Title: Nanotori of semiconductor material for use in diagnostics and in the anti-tumor therapy and process for the production thereof

DESCRIPTION

1. FIELD OF APPLICATION

The present invention generally refers to the pharmaceutical industry and semiconductor materials fields.

In particular, the invention regards nanotori of semiconductor material functionalized for use as diagnostic and therapeutic agents for the treatment of neoplasias and a process for the production thereof.

2. PRIOR ART

Several antineoplastic drugs are known, and it is also known that such drugs are all characterized by a high cytotoxicity. In tumor chemotherapy, the need to make such drugs selectively act on the cancer cells without excessively increasing their systematic concentration has always been felt.

Generally, however, these drugs are strongly stereospecific, and consequently a modification thereof aimed at allowing their selective attachment to the cancerous cells considerably reduces or even often destroys their antineoplastic activity.

One approach used to overcome this drawback is the conjugation of the antineoplastic drugs, in such conditions not to significantly alter the drug activity, to nanoparticles (NP) and the conjugation of such NPs to molecules which allow their preferential segregation on the membrane of cancerous cells or, better yet, their absorption via receptor-mediated endocytosis.

Such doubly conjugated NPs can be delivered to tissues through the circulatory system, which is indeed able to transport any particle with size lower than the red blood cells close to any cell (i.e. at a short enough distance to allow oxygen and glucose to diffuse from blood to

cells and vice versa for CO_2). Red blood cells have a diameter that, although varying with age, is anyway close to 5 μm, while the oxygen diffusion distance is around 50 μm [1].

NPs found their first application in medicine as a tool for the early stage imaging of solid tumors thanks to the possibility of their conjugation to antibodies or peptides to bond with tumor cells. An additional conjugation to antineoplastic agents thus seems a way for a selective and efficient release of such agents. *In vitro* and *in vivo* studies based on this hypothesis have given very promising results [2].

Currently, NP research is focused on the following topics: reanalysis of old therapeutic agents that, although biologically active, could only be delivered at pharmaceutically suboptimal dosage in order to avoid side effects [3,4]; multiple functionalization, for improving the selective segregation on the target tissue or even to overcome the blood-brain barrier [5]; and shape optimization, to improve the amount of delivered drug [6].

Nanoparticles, however, have several drawbacks, which will be clear from the following discussion.

Any medium or carrier for drug delivery can be associated with two contrasting parameters: efficiency and invasiveness.

Efficiency is measured by the agent's ability to transport molecules and invasiveness is measured by the agent volume. For a given agent, selectivity increases efficiency and decreases invasiveness. If the antineoplastic molecules are delivered conjugating them to the surface of a carrier, the efficiency is determined by the surface area of the carrier and by the physical-chemical properties of such area. If the physical-chemical properties do not depend on the carrier shape (that happens for sufficiently large carriers), the efficiency is controlled by the surface area alone.

NPs have nearly spherical form. Given that the sphere is the solid with the least area/volume ratio, the NPs generally have the shape of least

efficiency of drug delivery [7]. This difficulty is partially removed reducing the diameter d_p of the carrier, because for bodies of regular shape, and for spherical bodies in particular, the area/volume ratio diverges in the limit for $d_p \rightarrow 0$. Although a small size facilitates the movement in interstitial fluids, it suffers however from the following disadvantages: (i) the smaller d_p, the faster the secretion of the NP from the organism [8]; (ii) the number of molecules that can be accommodated at the NP surface vanishes as d^2_p (for example, for an NP with d_p = 50 nm this number cannot be higher than 10^4); and (iii) although the NP can be multifunctionalized with different molecules (antibodies, biomimetic molecules, antineoplastic drugs) [6,9], their relative abundances are controlled by the corresponding reaction kinetics.

It was sought to at least partially remove these disadvantages by giving a suitable shape to the carrier: for example, evidence has recently indicated that discoidal particles are accumulated in cancerous zones in a larger number than nearly hemispherical and spherical particles, and they may be useful in drug delivery as well as in imaging [10]. Also for these NP, though, the area/volume ratio remains rather low.

3. SUMMARY OF THE INVENTION

The problem underlying the present invention was that of providing a new type of carrier for detecting and treating tumor cells of a tissue, which might overcome the drawbacks outlined above with reference to the NPs of substantially spherical or discoidal shape.

Such a problem was solved, according to the present invention, by providing nanotori (NT) of semiconductor material with diameter on the scale of 10 to 10^2 nm and gyration radius of 1-10 μm (and hence with a higher area/volume ratio than the NPs) bearing at least two different functionalizations on the surface (by the term "nanotori" it is intended nanowires with ends fused to form a ring).

Preferably, nanotori have three or four functionalizations on their surface, adapted to control the hydrophilicity/hydrophobicity

characteristics of the aforesaid nanotori, bind molecules provided with anti-tumor activity, control the folding of the nanotori on themselves (preventing the possible formation of globular structures), allow their selective coupling on the tumor cells and/or increase their *in vivo* directed motility.

The aforesaid semiconductor material can be an intrinsic or doped semiconductor, and it is preferably selected from intrinsic or doped monocrystalline or polycrystalline silicon, as it is clear from the detailed description of two variants of the invention.

The present invention also regards a process for the production of the aforesaid functionalized nanotori according to claim 5. Preferred embodiments of the process according to the invention are reported in claims 6 to 11.

An alternative process for the production of functionalized nanotori is reported in claim 12.

4. BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 comprises a plan view and a section view of a functionalized nanotorus according to the invention and an enlarged detail of the latter.

Figure 2 schematically shows the steps of a process for the production of a nanotorus according to the invention.

Figure 3 shows, in a schematic manner, several steps of a process for the production of a vertical array of nanotori according to the invention.

Figure 4 is a scanning electron microscope (SEM) photograph of nanotori obtained at the end of the process schematized in figure 3.

Figure 5 is a SEM image of nanotori after their complete separation from the structure represented in figure 3.

Figure 6 is a scheme of a process for the formation of recess zones which house nanotori and for the functionalization of the latter.

Figure 7 is a schematic representation of the interaction between a nanotorus according to the present invention, functionalized with a quinoxaline cavitand and a cell membrane.

5. DETAILED DESCRIPTION

The treatment of solid tumors (except those of brain tumors) does not necessarily require the passage of the drug carrier into the interstitial fluids, since most of the tumor mass is hit by the blood circulation. NPs are generally designed to be coupled to tumor cells and to enter their interior via receptor-mediated endocytosis. However, the use of NTs allows different actions, as it is described in point 5.3.

Let us examine now how the NTs of the present invention can be obtained, which NTs, as indicated above, are: (a) deformable micrometer-sized carriers, (b) with optimal area/volume ratio, and (c) with at least two functionalizations, controlled on the length scale of tens of nanometers.

The target to be achieved is schematized in figure 1, where a nanotorus with silicon core and threefold organic functionalization is shown.

The possibility of preparing, even on a large scale, nanometer-sized rod-like flexible NTs with controlled gyration radius of the same order of magnitude as half the diameter of tissue cells has already been demonstrated [11]. In the light of their size and deformability, such NTs are capable of nearly free movement in the circulatory system, until they are captured by cells with the suitable receptor.

An innovative aspect of the present invention consists of a process for the functionalization of the nanotorus with three or even four controlled functionalizations on the length scale of 10 nm.

5.1 First Variant

A process for the production of a nanotorus with three functionalizations is schematized in figure 2.

According to such a process, one starts from a silicon substrate on an insulator (single crystalline silicon with SOI (silicon-on-insulator) structure, with (100) or (111) orientation, or polycrystalline silicon deposited on SiO_2), whose thickness is brought to the desired value *a* by controlled oxidation and etching.

A subsequent deposition of a thin Si_3N_4 film produces the starting substrate.

The process comprises the following steps:

(a) photolithographic definition of a circle of radius *R* and etching of the Si_3N_4 and Si layers outside the mask;

(b) functionalization of the outer region of the circle;

(c) lithographic definition of the complementary zone of a concentric circle of radius *R* - *b* and etching of the Si_3N_4 and Si layers in the unprotected region;

(d) second functionalization, imparted to the inner region of the silicon ring;

(e) etching of the thin Si_3N_4 layer;

(f) third functionalization, imparted to the top size region of the silicon ring;

(g) etching of the SiO_2 substrate and fourth functionalization of the bottom side of the silicon ring.

In the above-described process, the aspect ratio *a*/*b* of the cross section (see figure 1) is thus determined by the thickness of the starting silicon film (for *a*) and by the lithographic definition of the second mask with respect to the first (for *b*); if *b* is on the 10-nm length scale (as required for the application as therapeutic agent), the lithographic step must involve advanced lithography.

Generally but not necessarily, with the first functionalization, molecules

are inserted that are aimed at controlling the hydrophilicity/hydrophobicity characteristics; the second functionalization serves to insert groups adapted to transport anti-tumor molecules; while the third and the fourth functionalizations serve to stabilize the nanotorus with regard to folding, which could lead to globular structures, as well to insert molecular groups adapted to facilitate the movement of the NT towards the tumor cells and the specific docking onto the same.

The above-described process, although it meets the pre-established aim, allows producing only relatively limited quantities of nanotori. Assuming that each NT holds an area of 5 μm^2 and assuming that the nanotori are producible via a tessellation of a surface of 100 cm^2 (of a 4-inch wafer), the number of producible NTs should be $2x10^9$ per wafer.

It has been estimated that the number of capillaries present in an adult subject is on the order of 10^{10} [12] and that a capillary is capable of feeding $2x10^3$ cells with oxygen and energy-rich substances (in particular glucose). Since a cancerous cell has a metabolism that is about 50 times faster than that of a healthy cell [13], a capillary is able to feed only about 40 cancerous cells ("tumorlet") while it can be assumed that a tumor at the imaging limit contains 10^7 cancerous cells.

In all stages, the tumor is characterized by a large exposure to the blood stream, so that it can be reached by agents circulating in the blood. Assuming that the nanotori are injected in the organism via intravenous injection and are transported by the blood at its circulation velocity until they are captured by a cancerous cell or eliminated via the excretory system, they will perform an entire cycle in about 1 min. Assume moreover that the nanotori have a clearance time of 24 hours and consider now the capillary involved in the growth of the "tumorlet"; in one day, it will have a probability to be visited by a given NT of approximately $5x10^{-8}$. The minimum number of NTs necessary for obtaining a probability close to 1 is thus $2x10^7$. Therefore $Q^* \approx 8x10^8$, where Q^* is the number of NTs required for the passivation of all 40

cells forming the "tumorlet". Since each "tumorlet" is fed by the orifice of the original capillary, the same probably extends even after the angiogenic switch (because any tissue growth is ultimately limited by the supply of O_2 and glucose), provided that Q^* is in large excess with respect to the number of cancerous cells. A comparison of Q^* with the number of cells of the tumor (40 in tumorlet and of the order of 10^7 at the imaging limit) suggests that the NT strategy is adequate for the treatment of tumors, although in the second case the treatment might be quite invasive.

This optimistic result is however in contrast with the NT productivity for the process sketched in fig. 2. In fact, the comparison of Q^* with the number of producible NTs in a single wafer, $2x10^9$, shows that the agents taken from a single wafer would be sufficient to treat at most two tumors in the dormant phase, but likely insufficient to passivate a single massive cancer after the angiogenic shift.

This comparison clearly shows on one hand that the effort towards cancer diagnosis must be shifted to earlier and earlier levels, and on the other hand that the technology must succeed in increasing the nanowires productivity. Moreover, the technology should avoid the use of advanced lithography to avoid excessively high production costs.

Below, we will describe a process that does not require any advanced lithography, for the preparation of NTs with density so high as to allow the preparation of about 10^{12} NTs per 4-inch wafer.

5.2 Second Variant ("Preferred Embodiment")

The process described hereinbelow allows economically producing silicon nanotori with multiple functionalization and desired aspect ratio a/b and gyration ratio R. This process is based on the technique of controlled etching and filling of recessed regions (CEFRR) [11] described in patent application VA2009A000082.

5.2.1 NT Preparation

The CEFRR technique requires a multilayered film formed by bilayers

A|B, characterized by a selective etching for both A and B. For example, let us examine the familiar case in integrated-circuit processing of the $SiO_2|Si_3N_4$ bilayers, which can be easily prepared with pitch of 50 nm (as demonstrated below) and for which the layers can be selectively removed via wet chemistry (using HF_{aq} for SiO_2 or H_3PO_4 for Si_3N_4).

The basic idea, exemplified for the provided case, is schematized in fig. 3, in which 1 indicates a substrate, e.g. glass or ceramic, 2 a layer of silicon oxide, 3 a layer of silicon nitride and 4 a layer of polycrystalline silicon:

(a) the process starts with the deposition on the substrate of a stack of N insulating bilayers

$$\overbrace{\underbrace{\mathrm{SiO_2}|\mathrm{Si_3N_4}|}_{1}\ \underbrace{\mathrm{SiO_2}|\mathrm{Si_3N_4}|}_{2}\cdots\underbrace{\mathrm{SiO_2}|\mathrm{Si_3N_4}|}_{N}}^{N\left(t^{\mathrm{SiO_2}}+t^{\mathrm{Si_3N_4}}\right)},$$

where t^{SiO2} and t^{Si3N4} denote the thickness of SiO_2 and Si_3N_4, respectively.

(b) the film is patterned via highly directional attack (reactive ion etching, RIE) with the formation of deep trenches;

(c) the exposed walls are selectively and partially etched in HF_{aq} with the formation of recessed regions,

(d) the recessed regions are filled via conformal chemical vapor deposition (CVD) of a poly-Si film; and

(e) the poly-Si undergoes controlled oxidation to the desired amount and the SiO_2 so formed is selectively etched away with HF_{aq}. The practical feasibility of the idea was verified by experimentally implementing the following process:

(a') The stack was formed by depositing bilayers of SiO_2 and Si_3N_4 on an oxidized silicon wafer: the Si_3N_4 films were deposited via low pressure (170 Torr) CVD from an atmosphere of SiH_2Cl_2 and NH_3 at 790°C, whereas the SiO_2 film was obtained by partial oxidation in steam of the underlying Si_3N_4 film. The process was modulated to have t^{SiO2} = 30 nm and t^{Si3N4} = 20 nm. No attempt was made to further optimize the technology by reducing t^{SiO2} or t^{Si3N4}, and stacks with 2 or 4 bilayers were considered. Since differences in the two cases were not observed, the process can be extended to very large *N*: the difficulties of developing the process on a larger scale can arise due to the accumulated stress, essentially due to Si_3N_4; this stress can however be reduced by intermittent depositions of relatively thick, stress-relieving SiO_2 layers.

(b') After the definition of a poly-Si hard mask, the trench was formed by reactive ion etching with fluorine chemistry to selectively and directionally attack the unmasked $SiO_2|Si_3N_4$ stack.

(c') The recessed regions were then formed by selective HF_{aq} etching and rinsing; the extent of the recessed regions was controlled by the duration of the attack.

(e') The poly-Si underwent controlled oxidation in O_2 at 950°C for a duration sufficient to form dielectrically separated nanowires and the grown oxide was then etched away using HF_{aq}.

5.2.2 NT Release

In Fig. 4, a SEM image is shown of the poly-Si NTs obtained after process completion, in the recesses which surround a rectangular micrometer-sized pattern. What is interesting for the considered application is that an additional prolonged etching of SiO_2 releases the NTs from their seats without destroying their integrity.

Figure 5 indeed shows three NTs close to the photolithographic pattern that served for their definition. Although the etching modified the shape, it left the toroidal typology unchanged.

The comparison of the original and final shapes (showing the formation of regions where the curvature radius has increased and regions where it has appreciably decreased) suggests that the NTs have the high flexibility required for the hypothesized use as drug carriers.

The NT cross section can be varied almost at will simply by varying the duration of the etch in step (c'). In this manner, one can control the mechanical properties of the nanotori.

5.2.3 Functionalization

Starting from the recessed regions as template, (a) in fig. 6, the poly-Si is deposited up to their complete filling and the amount in excess is etched away, (b) in fig. 6, by controlled oxidation and etching of the grown oxide. The exposed surface of the NTs then undergoes the first functionalization, (c) in fig. 6. After that the NT sides are exposed by attacking the Si_3N_4 walls (for example, with HF_{aq}) for a duration tuned not to expose the SiO_2, (d) in fig. 6, and the newly exposed poly-Si NT sides undergo the second functionalization, (e) in fig. 6. Only after completion of this process, the NTs are totally released and the newly exposed inner sides are eventually functionalized with a further molecule, as sketched in (f) in fig. 6. This process provides a strategy for controlling the composition (and thus imparting desired properties like hydrophobic-hydrophilic, etc.) in the neighboring region on the 10 nm length scale.

It is noted that the order of functionalization in this process is not the same as that described in the first variant. We mention that a fourfold functionalization might be possible via a moderate sophistication of the process. For that it would be sufficient to deposit a sequence of trilayers A|B|C, with A = SiO_2, B = Si_3N_4 (as seen above) and C another material that can be selectively etched with respect to SiO_2, Si_3N_4 and poly-Si.

With the process just described, $2x10^{11}$ nanotori can be produced from a 4-inch wafer, and this number can be increased by optimizing the process, always using non-lithographic techniques for submicrometer-sized structures and without having the cost explosion generated by the

passage from standard lithography to advanced lithography.

The choice of the functionalizing agents for the nanotori and of the corresponding strategies is a key point. Generally, it is preferred to orient the functionalization along the following principles:

1. the outer side of the nanotori is addressed to control the hydrophobic-hydrophilic characteristics;

2. the adhesion to the cell surface is facilitated if the docking molecules are arranged on the side walls of the nanotori; and

3. the drug delivery, if any, is thus left to the inner part of the NT.

Of course, the choice of the appropriate groups that allow carrying out the above tasks is essential for any therapeutic treatment of cancer.

All the moieties which are currently introduced into the nanoparticles to allow them to segregate in the cancerous domain, to recognize the cancerous cells and to deliver drugs to them, can be used for the nanotori, with the additional advantage that such moieties can be spatially arranged in the most appropriate manner. All the molecules suitable for the functionalization will not be taken under consideration in detail, since these are already known for the application to nanoparticles and are certainly also suitable for the application to nanotori according to the present invention.

The major difficulty related to the functionalization of NTs is however the conjugation of organic molecules to silicon, while preserving their function. Indeed, the control of hydrophobicity-hydrophilicity, the ability to dock cancerous cells and to deliver drugs to them may be generally imparted with fragile molecules. However, at least two types of derivatizing molecules, those grafted in steps (c) and (e), must tolerate the exposure to a very aggressive environment (the HF_{aq} etching solution). This difficulty can be overcome by grafting robust linkers to the surface and using them after completion of step (f) for the final functionalization. In this way, the linkers decouple the "hard" silicon chemistry from the “delicate” carbon chemistry.

In order to resist the aggressive environment of the blood, the molecules must be bound to the surface with Si-C bonds, in turn obtainable by derivatizing surfaces with Si-H terminations with known processes such as thermal hydrosilation [14] or arylation with diazonium salts [15] or triazenes [16]. These processes are conducted in aggressive conditions (the first around 200°C, the second in HF environment), therefore poorly compatible with the presumable fragility of the drug, so that they will be dedicated to the insertion of suitable linkers onto the silicon [15,16].

Each derivatization must meet the following conditions: (i) the organic moiety binds to the surface through environmentally robust Si-C bonds; (ii) each linker does not interact with HF_{aq}; and (iii) the linkers have different terminations.

Limited to the coupling function, the docking mechanism could involve quinoxaline cavitands, as shown in fig. 7. Due to the hydrophobic character in "cave" conformation (to the left in fig. 7), this termination will prevent the docking to epithelial cells. However, water in vicinity of cancerous cells has a pH much lower than in the healthy tissue [17] so that if the basicity of the cavitand is carefully designed, the nitrogen atoms of the cavitands will capture H^+ ions from the medium, which in turn will cause the opening of the cavity in the "kite" position (to the right in fig. 7), due to the Coulomb repulsion force between positively charged nitrogen atoms [18]. The protonated nitrogen atoms will then be attracted by the negatively charged cell membrane sites, forming the “glue” for the attachment of the NT to a nearby cancerous cell.

A further functionalization strategy could provide for the use of molecules adapted to facilitate the docking of the NT once this is close to a tumor cell. The use of the so-called “Brownian motors” [19] makes it possible to impart to suitable “cargos” (large size molecules, but also nano-objects) a quantity of oriented motion whose direction and sense depends on the local chemical potential profiles. Biological examples of systems of this type are provided by molecules such as kinesin and myosin V, which are provided with helical tails capable of causing the movement of the entire molecule on the cytoskeletal microtubules [20].

5.3 Treatment strategies

The use of the NTs allows extending the array of therapeutic countermeasures against the growth of cancerous tissue. In particular, three modes of attack against the disease can be carried out:

1. The first is based on the conjugation of the NT with antineoplastic drugs that have already been identified or will be identified in the future, with the further advantage that they can be imparted to the diseased cell in an optimal concentration.

2. The second is based on the fact that the formation of an exoskeleton on the cancerous cell limits if not actually blocks its reproductive process.

3. The third is based on the possibility to dope the NTs with ^{10}B (via gas phase doping from a solid source, specific for the NTs of the second variant, or by ionic implant).

The doping with isotopically-pure ^{10}B can indeed be employed in the treatment with thermal neutrons. With this technique, one can obtain controlled concentrations up to $4x10^{20}$ cm^{-3} in a manner such that an NT with 10 nm diameter and 10 μm length could contain $4x10^5$ atoms of ^{10}B. In order to have a probability of the order of unity of activating the reaction

$$^{10}B + {}^{1}n \rightarrow {}^{7}Li + \alpha + 2.3\ MeV$$

(able by itself to heavily damage nearby cells, due to the high energy released therein by the ^7Li and α), the tissue should be exposed to a neutron fluence of about 10^{15} cm^{-2}.

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CLAIMS

1. A nanotorus of semiconductor material, with a diameter on the scale of 10 to 10^2 nm and a gyration radius of 1-10 μm bearing on its surface a plurality of functionalizations adapted to prevent the folding of the nanotorus on itself, facilitate the approach to the tumor cells, allow the docking thereof and/or transport molecules provided with anti-tumor activity.

2. Nanotorus according to claim 1, wherein said semiconductor material is an intrinsic or doped semiconductor.

3. Nanotorus according to claim 2, wherein said semiconductor material is monocrystalline or polycrystalline silicon.

4. Nanotorus according to claim 3, wherein said semiconductor material is constituted by polycrystalline silicon doped with ^{10}B.

5. A process for the production of functionalized nanotori comprising:

a) depositing a first layer of one or the other of a first silicon compound (2), depositable in a film of thickness less than or equal to 50 nm and etchable by a solution of a first chemical compound, and a second silicon compound (3) not etched by said solution, on a flat substrate (1) made of a material resistant to said etching solution;

b) depositing, over said first layer of one of said two different silicon compounds, a layer of the other silicon compound and repeating operations a) and b) for a number of times sufficient to reach a desired height of the stack of alternated layers;

c) forming or applying a mask over the surface of the stack defining parallel etch openings, the lower width limit of which is equivalent to the minimum linewidth of the defining lithographic process, spaced from each other by at least 1 μm, extending for the entire length of the stack;

d) etching, by sputtering, reactive plasma or plasma through the

openings of the mask, the multilayered stack, forming deep parallel trenches until the surface of the substrate is uncovered;

e) etching, in said solution, the edgeways exposed surfaces of the layers of said first silicon compound (2) until the progression surfaces of the etching back away between the adjacent layers of said second silicon compound (3), for an average distance of about 20 nm, forming parallel cavities on the opposite edgeways faces of each trench;

f) after removing any residues of said mask from the stack surface, depositing polycrystalline Si (4) via chemical vapor deposition, filling said parallel cavities until a conformal layer free of discontinuities is grown on top of the vertical and horizontal flat faces;

g) completely oxidizing the polycrystalline Si (4) which is located outside said parallel cavities and removing the oxide thus formed by means of etching with said solution, nanowires (4a) of polycrystalline Si thus remaining inside said parallel cavities;

h) functionalizing the exposed surface of said nanowires (4a), by inserting first molecular moieties thereon;

i) selectively etching said second silicon compound (3) in a manner so as to expose a further surface of said nanowires;

l) functionalizing said further exposed surface of said nanowires, by inserting second molecular moieties thereon that are different from said first molecular moieties;

m) etching both said first silicon compound (2) and said second silicon compound (3), causing the release of nanotori (4a) of polycrystalline Si that are partially functionalized on their surface;

n) inserting, on the non-functionalized surface of said nanotori, third molecular moieties that are different from said first and second molecular moieties.

6. The process according to claim 5, wherein said silicon is doped with

^{10}B.

7. The process according to claim 5, wherein said first silicon compound (2) is SiO_2, said second silicon compound (3) is Si_3N_4 and said etching solution is an aqueous solution of hydrofluoric acid.

8. The process according to claim 5, wherein said first silicon compound (2) is Si_3N_4, said second silicon compound (3) is SiO_2 and said etching solution is an aqueous solution of phosphoric acid.

9. The process according to any one of claims 5-8, wherein said functionalization step h) involves the insertion of molecular moieties adapted to confer adequate hydrophilicity/hydrophobicity properties.

10. The process according to claim 9, wherein said functionalization step l) involves the insertion of molecular moieties adapted to stabilize said functionalized nanotori.

11. The process according to claim 10, wherein said functionalization step n) involves the insertion of molecular moieties adapted to bind compounds provided with anti-tumor activity.

12. A process for the production of functionalized nanotori, which comprises

- providing a layer of crystalline or polycrystalline silicon of a defined thickness, arranged on an insulating substrate of SiO_2;

- depositing a thin layer of Si_3N_4 on said silicon layer;

- photolithographically defining a circle of predetermined radius *R* and etching said layers of Si_3N_4 and Si outside said circle;

- functionalizing the exposed surface of said silicon layer, inserting first molecular moieties thereon;

- photolithographically defining a concentric circle of radius *R* - *b* and etching said layers of Si_3N_4 and Si inside said circle of radius *R* - *b*;

- functionalizing the exposed surface of said silicon layer, inserting second molecular moieties thereon that are different from said first molecular moieties;

- etching said thin layer of Si_3N_4;

- functionalizing the surface of said layer of Si_3N_4, inserting third molecular moieties thereon that are different from said first and second molecular moieties;

- etching said insulating substrate of SiO_2 and functionalizing the silicon surface that is not yet functionalized, inserting fourth molecular moieties thereon that are different from said first and second moieties and different or equal to said third molecular moieties.

ABSTRACT

Nanotori (4a) of semiconductor material are described, useful in the treatment of tumor pathologies, having diameter on the scale of 10 to 10^2 nm and gyration radius of 1-10 μm and bearing on their surface a plurality of functionalizations adapted to prevent the folding of the nanotorus on itself, facilitate the approach to the tumor cells, allow the docking thereof and/or transport molecules provided with anti-tumor activity; a process for the production of such nanotori is also described.

(Fig. 1)