiguously not only homozygous sequence variations but also heterozygous variations. The details of the different steps in the identification and characterization of the polymorphisms in the MDR1 gene (homozygous and heterozygous) are described in the Examples below.

Over the past 20 years, genetic heterogeneity has been increasingly recognized as a significant source of variation in drug response. Many scientific communications (Meyer, Ann. Rev. Pharmacol. Toxicol. 37 (1997), 269-296 and West, J. Clin. Pharmacol. 37 (1997), 635-648) have clearly shown that some drugs work better in some patients than in others or may even be highly toxic and that such variations in patients' responses to drugs can be correlated to a molecular basis. This "pharmacogenomic" concept spots correlations between responses to drugs and genetic profiles of patient's (Marshall, Nature Biotechnology, 15 (1997), 954-957; Marshall, Nature Biotechnology, 15 (1997), 1249-1252). In this context of population variability with regard to drug therapy, pharmacogenomics has been proposed as a tool useful in the identification and selection of patients which can

respond to a particular drug without side effects. This identification/selection can be based upon molecular diagnosis of genetic polymorphisms by genotyping DNA from leukocytes in the blood of a patient, for example, and characterization of disease (Bertz, Clin. Pharmacokinet. 32 (1997), 210-256; Engel, J. Chromatogra. B. Biomed. Appl. 678 (1996), 93-103). For the founders of health care, such as health maintenance organizations in the US and government public health services in many European countries, this pharmacogenomics approach can represent a way of both improving health care and reducing costs related to health care caused by the development of unnecessary drugs, by ineffective drugs and by side effects due to drug administration.

The mutations in the variant genes of the invention sometimes result in amino acid deletion(s), insertion(s) and in particular in substitution(s) either alone or in combination. It is of course also possible to genetically engineer such mutations in wild type genes or other mutant forms. Methods for introducing such modifications in the DNA sequence of said genes are well known to the person skilled in the art; see, e.g., Sambrook, Molecular Cloning A Laboratory Manual, Cold Spring Harbor Laboratory (1989) N.Y.

For the investigation of the nature of the alterations in the amino acid sequence of the polypeptides of the invention may be used such as BRASMOL that are obtainable from the Internet. Furthermore, folding simulations and computer redesign of structural motifs can be performed using other appropriate computer programs (Olszewski, Proteins 25 (1996), 286-299; Hoffman, Comput. Appl. Biosci. 11 (1995), 675-679). Computers can be used for the conformational and energetic analysis of detailed protein models (Monge, J. Mol. Biol. 247 (1995), 995-1012; Renouf, Adv. Exp. Med. Biol. 376 (1995), 37-45). These analysis can be used for the identification of the influence of a particular mutation on metabolism, binding, inhibition, mediating of therapeutic action and/or transport of drugs. Moreover, based on the knowledge of the altered structure of the polypeptides which are encoded by the polynucleotides specified in the use of the present invention derivatives of the substances referred to above can be designed and synthesized which can be more efficiently metabolized, modified, transported, eliminated, and/or binded. Thereby, drugs or pro-drugs can be designed on the basis of the substances referred to herein which are more efficient in therapy of colorectal

cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genotype characterized by the presence of one or more polynucleotides of the invention.

Usually, said amino acid deletion, addition or substitution in the amino acid sequence of the protein encoded by the polynucleotide referred to in accordance with the use of the present invention is due to one or more nucleotide substitution, insertion or deletion, or any combinations thereof. Preferably said nucleotide substitution, insertion or deletion may result in an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118). The polypeptides encoded by the polynucleotides referred to in accordance with the use described herein have altered biological properties due to the mutations referred to in accordance with the present invention. Examples for said altered properties are stability of the polypeptides or amount of the polypeptides which may be effected resulting in, e.g. an altered drug metabolism or an altered transport of drugs or an altered substrate specificity or an altered catalytic activity characterized by, e.g. insufficiencies in drug metabolism or a complete loss of the capability to metabolize drugs or an enhanced capacity to metabolize drugs or an altered transport activity characterized by, e.g., insufficiencies in drug transport or a complete loss of the capability of transporting drugs or an altered substrate binding characterized by, e.g. an altered drug action or an altered inhibition or induction of transport or an altered binding to receptors or other target molecules characterized by, e.g. an altered activation of signal

transduction pathways or an altered protein or enzyme function. These altered properties result in an impaired pharmacological response to the substances referred to above of the subject to be treated in accordance with the use of the present invention. Moreover, due to said altered properties of the polypeptides encoded by the variant alleles specified herein the substances may be chemically modified in a way resulting in derivatives of the substances which are harmful or toxic for the subject or which cause undesirable side effects.

The mutations in the MDR1 gene detected in accordance with the present invention are listed in Tables 1 and 2. As is evident to the person skilled in the art, the genetic knowledge of the polynucleotides specified herein above can be used to exactly and reliably characterize the genotype of a patient.

Advantageously, therapeutical measures which are based on irinotecan or a derivative thereof can be more efficiently applied when taking into consideration said genetic knowledge. Undesirable side effects of said substances can be avoided and an effective but not harmful dosage can be calculated individually due the knowledge of the genetic makeup of the subject. Moreover in accordance with the foregoing, in cases where a given drug causes an unusual effect, a suitable individual therapy can be designed based on the knowledge of the individual genetic makeup of a subject. This tailored therapy will also be suitable to avoid the occurance of therapy resistances. Said resistances are one major problem in cancer chemotherapy with various chemotherapeutic agents, this fact being well known in the art. The use of the present invention, therefore, provides an improvement of the therapeutic applications which are based on the known therapeutically desirable effects of the substances referred to herein above since it is possible to individually treat the subject with an appropriate dosage and/or an appropriate derivative of said substances. Thereby, undesirable, harmful or toxic effects are efficiently avoided. Furthermore, the use of the present invention provides an improvement of the therapeutic applications which are based on the known therapeutically desirable effects of the substances referred to herein above since it is possible to identify those subject prior to onset of drug therapy and treat only those subjects with an appropriate dosage and/or an appropriate derivative of said substances who are most likely to benefit from therapy with said substances. Thereby, the unnecessary and potentially harmful treatment of those subjects who do not respond to the treatment with said substances (nonresponders), as well as

the development of drug resistances due to suboptimal drug dosing can be avoided.

In a preferred embodiment of the use of the present invention said first variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 345, 417 or 636:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 612 or 618;

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432), 176 of the MDR1 gene (Accession No: M29445), or 88883 of the MDR1 gene (Accession No: GI:10122135);

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having an A at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432) or 88883 of the MDR1 gene (Accession No: GI:10122135), or a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) or 88883 of the MDR1 gene (Accession No: GI:10122135);

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 400 or 893 of the MDR1 polypeptide (Accession No: G2506118); and

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Ser to Asn at a position corresponding to position 400 or Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118).

More preferably, said first variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of SEQ ID NO: 417 or 636;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 618;

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445), 88883 of the MDR1 gene (Accession No: GI:10122135);

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) or 88883 of the MDR1 gene (Accession No: GI:10122135);

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118); and

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118).

Most preferably, said first variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of SEQ ID NO: 417;

(b) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445); and

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445).

In a preferred embodiment of the use of the present invention said subject having a genome with a second variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 and/or 334;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 600, 602 and/or 604;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance Protein 1 (MRP1) gene, wherein said polynucleotide is having at a position corresponding to positions 57998, 57853, 53282, and/or 39508 of the MRP1 gene (Accession No: GI:7209451), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 137667, 137647, 137710, 124667, and/or 38646 of the MRP1 gene (Accession No: AC026452), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 27258, 27159, 34218, 34215, 55472, and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 21133, 14008, 18067, 17970, and/or 17900 of the MRP1 gene (Accession No: U91318), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 79, 88, and/or 249 of the MRP1 gene (Accession No: AF022830), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 95 and/or 259 of the MRP1 gene (Accession No: AF022831), a substitution or deletion

of at least one nucleotide or at a position corresponding to positions 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277), a substitution or deletion of at least one nucleotide or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 248 and/or 258 of the MRP1 gene (Accession No: AF022829), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 1884, 1625, 1163, 381, 233, 189, 440, and/or 1720 to 1723 of the MRP1 gene (Accession No: U07050), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 926/927 and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of at least one nucleotide or at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having at a position corresponding to position 21133, 14008 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 27258 and/or 34218 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 79 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 57998, and/or 57853 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137667 and/or 137647 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277) or at a position corresponding to position 248 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 1884, 1625, 233, and/or 189 of the MRP1 gene (Accession No: U07050) an A, at a position corresponding to position 39508 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 17900, 18067 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828) or at a position corresponding to position 440 and/or 1163 of the MRP1 gene (Accession No: U07050) a T, at a position corresponding to position 88 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 95 of the MRP1 gene

(Accession No: AF022831) or at a position corresponding to position 27159, 55472 and/or 34215 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 124667 and/or 38646 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137710 of the MRP1 gene (Accession No: AC026452) a C, at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 258 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 259 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 381 of the MRP1 gene (Accession No: U07050) a G, at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) a deletion of a T or at a position corresponding to position 34206 to 34207 of the MRP1 gene (Accession No: AC003026) a deletion of a AT or at a position corresponding to position 1720 to 1723 of the MRP1 gene (Accession No: U07050) a deletion of GGTA, at a position corresponding to position 926/927 a insertion of a T and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of a TCCTTCC, at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of TGGGGC;

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 239 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Ser at a position corresponding to position 433 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Gln at a position corresponding to position 723 of the MRP1 polypeptide (Accession No: G2828206).

The explanations and interpretations of the terms made above can be applied mutatis mutandis.

The term "second variant allele" refers to an allele of a second gene being different from said first gene corresponding to said first allele described herein above.

According to the present invention said second variant allele corresponds to a MRP1 gene comprising one or more of the polynucleotides specified above.
In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and a second variant allele corresponding to the MRP1 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. Hence, in accordance with the use of the present invention the diseases and disorders referred to herein can be more efficiently treated or prevented whereby said therapies or preventive measures are more convenient for the subject. Moreover, the applicability of therapeutic measures comprising administration of the substances referred to herein above can be efficiently predicted.

Preferred deletions in accordance with the invention are a T or AT deletion at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), preferred insertion is a TCCTTCC at a position corresponding to position 437/438 of the MRP1 gene (Accession No: GI: U07050) and/or a TGGGGC insertion at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026).

In a preferred embodiment of the use of the present invention said second variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 181, 209, 217, 205, 277, 281, 301, 325, 229, 193, 313, 293 or 253:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 600;

(c) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 95 of the MRP1 gene (Accession No: AF022831), 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene

(Accession No: AC026452), 381, 440,1625 of the MRP1 gene (Accession No: U07050), 34218 of the MRP1 gene (Accession No: AC003026), 18067 or 17900 of the MRP1 gene (Accession No: U91318) or an insertion of at least one nucleotide at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a T at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 18067 or 17900 of the MRP1 gene (Accession No: U91318), 440 of the MRP1 gene (Accession No: U07050), a C at a position corresponding toposition 95 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), a G at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 381 of the MRP1 gene (Accession No: U07050), or an A at a position corresponding to position 34218 of the MRP1 gene (Accession No: AC003026) or 1625 of the MRP1 gene (Accession No: U07050) or an insertion of a T at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206); and

(f) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206).

More preferably, said second variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 209, 205, 277, 281, 301 or 325;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 600;

(c) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), 381 of the MRP1 gene (Accession No: U07050), or an insertion of at least one nucleotide at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a C at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), a G at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 381 of the MRP1 gene (Accession No: U07050), or an insertion of a T at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206); and

(f) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206).

In a preferred embodiment of the use of the present invention said subject having a genome with a third variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 137, 138, 141, 142, 145, 146, 149 and/or 150;

(b) a polynucleotide capable of hybridizing to a Cytochrome P450, subfamily IIIA (nifedipene oxidase), polypeptide 5 (CYP3A5) gene, wherein said polynucleotide is having at a position corresponding to positions 47518 and/or 9736 of the CYP3A5 gene (Accession No: GI:10281451), a substitution of at least one nucleotide or at a position corresponding to positions 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452), a substitution of at least one nucleotide;

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) a C, at a position corresponding to position 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452) a G or at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451) a G.

The explanations and interpretations of the terms made above can be applied mutatis mutandis.

The term " third variant allele" refers to an allele of a third gene being different from said first gene corresponding to said first allele and said second gene corresponding to said second allele described herein above. According to the present invention said third variant allele corresponds to a CYP3A5 gene comprising one or more of the polynucleotides specified above.

In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and optionally a second variant allele corresponding to the MRP1 gene and a third variant allele corresponding to the CYP3A5 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. Hence, in accordance with the use of the present invention the diseases and disorders referred to herein can be more efficiently treated or prevented whereby said therapies or preventive measures are more convenient for the subject. Moreover, the applicability of therapeutic measures comprising administration of the substances referred to herein above can be efficiently predicted.

In a preferred embodiment of the use of the present invention said third variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 137, 141, 145 or 149:

(b) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 47518 or 9736 of the CYP3A5 gene (Accession No: GI:10281451) or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452);

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a C at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) or a G at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451), or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452).

More preferably, said third variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 137, 145 and/or 149;

(b) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 47518 or 9736 of the CYP3A5 gene (Accession No: GI:10281451) or 145929 of the CYP3A5 gene (Accession No: GI:11177452);

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a C at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) or a G at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451), or 145929 of the CYP3A5 gene (Accession No: GI:11177452).

In a preferred embodiment of the use of the present invention said subject having a genome with a fourth variant allele which comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 and/or 134;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 and/or 598;

(c) a polynucleotide capable of hybridizing to a Uridine Diphosphate Glycosyltransferase1 Member A1 (UGT1A1) gene, wherein said polynucleotide is having at a position corresponding to positions 59, 160, 226, 539, 544, 640, 701, 841, 855, 890, 938, 1006, 1007, 1020, 1084, 1085, 1114, 1117, 1139, 1158, 1175 to 1176, 1216, 1297, 1324, 1471, 1478, 372 to 373, 523 to 525, and/or 892 to 905 of the UGT1A1 gene (Accession No. GI:8850235), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 470/471, and/or 1222/1223 of the UGT1A1 gene (Accession No. GI:8850235) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having at a position corresponding to position 226, 539, 701, 855, 938, 1020, and/or 1117 of the UGT1A1 gene (Accession No: GI:8850235) an A, at a position corresponding to position 160, 640, 890, 1006, 1084, 1139, 1176, 1324, and/or 1478 of the UGT1A1 gene (Accession No: GI: 8850235) a T, at a position corresponding to position 544, 841, and/or 1216 of the UGT1A1 gene (Accession No: GI: 8850235) a C, at a position corresponding to position 59, 1007, 1085, 1114, 1158, 1175, 1297, and/or 1471 of the UGT1A1 gene (Accession No: GI:181303) a G, and/or at

a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TTC, at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TACATTAATGCTTC, at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a T, and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a G;

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Leu to Arg at a position corresponding to position 15 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 71 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Leu to Gln at a position corresponding to position 175 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Cys to Arg at a position corresponding to position 177 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Trp at a position corresponding to position 209 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Gln at a position corresponding to position 229 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 276 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Val at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Trp at a position corresponding to position 293 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Glu at a position corresponding to position 308 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 331 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 357 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Gly at a position corresponding to position 367 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Thr at a position corresponding to position 368 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Arg at a position corresponding to position 387 of

the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 375 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Arg at a position corresponding to position 381 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Pro at a position corresponding to position 401 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Lys to Glu at a position corresponding to position 428 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 488 of the UGT1A1 polypeptide (Accession No: G8850236);

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide is having at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, whereby in said polypeptide one or more amino acids following amino acid Asp at a position corresponding to position 119 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a T, whereby in said polypeptide one or more amino acids following amino acid Pro at a position corresponding to position 152 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TTC, whereby in said polypeptide one or more amino acids following amino acid Thr at a position corresponding to position 168 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TACATTAATGCTTC, whereby in said polypeptide one or more amino acids following amino acid Ala at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a G, whereby in said polypeptide one or more

amino acids following amino acid Lys at a position corresponding to position 402 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted; and

(g) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide comprises an amino acid substitution of Gln to a stop codon at a position corresponding to position 49 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Cys to a stop codon at a position corresponding to position 280 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 331 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Trp to a stop codon at a position corresponding to position 335 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 357 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Lys to a stop codon at a position corresponding to position 437 of the UGT1A1 gene (Accession No: G8850236).

The explanations and interpretations of the terms made above can be applied mutatis mutandis.

The term "fourth variant allele" refers to an allele of a fourth gene being different from said first gene corresponding to said first allele and said second gene corresponding to said second allele and said third gene corresponding to said third allele described herein above. According to the present invention said fourth variant allele corresponds to a UGT1A1 gene comprising one or more of the polynucleotides specified above.

In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and optionally a second variant allele corresponding to the MRP1 gene and a third variant allele corresponding to the CYP3A5 gene and a fourth variant allele corresponding to the UGT1A1 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. Hence, in accordance with the use of the present invention the

diseases and disorders referred to herein can be more efficiently treated or prevented whereby said therapies or preventive measures are more convenient for the subject. Moreover, the applicability of therapeutic measures comprising administration of the substances referred to herein above can be efficiently predicted.

In a preferred embodiment of the use of the present invention said fourth variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 37, 69 or 97;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 558, 570 or 584;

(c) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 890, 1117 or 1471 of the UGT1A1 gene (Accession No: GI: 8850235);

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having an A at a position corresponding to position 1117, a T at a position corresponding to position 890 or a G at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI:8850235);

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 292, 368 or 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236); and

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises amino acid substitution of Ala to Val at a position corresponding to position 292, Ala to Thr at aposition corresponding to position 368 or Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236).

More preferably, said fourth variant allele comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 97;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 584;

(c) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI: 8850235);

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a G at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI:8850235);

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236); and

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises amino acid substitution of Ala to Thr at a position corresponding to position 368 or Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236).

In accordance with the present invention it has been surprisingly found that a first variant allele corresponding to the MDR1 gene and optionally a second variant allele corresponding to the MRP1 gene and a third variant allele corresponding to the CYP3A5 gene and a fourth variant allele corresponding to the UGT1A1 gene, if present in combination in the genome of a subject, synergistically alter the pharmacological response of said subject to the administration of irinotecan or a derivative thereof. As has been found in accordance with he present invention, the pharmacokinetics of a drug which is based on irinotecan or a derivative thereof and the pharmacological response of a subject is mainly governed by the polypeptides

encoded by the MDR1, MRP1, CYP3A5 and UGT1A1 genes. Therefore, in order to increase the predictability and/or efficiency of therapeutic measures applied in accordance with the present invention, the genetic constitution of a subject as regards the present or absence of the first, second, third, and/or variant alleles referred to herein has to be determined and based on that knowledge an individual therapy can be developed which is therapeutically most effective and which avoids toxic or undesirable side effects caused by the substances according to the invention.

The present invention also relates to a method of treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer comprising:

(a) determining the presence or absence of a first, a second, a third and/or a fourth variant allele comprising a polynucleotide referred to herein; and

(b) administering to a subject a therapeutically effective dosage of irinotecan.

The definitions used in accordance with the use of the present invention apply mutatis mutandis to the above method. Further, all embodiments described in accordance with the use of the present invention can be applied mutatis mutandis to the method of the present invention. Moreover, also encompassed by the method of the present invention are any further developments of said method which the person skilled in the art can make without undue burden based on its knowledge and the prior art, such as those documents referred to throughout this specification.

In a preferred embodiment of the use of the present invention a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first, second or third variant allele compared to the corresponding wild type allele.
As discussed above, the alleles referred to in accordance with the use of the present invention correspond to the MDR1, MRP1, CYP3A5 and/or UGT1A1 gene. It is well known in the art that genes comprise structural elements which encode an amino acid sequence as well as regulatory elements which are involved in the regulation of the expression of said genes. Structural elements are represented by

exons which may either encode an amino acid sequence or which may code for RNA which is not encoding an amino acid sequence but is nevertheless involved in RNA function, e.g. by regulating the stability of the RNA or the nuclear export of the RNA.

Regulatory elements of a gene may comprise promoter elements or enhancer elements both of which could be involved in transcriptional control of gene expression. It is very well known in the art that a promoter is to be found upstream of the structural elements of a gene. Regulatory elements such as enhancer elements, however, can be found distributed over the entire locus of a gene. Said elements could reside, e.g., in introns, regions of genomic DNA which separate the exons of a gene. Promoter or enhancer elements correspond to polynucleotide fragments which are capable of attracting or binding polypeptides involved in the regulation of the gene comprising said promoter or enhancer elements. For example, polypeptides involved in regulation of said gene comprise the so called transcription factors.

Said introns may comprise further regulatory elements which are required for proper gene expression. Introns are usually transcribed together with the exons of a gene resulting in a nascent RNA transcript which contains both, exon and intron sequences. The intron encoded RNA sequences are usually removed by a process known as RNA splicing. However, said process also requires regulatory sequences present on a RNA transcript said regulatory sequences may be encoded by the introns.

In addition, besides their function in transcriptional control and control of proper RNA processing and/or stability, regulatory elements of a gene could be also involved in the control of genetic stability of a gene locus. Said elements control, e.g., recombination events or serve to maintain a certain structure of the DNA or the arrangement of DNA in a chromosome.

Therefore, single nucleotide polymorphisms can occur in exons of an allele of a gene which encode an amino acid sequence as discussed supra as well as in regulatory regions which are involved in the above discussed process. The polymorphisms comprised by the polynucleotides referred to in accordance with the use of the present invention can influence the expression level of MDR1, MRP1,

CYP3A5, and/or UGT1A1 protein via mechanisms involving enhanced or reduced transcription of the MDR1, MRP1, CYP3A5 and/or UGT1A1 gene, stabilization of the gene's RNA transcripts and alteration of the processing of the primary RNA transcripts.

Methods for the determination of an altered expression of a variant allele when compared to its wild type counterpart are well known in the art and comprise inter alia those referred to herein above, e.g., PCR based techniques, RFLP-based techniques, DNA sequencing-based techniques, hybridization techniques, Single strand conformational polymorphism (SSCP), denaturating gradient gel electrophoresis (DGGE), mismatch cleavage detection, heteroduplex analysis, techniques based on mass spectroscopy, HPLC-based techniques, primer extension-based techniques, and 5'-nuclease assay-based techniques. It might be necessary to obtain a sample comprising biological material, such as isolated cells or tissue from the subject prior to perform said methods for determination of the expression levels of the wild type and the variant alleles, respectively. An altered expression in accordance with the use of the present invention means that the expression of the wild type allele differs significantly from the expression of the variant allele. A significant difference can be determined by standard statistical methods, such as Student´s t-test, chi^2-test or the U-test according to Mann and Whitney. Moreover, the person skilled in the art can adopt these and other statistical method known in the art individually without an undue burden.

In a more preferred embodiment of the use of the invention said altered expression is decreased or increased expression.

To determine whether the expression of an allele referred to in accordance to the present invention is increased or decreased in comparison to the corresponding wild type allele well known methods such as PCR based techniques, RFLP-based techniques, DNA sequencing-based techniques, hybridization techniques, Single strand conformational polymorphism (SSCP), denaturating gradient gel electrophoresis (DGGE), mismatch cleavage detection, heteroduplex analysis, techniques based on mass spectroscopy, HPLC-based techniques, primer extension-based techniques, and 5'-nuclease assay-based techniques can be applied. As discussed above, it might be necessary to obtain a sample comprising cells or tissue from the subject in order to determine the expression level of the

variant allele referred to in the use of the invention. A decrease or increase of the expression is characterized by a significant difference in the expression level of the variant versus the wild type allele in those assays. Also encompassed by decreased expression is the absence detectable expression of a variant allele.

In a furthermore preferred embodiment of the use of the present invention a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered activity of the polypeptide encoded by the first, second, third, and/or fourth variant allele compared to the polypeptide encoded by the corresponding wild type allele.

As discussed supra, the variant alleles comprising those polynucleotides specified herein which correspond to coding regions of the MDR1, MRP1, CYP3A5 and/or UGT1A1 gene effect the amino acid sequences of the polypeptides encoded by said variant alleles. The variant polypeptides, therefore, exhibit altered biological and/or immunological properties when compared to their corresponding wild type counterpart. Preferred variant polypeptides in accordance with the use of the invention are those, which exhibit an altered biological activity, i.e. altered enzymatic function resulting in reduced, enhanced or complete loss of catalytic activity or altered transport function resulting in reduced, enhanced or complete loss of transport activity or altered binding to receptors or other drug targets resulting in altered activation of signal transduction pathways or altered inhibition of transporter or enzyme function. It might be necessary to obtain a sample comprising biological material such as isolated cells or tissue from the subject prior to perform said methods for determination of the activities of the wild type and the variant polypeptides, respectively. Whether a variant polypeptide has an altered activity or level of expression compared to its wild type corresponding counterpart can be determined by standard techniques well known in the art. Such standard techniques may comprise, e.g., ELISA based assays, RIA based assays, HPLC-based assays, mass spectroscopy-based assays, western blot analysis or assays which are known in the art and described in [Hitzl, *et al.*, 2001, Pharmacogenetics 11:293-8]; Hoffmeyer, 2000 #77; van Helvoort, 1996 #115; Schumacher, 1997 #116; Cordon-Cardo, 1990 #117; Hafkemeyer, 1998 #118] for MDR1, [Keppler, *et al.*, 1997, Biol Chem 378:787-91, Suzuki, *et al.*, 1994, Adv Prostaglandin Thromboxane Leukot Res 22:83-9, Scheffer, *et al.*, 2000, Cancer Res 60:5269-77,

Konig, *et al.*, 1999, Biochim Biophys Acta 1461:377-94, Kool, *et al.*, 1997, Cancer Res 57:3537-47, Bakos, *et al.*, 2000, Mol Pharmacol 57:760-8, Keppler, *et al.*, 1998, Chem Biol Interact 112:153-61, Leier, *et al.*, 2000, Kidney Int 57:1636-42, Evers, *et al.*, 2000, Br J Cancer 83:366-74, Evers, *et al.*, 2000, Br J Cancer 83:375-83] for MRP1, [Janardan, *et al.*, 1996, Pharmacogenetics 6:379-85, Kivisto, *et al.*, 1996, Br J Clin Pharmacol 42:387-9, Lown, *et al.*, 1994, Drug Metab Dispos 22:947-55, Anttila, *et al.*, 1997, Am J Respir Cell Mol Biol 16:242-9, Tateishi, *et al.*, 1999, Biochem Pharmacol 57:935-9, Gibbs, *et al.*, 1999, Drug Metab Dispos 27:180-7, Maenpaa, *et al.*, 1998, Pharmacogenetics 8:137-55, Haehner, *et al.*, 1996, Mol Pharmacol 50:52-9, Lown, *et al.*, 1994, Drug Metab Dispos 22:947-55] for CYP3A5, [Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202, Iyer, *et al.*, 1999, Clin Pharmacol Ther 65:576-82, Iolascon, *et al.*, 2000, J Med Genet 37:712-3, Raijmakers, *et al.*, 2000, J Hepatol 33:348-51, von Ahsen, *et al.*, 2000, Clin Chem 46:1939-45, Beutler, *et al.*, 1998, Proc Natl Acad Sci U S A 95:8170-4, Kadakol, *et al.*, 2000, Hum Mutat 16:297-306] for UGT1A1.

An altered activity in accordance with the use of the present invention means that the activity of the wild type polypeptide differs significantly from the variant polypeptide. A significant difference can be determined by standard statistical methods referred to herein above.

Most preferably, said altered activity is decreased or increased activity.
As discussed for the increase or decrease of expression, a decrease or increase of the activities is characterized by a significant difference in the activity of the variant versus the wild type polypeptide in the assays referred to herein. Also encompassed by decreased activity is the absence detectable activity of a variant allele.

Moreover, in a further preferred embodiment of the use of the present invention said subject is an animal.
As described supra, the subject in accordance with the use of the present invention encompasses animals. The term "animal" as used herein encompasses all animals, preferably animals belonging to the vertebrate family, more preferably mammals. Moreover, the animals can be genetically engineered by well known techniques

comprising transgenesis and homologous recombination in order to incorporate one or more of the polynucleotides referred to supra into the genome of said animals. Said animals comprising the genetically engineered animals can be used to study the pharmacological effects of drugs or pro-drugs which are based on the substances or derivatives thereof referred to herein, preferably irinotecan.

In accordance with the foregoing, most preferably, said animal is a mouse or rat.
Said animals are particularly well suited for assaying the pharmacological properties of the substances or derivatives referred to in accordance with the use of the present invention as described in detail in Giovanella, *et al.*, 1991, Cancer Res 51:3052-5, Kunimoto, *et al.*, 1987, Cancer Res 47:5944-7, Kaneda, *et al.*, 1990, Cancer Res 50:1715-20.
Preferably, said mouse is lacking functional cytochrome P450, MRP1, or MDR1. It is well known in the art how said mice lacking functional cytochrome P450, MRP1 or MDR1 can be obtained. For instance said mice might be generated by homologous recombination as described for cytochrome P450 in Pineau, *et al.*, 1998, Toxicol Lett 103:459-64, MRP1 in Rappa, *et al.*, 2000, Biochemistry 39:3304-10, and MDR1 in Schinkel, 1998, Int J Clin Pharmacol Ther 36:9-13, Schinkel, *et al.*, 2000, Pharmacogenetics 10:583-90.

Moreover, in another preferred embodiment of the use of the present invention said subject is a human.
In particular, the present invention is applicable to humans as is evident from the above. The use of the present invention is to be applied in order to treat or prevent side effects in patients which suffer from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer. The pharmacological effects of the above substances or derivatives thereof are well described in humans. However, the conventional therapies do not take into account the individual genetic makeup of the patient. Ethnical populations have different genetic backgrounds, which can also influence the function or regulation of a variant allele and thereby alter the pharmacological response of a patient to a substance or derivative used as a basis for a drug or pro-drug in accordance with the invention.

In light of the foregoing, most carefully, said human is selected from the African population who shows compared to Caucasians or Japanese (approx. 50 %) a higher frequency (approx. 80%) of the MDR1 high expressor allele (nucleotide C at a position corresponding to position 137 of the MDR1 gene Acc. No. M29445) and are therefore more likely to suffer from irinotecan toxicity. (population frequency data are from [Cascorbi, *et al.*, 2001, Clin Pharmacol Ther 69:169-74, Ameyaw, *et al.*, 2001, Pharmacogenetics 11:217-21, Ito, *et al.*, 2001, Pharmacogenetics 11:175-84].

In light of the foregoing, most preferably, said human is African or Asian.
The Asian population (16 %) who shows compared to Caucasians (39 %) a lower frequency of the UGT1A1 low expressor genotype (homozygously wildtype at positions corresponding to positions 174990 to 174993 of the UGT1A1 gene Acc. No. GI:11118740) and is therefore less likely to suffer from irinotecan toxicity. On the other hand, this allele is more common in Africans (43 %) who have additionally another low expressor allele (insertion of TA at positions corresponding to positions 174989/174990 of the UGT1A1 gene Acc. No. GI:11118740) the homozygous genotype of which occurs in 7 %. Africans are therefore more susceptible to irinotecan-related adverse events (population frequency data are from [Beutler, *et al.*, 1998, Proc Natl Acad Sci U S A 95:8170-4, Lampe, *et al.*, 1999, Pharmacogenetics 9:341-9, Hall, *et al.*, 1999, Pharmacogenetics 9:591-9]).

The present invention also relates to a method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer, wherein said method comprises:

(a) determining the presence or absence of a first, second, third and/or fourth variant allele referred to above in the genome of a subject in a sample obtained from said subject; and

(b) selecting a suitable therapy for said subject based on the results obtained in (a).

The definitions and explanations of the terms made above apply mutatis mutandis to the above method.

The term "suitable therapy" as used herein means that a substance according to the invention is selected and said substance being administered in a certain dosage to a subject, wherein said substance and said dosage are selected based on the knowledge of the presence or absence of a first, second, third and/or fourth variant allele referred to in accordance with the use of the invention. Said substance and said dosage of the substance are selected in a way that on one hand they are most effective in treating or preventing colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer on the other hand they do not cause toxic or undesirable side effects.
As is evident from the above, a prerequisite for selecting a suitable therapy is the knowledge of the presence or absence of a first, second, third, and/or fourth variant allele referred to in accordance with the use of the invention. Therefore, the method of the present invention encompasses the determination of the presence or absence of said variant alleles in a sample which has been obtained from said subject. The sample which is obtained by the subject comprises biological material which is suitable for the determination of the presence or absence of said variant alleles, such as isolated cells or tissue. Methods for the determination of the presence or absence of the variant alleles of the method of the invention comprise those methods referred to herein above.

Thanks to the method of the present invention, it is possible to efficiently select a suitable therapy for a subject, preferably a human, suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer Thereby, mistreatment of patients based on wrong medications and the results thereof, such as development of resistance towards cancer therapy, and subsequent increased costs in health care, can be efficiently avoided. Furthermore, patients that are at high risk can be excluded from therapy prior to the first dose and/or dosage can be adjusted according to the individual's genetic makeup prior to the onset of drug therapy. Also, inhibitors for the mentioned transporter genes (e.g. MDR1) can be applied in genetically defined patient subpopulations. Thus, adverse effects can be avoided and the optimal drug level can be reached faster without time-consuming and expensive drug monitoring-

based dose finding. This can reduce costs of medical treatment and indirect costs of disease (e.g. shorter time and less frequent hospitalization of patients).

As described supra, the present invention preferably encompasses the use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genome with a first variant allele of MDR1, optionally a second allele of MRP1, optionally a third variant allele of CYP3A5 and optionally a fourth variant allele of UGT1A1. However, other combinations of rank orders are also within the scope of the present invention. In said combinations of rank orders MRP1, UGT1A1 or CYP3A5 may be chosen as the first variant allele, while the remaining variant alleles, i.e. the second, the third and the fourth variant allele may be chosen from the group of genes including MDR1 but lacking the gene chosen as the first variant allele. In conclusion, the first variant allele may be MDR1, MRP1, UGT1A1 or CYP3A5, the second variant allele is selected from the same group of genes excluding the gene chosen as the first variant allele, the third variant allele is selected from the same group of genes excluding the gene chosen as the first and second variant allele and the fourth variant allele is the gene which has not selected as first, second or third variant allele. The explanations and definitions made before apply mutatis mutandis in such cases.

The following 59 items are also encompassed by the present invention. The definitions and explanations made supra apply mutatis mutandis to the terms used to characterize the claims.

1. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) assaying the genotype of the patient to determine if the patient has variant alleles of two or more of the MDR1 gene, the MRP1 gene, the CYP3A5 gene, and the UGT1A1 gene; and

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in

the two or more of the MDR1 gene, the MRP1 gene, the CYP3A5 gene, and the UGT1A1 gene.

2. The method of item 1 wherein the MDR1 gene is one of the two or more genes.

3. The method of item 1 wherein the genes are MDR1 and MRP1.

4. The method of item 1 wherein the genes are MDR1 and CYP3A5.

5. The method of item 1 wherein the genes are MDR1 and UGT1A1.

6. The method of item 1 wherein the genes are MDR1, MRP1 and CYP3A5.

7. The method of item 1 wherein the genes are MDR1, MRP1, and UGT1A1.

8. The method of item 1 wherein the genes are MDR1, MRP1, and CYP3A5.

9. The method of item 1 wherein the genes are MDR1, CYP3A5, and UGT1A1.

10. The method of item 1 wherein the genes are MRP1 and UGT1A1.

11. The method of item 1 wherein the genes are MRP1 and CYP3A5.

12. The method of item 1 wherein the genes are MRP1, CYP3A5 and UGT1A1.

13. The method of item 1 wherein the genes are MRP1 and UGT1A1.

14. The method of item 1 wherein the genes are CYP3A5 and UGT1A1.

15. The method of any one of items 1 wherein the cancer is colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, or pancreatic cancer.

16. The method of item 15 in which:

(a) the one or more variant alleles result in the patient expressing low amounts of the MDR1 gene product, whereby the amount of irinotecan administered to the patient is decreased to avoid toxicity; or

(b) the one or more variant alleles result in the patient expressing high amounts of the MDR1 gene product, whereby the amount of irinotecan administered to the patient is increased to enhance efficacy.

17. The method of item 16 wherein the variant alleles are in the promoter regions of the two or more genes.

18. The method of item 16 wherein the variant alleles are in the coding regions of the two or more genes.

19. The method of item 16 wherein each of the two or more genes has two or more variant alleles.

20. The method of item 16 wherein each of the two or more genes has one or more variant alleles in the promoter region and one or more variant alleles in the coding region.

21. The method of item 16 wherein each of the two or more genes has one or more variant alleles in the promoter region or one or more variant alleles in the coding region.

22. The method of item 16 wherein the one or more variant alleles are not in either the promoter region or the coding region of the two or more genes.

23. The method of item 16 wherein when MDR1 is one of the two or more genes the one or more variant alleles comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422,

425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482, 485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 and/or 641;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 606, 608, 610, 612, 618, 620, 622, 624, and/or 628;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance 1 (MDR1) gene, wherein said polynucleotide is having at a position corresponding to positions 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619 of the MDR1 gene (Accession No: AC002457) and/or 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162 of the MDR1 gene (Accession No: AC005068) and/or 101, 308 of the MDR1 gene (Accession No: M29432) and/or 137, 176 of the MDR1 gene (Accession No: M29445), a substitution or deletion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having at a position corresponding to position 83946, 70200, 70237, 65241 of the MDR1 gene (Accession No: AC005068) and/or 101 of the MDR1 gene (Accession No: M29432) and/or 141529, 174901, 139177, 140118, 140568, 140727, 139479 of the MDR1 gene (Accession No: AC002457) an A, at a position corresponding to position 308 of the MDR1 gene (Accession No: M29432) and/or 84701, 83973, 84074, 84119, 78170, 70204, 70253, 70371, 50537, 43162 of the MDR1 gene (Accession No: AC005068) and/or 137 or 176 of the MDR1 gene (Accession No: M29445) and/or 145984, 171466, 175068, 175074, 139064, 139276, 140576 of the MDR1 gene (Accession No: AC002457) a T, at a position corresponding to position 140837, 171404, 171456, 171511, 171512, 139119, 140490, 139619 of the MDR1 gene (Accession No: AC002457) and/or 43263 of the MDR1 gene (Accession No: AC005068) a C, at a position corresponding to position 84032, 77811, 73252 of the MDR1 gene

(Accession No: AC005068) and/or 141590, 175142, 175180, 139015, 140216, 140595 of the MDR1 gene (Accession No: AC002457) a G;

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to positions 21, 103, 168, 400, 893, 999, 1001, 1107, and/or 1141 of the MDR1 polypeptide (Accession No: G2506118);

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118).

24. The method of item 23 wherein when the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 345, 417 or 636:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 612 or 618;

(c) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432), 176 of the MDR1 gene

(Accession No: M29445), or 88883 of the MDR1 gene (Accession No: GI:10122135);

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having an A at a position corresponding to position 101 of the MDR1 gene (Accession No: M29432) or 88883 of the MDR1 gene (Accession No: GI:10122135), or a T at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) or 88883 of the MDR1 gene (Accession No: GI:10122135);

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 400 or 893 of the MDR1 polypeptide (Accession No: G2506118); and

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Ser to Asn at a position corresponding to position 400 or Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118).

25. The method of item 16 wherein when MRP1 is one of the two or more genes the one or more variant alleles of MRP1 comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 and/or 334;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 600, 602 and/or 604;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance Protein 1 (MRP1) gene, wherein said polynucleotide is having at a position corresponding to positions 57998, 57853, 53282, and/or 39508 of the MRP1 gene (Accession No: GI:7209451), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 137667, 137647, 137710, 124667, and/or 38646 of the MRP1 gene (Accession No: AC026452), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 27258, 27159, 34218, 34215, 55472, and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 21133, 14008, 18067, 17970, and/or 17900 of the MRP1 gene (Accession No: U91318), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 79, 88, and/or 249 of the MRP1 gene (Accession No: AF022830), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 95 and/or 259 of the MRP1 gene (Accession No: AF022831), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277), a substitution or deletion of at least one nucleotide or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 248 and/or 258 of the MRP1 gene (Accession No: AF022829), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 1884, 1625, 1163, 381, 233, 189, 440, and/or 1720 to 1723 of the MRP1 gene (Accession No: U07050), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 926/927 and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of at least one nucleotide or at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having at a position corresponding to position 21133, 14008 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 27258 and/or 34218 of the MRP1 gene (Accession

No: AC003026) or at a position corresponding to position 79 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 57998, and/or 57853 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137667 and/or 137647 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277) or at a position corresponding to position 248 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 1884, 1625, 233, and/or 189 of the MRP1 gene (Accession No: U07050) an A, at a position corresponding to position 39508 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 17900, 18067 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828) or at a position corresponding to position 440 and/or 1163 of the MRP1 gene (Accession No: U07050) a T, at a position corresponding to position 88 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 27159, 55472 and/or 34215 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 124667 and/or 38646 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137710 of the MRP1 gene (Accession No: AC026452) a C, at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 258 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 259 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 381 of the MRP1 gene (Accession No: U07050) a G, at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) a deletion of a T or at a position corresponding to position 34206 to 34207 of the MRP1 gene (Accession No: AC003026) a deletion of a AT or at a position corresponding to position 1720 to 1723 of the MRP1 gene (Accession No: U07050) a deletion of GGTA, at a position corresponding to position 926/927 a insertion of a T and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of a TCCTTCC, at a

position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of TGGGGC;

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 239 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Ser at a position corresponding to position 433 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Gln at a position corresponding to position 723 of the MRP1 polypeptide (Accession No: G2828206).

26. The method of item 25 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 181, 209, 217, 205, 277, 281, 301, 325, 229, 193, 313, 293 or 253:

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 600;

(c) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 95 of the MRP1 gene (Accession No: AF022831), 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), 381, 440,1625 of the MRP1 gene (Accession No: U07050), 34218 of the MRP1 gene (Accession No: AC003026), 18067 or 17900 of the MRP1 gene (Accession No: U91318) or an insertion of at least one nucleotide at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having a T at a position corresponding to position 137647 of the MRP1 gene (Accession No: AC026452), 18067 or 17900 of the MRP1 gene (Accession No: U91318), 440 of the MRP1 gene (Accession No: U07050), a C at a position corresponding toposition 95 of the MRP1 gene

(Accession No: AF022831), 124667 of the MRP1 gene (Accession No: AC026452), a G at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451), 249 of the MRP1 gene (Accession No: AF022830), 259 of the MRP1 gene (Accession No: AF022831), 381 of the MRP1 gene (Accession No: U07050), or an A at a position corresponding to position 34218 of the MRP1 gene (Accession No: AC003026) or 1625 of the MRP1 gene (Accession No: U07050) or an insertion of a T at a position corresponding to position 926/927 of the MRP1 gene (Accession No: U07050);

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206); and

(f) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 329 of the MRP1 polypeptide (Accession No: G2828206).

27. The method of item16 wherein when CYP3A5 is one of the two or more genes the one or more variant alleles of CYP3A5 comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 137, 138, 141, 142, 145, 146, 149 and/or 150;

(b) a polynucleotide capable of hybridizing to a Cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 5 (CYP3A5) gene, wherein said polynucleotide is having at a position corresponding to positions 47518 and/or 9736 of the CYP3A5 gene (Accession No: GI:10281451), a substitution of at least one nucleotide or at a position corresponding to positions 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452), a substitution of at least one nucleotide;

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having at a position corresponding to position 47518 of the

CYP3A5 gene (Accession No: GI:10281451) a C, at a position corresponding to position 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452) a G or at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451) a G.

28. The method of item 27 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 137, 141, 145 or 149:

(b) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 47518 or 9736 of the CYP3A5 gene (Accession No: GI:10281451) or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452);

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having a C at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) or a G at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451), or 145601 or 145929 of the CYP3A5 gene (Accession No: GI:11177452).

29. The method of item 16 wherein when UGT1A1 is one of the two or more genes the one or more variant alleles comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 and/or 134;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556,

558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 and/or 598;

(c) a polynucleotide capable of hybridizing to a Uridine Diphosphate Glycosyltransferase1 Member A1 (UGT1A1) gene, wherein said polynucleotide is having at a position corresponding to positions 59, 160, 226, 539, 544, 640, 701, 841, 855, 890, 938, 1006, 1007, 1020, 1084, 1085, 1114, 1117, 1139, 1158, 1175 to 1176, 1216, 1297, 1324, 1471, 1478, 372 to 373, 523 to 525, and/or 892 to 905 of the UGT1A1 gene (Accession No. GI:8850235), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 470/471, and/or 1222/1223 of the UGT1A1 gene (Accession No. GI:8850235) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having at a position corresponding to position 226, 539, 701, 855, 938, 1020, and/or 1117 of the UGT1A1 gene (Accession No: GI:8850235) an A, at a position corresponding to position 160, 640, 890, 1006, 1084, 1139, 1176, 1324, and/or 1478 of the UGT1A1 gene (Accession No: GI: 8850235) a T, at a position corresponding to position 544, 841, and/or 1216 of the UGT1A1 gene (Accession No: GI: 8850235) a C, at a position corresponding to position 59, 1007, 1085, 1114, 1158, 1175, 1297, and/or 1471 of the UGT1A1 gene (Accession No: GI:181303) a G, and/or at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TTC, at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TACATTAATGCTTC, at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a T, and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a G;

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Leu to Arg

at a position corresponding to position 15 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 71 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Leu to Gln at a position corresponding to position 175 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Cys to Arg at a position corresponding to position 177 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Trp at a position corresponding to position 209 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Gln at a position corresponding to position 229 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 276 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Val at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Trp at a position corresponding to position 293 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Glu at a position corresponding to position 308 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 331 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 357 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Gly at a position corresponding to position 367 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Thr at a position corresponding to position 368 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Arg at a position corresponding to position 387 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 375 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Arg at a position corresponding to position 381 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Pro at a position corresponding to position 401 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Lys to Glu at a position corresponding to position 428 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 488 of the UGT1A1 polypeptide (Accession No: G8850236);

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide is having at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, whereby in said polypeptide one or more amino acids following amino acid Asp at a position corresponding to position 119 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a T, whereby in said polypeptide one or more amino acids following amino acid Pro at a position corresponding to position 152 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TTC, whereby in said polypeptide one or more amino acids following amino acid Thr at a position corresponding to position 168 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TACATTAATGCTTC, whereby in said polypeptide one or more amino acids following amino acid Ala at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a G, whereby in said polypeptide one or more amino acids following amino acid Lys at a position corresponding to position 402 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted; and

(g) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide comprises an amino acid substitution of Gln to a stop codon at a position corresponding to position 49 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Cys to a stop codon at a position corresponding to position 280 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 331 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Trp to a stop

codon at a position corresponding to position 335 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 357 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Lys to a stop codon at a position corresponding to position 437 of the UGT1A1 gene (Accession No: G8850236).

30. The method of item 29 wherein the polynucleotide is selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NO: 37, 69 or 97;

(b) a polynucleotid encoding a polypeptide having the amino acid sequence of SEQ ID NO: 558, 570 or 584;

(c) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having a substitution at a position corresponding to position 890, 1117 or 1471 of the UGT1A1 gene (Accession No: GI: 8850235);

(d) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having an A at a position corresponding to position 1117, a T at a position corresponding to position 890 or a G at a position corresponding to position 1471 of the UGT1A1 gene (Accession No: GI:8850235);

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to position 292, 368 or 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236); and

(f) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises amino acid substitution of Ala to Val at a position corresponding to position 292, Ala to Thr at aposition corresponding to position 368 or Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: GI: 8850236).

31. A method for determining whether a patient is at risk for a toxic reaction to treatment with irinotecan which comprises determining if the patient has one or more variant alleles of two or more genes, wherein the genes comprise an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene.

32. The method of item 31 which further comprises administering to the patient reduced amounts of irinotecan.

33. A method for determining the optimum treatment regimen for administering irinotecan to a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;
(b) in a patient having one or more such alleles of each of the two or more genes, altering the regimen to reduce peak amounts of irinotecan in the patient in comparison to the peak amount in the patient when irinotecan is administered without regard to the patient's alleles in the two or more genes.

34. The method of item 33 wherein MDR1 is one of the two or more genes.

35. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two or more genes are lower than in the general population and so indicates high sensitivity to irinotecan, the method comprises administering to the patient a decreased amount of irinotecan.

36. The method of item 35 wherein MDR1 is one of the two or more genes.

37. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two

or more genes are higher than in the general population and so indicates resistance or predisposition to resistance to irinotecan, the method comprises administering to the patient an increased amount of irinotecan.

38. The method of item 37 wherein MDR1 is one of the two or more genes.

39. The method of item 37 wherein the patients are treated with one or more inhibitors, further wherein the inhibitors are selected from the group consisting of an inhibitor of MDR1, MRP1, CYP3A5, and UGT1A1.

40. The method of item 39 wherein one of the inhibitors is an MDR1 inhibitor.

41. The method of item 40 wherein the MDR1 inhibitor is selected from the group consisting of: GF120918, LY335979, XR 9576, XR 9051, flavonoids (e.g. apigenin, genistin, naringin, quercetin, flavone, flavonone, flavopiridol), bergamottin, Clarithromycin, Ketoconazole, Reserpine, 1,9-dideoxyforskolin, Azidopine, Dimethyl-b-cyclodextrin, Ivermectin, SDZ PSC 833, SDZ 280-446, B669, B-859-35 (R-enantiomere) and its major metabolite, MS-209 (quinolone derivative), PAK-104p, Amiloride, Amytriptyline, Atorvastatin, Aureobasidin & analogues, Berrylium fluoride (BeFx), Calmodulin inhibitors, Chloroquine, Chloropromazine, Clofazimine, Cremophor EL, Diltiazem, Verapamil, Nifedipine, Bepridil, Nicardipine, Niguldipine, Nitrendipine, Trifluoperazine, Felodipine, Valinomycin, Dipyridamole, Erythromycine, Fluoroquinolones: Fleroxacin, Eenoxacin, Grepafloxacin, Levofloxacin, Norfloxacine, Glibenclamides & analogues, Gluconate salts, Gramicidin, Hydrocortisone, Itraconazole, Lidocaine, Phosphatidyl-choline, Pristinamycin Ia, Propafenone, Propranolol, Talinolol, Pyridine analogue, Quercetin 4'-b-glucoside, Quinine & quinidine, Quinacrine, Cinchonine, Ritonavir , Saquinavir, Nelfinavir, Tamoxifen and metabolites, Taxoid (Tetracyclic taxopine C & derivatives), Terfenadine.

42. The method of item 35 which further comprises monitoring the patient during treatment by assaying for changes in expression levels of the two or more genes in the cancerous cells whereby an increase in the expression level of

the two or more genes is compensated for by an increase in the amount of irinotecan administered to the patient.

43. The method of item 42 wherein MDR1 is one of the two or more genes.

44. A method of treating cancer in a patient which comprises internally administering to the patient an effective amount of irinotecan, wherein the treatment regimen is modified based upon the patient's genotype of genes comprising MDR1, MRP1, CYP3A5, and UGT1A1.

45. A method of treating a population of patients suffering from cancer which comprises:

(a) determining, on a patient by patient basis, if the patient has one or more variant alleles of each of two or more genes comprising an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;

(b) in a patient having one or more of such variant alleles of the two or more genes, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount without regard to the patient's alleles of the two or more genes.

46. The method of item 45 wherein MDR1 is one of the two or more genes.

47. A method for predicting sensitivity to irinotecan in a patient suffering from cancer which comprises determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, which alleles indicate that the cancerous cells express low or high amounts of the proteins of the two or more genes, whereby low expression indicates high sensitivity to irinotecan and high expression indicates resistance or predisposition to resistance to irinotecan.

48. The method of item 47 which further comprises administering to patients that have a genotype that indicates resistance or predisposition to resistance one

or more inhibitors selected from the group consisting of an MDR1 inhibitor, an MRP1 inhibitor, a CYP3A5 inhibitor, and a UGT1A1 inhibitor.

49. The method of item 48 wherein at least one inhibitor is an MDR1 inhibitor.

50. The method of item 49 wherein the MDR1 inhibitor is selected from the group consisting of: GF120918, LY335979, XR 9576, XR 9051, flavonoids (e.g. apigenin, genistin, naringin, quercetin, flavone, flavonone, flavopiridol), bergamottin, Clarithromycin, Ketoconazole, Reserpine, 1,9-dideoxyforskolin, Azidopine, Dimethyl-b-cyclodextrin, Ivermectin, SDZ PSC 833, SDZ 280-446, B669, B-859-35 (R-enantiomere) and its major metabolite, MS-209 (quinolone derivative), PAK-104p, Amiloride, Amytriptyline, Atorvastatin, Aureobasidin & analogues, Berrylium fluoride (BeFx), Calmodulin inhibitors, Chloroquine, Chloropromazine, Clofazimine, Cremophor EL, Diltiazem, Verapamil, Nifedipine, Bepridil, Nicardipine, Niguldipine, Nitrendipine, Trifluoperazine, Felodipine, Valinomycin, Dipyridamole, Erythromycine, Fluoroquinolones: Fleroxacin, Eenoxacin, Grepafloxacin, Levofloxacin, Norfloxacine, Glibenclamides & analogues, Gluconate salts, Gramicidin, Hydrocortisone, Itraconazole, Lidocaine, Phosphatidyl-choline, Pristinamycin Ia, Propafenone, Propranolol, Talinolol, Pyridine analogue, Quercetin 4'-b-glucoside, Quinine & quinidine, Quinacrine, Cinchonine, Ritonavir , Saquinavir, Nelfinavir, Tamoxifen and metabolites, Taxoid (Tetracyclic taxopine C & derivatives), Terfenadine.

51. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the MDR1 gene product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

52. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the MRP1 gene

product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

53. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the CYP3A5 gene product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

54. The method of item 47 wherein the patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of the UGT1A1 gene product in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

55. The method of item 47 wherein patients that have a genotype that indicates resistance or predisposition to resistance are monitored during treatment by assaying for changes of expression levels of two or more of the gene products selected from the group consisting of the MDR1 gene, the MRP1 gene, the CYP3A5 gene, and the UGT1A1 gene in the cancerous cells so that an updated prediction of sensitivity to irinotecan may be determined.

56. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MDR1 gene in the cancerous tissue;
(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MDR1 gene.

57. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MRP1 gene in the cancerous tissue;
(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MRP1 gene.

58. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the UGT1A1 gene in the cancerous tissue;
(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the UGT1A1 gene.

59. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the CYP3A5 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the CYP3A5 gene.

The decreased expression as referred to herein above includes in addition to a significantly decreased amount of transcripts encoding a functional gene product also a normal or even elevated amount of transcripts encoding a gene product which has no activity or a significantly decreased activity.

By "in comparison to the amount that is administered without regard to the patient's alleles in the MDR1 gene" a standard dose is meant which is routinely administered to patients in need thereof without regarding the genotype. Such a general

population of patients is considered as having the normal genotype, i.e. wildtype genotype.

Further, the present invention encompasses a method for improving and/or modifying a therapy comprising determining the expression levels of MDR1, MRP1, UGT1A1, and/or CYP3A5, hereinafter referred to as expression profile or the protein level of the MDR1, MRP1, UGT1A1, and/or CYP3A5 proteins, hereinafter referred to as the protein profile, or the activity level of the said proteins, hereinafter referred to as the activity profile.

The term "expression level" as referred to in the context of the present invention means the detectable amount of transcripts of the MDR1, MRP1, CYP3A5 or UGT1A1 genes relative to the amount of transcripts for a housekeeping gene, such as PLA2. The amount of transcripts can be determined by standard molecular biology techniques including Northern analysis, RNAse protection assays, PCR based techniques encompassing Taq-Man analysis. Preferably, the determination can be carried out as described in the accompanied Examples 4 and 5. The term "expression profile" means that the expression level of a panel of the aforementioned genes is determined and the expression levels are compared to a reference standard. As a reference standard, preferably transcripts are obtained from cells or tissues of a subject having the aforementioned wildtype alleles of the respective genes in their genomes.
The term "protein level" refers to the detectable amount of MDR1, MRP1, CYP3A5 or UGT1A1 relative to the amount of a protein encoded by a housekeeping gene, such as PLA2. The amount of proteins can be determined by standard biochemical techniques, such as Western analysis, ELISA, RIA or other antibody based techniques known in the art. The term "protein profile" means that the protein level of a panel of the aforementioned proteins is determined and the protein levels are compared to a reference standard. As a reference standard, preferably proteins are obtained from cells or tissues of a subject having the aforementioned wildtype alleles of the respective genes in their genomes.

The term "activity level" means the detectable biological activity of MDR1, MRP1, CYP3A5 or UGT1A1 relative to the activity or amount of a encoded by the allelic variants of these genes as disclosed in the present invention relative to the activity of the protein encoded by the corresponding wild-type allele of the gene. Biological assays for the aforementioned proteins are well known in the art and described in Hitzl *et al.*, 2001, Pharmacogenetics 11:293-8, Cuff *et al.*, Toxicol Lett., 2001,

120:43-9, Stevens *et al.*, Drug Metab Dispos., 2001, 29:289-95, Barbier *et al.*, Mol Pharmacol., 2001, 59:636-45, Hanioka *et al.*, Xenobiotica. 2001, 31:687-99, Hallo *et al.*, Anticancer Res. 1998, 18:2981-7. As a reference standard, preferably proteins are obtained from cells or tissues of a subject having the aforementioned wildtype alleles of the respective genes in their genomes.

The aforementioned methods, preferably, comprise the steps (i) obtaining a tumor sample from a patient during specific stages of a tumor therapy; and (ii) determining the expression profile, protein profile or activity profile for MDR1, MRP1, UGT1A1, and/or CYP3A5. Based on the expression profiles a clinician can efficiently adapt the therapy. This comprises inter alia dosage adjustment and/or including administration of an MDR1, MRP1, UGT1A1 or CYP3A5 inhibitor. Preferably, said inhibitor is selected from the following group of inhibitors: for MDR1: GF120918, LY335979, XR 9576, XR 9051, flavonoids (e.g. apigenin, genistin, naringin, quercetin, flavone, flavonone, flavopiridol), bergamottin, Clarithromycin, Ketoconazole, Reserpine, 1,9-dideoxyforskolin, Azidopine, Dimethyl-b-cyclodextrin, Ivermectin, SDZ PSC 833, SDZ 280-446, B669, B-859-35 (R-enantiomere) and its major metabolite, MS-209 (quinolone derivative), PAK-104p, Amiloride, Amytriptyline, Atorvastatin, Aureobasidin & analogues, Berrylium fluoride (BeFx), Calmodulin inhibitors, Chloroquine, Chloropromazine, Clofazimine, Cremophor EL, Diltiazem, Verapamil, Nifedipine, Bepridil, Nicardipine, Niguldipine, Nitrendipine, Trifluoperazine, Felodipine, Valinomycin, Dipyridamole, Erythromycine, Fluoroquinolones: Fleroxacin, Eenoxacin, Grepafloxacin, Levofloxacin, Norfloxacine, Glibenclamides & analogues, Gluconate salts, Gramicidin, Hydrocortisone, Itraconazole, Lidocaine, Phosphatidyl-choline, Pristinamycin Ia, Propafenone, Propranolol, Talinolol, Pyridine analogue, Quercetin 4'-b-glucoside, Quinine & quinidine, Quinacrine, Cinchonine, Ritonavir , Saquinavir, Nelfinavir, Tamoxifen and metabolites, Taxoid (Tetracyclic taxopine C & derivatives), Terfenadine, for MRP1: SDZ-PSC 833, SDZ 280-446, MK571, MS209 (quinolone derivative), PAK-104p, Verapamil, Benzbromarone, Dipyridamole, Furosemide, Gamma-GS(naphtyl)cysteinyl-glycine diethyl ester, Genistein, Quinidine, Rifampicin, RU 486, Sulfinpyrazone, tricyclic isoxazole (e.g. LY 402913) (http://bigfoot.med.unc.edu/watkinsLab/intesinfo.htm, Paul Watkins, University of North Carolina); for UGT1A1: ß-estradiol, 4-hydroxyestrone, 2-hydroxyestrone, 7,8-Benzoflavone, Quercetin, Naringenin, Chrysin, Bilirubin, Octylgallate (Broudy M

(2001), BD Gentest, Woburn MA, USA); and for CYP3A5: Clarithromycin, Erythromycin, Diltiazem, Mibefradil, grapefuit juice, Cimetidine, Ciprofloxacin, Norfloxacin, Fluconazole, Itraconazole, Ketoconazole, Fluvoxamine, Norfluoxetine, Nefazodone, Troleandomycin, Delaviridine, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Mifepristone, gestodene (http://medicine.iupui.edu/flockhart).
The term inhibitor as used herein encompasses competitive and non-competitive inhibitors. Preferably competitive inhibitors are substrates such as (GF120918, LY335979, XR 9576, XR 9051, flavonoids). Preferably non-competitive inhibitors are substrates such as (SDZ PSC 833, SDZ 280-446, B669, B-859-35, Verapamil, MS-209, PAK-104p).

Finally, the present invention encompasses a method for determining whether a patient has developed a resistance against the drugs referred to in the context of the present invention. Said method comprising the steps of (i) obtaining a tumor sample from a patient during specific stages of a tumor therapy; and (ii) determining the expression levels of MDR1, MRP1, UGT1A1, and/or CYP3A5. The expression of the respective genes can be determined as described in Examples 4 and 5 or as described above. Based on the evaluation of said expression profile, a clinician can more efficiently adapt the therapy. This comprises inter alia dosage adjustment and/or including administration of an MDR1, MRP1, UGT1A1 or CYP3A5 inhibitor as defined supra.

Each of the documents cited herein (including any manufacturer's specifications, instructions, etc.) are hereby incorporated by reference.

The nucleic acid and amino acid sequences referred to in this application by sequence identification numbers (SEQ ID NOs.) are listed in the following Tables 1 2, 3 and 4. For positions of polymorphic nucleotides, the following substitute letters are used in the nucleic acid sequences: R, G or A; Y, T or C; M, A or C; K, G or T; S, G or C; W, A or T.

Amino acid sequences are shown in the one letter code. The letter X at polymorphic amino acid positions represents the modified amino acid or its corresponding wild type amino acid (see accession numbers).

Moreover, all nucleic acid and amino acid sequences referred to herein by making reference to GenBank accession numbers are shown in Figures 4 to 29 below.

Table 1: The nucleic acid and amino acid sequences referred to in this application

Gene	Variation SNP	Acc.no.	SEQ ID No	Sequence forward	SEQ ID NO	Sequence reverse	SEQ ID NO	Sequence wt>mut	SEQ ID NO	Sequence wt>mut
UGT1A1	T>G	59GI:8850235	001	GTCCTGGGCC**G**	002	ACACAGCAGC**C**	003	GTCCTGGGCC**K**	004	ACACAGCAGC**M**
				GCTGCTGTGT		GGCCCAGGAC		GCTGCTGTGT		GGCCCAGGAC
UGT1A1	C>T	160GI:8850235	005	GGCCATCCAG**T**	006	TGCTGCAGCT**A**	007	GGCCATCCAG**Y**	008	TGCTGCAGCT**R**
				AGCTGCAGCA		CTGGATGGCC		AGCTGCAGCA		AGCTGCAGCA
UGT1A1	G>A	226GI:8850235	009	CATCAGAGAC**A**	010	TAAAATGCTC**T**G	011	CATCAGAGAC**R**	012	TAAAATGCTC**Y**G
				GAGCATTTTA		TCTCTGATG		GAGCATTTTA		TCTCTGATG
UGT1A1	T>A	539GI:8850235	013	TTGCATGCAC**A**	014	GCTGCATGGC**T**	015	TTGCATGCAC**W**	016	GCTGCATGGC**K**
				GCCATGCAGC		GTGCATGCAA		GCCATGCAGC		GTGCATGCAA
UGT1A1	T>C	544GI:8850235	017	TGCACTGCCA**C**	018	TCCAGGCTGC**G**	019	TGCACTGCCA**Y**	020	TCCAGGCTGC**R**
				GCAGCCTGGA		GTGCATGCAA		GCAGCCTGGA		GTGCATGCAA
UGT1A1	C>T	640GI:8850235	021	CTTCCTGCAG**T**	022	TTCTTCACCC**A**C	023	CTTCCTGCAG**Y**	024	TTCTTCACCC**R**C
				GGGTGAAGAA		TGCAGGAAG		GGGTGAAGAA		TGCAGGAAG

UGT1A1	C>A	701	GI:8850235	025	GTTTATTCCC**A**G TATGCAACC	026	GGTTGCATAC**T** GGGAATAAAC	027	GTTTATTCCC**M** GTATGCAACC	028	GGTTGCATAC**K** GGGAATAAAC
UGT1A1	G>C	841	GI:8850235	029	GGTTTTTGTT**C**G TGGAATCAA	030	TTGATTCCAC**G** AACAAAAACC	031	GGTTTTTGTT**S**G TGGAATCAA	032	TTGATTCCAC**S**A ACAAAAACC
UGT1A1	C>A	855	GI:8850235	033	GAATCAACTG**A** CTTCACCAAA	034	TTTGGTGAAG**T** CAGTTGATTC	035	GAATCAACTG**M** CTTCACCAAA	036	TTTGGTGAAG**K** CAGTTGATTC
UGT1A1	C>T	890	GI:8850235	037	GAATTTGAAG**T**C TACATTAAT	038	ATTAATGTAG**A**C TTCAAATTC	039	GAATTTGAAG**Y** CTACATTAAT	040	ATTAATGTAG**R**C TTCAAATTC
UGT1A1	G>A	938	GI:8850235	041	TTCTCTTTGG**A**A TCAATGGTC	042	GACCATTGAT**T**C CAAAGAGAA	043	TTCTCTTTGG**R**A TCAATGGTC	044	GACCATTGAT**Y** CCAAAGAGAA
UGT1A1	C>T	1006	GI:8850235	045	CAAAATCCCT**T**A GACAGTCCT	046	AGGACTGTCT**A** AGGGATTTTG	047	CAAAATCCCT**Y**A GACAGTCCT	048	AGGACTGTCT**R** AGGGATTTTG
UGT1A1	A>G	1007	GI:8850235	049	AAAATCCCTC**G** GACAGTCCTG	050	CAGGACTGTC**C** GAGGGATTTT	051	AAAATCCCTC**R** GACAGTCCTG	052	CAGGACTGTC**Y** GAGGGATTTT
UGT1A1	G>A	1020	GI:8850235	053	CAGTCCTGTG**A** CGGTACACTG	054	CAGTGTACCG**T** CACAGGACTG	055	CAGTCCTGTG**R** CGGTACACTG	056	CAGTGTACCG**Y** CACAGGACTG
UGT1A1	C>T	1084	GI:8850235	057	GTGGCTACCC**T** AAAACGATCT	058	AGATCGTTTT**A**G GGTAGCCAC	059	GTGGCTACCC**Y** AAAACGATCT	060	AGATCGTTTT**R** GGGTAGCCAC

UGT1A1	A>G	1085GI:8850235	061	TGGCTACCCC**G**	062	CAGATCGTTT**C**	063	TGGCTACCCC**R**	064	CAGATCGTTT**Y**
				AAACGATCTG		GGGGTAGCCA		AAACGATCTG		GGGGTAGCCA
UGT1A1	C>G	1114GI:8850235	065	CCCGATGACC**G**	066	ATAAAGGCAC**C**	067	CCCGATGACC**S**	068	ATAAAGGCAC**S**
				GTGCCTTTAT		GGTCATCGGG		GTGCCTTTAT		GGTCATCGGG

UGT1A1	G>A 1117	GI:885023 5	069	GATGACCCGT**A** CCTTTATCAC	070	GTGATAAAGG**T** ACGGGTCATC	071	GATGACCCGT**R** CCTTTATCAC	072	GTGATAAAGG**Y** ACGGGTCATC
UGT1A1	C>T 1139	GI:885023 5	073	CATGCTGGTT**T** CCATGGTGTT	074	AACACCATGG**A** AACCAGCATG	075	CATGCTGGTT**Y** CCATGGTGTT	076	AACACCATGG**R** AACCAGCATG
UGT1A1	C>G 1158	GI:885023 5	077	TTTATGAAAG**G** TATGCAATG	078	CATTGCATAT**C** TTTCATAAA	079	TTTATGAAAG**S** TATGCAATG	080	CATTGCATAT**S** TTTCATAAA
UGT1A1	CC> 1175 to GT 1176	GI:885023 5	081	AATGGCGTTC**G** TATGGTGATGA	082	TCATCACCAT**AC** GAACGCCATT	083	AATGGCGTTC**Y** ATGGTGATGA	084	TCATCACCAT**SR** GAACGCCATT
UGT1A1	G>C 1216	GI:885023 5	085	GATGGACAAT**C** CAAAGCGCAT	086	ATGCGCTTTG**G** ATTGTCCATC	087	GATGGACAAT**S** CAAAGCGCAT	088	ATGCGCTTTG**S** ATTGTCCATC
UGT1A1	A>G 1297	GI:885023 5	089	AAATGCTCTA**G** AGCAGTCAT	090	ATGACTGCTT**C** AGAGCATTT	091	AAATGCTCTA**R** AGCAGTCAT	092	ATGACTGCTT**Y** AGAGCATTT
UGT1A1	A>T 1324	GI:885023 5	093	CAAAAGTTAC**T** GGAGAACAT	094	ATGTTCTCCT**A** TAACTTTTG	095	CAAAAGTTAC**W** AGGAGAACAT	096	ATGTTCTCCT**W** GTAACTTTTG
UGT1A1	T>G 1471	GI:885023 5	097	CTGGTACCAG**G** ACCATTCCTT	098	AAGGAATGGT**C** CTGGTACCAG	099	CTGGTACCAG**K** ACCATTCCTT	100	AAGGAATGGT**M** CTGGTACCAG
UGT1A1	C>T 1478	GI:885023	101	CAGTACCATT**T**	102	CACGTCCAAG**A**	103	CAGTACCATT**Y**	104	CACGTCCAAG**R**

				5		TTGGACGTG		AATGGTACTG		TTGGACGTG		AATGGTACTG	
UGT1A1	*del*CT	372	to	GI:885023	105	TAAAAAAGG**AC**	106	AGCATAGC**AGT**	107	TAAAAAAGGA**n**C	108	AGCATAGCA**Gn**
		373		5		TGCTATGCT		CCTTTTTTA		TGCTATGCT		TCCTTTTTTA
UGT1A1	*del*TT	523 to 525		GI:885023	109	GCCCACTGT**AT**	110	CATGCAAGA**AT**	111	GCCCACTGTA**n**	112	CATGCAAGAA**nT**
		C		5		TCTTGCATG		ACAGTGGGC		TTCTTGCATG		ACAGTGGGC
UGT1A1	*del*	892 to 905		GI:885023	113	ATTTGAAGC**CT**	114	ATGTTCTCC**AG**	115	ATTTGAAGCC**nT**	116	ATGTTCTCCA**nG**
				5		GGAGAACAT		GCTTCAAAT		GGAGAACAT		GCTTCAAAT
		TACA										
		TTA										
		ATGC										
		TTC										
UGT1A1	*ins*T	470/471		GI:885023	129	CTGACGGACC**C**	130	AAGGAAGGAA**A**	131	CTGACGGACCC	132	AAGGAAGGAAA
				5		**TT**TCCTTCCTT		**TG**GTCCGTCA		**n**TTTCCTTCCTT		**n**GGGTCCGTCA
								G				G
UGT1A1	*ins*G	1222/1223		GI:885023	133	CAATGCAAAG**C**	134	AGTCTCCATG**C**	135	CAATGCAAAGC	136	AGTCTCCATGC
				5		**GG**CATGGAGAC		**CG**CTTTGCATT		**n**GCATGGAGAC		**n**GCTTTGCATTG
						T		G		T		
Cyp3A5	T>C	47518		GI:102814	137	AAGGA**C**TTCTA	138	TAGAA**G**TCCTT	139	AAGGA**Y**TTCTA	140	TAGAA**R**TCCTT
				51								
Cyp3A5	T>G	145601		GI:111774	141	TGGGC**G**TGCAA	142	TTGCA**C**GCCCA	143	TGGGC**K**TGCAA	144	TTGCA**M**GCCCA

52

Cyp3A5	A>G 145929	GI:111774	145	GCCCCGCCTCC	146	GGAGGCGGGG	147	GCCCCRCCTCC	148	GGAGGYGGGG
		52				C				C			
Cyp3A5	A>G 9736	GI:102814	149	CTCACGCTGGG	150	CCCAGCGTGAG	151	CTCACRCTGGG	152	CCCAGYGTCTC
		51											
MRP1	G>A 21133	U91318	169	CCCAAAACACA	170	GCACAGGGTGTGT	171	CCCAAAACACR	172	GCAGGGTGTGY
				CACACCCTGC		GTGTTTTGGG		CACACCCTGC		GTGTTTTGGG
MRP1	G>T 57998	GI:720945	173	ACGCTCAGAGT	174	AGTCCATGAAA	175	ACGCTCAGAGK	176	AGTCCATGAAM
		1		TTCATGGACT		CTCTGAGCGT		TTCATGGACT		CTCTGAGCGT
MRP1	C>T 137667	AC026452	177	GCAGGTGGCCT	178	AATGTGCACAA	179	GCAGGTGGCCY	180	AATGTGCACAR
				TGTGCACATT		GGCCACCTGC		TGTGCACATT		GGCCACCTGC
MRP1	C>T 137647	AC026452	181	TTGCCGTCTAT	182	CAATGGTCACA	183	TTGCCGTCTAY	184	CAATGGTCACR
				GTGACCATTG		TAGACGGCAA		GTGACCATTG		TAGACGGCAA
MRP1	G>A 27258	AC003026	185	GATTCTCTCCAA	186	GATGTTTTCTTG	187	GATTCTCTCCRA	188	GATGTTTTCTYG
				GAAAACATC		GAGAGAATC		GAAAACATC		GAGAGAATC
MRP1	G>A 14008	U91318	189	CTGGGAAGTCA	190	GGGTCAGGGAT	191	CTGGGAAGTCR	192	GGGTCAGGGAY
				TCCCTGACCC		GACTTCCCAG		TCCCTGACCC		GACTTCCCAG
MRP1	C>T 18067	U91318	193	CCACGGCAGCT	194	CCAGGTCCACA	195	CCACGGCAGCY	196	CCAGGTCCACR

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					TGGCCGGGTG	GTGAGTGCAC		TGGCCGGGTG		GTGAGTGCAC				
					ACGTGGCCGG	AGTGCACATG		ACGTGGCCGG		AGTGCACATG				
MRP1	G>C	34215	AC003026	233	CATGTGCACTCT	234	CCGGCCACGTGA	235	CATGTGCACTSS	236	CCGGCCACGTSS			
				237	GTTTCGTTGTA	238	TCCCACCCCCT	239	GTTTCGTTGTR	240	TCCCACCCCCY			
			1		GGGGGTGGGA		ACAACGAAAC		GGGGGTGGGA		ACAACGAAAC			
MRP1	T>C	55472	AC003026	241	TGTCTAATTACA	242	ATCCATTTCTGT	243	TGTCTAATTAYA	244	ATCCATTTCTRT			
					GAAATGGAT		AATTAGACA		GAAATGGAT		AATTAGACA			
MRP1	G>A	150727	AC025277	245	CCATGTCAGCA	246	ACCTGTGTCAT	247	CCATGTCAGCR	248	ACCTGTGTCAY			
					TGACACAGGT		GCTGACATGG		TGACACAGGT		GCTGACATGG			
MRP1	*del*T	17970	U91318	249	CTGGTTTTTTCT	250	TGACCGGAAGA	251	CTGGTTTTTTnC	252	TGACCGGAAGn			
					TCCGGTCA		AAAAACCAG		TTCCGGTCA		AAAAAAACCAG			
MRP1	C>T	17900	U91318	253	TGTCTCCTTTTG	254	TGGGAGAAGCA	255	TGTCTCCTTTYG	256	TGGGAGAAGCR			
					CTTCTCCCA		AAAGGAGACA		CTTCTCCCA		AAAGGAGACA			
MRP1	G>A	18195	U91318	257	CACTGGCACAA	258	CTAGAGGCCAT	259	CACTGGCACAR	260	CTAGAGGCCAY			
					TGGCCTCTAG		TGTGCCAGTG		TGGCCTCTAG		TGTGCCAGTG			
MRP1	G>A	33551	AC025277	261	TGTGACCACAA	262	ACACACTCATTT	263	TGTGACCACAR	264	ACACACTCATYT			
					ATGAGTGTGT		GTGGTCACA		ATGAGTGTGT		GTGGTCACA			
MRP1	C>T	174	AF022828	265	CCAGGCCCCCT	266	CCTGAGGTCTA	267	CCAGGCCCCCY	268	CCTGAGGTCTR			

				AGACCTCAGG		GGGGGCCTGG		AGACCTCAGG		GGGGGCCTGG	
MRP1	C>A 248	AF022829	269	CCTTTCCACT**A**C	270	GAGGCCACAG**T**	271	CCTTTCCACT**M**	272	GAGGCCACAG**K**	
				TGTGGCCTC		AGTGGAAAGG		CTGTGGCCTC		AGTGGAAAGG	
MRP1	C>G 258	AF022829	273	CCTGTGGCCT**G**	274	ATCCTGGATT**C**	275	CCTGTGGCCT**S**	276	ATCCTGGATT**S**A	
				AATCCAGGAT		AGGCCACAGG		AATCCAGGAT		GGCCACAGG	
MRP1	A>G 259	AF022831	277	AAGGTAGGGG**G**	278	TGGCACAGCG**C**	279	AAGGTAGGGG**R**	280	TGGCACAGCG**Y**	
				CGCTGTGCCA		CCCCTACCTT		CGCTGTGCCA		CCCCTACCTT	
MRP1	T>C 124667	AC026452	281	GCGTGCCCAG**C**	282	AAACCCCAGG**G**	283	GCGTGCCCAG**Y**	284	AAACCCCAGG**R**	
				CCTGGGGTTT		CTGGGCACGC		CCTGGGGTTT		CTGGGCACGC	
MRP1	G>A 1884	U07050	285	AGCCTTGGAG**A**	286	CACCCCAGAT**T**	287	AGCCTTGGAG**R**	288	CACCCCAGAT**Y**	
				ATCTGGGGTG		CTCCAAGGCT		ATCTGGGGTG		CTCCAAGGCT	
MRP1	G>C 38646	AC026452	289	CCTTAAACAG**C**	290	CTTTTCAAAT**G**C	291	CCTTAAACAG**S**A	292	CTTTTCAAAT**S**C	
				ATTTGAAAAG		TGTTTAAGG		TTTGAAAAG		TGTTTAAGG	
MRP1	C>A 1625	U07050	293	GGGAATCACT**A**	294	CAGAGAGGTT**T**	295	GGGAATCACT**M**	296	CAGAGAGGTT**K**	
				AACCTCTCTG		AGTGATTCCC		AACCTCTCTG		AGTGATTCCC	
MRP1	C>T 1163	U07050	297	TGTGATCGGC**T**	298	AGCCGAGGCG**A**	299	TGTGATCGGC**Y**	300	AGCCGAGGCG**R**	
				CGCCTCGGCT		GCCGATCACA		CGCCTCGGCT		GCCGATCACA	
MRP1	A>G 381	U07050	301	TGGGGGACCC**G**	302	TTTATTGGCC**C**	303	TGGGGGACCC**R**	304	TTTATTGGCC**Y**	

				GGCCAATAAA		GGGTCCCCCA		GGCCAATAAA		GGGTCCCCCA				
MRP1	G>A 233	U07050	305	AAGAGTAGCA**A**	306	CAAGATAAAA**T**T	307	AAGAGTAGCA**R**	308	CAAGATAAAA**Y**T				
				TTTTATCTTG		GCTACTCTT		TTTTATCTTG		GCTACTCTT				
MRP1	C>A 189	U07050	309	AAAAAAATCC**A**A	310	TTTTTGGATT**T**G	311	AAAAAAATCC**M**	312	TTTTTGGATT**K**G				
				ATCCAAAAA		GATTTTTTT		AATCCAAAAA		GATTTTTTT				
MRP1	C>T 440	U07050	313	CTCCTTCCCT**T**G	314	AGGACCTAGC**A**	315	CTCCTTCCCT**Y**	316	AGGACCTAGC**R**				
				CTAGGTCCT		AGGGAAGGAG		GCTAGGTCCT		AGGGAAGGAG				
MRP1	*del*AT 34206 to 34207	AC003026	317	AGTCTCACA**CG**	318	GTGAGTGCA**CG**	319	AGTCTCACA**C**n	320	GTGAGTGCA**C**n				
				TGCACTCAC		TGTGAGACT		GTGCACTCAC		GTGTGAGACT				
MRP1	*del*GG1720 to TA 1723	U07050	321	ACTCCAGGC**AG**	322	GAACGGAGC**CT**	323	ACTCCAGGC**A**n	324	GAACGGAGC**C**n				
				GCTCCGTTC		GCCTGGAGT		GCCTCCGTTC		TGCCTGGAGT				
MRP1	*ins*T 926/ 927	U07050	325	TTAATTTTTTTT**T**	326	AAATAATAA**TAA**	327	TTAATTTTTTTT**T**n	328	AAATAATAA**T**nA				
				ATTATTATTT		AAAAAAATTAA		ATTATTATTT		AAAAAAATTAA				
MRP1	*ins*TC 437/ 438	U07050	329	TTCCTCCTTC**CT**	330	ACCTAGCGA**GG**	331	TTCCTCCTTCC**n**	332	ACCTAGCGAG**A**				
	CTTC			**CCTTCCCT**CGC		**GAAGGAG**GAAG		CTCGCTAGGT		GGAAGGAGGAA				
	C			TAGGT		GAGGAA								
MRP1	*ins*TG 55156/	AC003026	333	GGGGCTGGGG	334	CACGCACCCG**A**	335	GGGGCTGGGG	336	CACGCACCCG**n**				
	GGG			**CTGGGGCT**GGG		**CCCCGA**CCCAG		C**n**TGGGTGCGT		ACCCAGCCCC				
	C 55157			TGCGTG		CCCC		G						

MDR1	T>C 140837	AC002457	337	GCTCATTCGAG	338	AGAGCCGCTGC	339	CTCATTCGAGY	340	AGAGCCGCTRC
				CAGCGGCTCT		TCGAATGAG		AGCGGCTCTT		TCGAATGAG
MDR1	G>A 84701	AC005068	341	AAAATTGCTATC	342	AGATAGTGATA	343	AAAATTGCTRTC	344	AGATAGTGAYA
				ACTATCT		GCAATTTT		ACTATCT		GCAATTTT
MDR1	G>A 101	M29432	345	TTCACTTCAATT	346	ATGGGTAATTG	347	TCACTTCARTTA	348	GATGGGTAAYT
				ACCCATC		AAGTGAA		CCCATC		GAAGTGAA
MDR1	C>T 308	M29432	349	CTTGAAGGGTC	350	TCAGGTTCAGA	351	TCTTGAAGGGY	352	TCAGGTTCAGR
				TGAACCTGA		CCCTTCAAGA		CTGAACCTG		CCCTTCAAGA
MDR1	C>T 83946	AC005068	353	TCAGCAGTTAC	354	TGCAATGTAACT	355	CAGCAGTYACA	356	TGCAATGTRAC
				ATTGCA		GCTGA		TTGCAC		TGCTGA
MDR1	G>A 83973	AC005068	357	GACCCATGCAA	358	GGTCTAGCTTG	359	GACCCATGCRA	360	GGTCTAGCTYG
				GCTAGACC		CATGGGTC		GCTAGACC		CATGGGTC
MDR1	A>G 84032	AC005068	361	GAGCACAACGG	362	CAGCTGGACGG	363	GAGCACAACRG	364	CAGCTGGACYG
				TCCAGCTG		TTGTGCTC		TCCAGCTG		TTGTGCTC
MDR1	G>A 84074	AC005068	365	TGGGCAGACAG	366	CAGGGCCACTG	367	TGGGCAGACRG	368	CAGGGCCACYG
				TGGCCCTG		TCTGCCCA		TGGCCCTG		TCTGCCCA
MDR1	G>A 84119	AC005068	369	CTCGTCCTGAT	370	CAAGATCTATCA	371	CTCGTCCTGRT	372	CAAGATCTAYCA
				AGATCTTG		GGACGAG		AGATCTTG		GGACGAG

MDR1	A>G	77811	AC005068	373	GGCTTGAAGGT	374	ATTCTTACACCT	375	GGCTTGAAGRT	376	ATTCTTACAYCT
					GTAAGAAT		TCAAGCC		GTAAGAAT		TCAAGCC
MDR1	T>A	78170	AC005068	377	TATTCCTTTACA	378	CAAAAATTTGTA	379	TATTCCTTTACW	380	ACAAAAATTWG
					AATTTTTG		AAGGAATA		AATTTTTG		TAAAGGAAT
MDR1	A>G	73252	AC005068	381	ACTTTGTCTGAT	382	GCAGGAGATCA	383	ACTTTGTCTRAT	384	GCAGGAGATYA
					CTCCTGC		GACAAAGT		CTCCTGC		GACAAAGT
MDR1	G>A	141529	AC002457	385	CTTCAGGTCGG	386	CAAGATCCATTC	387	CTTCAGGTCGG	388	CAAGATCCATY
					AATGGATCTTG		CGACCTGA		RATGGATCTTG		CCGACCTGAAG
MDR1	A>G	141590	AC002457	389	AAACTGAACGA	390	TACCTTTTATCG	391	AAACTGAACRAT	392	TACCTTTTATYG
					TAAAAGGTA		TTCAGTTTAA		AAAAGGTA		TTCAGTTTAA
MDR1	C>T	70200	AC005068	393	TTCTCCTTTATGG	394	CTAACACCCAT	395	TTCTCCTTTAYGG	396	CTAACACCCRT
					GTGTTAG		AAGGAGAA		GTGTTAG		AAGGAGAA
MDR1	C>A	70204	AC005068	397	AATTTTCTCATT	398	CACCCGTAATG	399	AATTTTCTCMTT	400	CACCCGTAAKG
					ACGGGTG		AGAAAATT		ACGGGTG		AGAAAATT
MDR1	C>T	70237	AC005068	401	TTAATTGGCTAT	402	GTCCAAAATAG	403	TTAATTGGCYAT	404	GTCCAAAATRG
					TTTGGAC		CCAATTAA		TTTGGAC		CCAATTAA
MDR1	G>A	70253	AC005068	405	TCTACTGGTATT	406	TAAGACAAATAC	407	TCTACTGGTRTT	408	TAAGACAAAYAC
					TGTCTTA		CAGTAGA		TGTCTTA		CAGTAGA

MDR1	C>A	70371	AC005068	409	AATCATTTTATG TGCCACA	410	TGTGGCACATA AAATGATT	411	AATCATTTTMTG TGCCACA	412	TGTGGCACAKA AAATGATT
MDR1	C>T	137	M29445	413	GAACATTGCTTA TGGAGAC	414	GTCTCCATAAG CAATGTTC	415	GAACATTGCYTA TGGAGAC	416	GTCTCCATARG CAATGTTC
MDR1	C>T	176	M29445	417	GAAGAGATTGT GAGGG	418	CCCTCACAATC TCTTC	419	GAAGAGATYGT GAGGGC	420	CCCTCACRATC TCTTC
MDR1	A>C	43263	AC005068	421	TGAATGTTCCG TGGCTCCG	422	CGGAGCCACCG AACATTCA	423	TGAATGTTCMG TGGCTCCG	424	CGGAGCCACKG AACATTCA
MDR1	T>A	43162	AC005068	425	CGGGTGGTGACAC ACAGGAAG	426	CTTCCTGTGTCA CCACCCG	427	CGGGTGGTGTGW CACAGGAAG	428	CTTCCTGTGWC ACCACCCG
MDR1	C>T	145984	AC002457	429	AAAATACTTTGG AAATTTG	430	CAAATTTCCAAA GTATTTT	431	AAAATACTTYGG AAATTTG	432	CAAATTTCCRAA GTATTTT
MDR1	T>C	171404	AC002457	433	ATCATTAAACGA AATGAGT	434	ACTCATTTCGTT TAATGAT	435	ATCATTAAAYGA AATGAGT	436	ACTCATTTCRTT TAATGAT
MDR1	G>C	171456	AC002457	437	GACTAAAGACA CATAAATG	438	CATTTATGTGTC TTTAGTC	439	GACTAAAGASA CATAAATG	440	CATTTATGTSTC TTTAGTC
MDR1	G>T	171466	AC002457	441	GACATAAATGTT ATGTTTGTTT	442	AAACAAACATAA CATTTATGTCT	443	AGACATAAATG KTATGTTTGT	444	AAACAAACATA MCATTTATGTC

MDR1	T>C	171511	AC002457	445	GATACAGGGCT CTTCATGA	446	TCATGAAGAGC CCTGTATC	447	GATACAGGGYT CTTCATGA	448	TCATGAAGARC CCTGTATC
MDR1	T>C	171512	AC002457	449	GATACAGGGTC CTTCATGAAT	450	ATTCATGAAGG ACCCTGTATC	451	GATACAGGGTY CTTCATGAAT	452	ATTCATGAAGR ACCCTGTATC
MDR1	G>A	174901	AC002457	453	GTGCACGATAT TGGGGAGC	454	GCTCCCCAATA TCGTGCAC	455	GTGCACGATRT TGGGGAGC	456	GCTCCCCAAYA TCGTGCAC
MDR1	C>T	175068	AC002457	457	TAAGCAGCAAT AATGTCGTGT	458	ACACGACATTA TGCTGCTTA	459	TAAGCAGCAAY AATGTCGTGT	460	ACACGACATTR TGCTGCTTA
MDR1	C>T	175074	AC002457	461	CAACAATGTTGT GTGCATC	462	GATGCACACAA CATTGTTG	463	CAACAATGTYGT GTGCATC	464	GATGCACACRA CATTGTTG
MDR1	A>G	175142	AC002457	465	CATTAAATGGA GGACTGGG	466	CCCAGTCCTCC ATTTAATG	467	CATTAAATGRAG GACTGGG	468	CCCAGTCCTYC ATTTAATG
MDR1	A>G	175180	AC002457	469	TCCTCTGAGGA TGTGCAGT	470	ACTGCACATCC TCAGAGGA	471	TCCTCTGAGRA TGTGCAGT	472	ACTGCACATYCT CAGAGGA
MDR1	A>G	139015	AC002457	473	AACTTACTTGTA TCTTTGA	474	TCAAAGATACAA GTAAGTT	475	AACTTACTTRTA TCTTTGA	476	TCAAAGATAYAA GTAAGTT
MDR1	A>T	139064	AC002457	477	AGAAATAGTTTA ATCAACA	478	TGTTGATTAAAC TATTTCT	479	AGAAATAGTWT AATCAACA	480	TGTTGATTAWA CTATTTCT

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MDR1	G>A	140727	AC002457	517	CCGGGCCGGAA	518	ATGACTGCTTC	519	CCGGGCCGGRA	520	ATGACTGCTYC
					GCAGTCAT		CGGCCCGG		GCAGTCAT		CGGCCCGG
MDR1	G>A	139479	AC002457	521	GAGGCGGGCA	522	CTCGTGATCTG	523	GAGGCGGGCR	524	CTCGTGATCYG
					GATCACGAG		CCCGCCTC		GATCACGAG		CCCGCCTC
MDR1	T>C	139619	AC002457	525	GGAGAATGGCG	526	CGGGTTCACGC	527	GGAGAATGGYG	528	CGGGTTCACRC
					TGAACCCG		CATTCTCC		TGAACCCG		CATTCTCC
MDR1	G>T	65241	AC005068	636	ACTAGAAGGTT	637	ACCTTCCCAGA	638	ACTAGAAGGTK	639	ACCTTCCCAGM
					CTGGGAAGGT		ACCTTCTAGT		CTGGGAAGGT		ACCTTCTAGT
MDR1	G>A	50537	AC005068	640	TCCTGACTATA	641	TTGGCTTTGGT	642	TCCTGACTATRC	643	TTGGCTTTGGY
					CAAAGCCAA		ATAGTCAGGA		CAAAGCCAA		ATAGTCAGGA
TOP1	1334	13341845	GI:112252	529	ACTTTTCCGTTG	530	TTGCCGCGGCA	531	ACTTTTCCGTKG	532	TTGCCGCGGCM
	G>T		59		CCGCGGCAACT		ACGGAAAAGTT		CCGCGGCAACT		ACGGAAAAGTT
							C				C
TOP1	1845	1845	GI:112252	533	CTCGGGAAGGG	534	TCTGATGGAGC	535	CTCGGGAAGGR	536	TCTGATGGAGY
	A>G		59		CTCCATCAGA		CCTTCCCGAG		CTCCATCAGA		CCTTCCCGAG

Table 2: The nucleic acid and amino acid sequences referred to in this application

Gene	AS change	Protein Acc No	SEQ ID NO	Protein	SEQ ID N=	Protein wt>mut
UGT1A1	L15R	G8850236	538	PLVLGRLLCVL	539	PLVLGXLLCVL
UGT1A1	G71R	G8850236	540	LYIRDRAFYTL	541	LYIRDXAFYTL
UGT1A1	D119Dframeshift	G8850236	542	KKIKKDCYAFC	543	KKIKKDX
UGT1A1	P152Pframeshift	G8850236	544	VMLTDPFPSLQ	545	VMLTDPX
UGT1A1	F170del	G8850236	546	LSLPTVFLHAL	547	LSLPTVFX
UGT1A1	L175Q	G8850236	548	FFLHAQPCSLE	549	FFLHAXPCSLE
UGT1A1	C177R	G8850236	550	LHALPRSLEFE	551	LHALPXSLEFE
UGT1A1	R209W	G8850236	552	MTFLQWVKNML	553	MTFLQXVKNML
UGT1A1	P229Q	G8850236	554	DVVYSQYATLA	555	DVVYSXYATLA
UGT1A1	G276R	G8850236	556	NMVFVRGINCL	557	NMVFVXGINCL
UGT1A1	A292V	G8850236	558	SQEFEVYINAS	559	SQEFEXYINAS

UGT1A1	Y293Wframeshift	G8850236	560	QEFEAWRTWN	561	QEFEAXINASG
UGT1A1	G308E	G8850236	562	VVFSLESMVSE	563	VVFSLXSMVSE
UGT1A1	Q331R	G8850236	564	LGKIPRTVLWR	565	LGKIPXTVLWR
UGT1A1	Q357R	G8850236	566	VKWLPRNDLLG	567	VKWLPXNDLLG
UGT1A1	R367G	G8850236	568	GHPMTGAFITH	569	GHPMTXAFITH
UGT1A1	A368T	G8850236	570	HPMTRTFITHA	571	HPMTRXFITHA
UGT1A1	P387R	G8850236	572	ICNGVRMVMMP	573	ICNGVXMVMMP
UGT1A1	S375F	G8850236	574	ITHAGFHGVYE	575	ITHAGXHGVYE
UGT1A1	S381R	G8850236	576	HGVYERICNGV	577	HGVYEXICNGV
UGT1A1	A401P	G8850236	578	DQMDNPKRMET	579	DQMDNXKRMET
UGT1A1	R403Rframeshift	G8850236	580	MDNAKRHGD.	581	MDNAKX
UGT1A1	K428E	G8850236	582	LENALEAVIND	583	LENALXAVIND
UGT1A1	Y486D	G8850236	584	LTWYQDHSLDV	585	LTWYQXHSLDV
UGT1A1	S488F	G8850236	586	WYQYHFLDVIG	587	WYQYHXLDVIG

UGT1A1	Q49stop	G8850236	588	LGAIQ*	589	LGAIQ*			
UGT1A1	C280stop	G8850236	590	VGGIN*	591	VGGIN*			
UGT1A1	Q331stop	G8850236	592	LGKIP*	593	LGKIP*			
UGT1A1	W335stop	G8850236	594	PQTVL*	595	PQTVL*			
UGT1A1	Q357stop	G8850236	596	VKWLP*	597	VKWLP*			
UGT1A1	K437stop	G8850236	598	NDKSY*	599	NDKSY*			
MRP1	F329C	G2828206	600	YFLMSCFFKAI	601	YFLMSXFFKAI			
MRP1	R433S	G2828206	602	SVDAQSFMDLA	603	SVDAQXFMDLA			
MRP1	R723Q	G2828206	604	QNDSLQENILF	605	QNDSLXENILF			
MDR1	N21D	G2506118	606	FFKLNDKSEKD	607	FFKLNXKSEKD			
MDR1	F103L	G2506118	608	INDTGLFMNLE	609	INDTGXFMNLE			
MDR1	V168I	G2506118	610	FDVHDIGELNT	611	FDVHDXGELNT			
MDR1	S400N	G2506118	612	RNVHFNYPSRK	613	RNVHFXYPSRK			
MDR1	G412G	G2506118	614	VKILKGLNLKV	615	VKILKXLNLKV			

MDR1	T436T	G2506118	616	CGKSTTVQLMQ	617	CGKSTXVQLMQ		
MDR1	A893S	G2506118	618	KELEGSGKIAT	619	KELEGXGKIAT		
MDR1	A999T	G2506118	620	FAPDYTKAKIS	621	FAPDYXKAKIS		
MDR1	A1001T	G2506118	622	PDYAKTKISAA	623	PDYAKXKISAA		
MDR1	Q1107P	G2506118	624	KRLNVPWLRAH	625	KRLNVXWLRAH		
MDR1	A1132A	G2506118	626	IAENIAYGDNS	627	IAENIXYGDNS		
MDR1	S1141T	G2506118	628	NSRVVTQEEIV	629	NSRVVXQEEIV		
MDR1	I1145I	G2506118	630	VSQEEIVRAAK	631	VSQEEXVRAAK		
TOP1	G363C	G12644118	632	PGLFRCRGNHP	633	PGLFRXRGNHP		
TOP1	D533G	G12644118	634	DFLGKGSIRYY	635	DFLGKXSIRYY		

Table 3: Selected nucleic acid sequences referred to in this application

Gene	Variation	SNP	Genbank Accession No	SEQ ID NO
UGT1A1	C>T	890	GI:8850235	037
UGT1A1	G>A	1117	GI:8850235	069
UGT1A1	T>G	1471	GI:8850235	097
Cyp3A5	T>C	47518	GI:10281451	137
Cyp3A5	T>G	145601	GI:11177452	141
Cyp3A5	A>G	145929	GI:11177452	145
Cyp3A5	A>G	9736	GI:10281451	149
MRP1	C>T	137647	AC026452	181
MRP1	T>C	95	AF022831	209
MRP1	C>G	53282	GI:7209451	217
MRP1	T>G	249	AF022830	205
MRP1	A>G	259	AF022831	277
MRP1	T>C	124667	AC026452	281
MRP1	A>G	381	U07050	301
MRP1	*ins*T	926/927	U07050	325
MRP1	G>A	34218	AC003026	229
MRP1	C>T	18067	U91318	193
MRP1	C>T	440	U07050	313
MRP1	C>A	1625	U07050	293
MRP1	C>T	17900	U91318	253
MDR1	G>A	101	M29432	345
MDR1	C>T	176	M29445	417
MDR1	G>T	88883	GI:10122135	636

Table 4 Selected amino acid sequences referred to in this application

Gene	AA change	Protein Genbank No	SEQ ID NO
UGT1A1	A292V	G8850236	558
UGT1A1	A368T	G8850236	570
UGT1A1	Y486D	G8850236	584
MRP1	F329C	G2828206	600
MDR1	S400N	G2506118	612
MDR1	A893S	G2506118	618

The figure show:

Figure 1 shows the correlation of the exon 26 SNP with inestinal MDR1 expression in 21 volunteres determined by Western blot analyses. The box plot shows the distribution of MDR1 expression clustered according to the MDR1 3435C>T genotype at position corresponding to position 176 of the MDR1 gene (GenBank Acc. No. M29445). The T allele was associated with a lower expression of p-glycoprotein.

Figure 2 shows the correlation of MDR1 3435C>T genotype and digoxin uptake in 14 healthy volunteers who participated in a clinical study that addresses peak plama levels of digoxin at steady state [Johne et al., 1999, Clin. Pharmacol. Ther 66:338-345]. Maximum digoxin levels were statistically significantly different (p=0.006, Mann Whitney U test) between the two groups which were homozygous for the T and C allele, respectively.

Figure 3 represent the correlation of the genotype (wt/wt: 1; wt/mut and mut/mut:2) with MRP1 mRNA content in duodenal biopsies from healthy volunteers derived from two independent experiments, before and after application of rifampicin. Treatment with rifampicin had no effect on MRP1 mRNA expression ($p<0.001$, paired t-test). A strong trend of an association of MRP1 genotype with MRP1 mRNA levels was detected (p=0.086, Kruskal-Wallis test).

Figures 4 to 28 show the nucleic acid and amino acid sequences referred to herein.

Figure 29 shows the expression profile of genes relevant to Irinotecan metabolism in carcinoma cell lines. This semiquantitativ RT-PCR shows amounts of transcripts for the genes indicated right to the amplicons. PCR products were analyzed by agarose electrophoresis, stained with ethidium bromid. The respective fragment sizes are indicated on the left in basepaires (bp).

Figure 30 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with epithelial carcinoma cell lines LS174T (colon), KB 3-1 (cervix) and RT112 (bladder). Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200

ng/ml. Cells were treated for three days. The data for each concentration are mean values of at least three wells.

Figure 31 growth inhibition curves for CPT-11 (A) and SN-38 (B) with a epithelial cervix carcinoma cell line KB 3-1 and two subclones expressing high amounts of MDR1, KB 3-1 (MDR1) and KB 3-1 (MDR1, CYP3A5). Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml. Cells were treated for three days. The data for each concentration are mean values and standard deviation of at least three wells.

Figure 32 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with the bladdercancer cell line RT112 and and its subclones RT112 (MDR1, UGT1A1) expressing MDR1 and higher amounts of UGT1A1. Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml. Cells were treated for three days. The data for each concentration are mean values and standard deviation of at least three wells.

Figure 33 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with inhibition of MDR1 by R-Verapamil. The epithelial cervix carcinoma cell line KB 3-1 and the two subclones KB 3-1 (MDR1) and KB 3-1 (MDR1, CYP3A5), with high MDR1 expression, were tested for the influence of MDR1 inhibition by R-Verapamil on drug sensitivity. Concentrations of CPT-11 ranged from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml and R-Verapamil was added to 10 μg/ml final concentration(+V). Cells were treated for three days. The data for each concentration are mean values of two wells.

Figure 34 shows growth inhibition curves for CPT-11 (A) and SN-38 (B) with inhibition of MDR1 by R-Verapamil. To circumvent the MDR1 effect on drug resistance cells were treated in parallel with R-Verapamil. The KB 3-1 (MDR1) and KB 3-1 (MDR1, CYP3A5), which differ in their CYP3A5 expression, were tested for remaining resistance after inhibition of MDR1. Concentrations of CPT-11 ranged

from 0 to 200 μg/ml and of SN-38 from 0 to 200 ng/ml and R-Verapamil was added to 10 μg/ml final concentration(+V). Cells were treated for three days. The data for each concentration are mean values of two wells.

The present invention is illustrated by reference to the following biological Examples which are merely illustrative and are not to be constructed as a limitation of the scope of the present invention.

Example 1: Phenotypically impact of the C to T substitution at position corresponding to position 176 of the MDR1 gene (Acc. No. M29445).

To investigate the influence of the single nucleotide C to T substitution at position corresponding to position 176 of the MDR1 gene (Acc. No. M29445) also referred to as MDR1 exon 26 SNP C3435T on intestinal P-glycoprotein (PGP) expression, samples from biopsies and duodenal enterocyte preparations from 21 were investigated at the Dr. Margarete Fischer-Bosch-Institute for Clinical Pharmacology in Stuttgart by quantitative immunohistochemistry and Western blots. The results are shown in Figure 1. Homozygous carriers of the T allele (having at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) a T) demonstrated significantly higher PGP levels compared to homozygous carriers of the C allele (having at a position corresponding to position 176 of the MDR1 gene (Accession No: M29445) a C). Individuals with heterozygous genotype showed an intermediate level of PGP expression.

Furthermore, the influence of the MDR1 genotype on intestinal uptake-related pharmacokinetics of digoxin was investigated in a clinical study at the University Medical Center, Charite in Berlin. Maximal digoxin blood levels (Cmax) at steady state were correlated with the MDR1 3435C>T genotype 14 healthy volunteers after oral application of digoxin. Figure 2 shows, volunteers homozygous for the T allele show statistically significantly lower digoxin levels than volunteers with a C/C genotype. (p=0.006, Mann Whitney U test) and reflects the impact of this polymorphism on digoxin pharmacokinetics.

Example 2: Correlation of MRP1 polymorphisms with MRP1 expression and side effects during therapy with MRP1 substrates

Functional polymorphisms in the MRP1 gene affect the transport activity which in consequence modulates plasma levels and/or intracellular concentrations of MRP1 substrate drugs. Increased levels of such drugs can lead to side effects whereas decreased levels may result in subtherapeutical drug levels and therapy failure. MRP1 polymorphisms were correlated with the occurence of drug-related adverse effects and therapeutic efficacy in patients treated with MRP1 substrate drugs. In a case-control study, the frequency distribution of MRP1 SNPs was compared between a group of patients who suffered from cisplatin-related nephrotoxicity and a group of patients with nephro- and hepatotoxicities caused from anti-cancer drugs with a group of healthy controls. Furthermore, samples of known MRP1 mRNA levels were screened for MRP1 genotype. The results in the group of patients demonstrating nephro- and hepatotoxicity during anti-cancer treatment, are listed in the following table for one MRP1 SNP:

SNP	group	Allele frequency [%]		Genotype frequency [%]		
		G allele	A allele	*G/A	*A/A	*A/A expected[2]
150727G>A[1]	Controls	66.7	33.3	50	8.3	10.9
	Cases	50.0	50.0	14.3	42.9	25.0

[1]according to Acc. No. AC025277

[2] calculated according to Hardy-Weinberg

In contrast to control samples, the A allele (substitution of G to A at position according to position 150727 of the MRP1 gene, Acc. No. AC025277) was statistically significantly overrepresented in patients suffering from drug-related kidney- and liver side effects compared to healthy controls ($p=0.044$, Chi^2 test) and was thus predictive for these side effects.

Furthermore, an association of MRP1 genotype with mRNA expression before and after rifampicin application was detected for two MRP1 SNP's, 95T>C (SEQ ID NOs. 209, 210, 211, and 212, nucleotide substitution of T to C at a position corresponding to position 95 of the MRP1 gene, Acc. No. AF022831) and 259A>G (SEQ ID NOs. 277, 278, 279, and 280, nucleotide substitution of A to G at a position corresponding to position 259 of the MRP1 gene, Acc. No. AF022831). These SNPs are linked and form one allele. The mutant allele (MRP1mut, C at position 95 and G at position 259 of the MRP1 gene, Acc. No. AF022831) is statistically significantly correlated with decreased MRP1 mRNA expression and the wildtype allele (MRP1wt, T at position 95 and A at position 259 of the MRP1 gene, Acc. No. AF022831) with increased MRP1 expression in two independent experiments (with and without rifampicin induction), as illustrated in figure 3.

The differences in the MRP1 mRNA content are based on MRP1 genotype-related interindividual differences and the analysis of these SNP's is of high diagnostic and prognostic value for MRP1 expression levels and to predict the therapeutic outcome and adverse effects of MRP1 substrate drugs.

Example 3: Dosage calculation

Therapeutic efficacy ans adverse effects of irinotecan depend on plasma levels and intracellular concentrations of the parent compound and the active metabolites (e.g. SN-38), processes which are controlled by CYP3A5- and UGT1A1-related metabolism and MRP1- and MDR1-related transport processes [Atsumi, *et al.*, 1991, Xenobiotica 21:1159-69, Iyer, *et al.*, 1998, J Clin Invest 101:847-54, Ciotti, *et al.*, 1999, Biochem Biophys Res Commun 260:199-202, Santos, *et al.*, 2000, Clin Cancer Res 6:2012-20, Kuhn, 1998, Oncology (Huntingt) 12:39-42, Chen, *et al.*, 1999, Mol Pharmacol 55:921-8, Chu, *et al.*, 1997, Cancer Res 57:1934-8, Chu, *et al.*, 1997, J Pharmacol Exp Ther 281:304-14; Chu, *et al.*, 1998, Cancer Res 58:5137-43, Chu, *et al.*, 1999, Drug Metab Dispos 27:440-1, Chu, *et al.*, 1999, J Pharmacol Exp Ther 288:735-41, Mattern, *et al.*, 1993, Oncol Res 5:467-74, Hoki, *et al.*, 1997, Cancer Chemother Pharmacol 40:433-8, Sugiyama, *et al.*, 1998, Cancer Chemother Pharmacol 42:S44-9]. For example, MRP1 works in close connection with glucuronosyltransferases as part of the cellular detoxification system and is known to transport glucuronosyl conjugates such as SN-38G [König

et al., 1999, Biochim Biophys Acta 1461:377-394, Kerb et al., 2001, Pharmacogenomics 2:51-64]. For example, the extend to which SN-38G is exported from the cell into bile greatly influences the rate of its formation. For an efficient detoxification of SN-38 both processes are necessary, conjugation by UGT1A1 and export of the glucuronide.

The 47518T>C (SEQ ID NOs.137, 138, 139, and 140) and 9736A>G (SEQ ID NOs. 149, 150, 151, 152) nucleotide substitutions of the CYP3A5 gene (Acc. No. GI:10281451), and the 145601T>G (SEQ ID NOs. 141, 142, 143, 144) and 145929A>G (SEQ ID NOs. 145, 146, 147, and 148) nucleotide substitutions of the CYP3A5 gene (Acc. No. GI:11177452) form an high CYP3A5 expression-related allele and are therefore associated with a higher metabolic inactivation of irinotecan. Individuals with this allele are extensive metabolizers (EMs) and are therefore in contrast the reminder poor metabolizers (PMs) less likely to suffer from irinotecan toxicity. Those with one high expressor and one low expressor-related allele are regarded as intermediate metabolizers (IMs).

The 176C>T nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MDR1 gene (Accession No: M29445) is associated with low PGP expression-related low drug efflux, and the 95T>C (SEQ ID NOs. 209, 210, 211, and 212) and the 259A>G (SEQ ID NOs. 277, 278, 279, and 280) nucleotide substitutions of the MRP1 gene (Acc. No. AF022831) are associated with low mRNA expression and the 150727G>A nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MRP1 gene (Accession No: M29445) is associated with low PGP expression-related low drug efflux and the 150727G>A nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MRP1 gene (Accession No: AC025277) is associated with adverse effects. Individuals carrying low transporter expression-related alleles are therefore less capable to clear cells from toxic compounds. Both, transport and metabolism are affected in a gene-dose dependant manner. According to the number of low expression-related alleles of the respective transport protein, individuals can be classified as having either extensive (ET), intermediate (IT) or poor transporter capacity (PT) of the respective gene.

By genetic testing prior to onset of treatment with irinotecan, the MDR1- and MRP1-related transport capacity of the patients can be predicted. The individual risk to adverse effects depends on the number of PM and/or PT alleles Individuals with

PM-related alleles of CYP3A5 and UGT1A1 and PT-related alleles of MDR1 and MRP1 are at the highest risk to suffer from irinotecan toxicity.

Based on this knowledge, the initial dose can be adjusted prior to the first dose as shown by Brockmöller et al. (2000, Pharmacogenomics 1:125) for substrate drugs of CYP2D6, CYP2C9, and CYP2C19.

Dose adjustment can be achieved using a scoring system. For each PM- or PT-related allele a certain score is assigned e.g. a score of 2 is assigned to UGT1A1 PM alleles 226A, (SEQ ID NOs 9, 10, 11, 12, 540, 541) and 701A (SEQ ID NOs. 25, 26, 27, 28, 554, 555), and a score of 1 is assigned to the CYP3A5 PM-related alleles (47523T plus 35649A plus 145601T plus 145929A, 47523T plus 35649G plus 145601G plus 145929G, and 47523C plus 35649A plus 145601T plus 145929A), to the MDR1 low expression allele 176T (SEQ ID NOs.: 417, 418, 419, and 420), to the MRP1 low expression alleles 150727A (SEQ ID NOs. 217, 218, 219, and 220) and 259G (SEQ ID NOs. 277, 278, 279, and 280), to the MRP1 150727A allele (SEQ ID NOs. 217, 218, 219, and 220). After genotyping the scores are summarized and irinotecan dosage is adjusted according to the sum. Each single score corresponds to a dose reduction of 10%, i.e. a score of one corresponds to a 10% dose reduction, a score of two to 20%, a score of 3 to 30%, etc.

Example 4: Culture conditions and biological assays

The human epithelial cervical cancer cell line KB 3-1 with two subclones (KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5)) and the bladder cancer cell line RT112, also with subclone (RT112 ($MDR1^{+}$, UGT1A1)), were cultured in Dulbecco's Modified Eagle Medium (DMEM) including 3.7 g/l $NaHCO_3$, 4.5 g/l D-Glucose, 1.028 g/l N-Acetyl-L-Alanyl-L-glutamine and supplemented with 10% fetal bovine, 1 mM Na-pyruvate and 1% non-essential amino acids. The human colon cancer cell line LS174T was cultured in Dulbecco's modified Eagle medium containing L-glutamine, pyridoxine hydrochloride and 25 mM Hepes buffer without phenol red, supplemented with 10% fetal bovine, 1 mM Na-pyruvate and 1% non-essential amino acids. All cells were incubated at 37°C with 5% CO_2 in a humidified atmosphere.

Drugs

Irinotecan (CPT-11) and its active metabolite SN-38 were provided by Pharmacia. For preparation of stock solutions the substances were dissolved in methanol, 10 mg/ml for CPT-11 and 1 mg/ml for SN-38 and stored at 4°C protected from light. Lower concentrated dilutions were prepared in PBS and cell culture medium. R-Verapamil was applied from SIGMA, dissolved in DMSO to 50 mg/ml and further diluted in PBS.

Treatment of cells with drugs

Cells were seeded in 96-well culture plates 24 h prior to treatment. With respect to differential growth rates KB 3-1 and RT112 cells were seeded at 700 cells/well, RT112 ($MDR1^{+}$, UGT1A1) at 1000 cells/well and KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) at 1200 cells/well. LS174T were seeded at 1.0×10^4 cells/well. Cells were treated with freshly prepared serial dilutions in culture medium, 0, 0.5, 1, 2.5, 5, 7.5, 10, 25, 50, 75, 100 and 200 μg/ml for CPT-11, and 0, 0.1, 0.25, 0.5, 1, 5, 10, 25, 50, 75, 100 and 200 ng/ml for SN-38. Four well were treated with the same drug dilution. Cells were incubated for 3 days at 37°C in a humidified 5% CO_2 atmosphere.

For MDR1 inhibition experiments R-Verapamil was added to 10 μg/ml final concentration in two wells of each drug dilution.

Cytotoxicity assay

A commercially available MTS assay system (Promega, Madison, USA) was used to determine growth inhibition and cell death according to the instructions of the manufacturer. Three days after adding the drugs, 20 μl of the combined MTS/PMS solution was added to each well of the 96-well culture plate. The plate was incubated for at least 45 min at 37°C in a humidified 5% CO_2 atmosphere and the absorbance at 492 nm was measured. The absorbance values of untreated control cells on each plate were set as 100% growth and used to calculate the remaining growth of drug treated cells. Untreated cells on the culture plates served as controls for unaffected growth and survival.

The drug concentration effecting a 50% inhibition of cell growth was defined as the IC_{50}.

RNA preparation and cDNA synthesis

From each cell batch used in these experiments messenger RNA was isolated from cell lysates by oligo-dT magnet beads (μMACS mRNA Isolation Kit; Miltenyi Biotech) following the instructions of the manufacturer. 250 ng mRNA of each cell line was applied in a 20 μl cDNA synthesis reaction with Superscript II reverse transcriptase (Gibco BRL). Dilutions of this cDNAs served as template in transcript specific amplification reactions.

PCR primers and reaction conditions

PCRs were set up in 25 μl reactions with 0.5 units Taq Polymerase (Qiagen), 200 μM nucleotide mix, 5 μl cDNA template dilution and 0.2 μM gene specific primers, as indicated in Table 5. All reactions were run under the same amplification conditions, differing only in number of cycles (table), 2 min pre-denaturation at 94°C, than for amplification: 45 sec denaturation at 94°C, 45 sec annealing at 62°C and 45 sec elongation at 72°C, except for UGT1A1 which needed longer elongation of 2 min.

Table 5: Sequences of gene specific primers and conditions for PCR reactions. F: forward primer; R: reverse primer for mRNA sequences.

Gene	Primer sequence (5'-3')	cDNA dilution	cycle number
MDR1	F: TGCCTTCATCGAGTCACTGCC R: TCACTGGCGCTTTGTTCCAGC	1:100	26
MRP1	F: TCTCCAAGGAGCTGGACACA R: CGTGGTGACCTGCAATGAGT	1:10	30
UGT1A	F: GATGATGCCCTTGTTTGGTG	1:100	30

	R: TGTTTTCAAGTTTGGAAATGACTAGGG		
UGT1A1	F: AACCTCTGGCAGGAGCAAAGG R: TGTTTTCAAGTTTGGAAATGACTAGGG	1:10	34
CYP3A4	F: TCAGCCTGGTGCTCCTCTATCTAT R: AAGCCCTTATGGTAGGACAAAATATTT	1:10	34
CYP3A5	F: TTGTTGGGAAATGTTTTGTCCTATC R: ACAGGGAGTTGACCTTCATACGTT	1:10	34
PLA2 (house keeping gene)	F: GCTGGTTCAGAAGGCCAAAC R: GGGCCAGACCCAGTCTGATA	1:100	26

Example 5: Expression of genes involved in irinotecan metabolism

Messenger RNA was isolated from the human bladder cancer cell line RT112, its subclone RT112 (MDR1, UGT1A1), the human epithelial cervical cancer cell line KB 3-1 and two subclones KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5), and the colon carcinoma cell line LS174T (ATCC CL-188). These mRNAs were reverse transcribed into cDNA and applied as templates in transcript-specific amplification reactions to determine the expression levels of genes involved in irinotecan transport and metabolism (MDR1, MRP1, UGT1A, UGT1A1, CYP3A4, CYP3A5). Amplification of the house keeping gene phospholipase A2 (PLA2) was used as a control for comparable cDNA amounts in the reactions.

The amplification reactions in figure 29 show that the carcinoma cell lines RT112, KB 3-1, and LS174T have no or very low expression of MDR1, respectively. RT112 (MDR1, UGT1A1) is a subclone of RT112, which was selected for resistance to cytotoxic drugs as described in Seemann et al. (Urol Res 1995; 22:353-360), and is characterised by a moderately increased MDR1 expression. The drug resistant subclones KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) were derived similarly from the original KB 3-1 cell line by exposure to MDR1 substrates. These subclones are characterized by highly increased MDR1 expression. They show >20-times more transcripts than the original KB 3-1 cells, implicating a very high

MDR1 activity. MRP1 is expressed at the same level in all cell lines. Transcripts of UGT1A enzymes are present only in RT112, RT112 (MDR1, UGT1A1), and LS174T cells. UGT1A1 is only weakly expressed in RT112, stronger expressed in RT112 (MDR1, UGT1A1) and shows highest expression in LS174T cells. CYP3A4 was solely detected in very small amounts in LS174T. RT112 cells, RT112 (MDR1, UGT1A1), and LS174T show a heterozygous expression of the functionally inactive splice variant and the functionally active transcript of CYP3A5. In contrast, KB 3-1 and KB 3-1 ($MDR1^{+++}$) cells have only the active CYP3A5 transcript and the KB 3-1 ($MDR1^{+++}$, CYP3A5) showed the highest expression of the active CYP3A5 transcript, implicating that the latter have the highest CYP3A5 activity.

Example 6: Colon and other epidermal cancer cell lines with no or low MDR1 and CYP3A5 activity are sensitive to CPT-11 and SN-38.

The colon cancer cell line LS174T, the cervical cancer cell line KB 3-1 and the bladder cancer cell line RT112 were seeded in 96-well culture plates 24 h prior to treatment. Four wells of each cell line were incubated with serial dilutions of CPT-11 and SN-38 and analysed as described above. Figure 30 shows that all three epidermal cancer cell lines stop proliferation and die upon treatment with CPT-11 and SN-38. The concentrations resulting in 50% inhibition (IC_{50}) for CPT-11 are 1.5 μg/ml for LS174T, 2.5 μg/ml for RT112 and 5 μg/ml for KB 3-1 cells. The active metabolite of CPT-11, SN-38 shows a 1000-fold higher efficacy than CPT-11, since 10^3-times lower concentrations cause the same degree of growth inhibition and cell death. The IC_{50} of SN-38 is 5 ng/ml for LS174T cells, 4 ng/ml for RT112 cells and 25 ng/ml for KB 3-1 cells.

These results show that all three epidermal cancer cell lines although derived from different tissues are similarly sensitive to CPT-11 and SN-38 treatment. This also indicates that cancer cells expressing no or only low levels of MDR1 (Figure 29) can be efficiently killed by CPT-11 and SN-38 (Figure 30).

Example 7: MDR1 activity correlates with resistance of cancer cells toward CPT-11 and SN-38

Cells of KB 3-1 and its strongly MDR1 expressing subclones KB 3-1 ($MDR1^{+++}$) and the KB 3-1 ($MDR1^{+++}$, CYP3A5) were seeded in 96-well culture 24 h prior to treatment. Four wells of each cell line were incubated with serial dilutions of CPT-11 and SN-38 and treated as described above. The inhibition curves (Figure 31) of the MDR1 high expresser KB 3-1 subclones (KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5)) (Figure 29) demonstrate a significant higher resistance to CPT-11 and SN-38 compared to the MDR1 low expresser KB 3-1 cell line (KB 3-1). The IC_{50} for CPT-11 increases 17 to 40 fold from 5 μg/ml in KB 3-1 to 85 μg/ml in KB 3-1 ($MDR1^{+++}$) and 200 μg/ml in KB 3-1 ($MDR1^{+++}$, CYP3A5) cells. The IC_{50} for SN-38 increases at least 8 times from 25 ng/ml in KB 3-1 to 200 ng/ml in KB 3-1 ($MDR1^{+++}$) and >200 ng/ml in KB 3-1($MDR1^{+++}$, CYP3A5).

CPT-11 and SN-38 are substrates of MDR1, and are therefore removed from the cells by MDR1 activity. The MDR1 expression level correlates inversely with the sensitivity of tumor cells towards CPT-11 and SN-38. Subsequently, the killing of cells with high MDR1 expresser phenotype requires much higher concentrations of CPT-11.

Example 8: UGT1A1 activity correlates with sensitivity towards SN-38 and not towards CPT-11

CPT-11 and SN-38 sensitivity was compared between RT112 cells and its subclone RT112 (MDR1, UGT1A1). Four wells of each cell line were incubated with serial dilutions of CPT-11 and SN-38 and treated as described above.
The difference in sensitivity against CPT-11 is only small as shown in Figure 32A. The IC_{50} of RT112(MDR1, UGT1A1) cells of 4 μg/ml CPT-11 is two-times higher compared to RT112 cells (IC_{50} of 2.5 μg/ml). In contrast to RT112 cells which express no MDR1, RT112 MDR1, UGT1A1) cells express an intermediate amount of MDR1 which can explain the small though significant increase of CPT-11

sensitivity. A much stronger difference exists between RT112 (IC_{50} of 4 ng/ml) and RT112 (MDR1, UGT1A1) cells (IC_{50} of 75 ng/ml) after treatment with SN-38 (Figure 32B). This 19-fold higher resistance of the RT112 (MDR1, UGT1A1) cell line can be explained by the additional detoxifying effect of UGT1A1 which is expressed at a higher level in RT112 (MDR1, UGT1A1) than in RT112 cells (Figure 29). In contrast to SN-38, CPT-11 is not metabolized by UGTs. Therefore, CPT-11-related toxicity is not affected by UGT1A1 expression and the resistance-enhancing capabilitiy of UGTs in RT112(MDR1, UGT1A1) cells is only detected by application of SN-38.

Example 9: MDR1 inhibition serves as sensitizer towards CPT-11 and SN-38 in MDR1 high expressing but not low expressing cancer cells.

The sensitivity of KB 3-1 cells and its subclones KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) against CPT-11 and SN-38 was assessed after blocking MDR1 function using the specific inhibitor R-Verapamil. Four wells of each cell line were incubated with serial dilutions of CPT-11, SN-38 and analysed as described above. Two wells were additionally treated with the MDR1 inhibitor R-Verapamil. Figure 33 shows that addition of R-Verapamil has only marginal effects on the CPT-11 and SN-38 sensitivity of MDR1 low expresser KB 3-1 cells (CPT-11 and SN-38 IC50s of 5 μg/ml and 25 ng/ml without R-Verapamil versus 4.5 μg/ml and 15 ng/m with R-Verapamil, respectively). In contrast, the sensitivity of the MDR1 expressing cells KB 3-1($MDR1^{+++}$) and KB 3-1($MDR1^{+++}$, CYP3A5) towards CPT-11 and SN-38 was 8-fold and 10-fold higher after inhibition of MDR1 transport function with R-Verapamil. The IC_{50} of KB 3-1($MDR1^{+++}$) cells for CPT-11 decreased from 85 μg/ml without to 10 μg/ml with R-Verapamil and from 200 μg/ml without to 25 μg/ml with R-Verapamil in KB 3-1 ($MDR1^{+++}$, CYP3A5) cells. The effect of MDR1 inhibition during SN-38 treatment is even stronger in these MDR1 high expresser cells, R-Verapamil blocked the MDR1 transport completely and they become as sensitive as KB 3-1 cells.

These results demonstrate that the MDR1 activity is relevant for resistance of cancer cells to CPT-11 and SN-38 and that inhibition of MDR1 sensitises the cells, so that they are more efficiently killed at lower drug concentrations.

Example 10: CYP3A5 activity influences resistance to CPT-11

KB 3-1 ($MDR1^{+++}$) and KB 3-1 ($MDR1^{+++}$, CYP3A5) cells which differ by their amounts of CYP3A5 (Figure 29). Four wells of each cell line were incubated with serial dilutions of CPT-11, SN-38 and analyzed as described above. Two wells were additionally treated with the MDR1 inhibitor R-Verapamil.

Because MDR1 activity is a major determinant of cellular sensitivity toward CPT11 and SN-38, the MDR1 activity in these MDR1 high expresser cell lines was completely blocked using an excess of the specific MDR1 inhibitor R-Verapamil to analyze the impact of CYP3A5 on CPT-11 and SN-38 sensitivity without interference of MDR1.

The high CYP3A5 expresser cell line KB 3-1 ($MDR1^{+++}$, CYP3A5) is with an IC_{50} of 25 μg/ml 2.5-times more resistant to CPT-11 than KB 3-1 ($MDR1^{+++}$) showing an IC_{50} of 10 μg/ml (Figure 34). No difference between these two cell lines can be observed regarding their sensitivity towards SN-38.

These experiments demonstrate a significant impact of CYP3A5 expression on the resistance to CPT-11 in contrast to SN-38. The fact that CYP3A5 activity had no influence on SN-38 toxicity further confirms the CYP3A5 effect, because CPT-11 but not SN-38 is metabolized by CYP3A5.

Example 11: MDR1 genotyping improves therapeutic efficacy of irinotecan by genotype-based prediction and monitoring of drug resistance.

Therapeutic efficacy and adverse effects of irinotecan depend on plasma levels and on intracellular tumor concentrations of the parent compound and the active metabolites (e.g. SN-38). The MDR1 gene controls the PGP-dependent penetration of irinotecan across membranes [Luo et al., Drug Metab Dispos 2002, 30:763-770; Jansen et al., Br J Cancer 1998, 77:359-65 Chu et al., J Pharmacol Exp Ther 1999; 288, 735-41; Sugiyama et al., Cancer Chemother Pharmacol 1998, 42 Suppl:S44-9] and is therefore an important determinant for its systemic availability and intracellular accumulation. The 176C>T nucleotide substitution (SEQ ID NOs. 217, 218, 219, and 220) of the MDR1 gene (Accession No: M29445) is associated with low PGP expression-related low drug efflux and patient carrying this substitution are

more likely to respond to irinotecan treatment for two reasons: 1) Due to the lower amount of PGP in enterocytes more irinotecan can enter the body across the intestinal barrier causing more irinotecan to reach its site of action, the tumor. 2) Due to the lower amount of PGP in the tumor cell membranes more irinotecan can penetrate into the tumor cells to deploy its cytotoxic effects. The currently used standard dose of irinotecan kills highly effective most tumor cells within the first cycles of chemotherapy with only very few surviving drug-resistant tumor cells and tolerable adverse events. Independently from the mechanisms of drug resistance, in these patients, the number of surviving cells is to small to develop into a drug-resistant tumor which does not respond any longer to irinotecan therapy.

Patients with the high expresser MDR1 genotype (nucleotide C at position 176 of the MDR1 gene, Accession No: M29445) are less likely to respond to irinotecan treatment. Higher doses would be necessary to achieve a sufficiently efficient killing of tumor cells in order to prevent the development of a drug-resistant tumor. However, elevation of irinotecan dosage is limited due to the occurrence of intolerable adverse events (e.g. diarrhea, neutropenia, or thromboembolic complications). Alternatively, efficacy of irinotecan treatment can be improved by addition of a PGP inhibitor. A PGP inhibitor blocks efficiently the PGP function in MDR1 high expresser patients in such a way as to enable irinotecan to concentrate in the tumor cells for exerting its cytotoxicity as effective as in MDR1 low expresser patients. Consequently, genotypically MDR1 high expresser patients become phenotypically comparable to MDR1 low expressers.

According to the number of low or high expresser alleles of the MDR1 gene, individuals can be classified as having either extensive (ET, two high expresser alleles), intermediate (IT, one high expresser, one low expresser allele) or poor transport capacity (PT, two low expresser alleles). By genetic testing prior to onset of treatment with irinotecan, patients can be classified as ET, IT, or PT and the MDR1-related transport capacity of the patients can be predicted. The individual risk of an insufficient anticancer treatment increases with the number of MDR1 high expresser alleles. Individuals with ET genotype are at the highest risk to suffer from insufficient response to irinotecan and are at the highest risk to develop a drug resistant tumor. ET patients should be treated with a PGP-inhibitor in addition to irinotecan and more closely monitored for adverse events and for the development of chemotherapy-related drug-resistance. Furthermore, these patients, who are at

high risk for developing a drug-resistant tumor, can particularly benefit from taking a tumor biopsy between each cycle of chemotherapy with subsequent individual profiling of tumor cells for drug resistance.

Claims

1. Use of irinotecan or a derivative thereof for the preparation of a pharmaceutical composition for treating colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer in a subject having a genome with a first variant allele which comprises a polynucleotide selected from the group consisting of:

   (a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 337, 338, 341, 342, 345, 346, 349, 350, 353, 354, 357, 358, 361, 362, 365, 366, 369, 370, 373, 374, 377, 378, 381, 382, 385, 386, 389, 390, 393, 394, 397, 398, 401, 402, 405, 406, 409, 410, 413, 414, 417, 418, 421, 422, 425, 426, 429, 430, 433, 434, 437, 438, 441, 442, 445, 446, 449, 450, 453, 454, 457, 458, 461, 462, 465, 466, 469, 470, 473, 474, 477, 478, 481, 482, 485, 486, 489, 490, 493, 494, 497, 498, 501, 502, 505, 506, 509, 510, 513, 514, 517, 518, 521, 522, 525, 526 636, 637, 640 and/or 641;

   (b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 606, 608, 610, 612, 618, 620, 622, 624, and/or 628;

   (c) a polynucleotide capable of hybridizing to a Multidrug Resistance 1 (MDR1) gene, wherein said polynucleotide is having at a position corresponding to positions 140837, 141529, 141590, 145984, 171404, 171456, 171466, 171511, 171512, 174901, 175068, 175074, 175142, 175180, 139015, 139064, 139119, 139177, 139276, 140118, 140216, 140490, 140568, 140576, 140595, 140727, 139479, 139619 of the MDR1 gene (Accession No: AC002457) and/or 84701, 83946, 83973, 84032, 84074, 84119, 77811, 78170, 73252, 70200, 70204, 70237, 70253, 70371, 65241, 50537, 43263, 43162 of the MDR1 gene (Accession No: AC005068) and/or 101, 308 of the MDR1 gene (Accession No: M29432) and/or 137, 176 of the MDR1 gene (Accession No: M29445), a substitution or deletion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MDR1 gene, wherein said polynucleotide is having at a position corresponding to position 83946, 70200, 70237, 65241 of the MDR1 gene (Accession No: AC005068) and/or 101 of the MDR1 gene (Accession No: M29432) and/or 141529, 174901, 139177, 140118, 140568, 140727, 139479 of the MDR1 gene (Accession No: AC002457) an A, at a position corresponding to position 308 of the MDR1 gene (Accession No: M29432) and/or 84701, 83973, 84074, 84119, 78170, 70204, 70253, 70371, 50537, 43162 of the MDR1 gene (Accession No: AC005068) and/or 137 or 176 of the MDR1 gene (Accession No: M29445) and/or 145984, 171466, 175068, 175074, 139064, 139276, 140576 of the MDR1 gene (Accession No: AC002457) a T, at a position corresponding to position 140837, 171404, 171456, 171511, 171512, 139119, 140490, 139619 of the MDR1 gene (Accession No: AC002457) and/or 43263 of the MDR1 gene (Accession No: AC005068) a C, at a position corresponding to position 84032, 77811, 73252 of the MDR1 gene (Accession No: AC005068) and/or 141590, 175142, 175180, 139015, 140216, 140595 of the MDR1 gene (Accession No: AC002457) a G;

(e) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution at a position corresponding to positions 21, 103, 168, 400, 893, 999, 1001, 1107, and/or 1141 of the MDR1 polypeptide (Accession No: G2506118);

(f) a polynucleotide encoding an MDR1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Asn to Asp at a position corresponding to position 21 of the MDR1 polypeptide (Accession No: G2506118) or/and Phe to Leu at a position corresponding to position 103 of the MDR1 polypeptide (Accession No: G2506118) or/and Val to Ile at a position corresponding to position 168 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Asn at a position corresponding to position 400 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Ser at a position corresponding to position 893 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a position corresponding to position 999 of the MDR1 polypeptide (Accession No: G2506118) or/and Ala to Thr at a

position corresponding to position 1001 of the MDR1 polypeptide (Accession No: G2506118) or/and Gln to Pro at a position corresponding to position 1107 of the MDR1 polypeptide (Accession No: G2506118) or/and Ser to Thr at a position corresponding to position 1141 of the MDR1 polypeptide (Accession No: G2506118).

2. The use of claim 1, wherein said subject having a genome with a second variant allele comprising a polynuncleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 169, 170, 173, 174, 177, 178, 181, 182, 185, 186, 189, 190, 193, 194, 197, 198, 201, 202, 205, 206, 209, 210, 213, 214, 217, 218, 221, 222, 225, 226, 229, 230, 233, 234, 237, 238, 241, 242, 245, 246, 249, 250, 253, 254, 257, 258, 261, 262, 265, 266, 269, 270, 273, 274, 277, 278, 281, 282, 285, 286, 289, 290, 293, 294, 297, 298, 301, 302, 305, 306, 309, 310, 313, 314, 317, 318, 321, 322, 325, 326, 329, 330, 333 and/or 334;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 600, 602 and/or 604;

(c) a polynucleotide capable of hybridizing to a Multidrug Resistance Protein 1 (MRP1) gene, wherein said polynucleotide is having at a position corresponding to positions 57998, 57853, 53282, and/or 39508 of the MRP1 gene (Accession No: GI:7209451), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 137667, 137647, 137710, 124667, and/or 38646 of the MRP1 gene (Accession No: AC026452), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 27258, 27159, 34218, 34215, 55472, and/or 34206 to 34207 of the MRP1 gene (Accession No: AC003026), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 21133, 14008, 18067, 17970, and/or 17900 of the MRP1 gene (Accession No: U91318), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 79, 88, and/or 249 of the MRP1 gene (Accession No:

AF022830), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 95 and/or 259 of the MRP1 gene (Accession No: AF022831), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277), a substitution or deletion of at least one nucleotide or at a position corresponding to position 174 of the MRP1 gene (Accession No: AF022828), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 248 and/or 258 of the MRP1 gene (Accession No: AF022829), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 1884, 1625, 1163, 381, 233, 189, 440, and/or 1720 to 1723 of the MRP1 gene (Accession No: U07050), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 926/927 and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of at least one nucleotide or at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of at least one nucleotide;

(d) a polynucleotide capable of hybridizing to a MRP1 gene, wherein said polynucleotide is having at a position corresponding to position 21133, 14008 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to position 27258 and/or 34218 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 79 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 57998, and/or 57853 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137667 and/or 137647 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 150727 and/or 33551 of the MRP1 gene (Accession No: AC025277) or at a position corresponding to position 248 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 1884, 1625, 233, and/or 189 of the MRP1 gene (Accession No: U07050) an A, at a position corresponding to position 39508 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 17900, 18067 and/or 18195 of the MRP1 gene (Accession No: U91318) or at a position corresponding to

position 174 of the MRP1 gene (Accession No: AF022828) or at a position corresponding to position 440 and/or 1163 of the MRP1 gene (Accession No: U07050) a T, at a position corresponding to position 88 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 95 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 27159, 55472 and/or 34215 of the MRP1 gene (Accession No: AC003026) or at a position corresponding to position 124667 and/or 38646 of the MRP1 gene (Accession No: AC026452) or at a position corresponding to position 53282 of the MRP1 gene (Accession No: GI:7209451) or at a position corresponding to position 137710 of the MRP1 gene (Accession No: AC026452) a C, at a position corresponding to position 249 of the MRP1 gene (Accession No: AF022830) or at a position corresponding to position 258 of the MRP1 gene (Accession No: AF022829) or at a position corresponding to position 259 of the MRP1 gene (Accession No: AF022831) or at a position corresponding to position 381 of the MRP1 gene (Accession No: U07050) a G, at a position corresponding to position 17970 of the MRP1 gene (Accession No: U91318) a deletion of a T or at a position corresponding to position 34206 to 34207 of the MRP1 gene (Accession No: AC003026) a deletion of a AT or at a position corresponding to position 1720 to 1723 of the MRP1 gene (Accession No: U07050) a deletion of GGTA, at a position corresponding to position 926/927 a insertion of a T and/or 437/438 of the MRP1 gene (Accession No: U07050) a insertion of a TCCTTCC, at a position corresponding to position 55156/55157 of the MRP1 gene (Accession No: AC003026) a insertion of TGGGGC;

(e) a polynucleotide encoding an MRP1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Phe to Cys at a position corresponding to position 239 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Ser at a position corresponding to position 433 of the MRP1 polypeptide (Accession No: G2828206) or/and Arg to Gln at a position corresponding to position 723 of the MRP1 polypeptide (Accession No: G2828206).

3. The use of claim 1 or 2, wherein said subject having a genome with a third variant allele comprising a polynuncleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 137, 138, 141, 142, 145, 146, 149 and/or 150;

(b) a polynucleotide capable of hybridizing to a Cytochrome P450, subfamily IIIA (niphedipine oxidase), polypeptide 5 (CYP3A5) gene, wherein said polynucleotide is having at a position corresponding to positions 47518 and/or 9736 of the CYP3A5 gene (Accession No: GI:10281451), a substitution of at least one nucleotide or at a position corresponding to positions 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452), a substitution of at least one nucleotide;

(c) a polynucleotide capable of hybridizing to a CYP3A5 gene, wherein said polynucleotide is having at a position corresponding to position 47518 of the CYP3A5 gene (Accession No: GI:10281451) a C, at a position corresponding to position 145601 and/or 145929 of the CYP3A5 gene (Accession No: GI:11177452) a G or at a position corresponding to position 9736 of the CYP3A5 gene (Accession No: GI:10281451) a G.

4. The use of any one of claims 1 to 3, wherein said subject having a genome with a fourth variant allele comprising a polynuncleotide selected from the group consisting of:

(a) a polynucleotide having the nucleic acid sequence of any one of SEQ ID NOs: 001, 002, 005, 006, 009, 010, 013, 014, 017, 018, 021, 022, 025, 026, 029, 030, 033, 034, 037, 038, 041, 042, 045, 046, 049, 050, 053, 054, 057, 058, 061, 062, 065, 066, 069, 070, 073, 074, 077, 078, 081, 082, 085, 086, 089, 090, 093, 094, 097, 098, 101, 102, 105, 106, 109, 110, 113, 114, 129, 130, 133 and/or 134;

(b) a polynucleotide encoding a polypeptide having the amino acid sequence of any one of SEQ ID NOs: 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 564, 566, 568, 570, 572, 574, 576, 578, 580, 582, 584, 586, 588, 590, 592, 594, 596 and/or 598;

(a) a polynucleotide capable of hybridizing to a Uridine Diphosphate Glycosyltransferase1 Member A1 (UGT1A1) gene, wherein said polynucleotide is having at a position corresponding to positions 59, 160, 226, 539, 544, 640, 701, 841, 855, 890, 938, 1006, 1007, 1020, 1084, 1085, 1114, 1117, 1139, 1158, 1175 to 1176, 1216, 1297, 1324, 1471, 1478, 372 to 373, 523 to 525, and/or 892 to 905 of the UGT1A1 gene (Accession No. GI:8850235), a substitution or deletion of at least one nucleotide or at a position corresponding to positions 470/471, and/or 1222/1223 of the UGT1A1 gene (Accession No. GI:8850235) a insertion of at least one nucleotide;

(b) a polynucleotide capable of hybridizing to a UGT1A1 gene, wherein said polynucleotide is having at a position corresponding to position 226, 539, 701, 855, 938, 1020, and/or 1117 of the UGT1A1 gene (Accession No: GI:8850235) an A, at a position corresponding to position 160, 640, 890, 1006, 1084, 1139, 1176, 1324, and/or 1478 of the UGT1A1 gene (Accession No: GI: 8850235) a T, at a position corresponding to position 544, 841, and/or 1216 of the UGT1A1 gene (Accession No: GI: 8850235) a C, at a position corresponding to position 59, 1007, 1085, 1114, 1158, 1175, 1297, and/or 1471 of the UGT1A1 gene (Accession No: GI:181303) a G, and/or at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TTC, at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of TACATTAATGCTTC, at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a T, and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850235) a insertion of a G;

(c) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polypeptide comprises an amino acid substitution of Leu to Arg at a position corresponding to position 15 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position

corresponding to position 71 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Leu to Gln at a position corresponding to position 175 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Cys to Arg at a position corresponding to position 177 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Trp at a position corresponding to position 209 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Gln at a position corresponding to position 229 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Arg at a position corresponding to position 276 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Val at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Trp at a position corresponding to position 293 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gly to Glu at a position corresponding to position 308 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 331 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Gln to Arg at a position corresponding to position 357 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Arg to Gly at a position corresponding to position 367 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Thr at a position corresponding to position 368 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Pro to Arg at a position corresponding to position 387 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 375 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Arg at a position corresponding to position 381 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ala to Pro at a position corresponding to position 401 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Lys to Glu at a position corresponding to position 428 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Tyr to Asp at a position corresponding to position 486 of the UGT1A1 polypeptide (Accession No: G8850236) or/and Ser to Phe at a position corresponding to position 488 of the UGT1A1 polypeptide (Accession No: G8850236);

(d) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide is having at a position corresponding to position 372 to 373 of the UGT1A1 gene (Accession No: GI:8850235) a deletion of CT, whereby in said polypeptide one or more amino acids following amino acid Asp at a position corresponding to position 119 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 470/471 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a T, whereby in said polypeptide one or more amino acids following amino acid Pro at a position corresponding to position 152 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 523 to 525 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TTC, whereby in said polypeptide one or more amino acids following amino acid Thr at a position corresponding to position 168 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 892 to 905 of the UGT1A1 gene (Accession No: GI:8850236) a deletion of TACATTAATGCTTC, whereby in said polypeptide one or more amino acids following amino acid Ala at a position corresponding to position 292 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted and/or at a position corresponding to position 1222/1223 of the UGT1A1 gene (Accession No: GI:8850236) a insertion of a G, whereby in said polypeptide one or more amino acids following amino acid Lys at a position corresponding to position 402 of the UGT1A1 polypeptide (Accession No: G8850236) are substituted, added, and/or deleted; and

(e) a polynucleotide encoding an UGT1A1 polypeptide or fragment thereof, wherein said polynucleotide comprises an amino acid substitution of Gln to a stop codon at a position corresponding to position 49 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Cys to a stop codon at a position corresponding to position 280 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position

331 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Trp to a stop codon at a position corresponding to position 335 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Gln to a stop codon at a position corresponding to position 357 of the UGT1A1 gene (Accession No: G8850236) and/or an amino acid substitution of Lys to a stop codon at a position corresponding to position 437 of the UGT1A1 gene (Accession No: G8850236).

5. The use of any one of claims 1 to 4, wherein a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered expression of the first, second, third and/or fourth variant allele compared to the corresponding wild type alleles.

6. The use of claim 5, wherein said altered expression is decreased or increased expression.

7. The use of any one of claims 1 to 7, wherein a nucleotide deletion, addition and/or substitution comprised by said polynucleotide results in an altered activity of the polypeptide encoded by the first, second, third and/or variant allele compared to the polypeptide encoded by the corresponding wild type allele.

8. The use of claim 6, wherein said altered activity is decreased or increased activity.

9. The use of any one of claims 1 to 8, wherein said subject is an animal.

10. The use of any one of claims 9, wherein said subject is a mouse.

11. The use of any one of claims 1 to 8, wherein said subject is a human.

12. The use of claim 11, wherein said human is African or Asian.

13. A method for selecting a suitable therapy for a subject suffering from colorectal cancer, cervical cancer, gastric cancer, lung cancer, malignant glioma, ovarian cancer, and pancreatic cancer, wherein said method comprises:

(a) determining the presence or absence of a first, second, third and/or fourth, variant allele as specified in any one of claims 1 to 4 in the genome of a subject in a sample obtained from said subject; and

(b) selecting a suitable therapy for said subject based on the results obtained in (a).

14. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) assaying the genotype of the patient to determine if the patient has one or more variant alleles of each of two or more genes, wherein the two or more genes comprise genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene; and

(b) in a patient having such variant alleles of the two or more genes, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the two or more of the genes.

15. A method for determining whether a patient is at risk for a toxic reaction to treatment with irinotecan which comprises determining if the patient has one or more variant alleles of two or more genes, wherein the genes comprise an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene.

16. A method for determining the optimum treatment regimen for administering irinotecan to a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;

(b) in a patient having one or more such alleles of each of the two or more genes, altering the regimen to reduce peak amounts of irinotecan in the patient in comparison to the peak amount in the patient when irinotecan is administered without regard to the patient's alleles in the two or more genes.

17. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two or more genes are lower than in the general population and so indicates high sensitivity to irinotecan, the method comprises administering to the patient a decreased amount of irinotecan.

18. A method of treating cancer in a patient having one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, wherein when expression levels of gene products of the two or more genes are higher than in the general population and so indicates resistance or predisposition to resistance to irinotecan, the method comprises administering to the patient an increased amount of irinotecan.

19. A method of treating cancer in a patient which comprises internally administering to the patient an effective amount of irinotecan, wherein the treatment regimen is modified based upon the patient's genotype of genes comprising MDR1, MRP1, CYP3A5, and UGT1A1.

20. A method of treating a population of patients suffering from cancer which comprises:

(a) determining, on a patient by patient basis, if the patient has one or more variant alleles of each of two or more genes comprising an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene;

(b) in a patient having one or more of such variant alleles of the two or more genes, administering to the patient an amount of irinotecan which is

sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount without regard to the patient's alleles of the two or more genes.

21. A method for predicting sensitivity to irinotecan in a patient suffering from cancer which comprises determining if the patient has one or more variant alleles of each of two or more genes comprising genes selected from the group consisting of an MDR1 gene, an MRP1 gene, a CYP3A5 gene, and a UGT1A1 gene, which alleles indicate that the cancerous cells express low or high amounts of the proteins of the two or more genes, whereby low expression indicates high sensitivity to irinotecan and high expression indicates resistance or predisposition to resistance to irinotecan.

22. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MDR1 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MDR1 gene.

23. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the MRP1 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the MRP1 gene.

24. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the UGT1A1 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the UGT1A1 gene.

25. A method of using irinotecan to treat a patient suffering from cancer which comprises:

(a) determining if the patient has one or more variant alleles of the CYP3A5 gene in the cancerous tissue;

(b) in a patient having one or more of such variant alleles, administering to the patient an amount of irinotecan which is sufficient to treat a patient having such variant alleles which amount is increased or decreased in comparison to the amount that is administered without regard to the patient's alleles in the CYP3A5 gene.

Figure 1

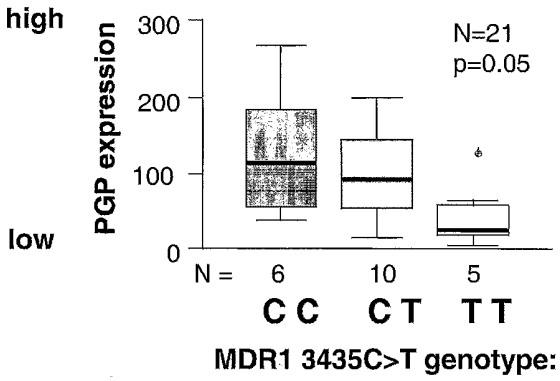
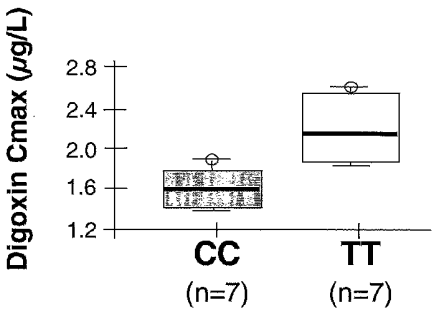

high
low
PGP expression
300
200
100
0
N=21
p=0.05
N = 6 10 5
C C C T T T
MDR1 3435C>T genotype:

Figure 2


Digoxin Cmax (µg/L)
2.8
2.4
2.0
1.6
1.2
CC
(n=7)
TT
(n=7)
MDR1 3435C>T genotype:

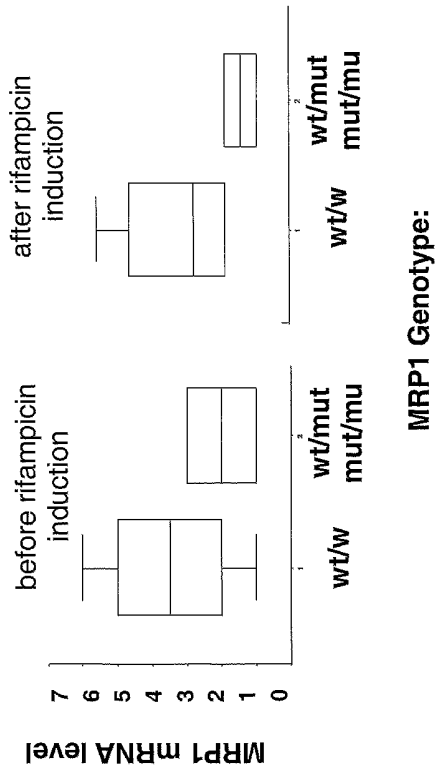

MRP1 mRNA level
0
1
2
3
4
5
6
7
before rifampicin induction
after rifampicin induction
wt/w
wt/mut
mut/mu
MRP1 Genotype:

Figure 3

Figures 4 to 28

represent sequence listings published separately in electronic form and are available upon request from the International Bureau or can be viewed from the following WIPO website :

http://www.wipo.int/pct/en/sequences/index.htm

Figure 29

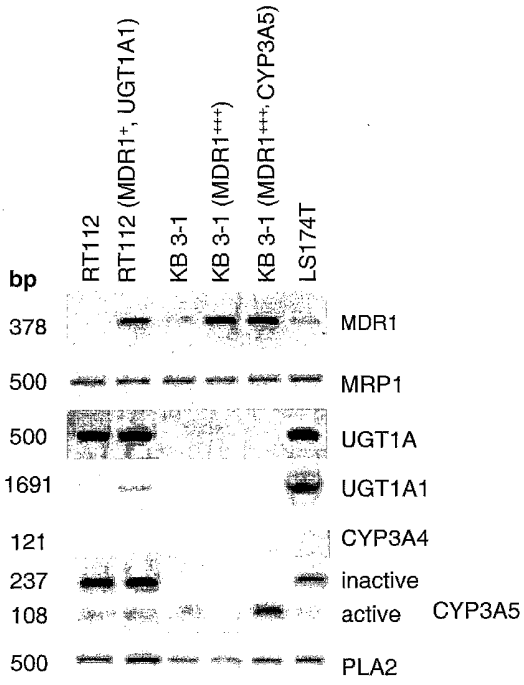
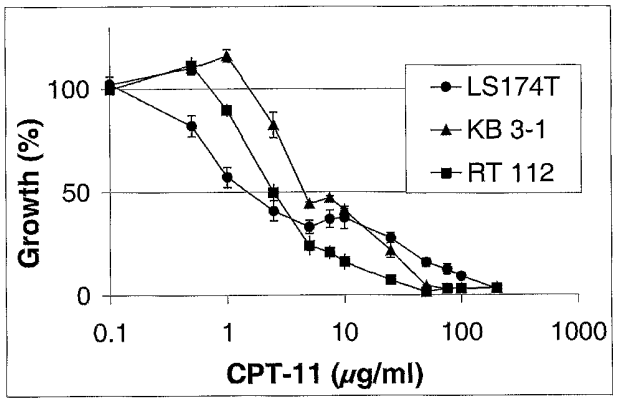

RT112
RT112 (MDR1+, UGT1A1)
KB 3-1
KB 3-1 (MDR1+++)
KB 3-1 (MDR1+++, CYP3A5)
LS174T
bp
378
MDR1
500
MRP1
500
UGT1A
1691
UGT1A1
121
CYP3A4
237
inactive
108
active
CYP3A5
500
PLA2

Figure 30


100
50
0
Growth (%)
0.1
1
10
100
1000
CPT-11 (μg/ml)
LS174T
KB 3-1
RT 112

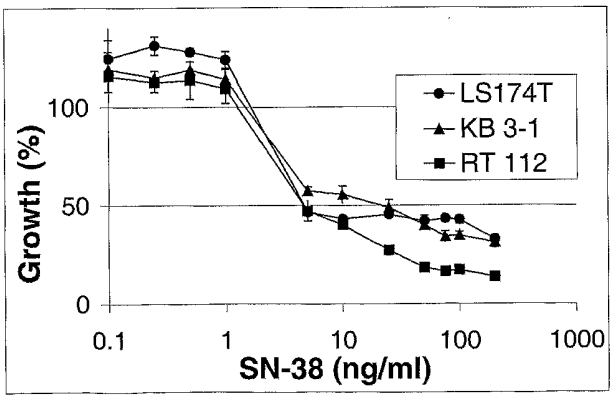
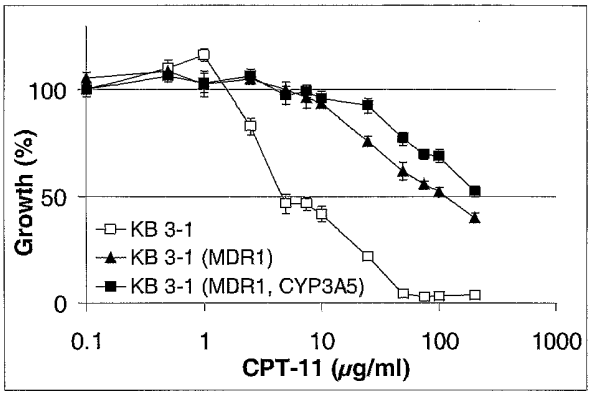

100
50
0
Growth (%)
0.1
1
10
100
1000
SN-38 (ng/ml)
LS174T
KB 3-1
RT 112

Figure 31


100
50
0
Growth (%)
KB 3-1
KB 3-1 (MDR1)
KB 3-1 (MDR1, CYP3A5)
0.1
1
10
100
1000
CPT-11 (μg/ml)

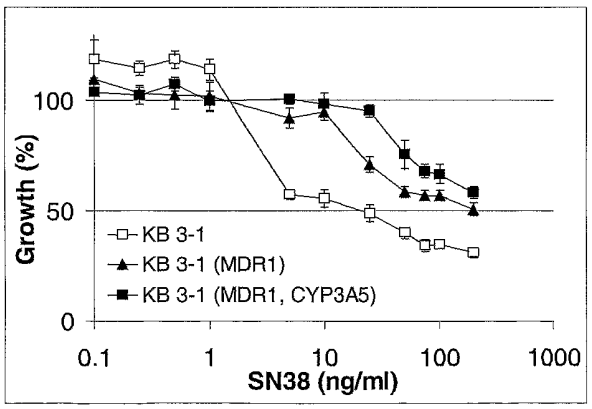

100
50
0
Growth (%)
KB 3-1
KB 3-1 (MDR1)
KB 3-1 (MDR1, CYP3A5)
0.1
1
10
100
1000
SN38 (ng/ml)

Figure 32

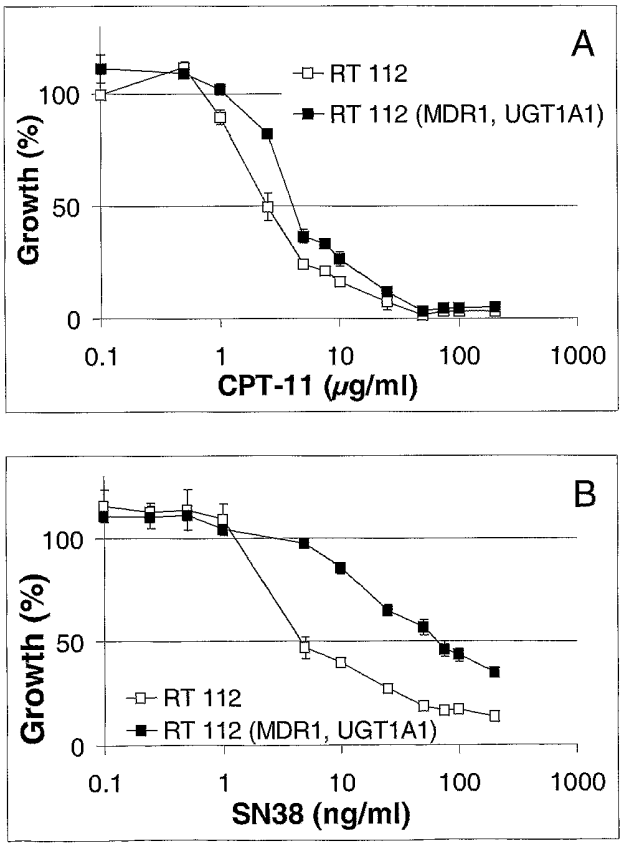
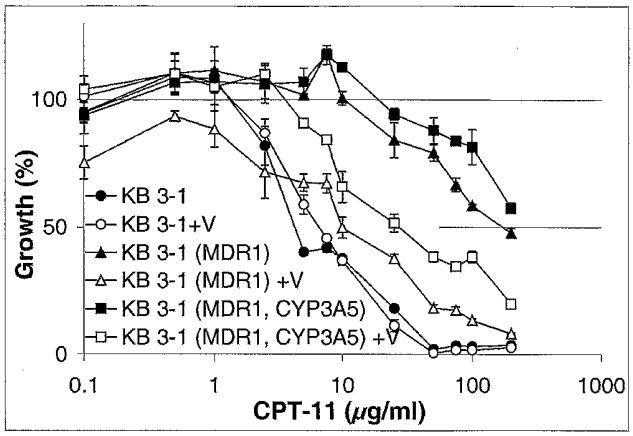

A
RT 112
RT 112 (MDR1, UGT1A1)
Growth (%)
100
50
0
0.1
1
10
100
1000
CPT-11 (μg/ml)
B
RT 112
RT 112 (MDR1, UGT1A1)
Growth (%)
100
50
0
0.1
1
10
100
1000
SN38 (ng/ml)

Figure 33


100
50
0
Growth (%)
KB 3-1
KB 3-1+V
KB 3-1 (MDR1)
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5)
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
CPT-11 (μg/ml)

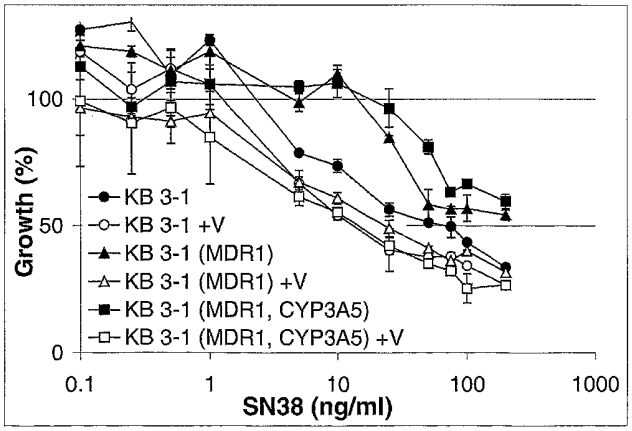
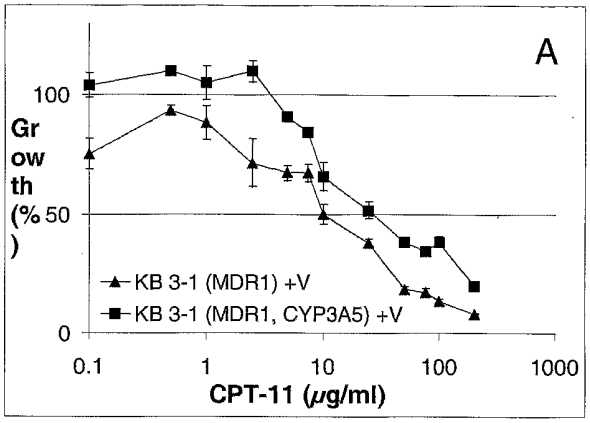
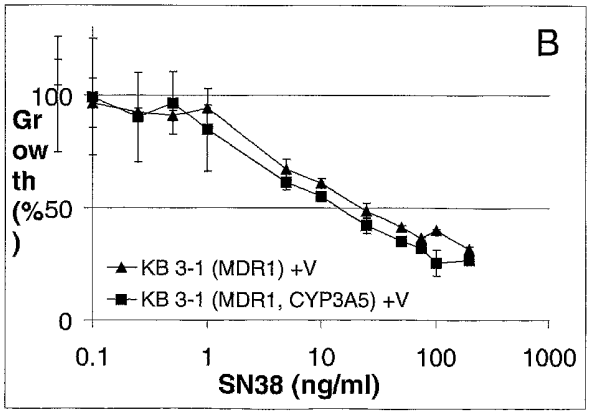

100
50
0
Growth (%)
KB 3-1
KB 3-1 +V
KB 3-1 (MDR1)
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5)
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
SN38 (ng/ml)

Figure 34


A
100
Gr
ow
th
(%
)
50
0
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
CPT-11 (μg/ml)


B
100
Gr
ow
th
(%
)
50
0
KB 3-1 (MDR1) +V
KB 3-1 (MDR1, CYP3A5) +V
0.1
1
10
100
1000
SN38 (ng/ml)

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/08218

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4745 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2003	02/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bonzano, C

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PCT/EP 02/08218

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Ａ６１Ｐ 25/00	Ａ６１Ｐ 25/00		
Ａ６１Ｐ 35/00	Ａ６１Ｐ 35/00		
Ｃ０７Ｄ 491/052	Ｃ０７Ｄ 491/052		
// Ｃ１２Ｎ 15/09	Ｃ１２Ｎ 15/00	ＺＮＡＡ	
Ｃ１２Ｑ 1/68	Ｃ１２Ｑ 1/68	Ａ	

(81)指定国 AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,SK,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OM,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZM,ZW

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(72)発明者 ケルブ，レインホルド
ドイツ国８１２４１ ミュンヘン，エルンスベルガーシュトラーセ １７

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