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(54) Title: VEHICLE FOR THE TRANSPORT OF A CHOSEN MOLECULE TO A CELL

(57) Abstract: Vehicle for the transport of a chosen molecule to a cell, consisting of a Saint-molecule which is bound to the chosen molecule by means of an electrostatic interaction, in which the Saint-molecule is coupled to the linker molecule and the linker molecule is coupled to the cell specific ligand and in which the Saint-molecule is covalently bound to the linker molecule.

WO 2006/043811 A1

Vehicle for the transport of a chosen molecule to a cell.

The presented invention relates to a vehicle for the transport of a chosen molecule to a cell, comprising a SAINT-molecule, which by means of an electrostatic interaction, more particular a non-covalent binding, for instance by hydrogen bonding, is bound to the chosen molecule. Further the invention relates to the application of the SAINT-molecule for a targeted transport of a chosen molecule to a cell.

It is known in the state of the art to administer chosen molecules to a body, in such a way that the chosen molecule has to perform its action in or near the preferred cell of the body. One possibility to deliver such molecules to a cell is the administration of considerable amounts of chosen molecules to the body, whereby, by diffusion, a required concentration of the chosen molecule will be obtained at the targeted cells. A problem of this process is that the chosen molecule might generate undesirable site effects in other parts of the body.

Therefore processes have been developed to deliver chosen molecules, for instance drugs, to a specific location in the body at a specific cell. A first method applied comprises the coupling of the chosen compound to antibodies. Such a coupling is covalent. As an effect, the activity of the chosen compound is substantially reduced in comparison with the activity of the free molecule. Another, currently applied method, is the packaging of the chosen molecules in liposomes. To the outside of the liposome, in which the molecule is packaged, an antibody can be coupled. This coupling of the antibody to the liposome occurs mostly after the inclusion of the chosen molecule in the liposome. In case the coupling of the antibody occurs before the chosen molecule has been included, it is possible that the antibody is located at the inner membrane of the liposome which might result in a

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decreased efficacy of the liposome. A general known disadvantage of inclusion of chosen molecules, for instance pharmaceutical compounds, in liposomes, is that pharmaceuticals will slowly leak from the liposome. A second disadvantage is that the formation of the packaging (the liposome containing the chosen compound inside) has to be performed in a solution containing the chosen compound. During packaging, not more than 5% of the chosen compounds will be included in the liposome. This means that 95% of the chosen compound is not included in the liposomes. Consequently, the efficacy of this method is very low.

Embodiments of the present invention may provide a vehicle which strongly improves the delivery of a chosen compound to a cell.

Embodiments of the present invention may provide a vehicle that enables long-lasting and stable binding to the chosen molecule.

In a first aspect, the present invention provides a vehicle for the transport of a chosen molecule to a cell, the vehicle comprising one or more SAINT-linker molecules, which is characterised in that the SAINT-molecule is covalently bound to the linker molecule which is covalently bound to an antibody or a derivate thereof, a protein, a peptide, a compound that targets a cell-surface, or other compounds with cell specificity. In this way, a very stable process is provided to deliver a chosen molecule at a cell.

Although below hydrogen interaction and hydrogen bonding will be mentioned in general, the interaction is not limited to this single form. In all cases, any kind of electrostatic interaction is referred to.

In this text the word "cell" is used in general. With this, however, as the person skilled in the art will clearly understand, a "specific cell" is mentioned towards which the chosen compound has to be transported to.

According to a second aspect, the present invention provides the application of a SAINT-molecule for the targeted transport of a chosen molecule to a cell, in which the SAINT-molecule is bound to the chosen molecule by means of an electrostatic interaction, and in which the SAINT-molecule is coupled to the linker molecule and the linker molecule is coupled to the cell specific ligand. SAINT-molecule are commonly known, also described as transport vehicle, and are extensively described in the European patent, publication number EP-0755924 B1 and in the American patents with publication numbers US 5,853,694 and US 6,726,894, which is registered to the present applicant. The description of these patent-applications is herewith included by reference, in the present application. SAINT-molecules are, according to a broad description, to be regarded as synthetic amphiphiles.

The way chosen molecules, for instance macromolecules or pharmaceuticals in general, are enwrapped in SAINT-molecules, is described extensively in the aforementioned European patent EP 0755924 B1 and the American Patents US 5,853,694 and US 6,726,894.

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According to a preferred embodiment, the SAINT-molecule is covalently bound to a linker molecule. By means of this covalently coupling it is assured that is an integrated and solid part of the stable vehicle. The linker molecules might be bound to the SAINT-molecules at the positions Rl, R2, R3, R4, R5 and R5' , taking into account that R5 and R5' either can be identical or different. For a more extended description of these type of SAINT-molecules reference is made to US 6,726,894. Examples of the linker molecules are for instance the following: 1-N'-Methyl-4-(aminobutyl, cis-9-oleyl)-methylpyrimidiniumchloride (SAINT-amino-linker), and 1-N'-methyl-4-(N-succinimidyl-S-acetylthio-acetate, cis-9-oleyl)-methylpyridiniumchloride (SAINT-SATA-linker). In these both cases the acetylthioacetate and the SATA group function as the linker (moiety). However equivalent compounds also might be applied as linker-moiety, including every chemical compound which can be covalently bound to SAINT-molecules. Although in general only one linker molecule will be bound to the SAINT-molecule, it might be possible that a combination of positions is occupied by a linker molecule, for example Rl, R2, R3, R4, R5 or R5' alone or a combination of these, with a maximum off all five linker positions.

According to a further preferred embodiment, the cell specific ligand is chosen from: an antibody or a derivate thereof, a protein, a peptide, a compound with a specific application as a target for a cell surface, and other compounds with the desired cell specificity.

The antibodies or derivates thereof may be generated synthetically, or naturally occurring variants.

Within the scope of the present invention we consider as a ligand, every compound which is able to bind to a receptor or protein of a cell. A precondition for the ligand is that it has a specificity for a receptor and/or a cell type. Examples for these types of ligands are L-Dopa or adrenaline derivates. This first type of ligands specifically binds the dopamine receptors in the substantia nigra; the second type of ligand specifically binds to the adrenergic receptors of the body. Of course, the invention is not restricted to this example.

More specifically, it is preferred that the molecule to be enwrapped binds at the active surface of the SAINT-molecule. Without to be restricted to this embodiment, here the positively charged pyridiniumgroup is used. This group binds to the negative charge of the macromolecule to be enwrapped. Furthermore it is possible that the SAINT-molecules will bind the macromolecule in an indirect manner, by interacting with the water-layer surrounding the macromolecule, in case the macromolecule has a positive charge. Consequently, the SAINT-molecules will bind the macromolecules by means of an electrostatic interaction, for instance by forming hydrogen-bonds, so preventing leakage of the chosen molecules from the SAINT-molecules.

Furthermore the possibility exists that electrostatic interaction from, for instance, the carbon-atoms or the ortho-electrons of the pyridinium-ring, is for binding.

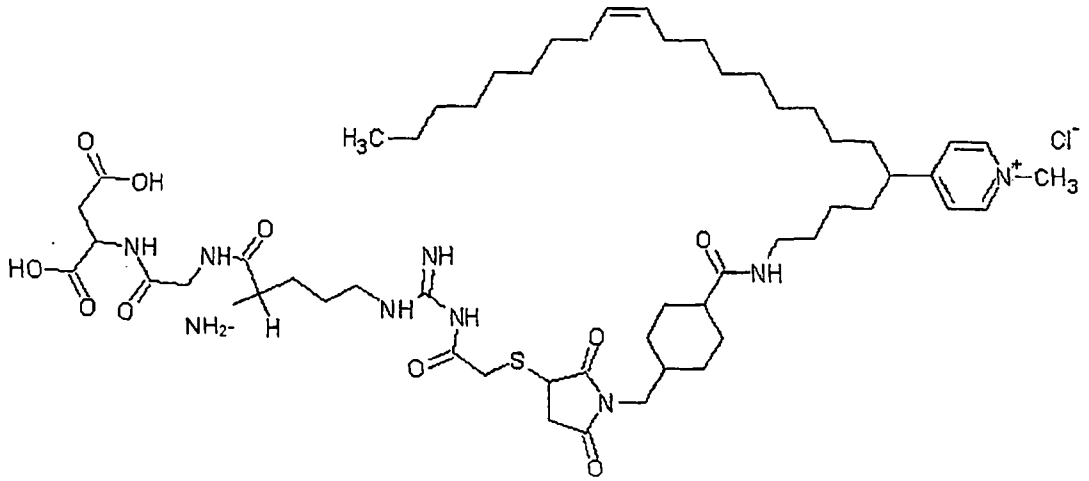
The present invention creates the possibility to deliver chosen molecules, for example a drug, at a specific place in the body at a specific cell. Hereby the advantage is generated that the amount of

drugs, which has to been administered to the body, can be geared exactly for the amount of cells which needs to be treated. By choosing the appropriate formulation between the SAINT-molecules and the enwrapped compound, leakage of the compound is prevented, and it is released after delivery to, fusion with, or uptake into the cell membrane, which also contains the receptor ligand that is complementary for the linker coupled ligand. In this way it is prevented that the chosen molecule is released at other places in the body. Here they stay included in the SAINT-molecule-vehicle.

The essence of the invention is described above. Based on the description above and the attached conclusions, a person skilled in the art will be able to simply develop further embodiments, which all will fall within the scope of the present invention.

EXAMPLE 1

Human Embryonic Kidney cells are difficult to be transfected. When using these cells, main competing transfection methods (of other manufacturers), require several micrograms of plasmid DNA for successful transfection. Combined with SAINT-18, 1 µg (per 12 wells) normally results in a transfection rate above 90%. To be able to visualise the enhancing effect of the targeting moiety SAINT-18-RGD, in this protocol we used a low amount of plasmid DNA (500 ng per 12 wells) . The structural formula of SAINT-linker-RGD is depicted in figure 1 below. In addition, an RGD-peptide is coupled to the SATA-group of the SAINT-Linker, as described in the present invention. The RGD group is a targeting moiety for the integrin receptor family and is though to increase the transfection efficacy. Human Embryonic Kidney cells, strain 293A, are cultured in 12 well plates and are transfected with 4 combinations of SAINT-molecules (i.e. SAINT-18, SAINT-18 coupled to RGD, a mixture of SAINT-18 and SAINT-18 coupled to RGD, and only a linker molecule as a reference) . 500 ng of CMV-GFP plasmid is complex with 3.75nm SAINT molecules or linker (per well). 48 hours after transfection GFP expression is measured by FACS analysis. The percentage of GFP positive cells in depicted in the graph below.

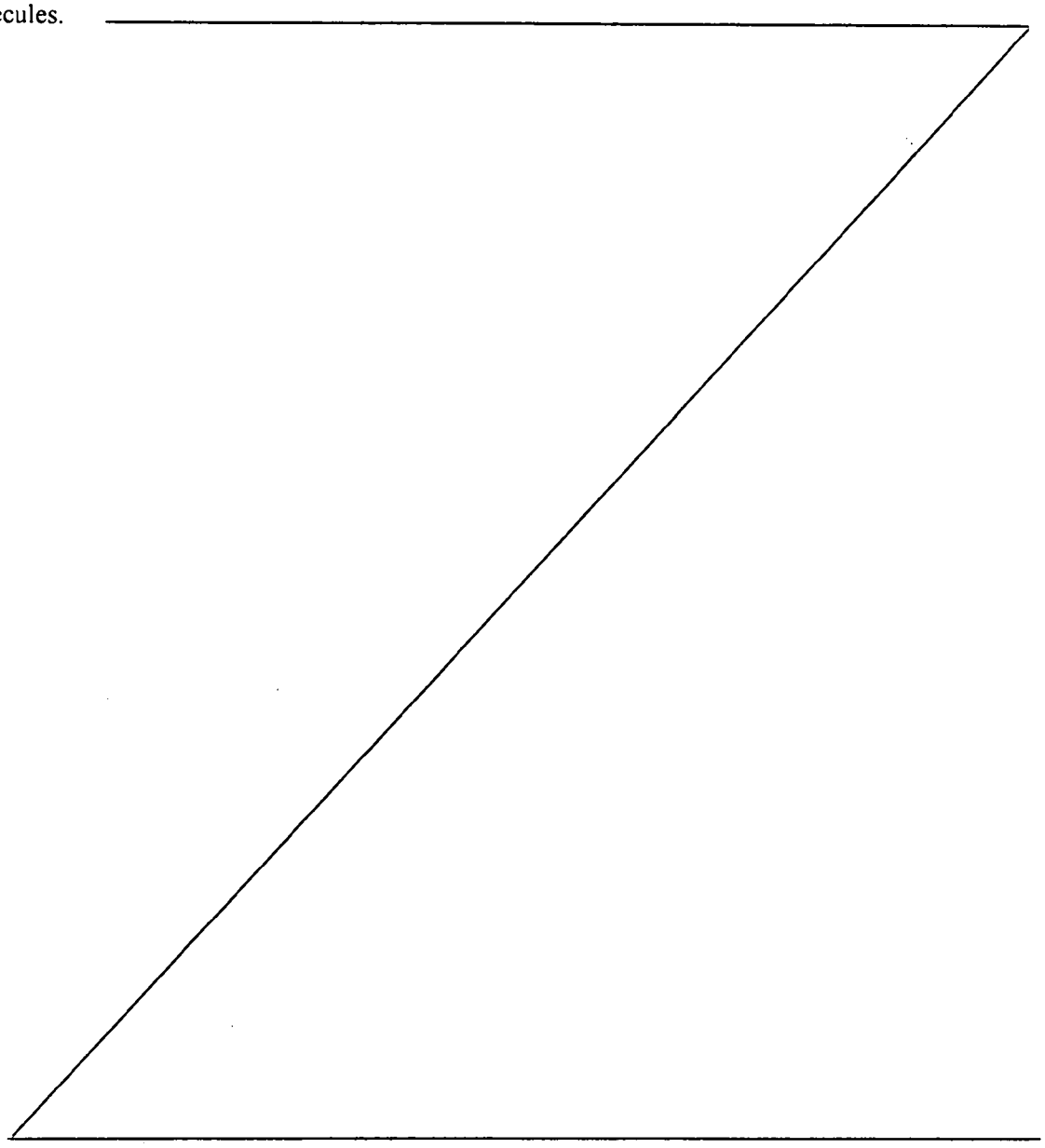


Structural formula of SAINT-linker-RGD.

The results depicted in Fig. 1 clearly show that

1. S18-linker (reference) functions poorly as a transfection reagent (column 4).
2. S18/RGD is able to transfect cells.
3. S18:S18RGD ratio 500:1 increases the transfection rate by approximately 33%.

S18-linker alone has no major transfection ability. We envision that 100% S18-RGD has a decreased transfection efficacy resulting from the sterical hindrance generated by the RGD group. However when S18RGD is mixed with S18 in a ratio of 500:1, transfection efficacy is greatly increased. A more optimised ratio will be determined. Similar results are obtained with targeting moieties other than RGD (such as a cell-specific ligand). However, in all cases, an optimisation will be needed to gain an optimal effect. This experiment greatly indicates the transfection enhancing characteristic of SAINT molecules.



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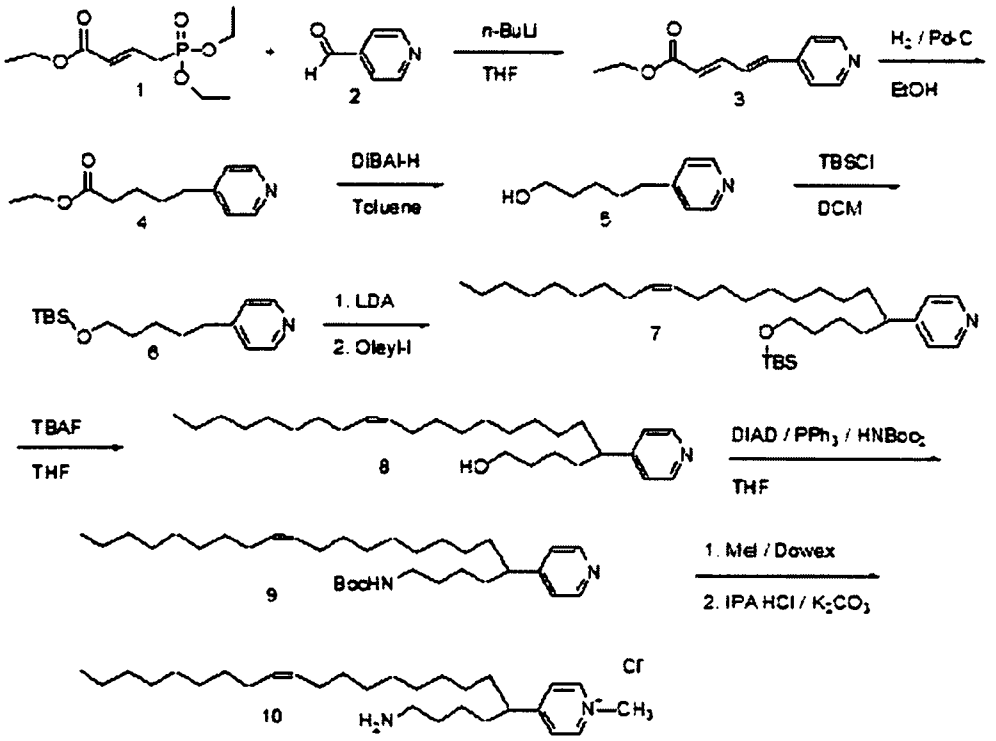
Example 2

Synthesis of 4-[1-(4-Amino-butyl)-nonadec-10-enyl]-1-methyl-pyridinium chloride (**SAINT-amino-linker**):

The synthesis of SAINT-amino-linker is performed according to scheme 1:



Scheme 1: synthesis of SAINT-amino-linker

5-Pyridin-4-yl-penta-2,4-dienoic acid ethyl ester (3). To 250 mL tetrahydrofuran at –70 °C was added 32 mL *n*-butyl lithium (2.5 M in hexanes) and 11.25 mL (80 mmol) diisopropylamine. After 15 min of stirring 17.8 mL (80 mmol) of phosphonocrotonate was added. Another 30 min of stirring were applied and next 7.6 mL (80 mmol) of 4-pyridinecarboxaldehyde was added dropwise. The mixture was allowed to heat up to r.t. The clear brown solution turned first into a yellow suspension, then in a brown suspension and was stirred overnight. The reaction was quenched with acetic acid and the solvents were evaporated. The resulting brown oil was neutralized with $NaHCO_3$ (saturated solution in water) and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The remaining brown oil was dissolved in ethyl acetate, filtered over silica and evaporated. The remaining orange oil, 16.7 g (82.3 mmol, >100%) contained some impurities but was used without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 9.00 (2H, d), 7.90-7.60 (1H, m), 7.70 (2H, d), 7.50-7.30 (1H, m), 7.19 (1H, d), 6.45 (1H, d), 4.60 (2H, q), 1.65 (3H, t) ppm.

5-Pyridin-4-yl-pentanoic acid ethyl ester (4). 5-Pyridin-4-yl-penta-2,4-dienoic acid ethyl ester (16.7 g, 82.3 mmol) was dissolved in 500 mL ethanol. After the addition of 3.0 g palladium on carbon the mixture was exposed to hydrogen pressure (1 bar) for 24 hours. The mixture was filtered over Celite and the yellowish filtrate was evaporated. The isolated product was a yellow oil 14.5 g (70.0 mmol, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (2H, d), 7.10 (2H, d), 4.05 (2H, q), 2.60 (2H, t), 2.25 (2H, t), 1.65-1.55 (4H, m), 1.20 (3H, t) ppm.

5-Pyridin-4-yl-pentan-1-ol (5). 5-Pyridin-4-yl-pentanoic acid ethyl ester (14.5 g, 70 mmol) was dissolved in toluene (250 mL) in a flame-dried 1 L flask under nitrogen atmosphere. The solution was cooled to –60 °C and DiBAl-H (250 mL, 1 M in toluene) was added dropwise. The mixture was stirred for 2 hours at –40°C and was allowed to warm up to r.t. Next methanol (250 mL) was added to the reaction. The mixture was stirred for 30 min, and changed into a yellow suspension. The mixture was filtered over Celite, dried (Na_2SO_4) and evaporated: 6.2 g brown oil (37.5 mmol, 54%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (2H, d), 7.18 (2H, d), 3.65 (2 H, t), 2.60 (2H, t), 1.70-1.25 (6H, m) ppm.

4-[5-(*t*-Butyl-dimethyl-silanyloxy)-pentyl]-pyridine (6). 5-Pyridin-4-yl-pentan-1-ol (3 g, 18.2 mmol) was dissolved in 100 mL DCM and triethylamine (2.80 mL, 19.9 mmol) was added. After 10 min of stirring *t*-butyldimethylsilyl chloride (3.0 g, 19.9 mmol) was added and the mixture was stirred at r.t. overnight. A volume-equivalent of water was added and the mixture was stirred for 5 min. The organic layer was separated and dried (Na_2SO_4). After evaporation of the solvent 5 g of crude **6** was isolated as a brown liquid. Column chromatography with heptane:ethylacetate (5:1, R_{fprod} = 0.22) yielded 2.5 g pure **6** (49%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (2H, d), 7.08 (2H, d), 3.60 (2 H, t), 2.60 (2H, t), 1.70-1.30 (6H, m), 0.93 (9H, s), 0.01 (6H, s) ppm.

4-{1-[4-(*t*-Butyl-dimethyl-silanyloxy)-butyl]-nonadec-10-enyl}-pyridine (7). Tetra-hydrofuran (200 mL) was cooled to –17 °C under a nitrogen-atmosphere. *n*-Butyllithium (8.6 mL, 2.5 M in hexanes) was added and after 5 min of stirring diisopropylamine (3.0 mL, 21.5 mmol) and

hexamethyl phosphoric acid triamide (3.75 mL, 21.5 mmol) were added. After 30 min of stirring 4-[5-(*t*-butyl-dimethyl-silanyloxy)-pentyl]-pyridine (2.0 g, 7.2 mmol) was added. After another 30 min of stirring oleyl iodide* (3.0 g, 7.94 mmol) was added and the mixture was allowed to heat up to r.t. and was stirred overnight. The mixture was diluted with *t*-butylmethylether and washed twice with ammonium chloride (saturated solution in water) and once with brine. After drying (Na_2SO_4) and concentration *in vacuo* 3.7 g of the crude product was isolated as a yellow oil. Purification by column chromatography (heptane:ethylacetate 5:1) yielded 1.6 of the pure product (42%).

*Oleyl iodide pas prepared from oleyl alcohol according to a procedure described in 'The synthesis of 1-methyl-4-(1-octadec-9-enyl-nonadec-10-enyl)-pyridinium chloride'.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (2H, d), 7.02 (2H, d), 5.38 (2H, t), 3.60 (2 H, t), 2.45 (1H, m), 2.05-1.95 (4H, m), 1.70-1.30 (6H, m), 1.20-1.00 (22H, m), 0.98-0.90 (15H, s), 0.01 (6H, s) ppm.

5-Pyridin-4-yl-tricos-14-en-1-ol (8). 4-{1-[4-(*t*-Butyl-dimethyl-silanyloxy)-butyl]-nonadec-10-enyl}-pyridine (1.6 g, 3.0 mmol) was dissolved in 5 mL of tetrahydrofuran. Tetrabutylammonium fluoride (2.0 g, 6.3 mmol) was added and the mixture was stirred overnight at r.t. When TLC (heptane:ethylacetate 1:1 R_{fprod}=0.22, R_{fsm}=0.78) showed complete conversion, one volume-equivalent of water was added. The mixture was extracted with *t*-butylmethylether. The organic layer was dried (Na_2SO_4) and evaporated, yielding 1.1 g (2.7 mmol) of the product as a yellow oil (88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (2H, d), 7.02 (2H, d), 5.38 (2H, t), 3.60 (2 H, t), 2.45 (1H, m) 2.05-1.95 (4H, m), 1.70-1.30 (6H, m), 1.20-1.00 (22H, m), 0.98-0.95 (3H, t) ppm.

(5-Pyridin-4-yl-tricos-14-enyl)-carbamic acid *t*-butyl ester (9). To a solution of 5-pyridin-4-yl-tricos-14-en-1-ol (415 mg, 1 mmol) in tetrahydrofuran (20 mL) at rt. was added di-*t*-butyl iminodicarboxylate (1.5 mmol, 325 mg), triphenylphosphine (1.5 mmol, 393 mg) and diethylazodicarboxylate (1.5 mmol, 261 mg) and the mixture was stirred overnight. Column chromatography with heptane:ethylacetate (1:1, R_{fprod} = 0.3, R_{fsm} = 0.14) yielded 200 mg (0.39 mmol, 39%) of the mono-Boc-protected amine (**9**) as a colorless oil.

^{1}H NMR (300 MHz, CD_3OD) δ 8.45 (2H, d), 7.02 (2H, d), 5.38 (2H, t), 3.55 (2 H, t), 2.45 (1H, m) 2.05-1.95 (4H, m), 1.70-1.00 (37H, m), 0.98-0.95 (3H, t) ppm.

4-[1-(4-Amino-butyl)-nonadec-10-enyl]-1-methyl-pyridinium chloride (10). 1.6 g (3.1 mmol) of (5-pyridin-4-yl-tricos-14-enyl)-carbamic acid *t*-butyl ester was dissolved in iodomethane (10 mL) and stirred for two hours. The iodomethane was removed *in vacuo* and the remaining yellow oil was dissolved in methanol and eluted over a Dowex column. After exporation of the solvent 1.5 g product remained (2.8 mmol, 91% over 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (2H, d), 8.70 (2H, d), 6.72 (1H, bs), 5.38 (2H, t), 4.70 (3H, s), 3.45 (2 H, t), 2.79 (1H, m) 2.05-1.95 (4H, m), 1.90-1.00 (37H, m), 0.98-0.95 (3H, t) ppm. 400 mg (0.9 mmol) of 4-[1-(4-*t*-butoxycarbonylamino-butyl)-nonadec-10-enyl]-1-methyl-pyridinium chloride was dissolved in a solution of 5-6 M of HCl in *i*-ipropanol (25 mL) and stirred for 1 hour at rt. Evaporation of the solvent yielded the HCl-salt of the deprotected amine. The residue was dissolved in methylene dichloride and 0.5 g of potassium carbonate was added and the suspension was stirred for 1 hour at rt. After filtration and removal of the solvent a white foam remained (130 mg, 0.3 mmol, 40% over 2 steps).

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

All publications mentioned in this specification are herein incorporated by reference. Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed in Australia or elsewhere before the priority date of each claim of this application.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A vehicle for the transport of a chosen molecule to a cell, the vehicle comprising one or more SAINT-linker molecules, which is characterised in that the SAINT-molecule is covalently bound to the linker molecule which is covalently bound to an antibody or a derivate thereof, a protein, a peptide, a compound that targets a cell-surface, or other compounds with cell specificity.

2. The application of a SAINT-molecule for the targeted transport of a chosen molecule to a cell, in which the SAINT-molecule is bound to the chosen molecule by means of an electrostatic interaction, and in which the SAINT-molecule is coupled to the linker molecule and the linker molecule is coupled to the cell specific ligand.

3. The application according to claim 2, using a vehicle according to claim 1.

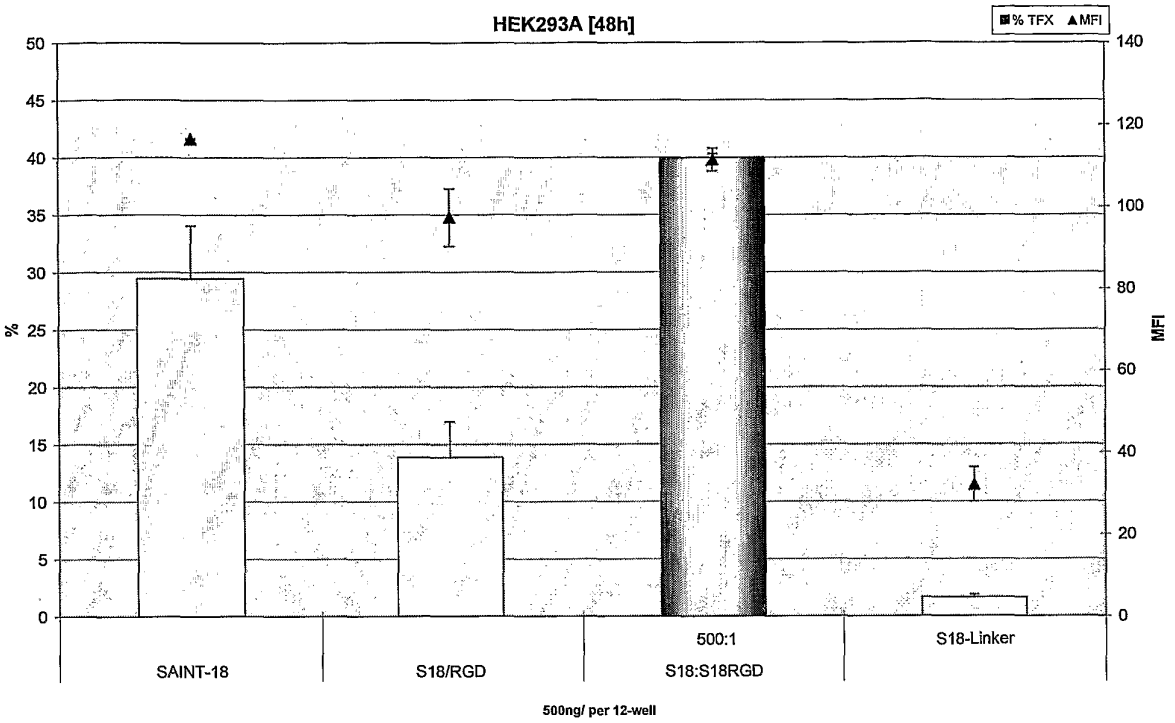
HEK293A [48h]
% TFX
MFI
%
MFI
SAINT-18
S18/RGD
500:1
S18:S18RGD
S18-Linker
500ng/ per 12-well

FIG. 1