CHAPTER 14

Medical Nanorobotics: The Long-Term Goal for Nanomedicine

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14.1 Introduction

Nanotechnology involves the engineering of molecularly precise structures and, ultimately, molecular machines. BCC Research [1] estimated the global market for nanotools and nanodevices was $1.5 billion in 2006 and projected to reach $8.6 billion by 2011, rapidly gaining on the slower-growing nanomaterials market, which is estimated at $9.0 billion (2006) and $16.6 billion (2011). As distinct from nanoscale materials and today's simple nanotools and nanodevices having nanoscale features, molecular nanotechnology encompasses the concept of engineering functional machine systems at the molecular scale—including mechanical systems designed and built to atomic precision. Molecular manufacturing (Section 14.4) would make use of positionally controlled mechanosynthesis (mechanically-mediated chemistry) guided by molecular machine systems to build complex products, including additional nanomachines.

Nanomedicine [2, 3] is the application of nanotechnology to medicine: the preservation and improvement of human health, using molecular tools and molecular knowledge of the human body. Nanomedicine encompasses at least three types of molecularly precise structures [4]—nonbiological nanomaterials, biotechnology materials and engineered organisms, and nonbiological devices including diamondoid nanorobotics. In the near term, the molecular tools of nanomedicine will employ biologically active nanomaterials and nanoparticles having well-defined nanoscale features. In the midterm (5–10 years), knowledge gained from genomics and proteomics will make possible new treatments tailored to specific individuals, new drugs targeting pathogens whose genomes have been decoded, and stem cell treatments. Genetic therapies, tissue engineering, and many other offshoots of biotechnology will become more common in therapeutic medical practice. We also may see biological robots derived from bacteria or other motile cells that have had their genomes reengineered and reprogrammed, along with artificial organic devices that incorporate biological motors or self-assembled DNA-based structures for a variety of useful medical purposes.

In the farther term (2020s and beyond), the first fruits of *medical nanorobotics*—the most powerful of the three classes of nanomedicine technology, though clinically the most distant and still mostly theoretical today–should begin to appear in the medical field. Nanotechnologists will learn how to build nanoscale

molecular parts like gears, bearings, and ratchets. Each nanopart may comprise a few thousand precisely placed atoms. These mechanical nanoparts will then be assembled into larger working machines such as nanosensors, nanomanipulators, nanopumps, nanocomputers, and even complete nanorobots which may be micron-scale or larger. The presence of onboard computers is essential because in vivo medical nanorobots will be called upon to perform numerous complex behaviors that must be conditionally executed on at least a semiautonomous basis, guided by receipt of local sensor data and constrained by preprogrammed settings, activity scripts and event clocking, and further limited by a variety of simultaneously executing real-time control protocols and by external instructions sent into the body by the physician during the course of treatment. With medical nanorobots in hand, doctors should be able to quickly cure most diseases that hobble and kill people today, rapidly repair most physical injuries our bodies can suffer, and significantly extend the human healthspan [5].

The early genesis of the concept of medical nanorobotics sprang from the visionary idea that tiny nanomachines could be designed, manufactured, and introduced into the human body to perform cellular repairs at the molecular level. Although the medical application of nanotechnology was later championed in the popular writings of Drexler [6] in the 1980s and 1990s and in the technical writings of Freitas [2, 3] in the 1990s and 2000s, the first scientist to voice this possibility was the late Nobel physicist Richard P. Feynman, who worked on the Manhattan Project at Los Alamos during World War II and later taught at CalTech for most of his professorial career.

In his prescient 1959 talk "There's Plenty of Room at the Bottom," Feynman proposed employing machine tools to make smaller machine tools, these to be used in turn to make still smaller machine tools, and so on all the way down to the atomic level [7]. He prophetically concluded that this is "a development which I think cannot be avoided." After discussing his ideas with a colleague, Feynman offered the first known proposal for a medical nanorobotic procedure of any kind–in this instance, to cure heart disease: "A friend of mine (Albert R. Hibbs) suggests a very interesting possibility for relatively small machines. He says that, although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and looks around. (Of course the information has to be fed out.) It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately functioning organ." Later in his historic 1959 lecture, Feynman urges us to consider the possibility, in connection with microscopic biological cells, "that we can manufacture an object that maneuvers at that level!"

14.2 From Nanoparticles to Nanorobots

The greatest power of nanomedicine will emerge when we can design and construct complete artificial medical nanorobots using rigid diamondoid nanometer-scale parts such as molecular gears and bearings. Diamondoid nanorobots may be constructed using future molecular manufacturing technologies such as diamond

mechanosynthesis that are currently being investigated theoretically using quantum ab initio and density-functional computational methods. Complete artificial nanorobots may possess subsystems including onboard sensors, pumps, motors, manipulators, clocks, power supplies, communication systems, navigation systems, and molecular computers. Conceptual designs for diamondoid nanorobots that can mimic important natural biological cells (e.g., erythrocytes and leukocytes) have been published, and other nanorobots could perform medical tasks not found in nature such as drug delivery or chromosome replacement in individual living cells in vivo.

To bridge the gap in our knowledge between present-day nanoparticle-based technologies and future nanorobotic technologies, a great deal of research remains to be done. In the relatively near term, over the next 5 years, pre-nanorobotic nanomedicine can address many important medical problems by using for drug delivery nanoscale-structured materials and basic nanodevices that can already be manufactured today—most notably organic polymer or lipid-based systems such as polymeric micelles, liposomes and solid lipid nanoparticles, and various nanocrystal-based systems, many of which have already advanced to marketed products. Surveys of these technologies are available elsewhere [4, 8], so here we report just a few selected examples of nanoparticle-related work that may exemplify early steps toward the more sophisticated capabilities that nanorobots will ultimately possess.

Kopelman's group at the University of Michigan has developed dye-tagged nanoparticles to be inserted into living cells as biosensors. This quickly led to more complex nanoparticle platforms incorporating a variety of plug-in modules, creating molecular nanodevices for the early detection and therapy of brain cancer [9]. In this instance, one type of nanoparticle is attached to a cancer cell antibody that adheres to cancer cells, but is also affixed with a contrast agent to make the particle highly visible during MRI while also enhancing the selective cancer-killing effect during subsequent laser irradiation of the treated brain tissue.

Baker's group at the University of Michigan works with dendrimers, tree-shaped synthetic molecules with a regular branching structure emanating outward from a core. The outermost layer can be functionalized with other useful molecules such as genetic therapy agents, decoys for viruses, or anti-HIV agents. The next step is to create dendrimer cluster agents, multicomponent nanodevices called tecto-dendrimers built up from a number of single-dendrimer modules [10, 11]. These modules may perform specialized functions such as diseased cell recognition, diagnosis of disease state, therapeutic drug delivery, location reporting, and therapy outcome reporting. The framework can be customized to fight a particular cancer simply by substituting any one of many possible distinct cancer recognition or "targeting" dendrimers. The larger trend in medical nanomaterials is to migrate from single-function molecules to multilayer or multimodule entities that can do many things but only at certain times, or under certain conditions, or in a particular sequence. This exemplifies a continuing and inevitable technological evolution toward a device-oriented nanomedicine, working from the bottom up.

On the top-down pathway, there are ongoing attempts to build microrobots for in vivo medical use. In 2002, Ishiyama et al. at Tohoku University developed tiny magnetically driven spinning screws intended to swim along veins and carry drugs

to infected tissues or even to burrow into tumors and kill them with heat [12]. In 2003, the "MR-Sub" project of Martel's group at the NanoRobotics Laboratory of Ecole Polytechnique in Montreal tested using variable MRI magnetic fields to generate forces on an untethered microrobot containing ferromagnetic particles, developing sufficient propulsive power to direct the small device through the human body [13]. Brad Nelson's team at the Swiss Federal Institute of Technology in Zurich has continued this approach. In 2005 they reported [14] the fabrication of a microscopic robot small enough (~200 μm) to be injected into the body through a syringe. They hope this device or its descendants might someday be used to deliver drugs or perform minimally invasive eye surgery. Nelson's simple microrobot has successfully maneuvered through a watery maze using external energy from magnetic fields, with different frequencies able to vibrate different mechanical parts on the device to maintain selective control of various functions. Gordon's group at the University of Manitoba has also proposed magnetically controlled "cytobots" and "karyobots" for performing wireless intracellular and intranuclear surgery [15]. These approaches illustrate the first steps toward developing the ability to externally control microscopic objects after they have been placed inside the human body, an important capability for future medical nanorobots.

Other methods for controlling the activity of the tiniest robotic devices—or even individual macromolecules—are being investigated in the laboratory. Most interestingly, Jacobson and colleagues [16] have attached tiny radio-frequency antennas—1.4-nm gold nanocrystals of less than 100 atoms—to DNA. When a ~1-GHz radio-frequency magnetic field is transmitted into the tiny antennas, alternating eddy currents induced in the nanocrystals produce highly localized inductive heating, causing the double-stranded DNA to separate into two strands in a matter of seconds in a fully reversible dehybridization process that leaves neighboring molecules untouched. The long-term goal is to apply the antennas to living systems and control DNA (e.g., gene expression, giving the ability to turn genes on or off) via remote electronic switching. Such a tool could give pharmaceutical researchers a way to simulate the effects of potential drugs, which also turn genes on and off. The gold nanocrystals can be attached to proteins as well as DNA, opening up the possibility of future radio frequency biology electronically controlling more complex biological processes such as enzymatic activity, protein folding and biomolecular assembly [17].

Motors and bearings for nanoscale machines have received a great deal of experimental attention, including the 78-atom chemically-powered rotating nanomotor synthesized in 1999 by Kelly [18], a chemically-powered rotaxane-based linear motor exerting ~100 pN of force with a 1.9 nm throw and a ~250-sec contraction cycle by Stoddart's group [19], a UV-driven catenane-based ring motor by Wong and Leigh [20], and an artificial 58-atom motor molecule that spins when illuminated by solar energy by Feringa [21]. Zettl's group at U.C. Berkeley has experimentally demonstrated an essentially frictionless bearing made from two corotating nested nanotubes [22], which can also serve as a mechanical spring because the inner nanotube "piston" feels a restoring force as it is extracted from the outer nanotube "jacket." Zettl's group then fabricated a nanomotor mounted on two of these nanotube bearings, demonstrating the first electrically powered nanoscale motor [23]. Deshpande and coworkers [24] have demonstrated a simple electrostatic

motor in which an inside nanotube "piston" is forced to slide out of its outer nanotube jacket by increasing the applied electrical voltage from 4.5 to 10 volts.

In 2005, Tour's group at Rice University reported [25] constructing a tiny molecular "nanocar" measuring 3 to 4 nm across that consists of a chassis, two freely rotating axles made of well-defined rodlike acetylenic structures with a pivoting suspension, and wheels made of C_{60} buckyball molecules that can turn independently because the bond between them and the axle is freely rotatable. Placed on a gold surface at 170°C, the nanocar spontaneously rolls on all four wheels, but only along its long axis in a direction perpendicular to its axles (a symmetrical three-wheeled variant just spins in place). When pulled with an STM tip, the nanocar cannot be towed sideways—the wheels dig in, rather than rolling. A larger, more functionalized version of the nanocar might carry other molecules along and dump them at will. Indeed, the Rice team has apparently "already followed up the nanocar work by designing a light-driven nanocar and a nanotruck that's capable of carrying a payload" [26].

14.3 Diamondoid Materials in Nanorobotics

Many theorists believe that the most reliable, durable, and efficacious medical nanorobots will be built using "diamondoid" materials [2–6, 27] that combine the key properties of high bond strength, high bond density, simplicity (hence predictability) of 3-D bonding chemistry, and maximum mechanical stiffness. What is diamondoid? First and foremost, diamondoid materials include pure diamond, the crystalline allotrope of carbon. Among other exceptional properties, diamond has extreme hardness, high thermal conductivity, low frictional coefficient, chemical inertness, a wide electronic bandgap, and (along with carbon nanotubes and fullerenes) is the strongest and stiffest material presently known at ordinary pressures. Diamondoid materials also may include any stiff covalent solid that is similar to diamond in strength, chemical inertness, or other important material properties, and possesses a dense three-dimensional network of bonds. Examples of such materials are single-crystal silicon and strong covalent ceramics such as silicon carbide, silicon nitride, and boron nitride, plus a few very stiff ionic ceramics such as sapphire (monocrystalline aluminum oxide). Many of these can be covalently or nanomechanically bonded to pure covalent structures such as diamond—for example, as in silicon-on-sapphire [28] and diamond-on-sapphire [29, 30] devices, diamond-Al composites [31], and both van der Waals [32] and mechanical [33] diamond-sapphire bonding. Of course, large pure crystals of diamond are brittle and easily fractured. The intricate molecular structure of a nanofactory-built diamondoid medical nanomachine will more closely resemble a complex composite material, not a brittle solid crystal. These products, and the nanofactories that build them, should be extremely durable in normal use.

Complex diamondoid medical nanorobots probably cannot be manufactured using the conventional techniques of self-assembly. As noted in the final report [34] of the 2006 congressionally mandated review of the U.S. National Nanotechnology Initiative by the National Research Council (NRC) of the National Academies and the National Materials Advisory Board (NMAB): "For the manufacture of more

sophisticated materials and devices, including complex objects produced in large quantities, it is unlikely that simple self-assembly processes will yield the desired results. The reason is that the probability of an error occurring at some point in the process will increase with the complexity of the system and the number of parts that must interoperate."

The opposite of self-assembly processes is positionally controlled processes, in which the positions and trajectories of all components of intermediate and final product objects are controlled at every moment during fabrication and assembly. Positional processes should allow more complex products to be built with high quality and should enable rapid prototyping during product development. Positional assembly is the norm in conventional macroscale manufacturing (e.g., cars, appliances, houses) but is only recently [35, 36] starting to be seriously investigated experimentally for nanoscale manufacturing. Of course, we already know that positional fabrication will work in the nanoscale realm. This is demonstrated in the biological world by ribosomes, which positionally assemble proteins in living cells by following a sequence of digitally encoded instructions (even though ribosomes themselves are self-assembled). Lacking this positional fabrication of proteins controlled by DNA-based software, large, complex, digitally specified organisms would probably not be possible and biology as we know it could not exist.

The most important materials for positional assembly may be the rigid covalent or diamondoid solids, since these could potentially be used to build the most reliable and complex nanoscale machinery [45]. Preliminary theoretical studies have suggested great promise for these materials in molecular manufacturing [37–55]. The NMAB/NRC Review Committee recommended [34] that experimental work aimed at establishing the technical feasibility of positional molecular manufacturing should be pursued and supported: "Experimentation leading to demonstrations supplying ground truth for abstract models is appropriate to better characterize the potential for use of bottom-up or molecular manufacturing systems that utilize processes more complex than self-assembly." Making complex nanorobotic systems requires manufacturing techniques that can build a molecular structure by positional assembly [37]. This will involve picking and placing molecular parts one by one, moving them along controlled trajectories much like the robot arms that manufacture cars on automobile assembly lines. The procedure is then repeated over and over with all the different parts until the final product, such as a medical nanorobot, is fully assembled using, say, a desktop nanofactory.

The development pathway for diamondoid medical nanorobots will be long and arduous. First, theoretical scaling studies [38–44] and basic experimental efforts are used to assess basic concept feasibility. These initial studies must then be followed by more detailed computational simulations of specific nanorobot components and assemblies, and ultimately full systems simulations, all thoroughly integrated with additional simulations of massively parallel manufacturing processes from start to finish consistent with a design-for-assembly engineering philosophy. Once molecular manufacturing capabilities become available, experimental efforts may progress from fabrication and testing of components (built from small-molecule or atomic precursors) to the assembly of components into nanomechanical devices and nanomachine systems, and finally to prototypes and mass manufacture of medical nanorobots, ultimately leading to clinical trials. As noted earlier there has been some

limited experimental work with microscale-component microscopic microrobots [12–15] but progress on nanoscale-component microscopic nanorobots today is largely at the concept feasibility and preliminary design stages and will remain so until experimentalists develop the capabilities required for molecular manufacturing, as reviewed below.

14.4 Early Steps Toward Diamondoid Molecular Manufacturing

It is worth taking a brief look at the earliest steps along the development pathway leading to diamondoid nanorobotics. The key threshold technology that must be mastered and demonstrated is called "mechanosynthesis." Mechanosynthesis, which involves molecular positional fabrication, is the formation of covalent chemical bonds using precisely applied mechanical forces to build, for example, diamondoid structures. Mechanosynthesis employs chemical reactions driven by the mechanically precise placement of extremely reactive chemical species in an ultra-high vacuum (UHV) environment. Mechanosynthesis can subsequently be automated via computer control, enabling programmable molecular positional fabrication. Molecularly precise fabrication involves holding feedstock atoms or molecules, and a growing nanoscale workpiece, in the proper relative positions and orientations so that when they touch they will chemically bond in the desired manner (because the reaction is arranged to be thermodynamically preferred). In this process, a mechanosynthetic tool is brought up to the surface of a workpiece. One or more transfer atoms are added to, or removed from, the workpiece by the tool. Then the tool is withdrawn and recharged. This process is repeated until the workpiece (e.g., a growing nanopart) is completely fabricated to molecular precision with each atom in exactly the right place. Note that the transfer atoms are under positional control at all times, in UHV, to prevent unwanted side reactions from occurring. Side reactions are also prevented using proper reaction design so that the reaction energetics help us avoid undesired pathological intermediate structures.

The positional assembly of diamondoid structures, some almost atom by atom, using molecular feedstock has been examined theoretically [45–55] via computational models of diamond mechanosynthesis (DMS). DMS is the controlled addition of carbon dimers (C_2), single methyl groups (CH_3), or other small molecular groups to the growth surface of a diamond crystal lattice workpiece in a vacuum manufacturing environment. Covalent chemical bonds are formed one by one as the result of positionally constrained mechanical forces applied at the tip of a scanning probe microscope (SPM) apparatus. For example, programmed sequences of carbon dimer placement on growing diamond surfaces in vacuo appear feasible in theory [51, 55], as illustrated by the hypothetical DCB6Ge tooltip which is shown depositing the first two carbon atoms on a clean diamond C(110) surface in Figure 14.1.

The first experimental proof that individual atoms could be manipulated was obtained by IBM scientists in 1989 when they used a scanning tunneling microscope to precisely position 35 xenon atoms on a nickel surface to spell out the corporate logo "IBM" (Figure 14.2). However, this feat did not involve the formation of cova-

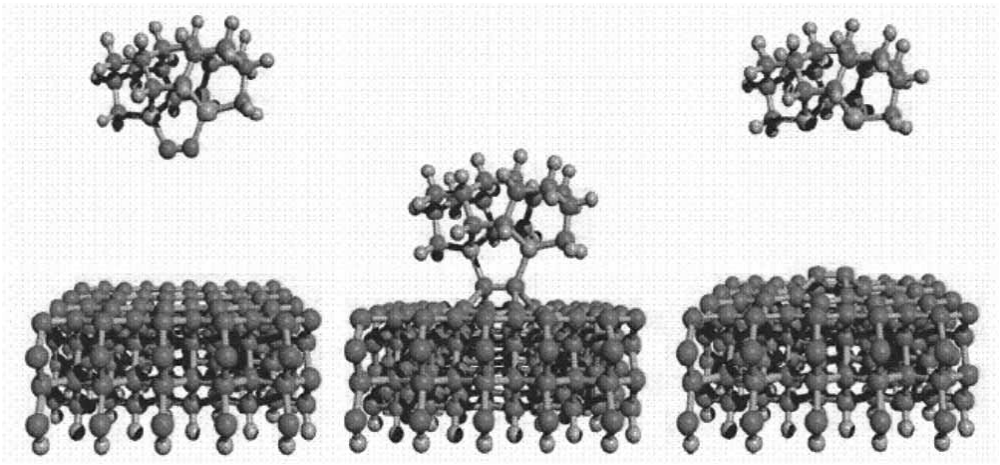


Figure 14.1 DCB6Ge tooltip shown depositing two carbon atoms on a diamond surface. (© 2004 Robert A. Freitas Jr. All Rights Reserved [29].)

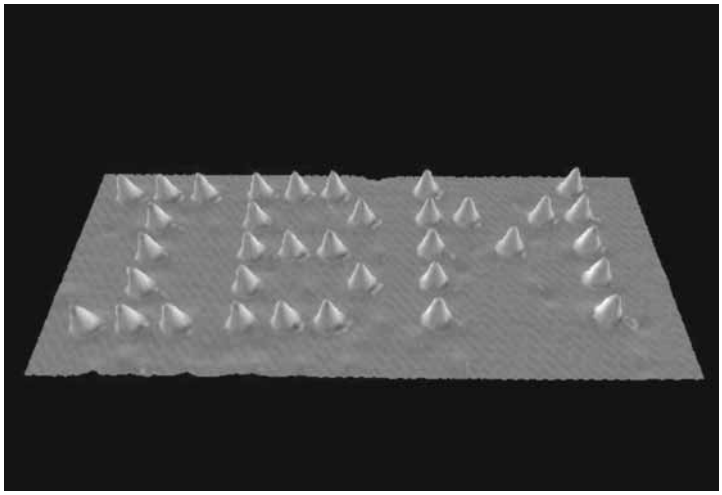


Figure 14.2 IBM logo spelled out using 35 xenon atoms arranged on a nickel surface by an STM. (Courtesy of IBM Research Division.)

lent chemical bonds. One important step toward the practical realization of DMS was achieved in 1999 by Ho and Lee [56], who achieved the first site-repeatable site-specific covalent bonding operation of a two diatomic carbon-containing molecules (CO), one after the other, to the same atom of iron on a crystal surface, using an SPM. SPM-mediated single-molecule chemistry is now an active research area. The first experimental demonstration of pure mechanosynthesis, establishing covalent bonds using only mechanical forces—albeit on silicon atoms, not carbon atoms—was reported in 2003 by Oyabu and colleagues [57] in the Custance group. In this landmark experiment, the researchers vertically manipulated single silicon atoms from the Si(111)–(7×7) surface, using a low-temperature near-contact atomic force microscope to demonstrate: (1) removal of a selected silicon atom from its

equilibrium position without perturbing the (7×7) unit cell, and (2) the deposition of a single Si atom on a created vacancy, both via purely mechanical processes. The same group later repeated this feat with germanium atoms [58], and in 2008 progressed to more complex 2-D structures fabricated entirely via mechanosynthesis [59]; the mechanosynthesis of carbon nanostructures is now being pursued by other groups [60].

To achieve molecularly precise fabrication, the first challenge is to make sure that all chemical reactions will occur at precisely specified places on the surface. A second problem is how to make the diamond surface reactive at the particular spots where we want to add another atom or molecule. A diamond surface is normally covered with a layer of hydrogen atoms. Without this layer, the raw diamond surface would be highly reactive because it would be studded with unused (or "dangling") bonds from the topmost plane of carbon atoms. While hydrogenation prevents unwanted reactions, it also renders the entire surface inert, making it difficult to add carbon (or anything else) to it.

To overcome these problems, we are developing a set of molecular-scale tools that would, in a series of well-defined steps, prepare the surface and create hydrocarbon structures on a layer of diamond, atom by atom and molecule by molecule. A mechanosynthetic tool typically has two principal components: a chemically active tooltip and a chemically inert handle to which the tooltip is covalently bonded. The tooltip is the part of the tool where chemical reactions are forced to occur. The much larger handle structure is big enough to be grasped and positionally manipulated using an SPM or similar macroscale instrumentality. At least three types of basic mechanosynthetic tools (Figure 14.3) have already received considerable theoretical (and some experimental) study [61] and are likely among those required to build molecularly precise diamond via positional control:

Hydrogen Abstraction Tools. The first step in the process of mechanosynthetic fabrication of diamond might be to remove a hydrogen atom from each of one or two specific adjacent spots on the diamond surface, leaving behind one or two reactive dangling bonds or a penetrable C=C double bond. This could be done using a

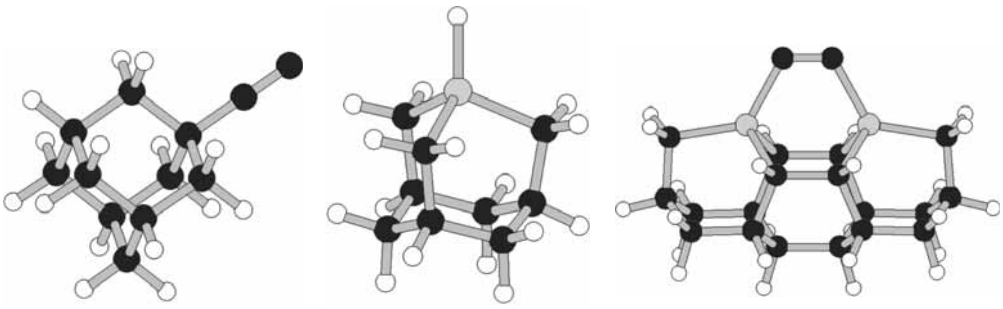


Figure 14.3 Examples of three basic mechanosynthetic tooltypes that are required to build molecularly precise diamond via positional control (black = C atoms, gray = Ge atoms, white = H atoms) [48]. (© 2007 Robert A. Freitas Jr. All Rights Reserved.)

hydrogen abstraction tool [52] that has a high chemical affinity for hydrogen at one end but is elsewhere inert (Figure 14.3(a)). The tool's unreactive region serves as a handle or handle attachment point. The tool would be held by a molecular positional device, initially perhaps a scanning probe microscope tip but ultimately a molecular robotic arm, and moved directly over particular hydrogen atoms on the surface. One suitable molecule for a hydrogen abstraction tool is the acetylene or "ethynyl" radical, comprised of two carbon atoms triply bonded together. One carbon of the two serves as the handle connection, and would bond to a nanoscale positioning tool through a much larger handle structure perhaps consisting of a lattice of adamantane cages as shown in Figure 14.4. The other carbon of the two has a dangling bond where a hydrogen atom would normally be present in a molecule of ordinary acetylene (C_2H_2). The working environment around the tool would be inert (e.g., vacuum or a noble gas such as neon).

Hydrogen Donation Tools. After a molecularly precise structure has been fabricated by a succession of hydrogen abstractions and carbon depositions, the fabricated structure must be hydrogen-terminated to prevent additional unplanned reactions or structural rearrangements. While the hydrogen abstraction tool is intended to make an inert structure reactive by creating a dangling bond, the hydrogen donation tool [54] does the opposite. It makes a reactive structure inert by terminating a dangling bond. Such a tool would be used to stabilize reactive surfaces and help prevent the surface atoms from rearranging in unexpected and undesired ways. The key requirement for a hydrogen donation tool is that it includes a weakly attached hydrogen atom. Many molecules fit that description, but the bond between hydrogen and germanium is sufficiently weak so that a Ge-based hydrogen donation tool (Figure 14.3(b)) should be effective.

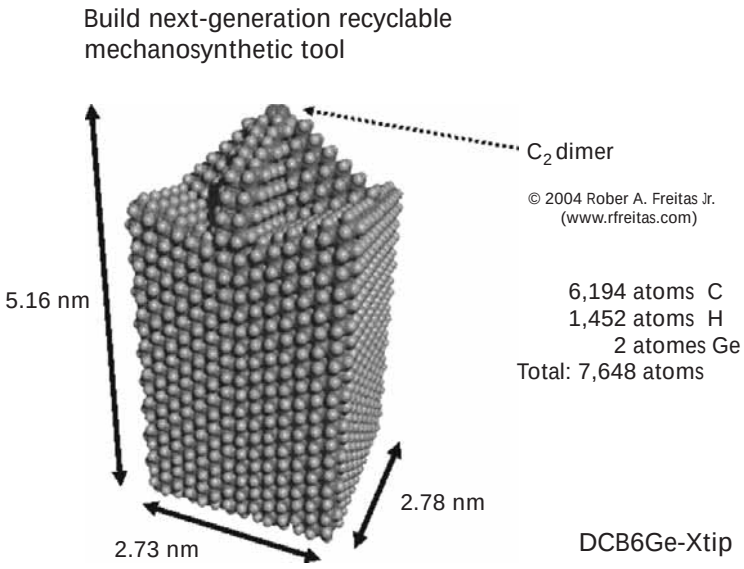


Figure 14.4 Recyclable DCB6Ge tooltip with crossbar handle motif [44]. (© 2004 Robert A. Freitas Jr. All Rights Reserved.)

Carbon Placement Tools. After the abstraction tool has created adjacent reactive spots by selectively removing hydrogen atoms from the diamond surface but before the surface is reterminated by hydrogen, carbon placement tools may be used to deposit carbon atoms at the desired reactive surface sites. In this way a diamond structure would be built on the surface, molecule by molecule, according to plan. The first *complete* tool ever proposed for this carbon deposition function is the "DCB6Ge" dimer placement tool [47]; in this example, a carbon (C_2) dimer having two carbon atoms connected by a triple bond, with each carbon in the dimer connected to a larger unreactive handle structure through two germanium atoms (Figure 14.3(c)). This dimer placement tool, also held by a nanoscale positioning device, is brought close to the reactive spots along a particular trajectory, causing the two dangling surface bonds to react with the ends of the carbon dimer. The dimer placement tool would then withdraw, breaking the relatively weaker bonds between it and the C_2 dimer and transferring the carbon dimer from the tool to the surface, as illustrated in Figure 14.1. A positionally controlled dimer could be bonded at many different sites on a growing diamondoid workpiece, in principle allowing the construction of a wide variety of useful nanopart shapes. As of 2009, the DCB6Ge dimer placement tool remains the most intensively studied of any mechanosynthetic tooltip to date [47, 48, 50, 51, 53, 55], having had more than 150,000 CPU-hours of computation invested thus far in its analysis, and it remains the only DMS tooltip motif that has been successfully simulated and validated for its intended function on a full 200-atom diamond surface model [51]. Other proposed dimer (and related carbon transfer) tooltip motifs [45–47, 49, 53, 55] have received less extensive study but are also expected to perform well.

In 2008, Freitas and Merkle [55] published the results of a three-year project to computationally analyze a comprehensive set of DMS reactions and an associated minimal set of tooltips that could be used to build basic diamond, graphene (e.g., carbon nanotubes and fullerenes), and all of the tools themselves including all necessary tool recharging reactions. The research defined 65 DMS reaction sequences incorporating 328 reaction steps, with 354 pathological side reactions analyzed and with 1,321 unique individual density functional theory (DFT)-based quantum chemistry reaction energies reported. (These mechanosynthetic reaction sequences range in length from 1–13 reaction steps (typically 4) with 0–10 possible pathological side reactions or rearrangements (typically 3) reported per reaction step.) For the first time, this toolset provides clear developmental targets for a comprehensive near-term DMS implementation program. Although the first practical proposal for building a DMS tool experimentally was published by Freitas in 2005 and was the subject of the first mechanosynthesis patent ever filed [50], the 2008 Freitas–Merkle study [55] provides even simpler practical proposals for building several DMS tools experimentally, also using only experimental methods that are already available today. Processes are identified for the experimental fabrication of a hydrogen abstraction tool, a hydrogen donation tool, and two alternative carbon placement tools (other than DCB6Ge), and these processes and tools are part of the second mechanosynthesis patent ever filed. Direct experimental tests of these proposals were underway by early 2009 [60].

14.5 Massive Parallelism Enables Practical Molecular Manufacturing

The ultimate goal of molecular nanotechnology is to develop a manufacturing technology able to inexpensively manufacture most arrangements of atoms that can be specified in molecular detail, including complex arrangements involving millions or billions of atoms per product object, as in the hypothesized medical nanorobots (Section 14.6). This will provide the ultimate manufacturing technology in terms of atomic precision, system flexibility, and low cost. But to be practical, molecular manufacturing must also be able to assemble very large numbers of identical medical nanorobots very quickly. Two central technical objectives thus form the core of our current strategy for diamondoid molecular manufacturing: (1) programmable positional assembly including fabrication of diamondoid structures using molecular feedstock, as discussed above, and (2) massive parallelization of all fabrication and assembly processes, briefly described below.

Molecular manufacturing systems capable of massively parallel fabrication [62] might employ, at the lowest level, large arrays of DMS-enabled scanning probe tips all building similar diamondoid product structures in unison. Analogous approaches are found in present-day larger-scale systems. For example, simple mechanical ciliary arrays consisting of 10,000 independent microactuators on a 1-cm^2 chip have been made at the Cornell National Nanofabrication Laboratory for microscale parts transport applications, and similarly at IBM for mechanical data storage applications [63]. Active probe arrays of 10,000 independently actuated microscope tips have been developed by Mirkin's group at Northwestern University for dip-pen nanolithography [64] using DNA-based "ink." Almost any desired 2-D shape can be drawn using 10 tips in concert. Another microcantilever array manufactured by Protiveris Corp. has millions of interdigitated cantilevers on a single chip [65]. Martel's group has investigated using fleets of independently mobile wireless instrumented microrobot manipulators called NanoWalkers to collectively form a nanofactory system that might be used for positional manufacturing operations [66]. Zyvex Corp. (www.zyvex.com) of Richardson TX received a $25 million, five-year, National Institute of Standards and Technology (NIST) contract to develop prototype microscale assemblers using microelectromechanical systems [62].

Eventually this research should lead to the design of production lines in a nanofactory, both for diamondoid mechanosynthesis and for component assembly operations. Making complex nanorobotic systems will require manufacturing techniques that can build a molecular structure via positional assembly. This will involve picking and placing molecular parts one by one, moving them along controlled trajectories much like the robot arms that manufacture cars on automobile assembly lines. The procedure is then repeated over and over with all the different parts until the final product, such as a medical nanorobot, is fully assembled. Ultimately, medical nanorobots will be manufactured in nanofactories efficiently designed for this purpose. The nanofactory system will likely include a progression of fabrication and assembly mechanisms at several different physical scales. At the smallest scale, molecular mills could manipulate individual molecules to fabricate successively larger submicron-scale building blocks. These could be passed to larger block assemblers that assemble still larger microblocks, which are themselves passed to

even larger product assemblers that put together the final product. The microblocks would be placed in a specific pattern and sequence following construction blueprints created using a modern "design for assembly" philosophy.

14.6 Examples of Diamondoid Medical Nanorobots

The greatest power of nanomedicine will emerge, perhaps in the 2020s, when we can design and construct complete artificial medical nanorobots using rigid diamondoid nanometer-scale parts such as molecular gears and bearings [45]. Complete artificial nanorobots may possess a full range of autonomous subsystems including onboard sensors, pumps, motors, manipulators, clocks, power supplies, communication systems, navigation systems, and molecular computers, as has been extensively described elsewhere [2].

Several conceptual designs of medical nanorobots have been published [38–44]. The first theoretical design study [38] of a complete medical nanorobot ever published in a peer-reviewed journal (in 1998) described a hypothetical artificial mechanical red blood cell or "respirocyte" made of 18 billion precisely arranged structural atoms. The respirocyte (Figure 14.5) is a bloodborne spherical 1-μm diamondoid 1,000-atmosphere pressure vessel with reversible molecule-selective pumps powered by endogenous serum glucose. This nanorobot would deliver 236 times more oxygen to body tissues per unit volume than natural red cells and would

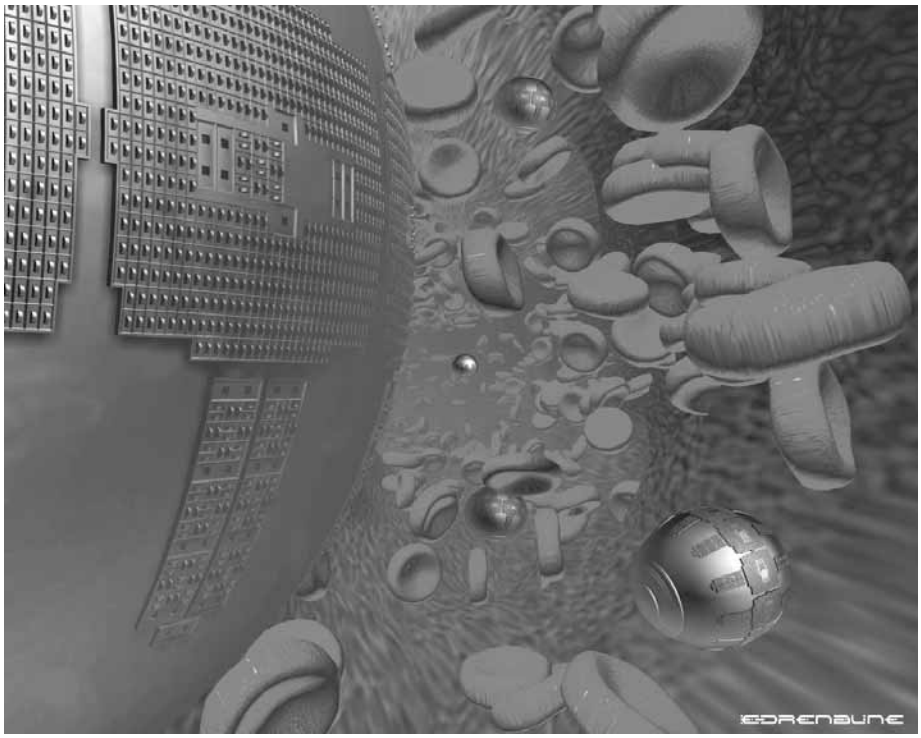


Figure 14.5 (Color plate 21) The respirocyte [31], an artificial mechanical red cell. (Designer Robert A. Freitas Jr. ©2000 E-spaces (3danimation.e-spaces.com) and Robert A. Freitas Jr. (www.rfreitas.com).

manage carbonic acidity, controlled by gas concentration sensors and an onboard nanocomputer. A mere 5-cc therapeutic dose of 50% respirocyte saline suspension containing 5 trillion nanorobots could exactly replace the gas carrying capacity of the patient's entire 5.4 liters of blood. Respirocytes could provide a universal blood substitute, quick treatment for asphyxia (e.g., monoxide poisoning), backup tissue oxygenation for heart and surgical patients, site-specific deoxygenation of tumors, and support for other nanorobots (e.g., augmenting local O_2, the limiting resource for oxyglucose nanorobot power). The supervising physician can transmit control commands via ultrasound signals that are received by acoustic sensors on the nanorobot hull.

Another conceptual design exists for the nanorobotic artificial phagocytes called "microbivores" [42] that could patrol the bloodstream, seeking out unwanted pathogens including bacteria, viruses, or fungi and then digesting them using a combination of onboard mechanical and artificial enzymatic systems (Figure 14.6). Nanorobots recognize a target bacterium by direct contact with its foreign surface coat antigen markers. Microbivores (2–3 μm oblate-shaped nanorobots with a mouth at one end) could achieve complete clearance of even the most severe septicemic infections in hours or less if a sufficient number of devices are employed [42]. This is far better than the weeks or months needed for antibiotic-assisted natural phagocytic defenses. Microbivores don't increase the risk of sepsis or septic shock because the pathogens are completely digested into harmless sugars, amino acids and the like, which are the only effluents from the nanorobot. The biocompatibility (including immunoreactivity, thrombogenicity, phagocytosis, and granulomatous reaction) of diamondoid medical nanorobots such as respirocytes and microbivores has been extensively reviewed in a book-length treatment elsewhere [3]. Note that such devices will likely require some form of biocompatible

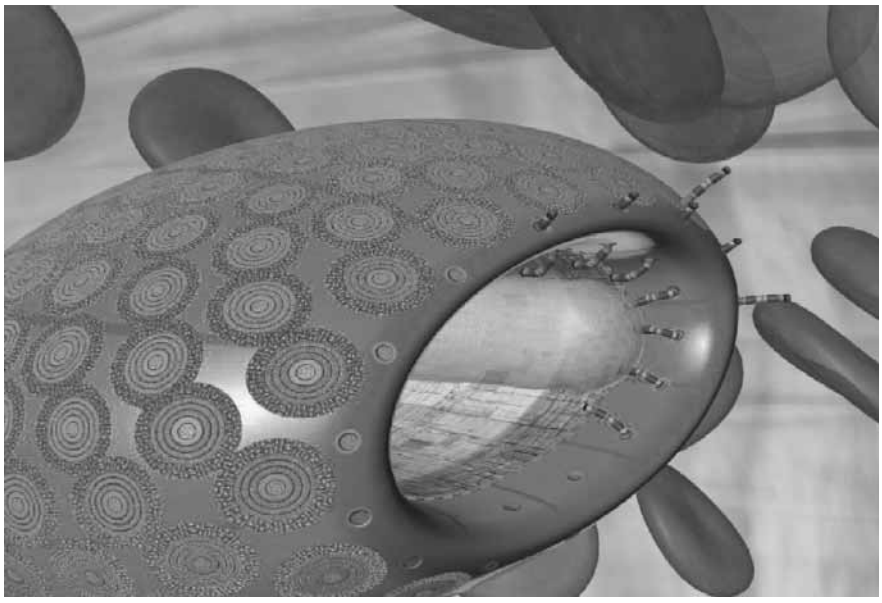
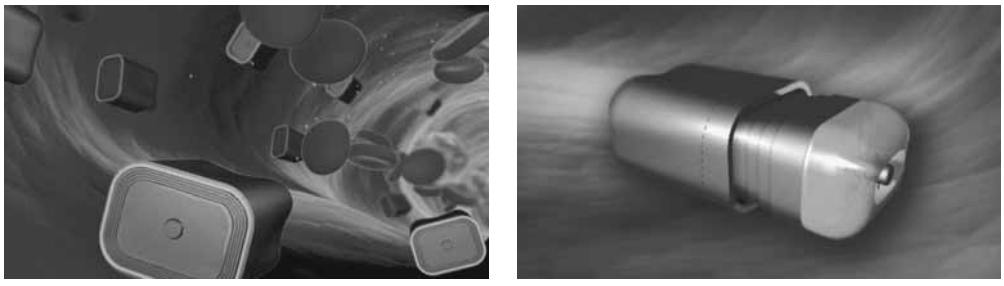


Figure 14.6 (Color plate 22) An artificial white cell—the microbivore [35]. (Designer Robert A. Freitas Jr., additional design by Forrest Bishop. ©2001 Zyvex Corp. Used with permission.)

coating [3] (depending on mission type and duration) to give them a high level of biocompatibility closer to that of lipid-based systems [67] than to that of uncoated fullerene- or carbon nanotube-based systems [68].

A conceptual design has also been published [44] for a very advanced medical nanorobot called the chromallocyte. This is a hypothetical mobile cell-repair nanorobot whose primary purpose is to perform chromosome replacement therapy (CRT). In CRT, the entire chromatin content of the nucleus in a living cell is extracted and promptly replaced with a new set of prefabricated chromosomes which have been artificially manufactured as defect-free copies of the originals. The chromallocyte (Figure 14.7) will be capable of limited vascular surface travel into the capillary bed of the targeted tissue or organ, followed by diapedesis (exiting a blood vessel into the tissues) [2], histonatation (locomotion through tissues) [2], cytopenetration (entry into the cell interior) [2], and complete chromatin replacement in the nucleus of the target cell [44]. The CRT mission ends with a return to the bloodstream and subsequent extraction of the device from the body at the original infusion site. Replacement chromosomes are manufactured in a desktop ex vivo chromosome sequencing and manufacturing facility, then loaded into the nanorobots for delivery to specific targeted cells during CRT. A single lozenge-shaped 69 micron^3 chromallocyte measures 4.18 microns and 3.28 microns along cross-sectional diameters and 5.05 microns in length, typically consuming 50 to 200 pW in normal operation and a maximum of 1,000 pW in bursts during outmessaging, the most energy-intensive task. Treatment of an entire large human organ such as a liver, involving simultaneous CRT on all 250 billion hepatic tissue cells, might require the localized infusion of a ~1 terabot (10^{12} devices) ~69 cm^3 chromallocyte dose in a 1-liter 7% saline suspension during a ~7-hour course of therapy.

The chromallocyte includes an extensible primary manipulator 4 microns long and 0.55 microns in diameter called the Proboscis that is used to spool up chromatin strands via slow rotation when inserted into the cell nucleus. After spooling, a segmented funnel assembly is extended around the spooled bolus of DNA, fully enclosing and sequestering the old genetic material. The new chromatin is then discharged into the nucleus through the center of the Proboscis by pistoning from internal storage vaults, while the old chromatin that is sequestered inside the sealed watertight



(a) (b)

Figure 14.7 (Color plate) Artist's conceptions of the basic chromallocyte [37] design: (a) devices walking along luminal wall of blood vessel ; and (b) schematic of telescoping funnel assembly and proboscis operation. (Image © 2006 Stimulacra LLC (www.stimulacra.net) and Robert A. Freitas Jr. (www.rfreitas.com).)

funnel assembly is forced into the storage vaults as space is vacated by the new chromatin that is simultaneously being pumped out. The chromallocyte includes a mobility system similar to the microbivore grapple system [42], along with a solvation wave drive [2] that is used to ensure smooth passage through cell plasma and nuclear membranes.

14.7 An Ideal Nanorobotic Pharmaceutical Delivery Vehicle

What would an ideal drug delivery vehicle look like? To start with, it would be targetable not just to specific tissues or organs, but to individual cellular addresses within a tissue or organ. Alternatively, it would be targetable to all individual cells within a given tissue or organ that possessed a particular characteristic (e.g., all cancer cells, or all bacterial cells of a defined species). This ideal vehicle would be biocompatible and virtually 100% reliable, with all drug molecules being delivered only to the desired target cells and none being delivered elsewhere so that unwanted side effects are eliminated. The ideal vehicle would remain under the continuous control of the supervising physician, including post-administration. Even after the vehicles had been injected into the body, the doctor would still be able to activate or inactivate them remotely, or alter their mode of action or operational parameters. Once treatment was completed, all of the vehicles could be removed intact from the body, leaving no lingering evidence of their passage. This hypothetical ideal drug delivery vehicle may be called a "pharmacyte" [43].

Pharmacytes will be self-powered, computer-controlled nanorobotic systems capable of digitally precise transport, timing, and targeted delivery of pharmaceutical agents to specific cellular and intracellular destinations within the human body. Drug molecules could be purposely delivered to one cell, but not to an adjacent cell, in the same tissue.

The exemplar pharmacyte would not be a relatively passive nanoparticle but rather would be an active medical nanorobot 1–2 μm in size, similar to the respirocyte but slightly larger. It would be capable of carrying up to ~1 μm^3 of pharmaceutical payload stored in onboard tanks that are mechanically offloaded using molecular sorting pumps [2, 45] mounted in the hull, operated under the control of an onboard nanocomputer. Depending on mission requirements, the payload could be discharged into the proximate extracellular fluid or delivered directly into the cytosol using a transmembrane injector mechanism [2, 3]. The sorting pumps are typically envisioned as ~1,000 nm^3-size devices that can transfer ~10^6 molecules/sec [2, 45]. Each pump employs reversible binding sites mounted on a rotating structure that cycles between the interior and exterior of the nanorobot, allowing transport of a specific molecule even against a considerable concentration gradient (Figure 14.8). Other reversible binding sites comprise sensors on the surface of the nanorobot in order to recognize the unique biochemical signature of specific vascular and cellular addresses [2], simultaneously testing encountered biological surfaces for a sufficiently reliable combination (at least 5–10 in number) of positive-pass and negative-pass molecular markers to ensure virtually 100% targeting accuracy. Onboard power may be provided by glucose and oxygen drawn from the local environment (e.g., circulating blood, interstitial fluid, or cytosol) that is metabolized using fuel

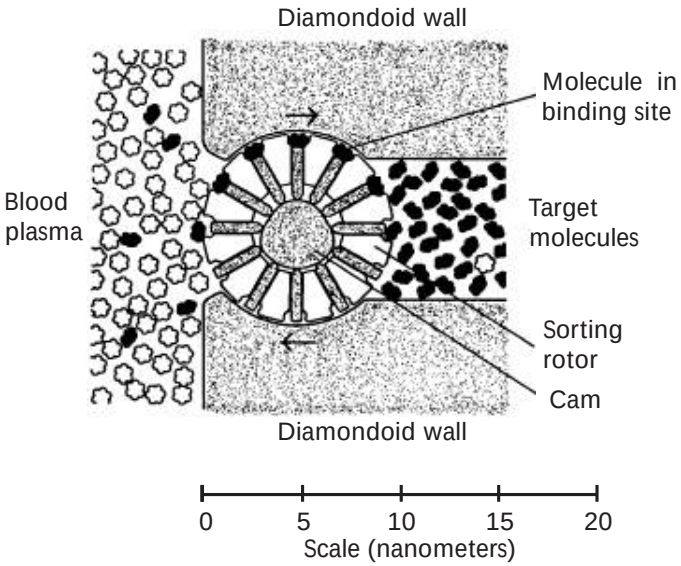


Figure 14.8 Individual sorting rotor. (Redrawn from Drexler [38]).

cells or other methods for biochemical energy conversion [2]. If needed for a particular application, deployable mechanical cilia and other locomotive systems can be added to the pharmacyte to permit transvascular and transcellular mobility [2], thus allowing delivery of pharmaceutical molecules to specific cellular and even intracellular addresses with negligible error. Because sorting pumps can be operated reversibly, pharmacytes could also be used to selectively extract specific molecules from targeted locations as well as deposit them. Pharmacytes, once depleted of their payloads or having completed their mission, would be recovered from the patient via centrifuge nanapheresis [2] or by conventional excretory pathways. The nanorobots might then be recharged, reprogrammed and recycled for use in a subsequent patient who may need a different pharmaceutical agent targeted to different tissues or cells than in the first patient.

Phagocytosis and foreign-body granulomatous reaction are major issues for all medical nanorobots intended to remain in the body for extended durations [3], though short-duration pharmacytes that can quickly be extracted from the body may face somewhat fewer difficulties. In either case, bloodborne 1 to 2 μm pharmacytes can avoid clearance by the RES (whether via geometrical trapping or phagocytic uptake [3]) and techniques have been proposed for phagocyte avoidance and escape at each step in the phagocytic process [3]. Modest concentrations of pharmacytes will not embolize small blood vessels because the minimum viable human capillary that allows passage of intact erythrocytes and white cells is 3 to 4 μm in diameter, which is larger than the largest proposed pharmacyte. Pharmacytes can also be equipped with mobility systems [2] to allow mechanically-assisted passage through partially occluded vessels or unusually narrow spaces such as the interendothelial slits of the spleen [3]. Targeting ligands or receptors in the cell membrane exterior can be recognized by chemotactic sensors [2] on the nanorobot surface, but note that the pharmacyte (as distinguished from conventional nanoparticles) need not always be endocytosed. For example, in some cases

nanorobots may use transmembrane mechanical nanoinjectors [3] to avoid having to enter a target cell. Alternatively, if the mission requires cytopenetration then endocytosis of the nanorobot may be purposely stimulated using biomimetic or completely artificial (including powered mechanical) methods [2]; after payload delivery, indigestible diamondoid nanorobots will require exocytosis by similar means. Nanorobot volume is only 1 to 10 μm^3 compared to 10^3 to 10^4 μm^3 for most human tissue cells so pharmacytes could be targeted to intracellular organelles, though nanorobots would have insufficient room to enter one (excepting perhaps the ER and nucleus) and would have to rely on nanoinjection in those cases.

There are many potential uses of pharmacytes but it will suffice to briefly mention just two general classes of applications.

First, it is often desired to deliver cytocidal agents to tumor cells. Current methods involve introducing large quantities of chemotherapy agents into the body in an effort to kill a relatively few cancerous cells, with numerous unwanted side effects on healthy cells. Precise targeting using pharmacytes can ensure delivery only to the correct cellular addresses, with presentation of cytocidal chemical agents literally on a cell-by-cell basis. In one trivial scenario, the targeted killing of 1 billion (10^9) cancer cells with each cell capable of being killed by ~10^6 precisely delivered ~1,000-dalton cytocidal molecules (i.e., lethality similar to bufagin toxin) would require a total whole-body treatment dose of just ~10^{15} cytocidal molecules or ~0.001 mm^3 (~2 μg) of delivered material. This dose could be carried and dispensed by one trillion pharmacyte nanorobots (total injected volume of therapeutic nanorobots ~2 cm^3) assuming that only 0.1% of the nanorobots encounter an acceptable target and are allowed to release a 0.001 μm^3 cytocidal payload into the targeted cell, while the remaining 99.9% of the nanorobots release nothing. After initiating cell death, unmetabolized free cytocidal molecules can be locally reacquired by the pharmacyte and subsequently transported out of the patient, thus minimizing any post-treatment collateral damage. Note that the strict size requirements for macromolecules to reach the leaky vasculature of a tumor and convectively enter its pores [69] may apply to passively-diffusing payload molecules that might be conveyed and released by pharmacytes, but these limits do not apply to the motorized active nanorobots themselves. Upon arriving in the vicinity of a tumor, the pharmacyte may deliver its payload either via direct nanoinjection [3] (for tumor cells adjoining the vasculature) or by progressive cytopenetration [2] through adjacent cells until the targeted tumor cell that awaits payload delivery is reached.

It is well-known that apoptotic cellular "death receptors" can be expressed on both normal and cancerous cells in the human body, so one challenge for conventional drug-based therapy is to find some way to activate death receptors selectively on cancer cells only [70]. With pharmacytes, such selectivity should be simple and routine using multiple chemosensors [2], a benefit that may be characteristic of most future nanorobot-based therapeutics. For example, if caspase cascade amplification is sufficient to permit single-site activation of the cascade, then in principle an extracellular nanorobot intending cytocide of a detected cancerous cell could press onto the outer surface of the target cell an appropriate ligand display tool. This tool might contain suitably exposed trimeric CD95L (aka FasL) ligand (binds to the extracellular domains of three CD95 death receptors), TNF or lymphotoxin alpha (binds to CD120a), Apo3L ligand aka TWEAK (binds to DR3), or Apo2L ligand

aka TRAIL (binds to DR4 and DR5) [70, 71]. The binding event would then activate a single death receptor complex, potentially triggering the entire irreversible cytocidal cascade. If necessary, multiple such display tools could be employed. This technique avoids much of the storage requirement for bulky consumables aboard the medical nanorobot. As yet another approach, molecular sorting pumps on the pharmacyte surface could be used to selectively extract from the cytoplasm of a target cell specific crucial molecular species of inhibitors of apoptosis (IAPs) that normally hold the apoptotic process in check. Examples include survivin, commonly found in human cancer cells [72], the transcription factor NF-κB, and Akt, which delivers a survival signal that inhibits the apoptosis induced by growth factor withdrawal in neurons, fibroblasts, and lymphoid cells. Conversely, decoy receptors (DcRs) [73] that compete with DR4 and DR5 for binding to Apo2L could be saturated with intrinsically harmless but precisely engineered intracellular "chaff" ligands. With IAPs removed or DcRs blockaded, apoptosis may be free to proceed.

Pharmacytes could also tag target cells with biochemical substances capable of triggering a reaction by the body's natural defensive or scavenging systems, a strategy called "phagocytic flagging" [2]. For example, novel recognition molecules are expressed on the surface of apoptotic cells. In the case of T lymphocytes, one such molecule is phosphatidylserine, a lipid that is normally restricted to the inner side of the plasma membrane [2] but, after the induction of apoptosis, appears on the outside [74]. Cells bearing this molecule on their surface can then be recognized and removed by phagocytic cells. Seeding the outer wall of a target cell with phosphatidylserine or other molecules with similar action could activate phagocytic behavior by natural macrophages that had mistakenly identified the target cell as apoptotic. Loading the target cell membrane surface with B7 costimulator molecules also permits T-cell recognition, allowing an immunologic response via the immunological synapse [75]. These tagging operations should work well against cells that have an apoptotic response that can be triggered by cytotoxic T cells, such as human cancer cells and cysts.

A second major application area of pharmacytes would be the control of cell signaling processes. As a trivial example, Ca^{++} serves as an intracellular mediator in a wide variety of cell responses including secretion, cell proliferation, neurotransmission, cellular metabolism (when complexed to calmodulin), and signal cascade events that are regulated by calcium-calmodulin-dependent protein kinases and adenylate cyclases. The concentration of free Ca^{++} in the extracellular fluid or in the cell's internal calcium sequestering compartment (which is loaded with a binding protein called calsequestrin) is ~10^{-3} ions/nm^3. However, in the cytosol, free Ca^{++} concentration varies from 6×10^{-8} ions/nm^3 for a resting cell up to 3×10^{-6} ions/nm^3 when the cell is activated by an extracellular signal; cytosolic levels >10^{-5} ions/nm^3 may be toxic (e.g., via apoptosis). To transmit an artificial Ca^{++} activation signal to a typical (20 μm)^3 tissue cell in ~1 msec, a single pharmacyte stationed in the cytoplasm must promptly raise the cytosolic ion count from 480,000 Ca^{++} ions to 24 million Ca^{++} ions. This is a transfer rate of ~2.4×10^{10} ions/sec that may be accomplished using ~24,000 hull-mounted molecular sorting pumps [2, 45] across a total nanorobot emission surface area of ~2.4 μm^2. Onboard storage volume of ~1 μm^3 can hold up to ~20 billion calcium atoms, enough to transmit up to ~1,000 arti-

ficial Ca^{++} signals into the cell even assuming no reabsorption and recycling of the ions.

Properly configured in cyto pharmacytes could also modify natural intracellular message traffic according to preprogrammed rules or by following external commands issued by the supervising physician. In the case of steroids and thyroid hormones, this may involve the direct manipulation of the signaling molecules themselves (after they have passed through the cell membrane) or their bound receptor complexes. However, most signaling molecules are absorbed at the cell surface, initiating a signal cascade which may be modulated by manipulating second-messenger molecules or other components of the in cyto signal cascade. A few basic examples [2] of signal modifying action involving cAMP would include:

Amplification. A single epinephrine molecule received by a beta adrenergic receptor at a cell surface transduces the activation of dozens of G-protein alpha subunits, each of which in turn activates a single adenylate cyclase enzyme which cyclizes hundreds of ATP molecules into cAMP molecules. The intracellular population of cAMP (in muscle or liver target cells) is normally $<10^{-6}$ M or ~5 million molecules for a typical $(20\ \mu m)^3$ tissue cell. Stimulation by epinephrine raises the cAMP population to ~25 million molecules in a few seconds. However, upon detecting this rising tide of cAMP during the first few msec, each in cyto pharmacyte could quickly amplify this existing chemical signal by releasing 20 million cAMP molecules (occupying a storage volume of ~0.01 μm^3) from onboard inventories in ~1 msec—thus accelerating cellular response time by several orders of magnitude.

Suppression. Similarly, upon detection of rising cAMP levels in target cells, resident pharmacytes could use molecular pumps to rapidly remove cAMP from the cytosol as quickly as it is formed, even under maximum adrenal stimulation. The diffusion-limited intake current at the basal concentration (~6×10^{-7} molecules/nm^3) for a cAMP-absorbing spherical nanodevice 1 μm in radius is ~4 million molecules/sec [2], so a single such device could probably keep up with natural cAMP production rates and thus completely extinguish the response by preserving a flat basal concentration even in the face of a maximum stimulus. (As a practical matter, it may be more efficient to control epinephrine generation at its glandular source unless it is desired to interface with just a single tissue type.) Simultaneously, the cAMP-absorbing nanorobot may hydrolyze the stored cAMP in the manner of the cAMP phosphodiesterases, then excrete these deactivated AMP messenger molecules back into the cytosol. Similar methods might be useful in ligand-gated ion channel desensitization or in disease symptom suppression, as, for example, in suppressing the prolonged elevation of cAMP in intestinal epithelial cells associated with the cholera toxin, which produces severe diarrhea by causing a large influx of water into the gut.

Replacement. Combining suppression and amplification, an existing chemical signal could be eliminated and replaced by a different—even an opposite—message pathway using resident pharmacyte mediators. Alternative pathways may be natural or wholly synthetic. Novel responses to existing signals may be established within the cell to enhance functionality or to improve stability or controllability. For

instance, detection of one species of cytokine by a pharmacyte could trigger rapid specific absorption of that cytokine and a simultaneous fast release of another (different) species of cytokine in its place. Such procedures must of course take into account the many redundant signaling pathways and backup systems (e.g., developmental signals, immune system, blood clotting) that exist within the body. Medical nanorobots can allow the replacement of many redundant pathways with more refined and specific responses.

Linkage. Previously unlinked signal cascades may be artificially linked using in cyto nanorobots. As a fanciful example, the receipt of epinephrine by pharmacytes located in the capillaries of the brain could trigger these devices to suppress the adrenalin response while simultaneously releasing chemical messengers producing message cascades that stimulate production of enkephalins or other opioids, thus encouraging a subjective state of psychological relaxation rather than the "fight or flight" response to certain stressful conditions.

14.8 Conclusion

Nanomedicine is the application of nanotechnology to medicine: the preservation and improvement of human health, using molecular tools and molecular knowledge of the human body. The greatest power of nanomedicine will emerge when we can design and construct complete artificial medical nanorobots using rigid diamondoid nanometer-scale parts such as molecular gears and bearings. These diamondoid nanorobots may be constructed using future molecular manufacturing technologies such as diamond mechanosynthesis which are currently being investigated theoretically using quantum ab initio and density-functional computational methods to design useful molecular toolsets, and early steps toward experimental validation of the basic principles of positionally controlled diamondoid mechanosynthesis are now in progress. Complete artificial nanorobots may possess a full panoply of autonomous subsystems including onboard sensors, pumps, motors, manipulators, clocks, power supplies, communication systems, navigation systems, and molecular computers. Conceptual designs for diamondoid nanorobots that can mimic important natural biological cells (e.g., erythrocytes and leukocytes) have been published, along with designs for other nanorobots that could perform medical tasks not found in nature such as drug delivery or chromosome replacement in individual living cells in vivo. Medical nanorobotics will become the foundational medical technology of 21st century medicine, allowing future physicians to quickly cure most diseases that hobble and kill people today, rapidly repair most physical injuries our bodies can suffer, and significantly extend the human healthspan.

Problems

14.1 What are the remaining technical challenges to achieving positionally controlled atomically precise diamondoid mechanosynthesis?

14.2 Unlike nanoparticles, nonbiological nanorobots are small machines with lots of mechanical moving parts. What mechanical subsystems would be required to ensure safe and correct functioning of a medical nanorobot placed inside a living human body?

14.3 Suggest and analyze possible methods by which nonbiological medical nanorobots could be safely removed from the human body.

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