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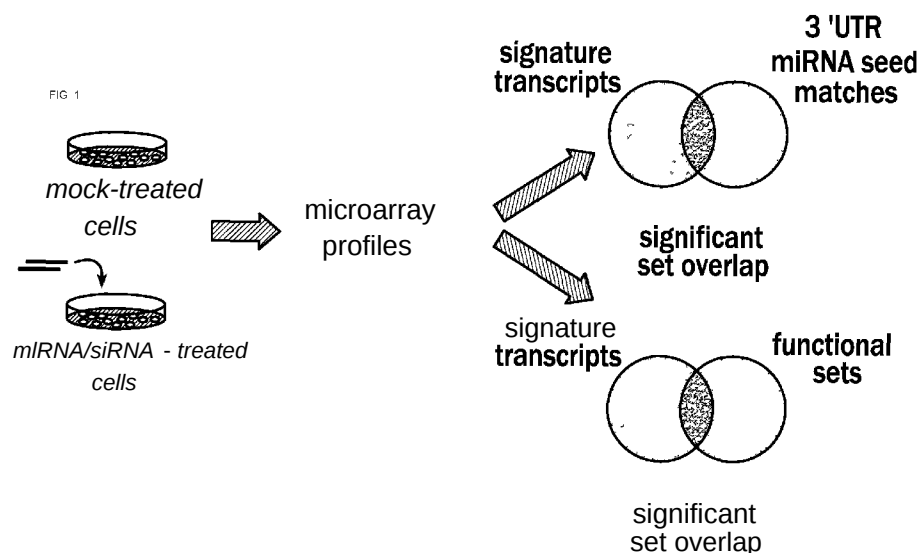
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[Continued on next page]

(54) **Title:** METHODS AND COMPOSITIONS FOR REGULATING CELL CYCLE PROGRESSION



(57) **Abstract:** In one aspect, a method is provided of inhibiting proliferation of a mammalian cell comprising introducing into said cell an effective amount of at least one at least one small interfering RNA agent (iRNA), wherein said iRNA comprises a nucleotide sequence of at least 15 nucleotides, wherein the nucleotide sequence comprises a seed region consisting of nucleotide positions 1 to 12, wherein position 1 represents the 5' end of the iRNA nucleotide sequence and wherein said seed region comprises a nucleotide sequence of at least six contiguous nucleotides that is complementary to six contiguous nucleotides within positions 1 to 12 of a nucleotide sequence, wherein position 1 represents the 5' end of the nucleotide sequence, wherein the nucleotide sequence is selected from the group consisting of SEQ ID NO: 1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7 and SEQ ID NO:8. In some embodiments, the method comprises introducing at least one iRNA that inhibits the expression of at least one miR-16 responsive gene selected from TABLE 5 into the mammalian cell.



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INTERNATIONAL SEARCH REPORT

International application No

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A CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07H 21/02, 21/04, C12Q 1/68 (2008.04)
USPC - 536/23.1

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)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 435/6, 7 23, 9 1 2 1, 536/25 1-25 2 (text search-see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB) and Google Patent/Scholar
Search terms RNA interference, siRNA, cell cycle, CARD10, CDC27, CDK6, m1R-16, kshv-m1R-K12-6-5p

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X ----- Y	US 2004/01521 12 A1 (Croce et al) 05 August 2004 (05 08 2004) para [001 1], [0019], [0038], [0070], [01 13], Fig 1b	1-2, 13-14, 19, 24 ----- 10-12, 15-18, 20-22
Y	US 2006/0019256 A1 (Clarke et al) 26 January 2006 (26 01 2006) para [0008], [0013], [0235], Table 5-6	10-12, 16-18, 20-22
Y	US 2005/0221293 A1 (Tuschl et al) 06 October 2005 (06 10 2005) para [0109], Table A 1	15

☐ Further documents are listed in the continuation of Box C

D

* Special categories of cited documents	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

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Name and mailing address of the ISA/US Mail Stop PCT, Attn ISA/US, Commissioner for Patents P O Box 1450, Alexandria, Virginia 22313-1450 Facsimile No 571-273-3201	Authorized officer Lee W Young PCT Helpdesk 571-272-4300 PCT OSP 571 272 7774

INTERNATIONAL SEARCH REPORT

International application No

PCT/US 07/71239

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

- 1 ☐ Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely

- 2 **D** Claims Nos
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

- 3 ☐ Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box No. IH Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows
see extra sheet

- 1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos
- 4 ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos 1-2, 10-22 and 24, limited to SEQ ID No 3

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation
- ☐ No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

International application No

PCT/US 07/71239

Group 1 claims 1-2, 10-22 and 24, directed to methods of inhibiting proliferation, etc limited to SEQ ID No 3
Group 2 claims 1, 3, 10-22 and 24 limited to SEQ ID No 1
Group 3 claims 1, 4, 10-22 and 24 limited to SEQ ID No 2
Group 4 claims 1, 5, 10-22 and 24 limited to SEQ ID No 4
Group 5 claims 1, 6, 10-22 and 24 limited to SEQ ID No 5
Group 6 claims 1, 7, 10-22 and 24 limited to SEQ ID No 6
Group 7 claims 1, 8, 10-22 and 24 limited to SEQ ID No 7
Group 8 claims 1, 9, 10-22 and 24 limited to SEQ ID No 8
Groups 9-58 claims 1 and 23, limited to one each of SEQ ID No 1-8 and one of SEQ ID No 272-277, 284-295, 248-253, or 344-361
Group 59 claims 25-40, directed to methods for identifying a subset of genes that are responsive to a selected microRNA species, etc
Group 60-101 claims 41-46, directed to compositions of comprising a combination of gene-specific agents, etc, limited to one of SEQ ID Nos 272-277, 284-295, 248-253, or 344-361
Groups 102-227 claims 46-48, directed to isolated dsRNA molecules, etc, limited to one of SEQ ID Nos 236-361

The inventions listed as Groups 1-227 do not relate to a single general inventive concept under PCT Rule 13 1 because under PCT Rule 13 2 they lack the same or corresponding special technical feature. According to PCT Rule 13 2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

Further, Groups 1-8, 9-58, 60-227 of this application contain claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13 1.

The subspecies of Groups 1-8, 9-58, 60-227 are the polynucleotide sequences represented by SEQ ID No 1-8 and 236-361.

The different physical characteristics of the sequences represent distinct traits that are measured using different techniques and compared using different criteria. The different polynucleotide sequences represented by the nucleic acid content of the species are different structures that are not common to one another but are different because they are composed of unique nucleotide sequences.

In addition, respecting Groups 1-8, 9-58 and 60-227, while it is apparent that each dsRNA with a particular SEQ ID NO in groups 9-58 shares a technical feature with same SEQ ID NO in 60-227 (for example, SEQ ID NO 272 is recited in groups 9, 60, and 137 etc), and likewise with respect to Group 2 and Group 9, which share a special technical feature (SEQ ID NO 1) (and the same for Groups 1 and 3 -8, with respect to SEQ ID Nos 3, 2 and 4-8, respectively, and Groups 10-58, the specification teaches how the siRNA were produced using prior art methods and materials. The specification uses the method taught by Jackson et al Nat Biotech 2003 and Genbank nos known in the prior art (see Tables 5 and 6 and page 64 of Jackson, et al). Thus, the groups do not share a special technical feature that defines a contribution over the prior art.

It will also be noted that the methods of the claims of group 1-58 are distinct from the methods of the claims of group 59. It will be readily understood that methods of inhibiting proliferation are distinct from methods for identifying a subset of genes that are responsive to a selected microRNA species in that do not share a common, unknown technical feature as required under PCT Rule 13 2 as described above. Further, it will be readily understood that the compositions of the claims of groups 60-101 are distinct from the isolated dsRNA molecules of the claims of groups 102-227, and further, the claims of each of these groups are distinct from the methods of the claims of groups 1-59, as described above. Thus, groups 1-227 do not share any common, unknown technical feature as required under PCT Rule 13 2 as described above.

In this case the first named invention and first named species that will be searched without additional fees is Group I represented by claims 1-2, 10-22 and 24, limited to SEQ ID No 3.

In order for more than one species to be examined, the appropriate additional examination fees must be paid and the desired species clearly identified.