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Original article

What is nanomedicine?

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Abstract

The early genesis of the concept of nanomedicine sprang from the visionary idea that tiny nanorobots and related machines could be designed, manufactured, and introduced into the human body to perform cellular repairs at the molecular level. Nanomedicine today has branched out in hundreds of different directions, each of them embodying the key insight that the ability to structure materials and devices at the molecular scale can bring enormous immediate benefits in the research and practice of medicine.

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In his January 2000 State of the Union speech, the US president announced that he would seek \$475 million for nanotechnology research and development (R&D) via the National Nanotechnology Initiative, effectively doubling federal nanotech funding for fiscal year (FY) 2001. The president never referred to “nanotechnology” by name, but he gushed about its capabilities, marveling at a technology that will someday produce “molecular computers the size of a tear drop with the power of today’s fastest super-computers.” Annual US federal funding for nanotechnology R&D exceeded \$500 million in 2002 [1], reached \$849 million in FY 2004 [2], and may approach \$1 billion in next year’s budget. The European Commission has set aside 1.3 billion euros for nanotechnology research during the 2003–2006 period [3], with annual nanotechnology investment worldwide reaching approximately \$3 billion in 2003. Private sector analysts estimate that the worldwide market for nanoscale devices and molecular modeling should experience an average annual growth rate of 28% per year, rising from \$406 million in 2002 to \$1.37 billion in 2007, with a 35% per year growth rate in revenues from biomedical nanoscale devices [4].

In December 2002, the US National Institutes of Health (NIH) announced a 4-year program for nanoscience and nanotechnology in medicine [3]. Burgeoning interest in the medical applications of nanotechnology has led to the emergence of a new field called nanomedicine [3,5–12]. Most broadly, nanomedicine [5] is the process of diagnosing [13], treating, and preventing disease and traumatic injury, relieving pain, and preserving and improving human health,

using molecular tools and molecular knowledge of the human body. In short, nanomedicine is the application of nanotechnology to medicine. The NIH Roadmap’s new Nanomedicine Initiatives, first released in late 2003, “envision that this cutting-edge area of research will begin yielding medical benefits as early as 10 years from now” and will begin with “establishing a handful of Nanomedicine Centers ... staffed by a highly interdisciplinary scientific crew including biologists, physicians, mathematicians, engineers and computer scientists ... gathering extensive information about how molecular machines are built” who will also develop “a new kind of vocabulary—lexicon—to define biological parts and processes in engineering terms” [14]. Even state-funded programs have begun, such as New York’s Alliance for Nanomedical Technologies [15]. The first 12 doctoral candidates in “nanobiotechnology” began laboratory work at Cornell University in June 2000, and many other universities have started similar programs as state, federal, and international funding has soared.

Feynman’s early vision

The early genesis of the concept of nanomedicine sprang from the visionary idea that tiny nanorobots and related machines could be designed, manufactured, and introduced into the human body to perform cellular repairs at the molecular level. Although this idea was later championed in the popular writings of Drexler [16,17] in the 1980s and 1990s, and in the technical writings of Freitas [5,7] in the 1990s and 2000s, the first scientist to voice these possibilities was the late Nobel physicist Richard P.

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77 Feynman, who worked on the Manhattan Project at Los
78 Alamos during World War II and later taught at CalTech for
79 most of his professorial career. In his prescient 1959 talk,
80 “There’s Plenty of Room at the Bottom,” Feynman proposed
81 using machine tools to make smaller machine tools, these to
82 be used in turn to make still smaller machine tools, and so on
83 all the way down to the atomic level [18]. Feynman
84 prophetically concluded that this is “a development which I
85 think cannot be avoided.” Such nanomachine tools, nano-
86 devices, and nanorobots could ultimately be used to develop
87 a wide range of atomically precise microscopic instrumen-
88 tation and manufacturing tools—that is, nanotechnology.

89 Feynman was clearly aware of the potential medical
90 applications of the new technology that he was proposing.
91 After discussing his ideas with a colleague, Feynman [18]
92 offered the first known proposal for a nanomedical
93 procedure of any kind—in this instance, to cure heart
94 disease: “A friend of mine (Albert R. Hibbs) suggests a
95 very interesting possibility for relatively small machines.
96 He says that, although it is a very wild idea, it would be
97 interesting in surgery if you could swallow the surgeon.
98 You put the mechanical surgeon inside the blood vessel
99 and it goes into the heart and looks around. (Of course the
100 information has to be fed out.) It finds out which valve is
101 the faulty one and takes a little knife and slices it out.
102 Other small machines might be permanently incorporated
103 in the body to assist some inadequately functioning
104 organ.” Later in his historic lecture in 1959, Feynman
105 urged us to consider the possibility, in connection with
106 biologic cells, “that we can manufacture an object that
107 maneuvers at that level!”

108 Without losing sight of Feynman’s original long-term
109 vision of medical nanorobotics, nanomedicine today has
110 branched out in hundreds of different directions, each of
111 them embodying the key insight that the ability to structure
112 materials and devices at the molecular scale can bring
113 enormous immediate benefits in the research and practice of
114 medicine. In general, miniaturization of our medical tools
115 will provide more accurate, more controllable, more
116 versatile, more reliable, more cost-effective, and faster
117 approaches to enhancing the quality of human life [5].
118 Table 1 gives an overview of this rapidly expanding and
119 exciting field. Over the next 5 to 10 years, nanomedicine
120 will address many important medical problems by using
121 nanoscale-structured materials and simple nanodevices that
122 can be manufactured today.

123 There is space here to briefly describe only a few of the
124 most interesting and diverse current research projects within
125 several of the 96 subcategories listed in Table 1 because
126 each subcategory may represent up to a dozen or more
127 projects of which I am aware.

128 Nanomedicine today

129 Many approaches to nanomedicine being pursued today
130 are already close enough to fruition that it is fair to say that

their successful development is almost inevitable, and their
subsequent incorporation into valuable medical diagnostics
or clinical therapeutics is highly likely and may occur
very soon.

135 Immunoisolation

136 One of the simplest medical nanomaterials is a surface
137 perforated with holes, or nanopores. In 1997, Desai et al [19]
138 created what could be considered one of the earliest
139 therapeutically helpful nanomedical devices, using bulk
140 micromachining to fabricate tiny chambers within single
141 crystalline silicon wafers in which biologic cells can be
142 placed. The chambers interface with the surrounding
143 biologic environment through polycrystalline silicon filter
144 membranes micromachined to present a high density of
145 uniform nanopores as small as 20 nm in diameter. These
146 pores are large enough to allow small molecules such as
147 oxygen, glucose, and insulin to pass but are small enough to
148 impede the passage of much larger immune system
149 molecules such as immunoglobulins and graft-borne virus
150 particles. Behind this artificial barrier, immunoisolated
151 encapsulated rat pancreatic cells may receive nutrients and
152 remain healthy for weeks, secreting insulin through the pores
153 while remaining hidden from the immune system, which
154 would normally attack and reject the foreign cells. Micro-
155 capsules containing easily harvested replacement pig islet
156 cells could be implanted beneath the skin of some diabetes
157 patients [20], temporarily restoring the body’s glucose
158 control feedback loop, while avoiding the use of powerful
159 immunosuppressants that can leave the patient at serious
160 risk for infection. Supplying encapsulated new cells to the
161 body could also be a valuable way to treat other enzyme- or
162 hormone-deficiency diseases, including encapsulated neu-
163 rons that could be implanted in the brain and then be
164 electrically stimulated to release neurotransmitters, possibly
165 as part of a future treatment for Alzheimer’s or Parkinson’s
166 diseases. In conjunction with the biomedical company
167 iMEDD (Columbus, Ohio), Desai has been active in
168 continuing this work for immunoisolation [21], drug
169 delivery [22,23] and cell-based sensing [24,25].

170 Gated nanosieves

171 The flow of materials through nanopores can also be
172 externally regulated [26]. The first artificial voltage-gated
173 molecular nanosieve was fabricated by Nishizawa et al [27]
174 at Colorado State University in 1995; it had an array of
175 cylindric gold nanotubules with inside diameters as small as
176 1.6 nm. When tubules were positively charged, positive
177 ions were excluded and only negative ions were transported
178 through the membrane; with a negative voltage, only
179 positive ions could pass. Similar nanodevices are now
180 combining voltage gating with pore size, shape, and charge
181 constraints to achieve precise control of ion transport with
182 significant molecular specificity [28]. Martin and Kohli’s
183 [29] recent efforts have been directed at immobilizing
184 biochemical molecular- recognition agents such as

Table 1

A partial nanomedicine technologies taxonomy

t1.1	Raw nanomaterials	Cell simulations and cell diagnostics	Biological research
t1.2	Nanoparticle coatings	Cell chips	Nanobiology
t1.3	Nanocrystalline materials	Cell simulators	Nanoscience in life sciences
t1.4			
t1.5	Nanostructured materials	DNA manipulation, sequencing, diagnostics	Drug delivery
t1.6	Cyclic peptides	Genetic testing	Drug discovery
t1.7	Dendrimers	DNA microarrays	Biopharmaceutics
t1.8	Detoxification agents	Ultrafast DNA sequencing	Drug delivery
t1.9	Fullerenes	DNA manipulation and control	Drug encapsulation
t1.10	Functional drug carriers		Smart drugs
t1.11	MRI scanning (nanoparticles)	Tools and diagnostics	Molecular medicine
t1.12	Nanobarcodes	Bacterial detection systems	Genetic therapy
t1.13	Nanoemulsions	Biochips	Pharmacogenomics
t1.14	Nanofibers	Biomolecular imaging	
t1.15	Nanoparticles	Biosensors and biodetection	Artificial enzymes and enzyme control
t1.16	Nanoshells	Diagnostic and defense applications	Enzyme manipulation and control
t1.17	Carbon nanotubes	Endoscopic robots and microscopes	
t1.18	Noncarbon nanotubes	Fullerene-based sensors	Nanotherapeutics
t1.19	Quantum dots	Imaging (cellular, etc.)	Antibacterial and antiviral nanoparticles
t1.20		Lab on a chip	Fullerene-based pharmaceuticals
t1.21	Artificial binding sites	Monitoring	Photodynamic therapy
t1.22	Artificial antibodies	Nanosensors	Radiopharmaceuticals
t1.23	Artificial enzymes	Point of care diagnostics	
t1.24	Artificial receptors	Protein microarrays	Synthetic biology and early nanodevices
t1.25	Molecularly imprinted polymers	Scanning probe microscopy	Dynamic nanoplatform “nanosome”
t1.26			Tecto-dendrimers
t1.27	Control of surfaces	Intracellular devices	Artificial cells and liposomes
t1.28	Artificial surfaces—adhesive	Intracellular assay	Polymeric micelles and polymersomes
t1.29	Artificial surfaces—nonadhesive	Intracellular biocomputers	
t1.30	Artificial surfaces—regulated	Intracellular sensors/reporters	Biotechnology and biorobotics
t1.31	Biocompatible surfaces	Implants inside cells	Biologic viral therapy
t1.32	Biofilm suppression		Virus-based hybrids
t1.33	Engineered surfaces	BioMEMS	Stem cells and cloning
t1.34	Pattern surfaces (contact guidance)	Implantable materials and devices	Tissue engineering
t1.35	Thin-film coatings	Implanted bioMEMS, chips, and electrodes	Artificial organs
t1.36		MEMS/Nanomaterials-based prosthetics	Nanobiotechnology
t1.37		Sensory aids (artificial retina, etc.)	Biorobotics and biobots
t1.38	Nanopores	Microarrays	
t1.39	Immunoisolation	Microcantilever-based sensors	Nanorobotics
t1.40	Molecular sieves and channels	Microfluidics	DNA-based devices and nanorobots
t1.41	Nanofiltration membranes	Microneedles	Diamond-based nanorobots
t1.42	Nanopores	Medical MEMS	Cell repair devices
t1.43	Separations	MEMS surgical devices	
t1.44			
t1.45			

185 enzymes, antibodies, and other proteins, and DNA, inside
 186 the nanotubes to make active biologic nanosensors [30–32]
 187 and also to perform drug separations [33,34] or to allow
 188 selected biocatalysis [34].

189 *Ultrafast DNA sequencing*

190 Branton’s [35,36] team at Harvard University uses an
 191 electric field to drive a variety of RNA and DNA polymers
 192 through the central nanopore of an α -hemolysin protein
 193 channel mounted in a lipid bilayer similar to the outer
 194 membrane of a living cell. Branton first showed that the
 195 nanopore could rapidly discriminate between pyrimidine and
 196 purine segments along a single RNA molecule and then in
 197 2000 demonstrated discrimination between DNA chains of
 198 similar length and composition differing only in base pair
 199 sequence. Reliability and resolution are the biggest chal-

200 lenges, and Branton’s [37–41] group continues to perfect this
 201 approach. Current research is directed toward fabricating
 202 pores with specific diameters and repeatable geometries at
 203 high precision [42–45], understanding the unzipping of
 204 double-stranded DNA as one strand is pulled through the
 205 pore [46] and the recognition of folded DNA molecules
 206 passing through a pore [41], and investigating the benefits of
 207 adding electrically conducting electrodes to pores to improve
 208 longitudinal resolution “possibly to the single-base level for
 209 DNA” [41]. If these difficult challenges can be surmounted,
 210 nanopore-based DNA-sequencing devices could allow per-
 211 pore read rates potentially up to 1000 bases per second [47].

Fullerene-based pharmaceuticals 212

213 Soluble derivatives of fullerenes such as C₆₀—a soccer-
 214 ball-shaped arrangement of 60 carbon atoms per mole-

cule—show great promise as pharmaceutical agents. These derivatives, many already in clinical trials, have good biocompatibility and low toxicity even at relatively high dosages. Fullerene compounds may serve as antiviral agents (most notably against human immunodeficiency virus [48]), antibacterial agents (*Escherichia coli* [49], *Streptococcus* [50], *Mycobacterium tuberculosis* [51]), photodynamic anti-tumor [52,53] and anticancer [54] therapies, antioxidants and antiapoptosis agents as treatments for amyotrophic lateral sclerosis [55] and Parkinson's disease, and other applications—most being pursued by C Sixty (www.csixty.com), the leading company in this area.

227 *Nanoshells*

228 Halas and West [56,57] at Rice University in Houston
229 have developed a platform for nanoscale drug delivery called
230 the nanoshell—dielectric metal (gold-coated silica) nano-
231 spheres whose optical resonance is a function of the relative
232 size of the constituent layers. These nanoshells, embedded in
233 a drug-containing tumor-targeted hydrogel polymer, and
234 then injected into the body, accumulate near tumor cells.
235 When heated with an infrared laser, the nanoshells (each
236 slightly larger than a polio virus) selectively absorb a specific
237 infrared frequency, melting the polymer and releasing the
238 drug payload at a specific site. Nanoshells might prove
239 useful in treating diabetes—a patient would use a ballpoint-
240 pen-sized infrared laser to heat the skin site where nanoshell
241 polymer had been injected, releasing a pulse of insulin.
242 Unlike injections, which are taken several times a day, the
243 nanoshell-polymer system could remain in the body for
244 months. Nanospectra Biosciences (www.nanospectra.com)
245 is conducting animal studies at the MD Anderson Cancer
246 Center at the University of Texas in a related application
247 specifically targeting micrometastases, tiny aggregates of
248 cancer cells too small for surgeons to find and remove with a
Q2 249 scalpel. The company hopes to start clinical trials for the
250 cancer treatment in 2004–2005 and for an insulin-delivery
251 system by 2006. Rice University researchers have also
252 developed a point-of-care whole-blood immunoassay using
253 antibody-nanoparticle conjugates of gold nanoshells, suc-
254 cessfully detecting subnanogram-per-milliliter quantities of
255 immunoglobulins in saline, serum, and whole blood within
256 10 to 30 minutes of sample acquisition [58].

257 *Single-virus detectors*

258 Lieber's [59] group has recently reported direct, real-time
259 electrical detection of single virus particles with high
260 selectivity using nanowire field-effect transistors to measure
261 discrete conductance changes characteristic of binding and
262 unbinding on nanowire arrays modified with viral anti-
263 bodies. The arrays detect viruses suspended in fluids,
264 whether bodily or otherwise. The Lieber group tested
265 nanowire arrays having receptors specific to influenza A,
266 paramyxovirus, and adenovirus and found that the detectors
267 could differentiate among the 3 viruses, both because of the

specific receptors used to bind them and because each virus
binds to its receptor for a characteristic length of time before
dislodging, giving only a small risk of a false positive
reading. Note the researchers' comment: "The possibility of
large-scale integration of these nanowire devices suggests
potential for simultaneous detection of a large number of
distinct viral threats at the single virus level." Incorporation
into practical clinical diagnostic devices seems within reach
within the next few years.

Tectodendrimers

Starburst dendrimers [60] are tree-shaped synthetic
molecules up to a few nanometers in diameter that are
formed with a regular branching structure. Baker's [61–63]
and Tomalia's [62–64] groups are synthesizing multicompo-
nent nanodevices called tectodendrimers, which have a
single core dendrimer to which additional dendrimer
modules of different types are affixed, each type designed
to perform a function necessary to a smart therapeutic
nanodevice. A combinatorially large number of smart
therapeutic nanodevices can easily be synthesized from a
library of dendrimeric components performing the follow-
ing tasks: (1) diseased cell recognition, (2) diagnosis of
disease state, (3) drug delivery, (4) location reporting, and
(5) reporting outcome of therapy. For instance, once
apoptosis-reporting, contrast-enhancing, and chemothera-
peutic-releasing dendrimer modules are made and attached
to the core dendrimer, it should be possible to make large
quantities of this tectodendrimer as a starting material. This
framework structure can be customized to fight a particular
cancer simply by substituting any one of many possible
distinct cancer recognition or "targeting" dendrimers,
creating a nanodevice customized to destroy a specific
cancer type and no other, while also sparing the healthy
normal cells. In 3 nanodevices synthesized using a 5-
generation, ethylenediamine-core polyamidoamine den-
drimer with folic acid, fluorescein, and methotrexate
covalently attached to the surface to provide targeting,
imaging, and intracellular drug delivery capabilities, the
"targeted delivery improved the cytotoxic response of the
cells to methotrexate 100-fold over free drug" [61]. At least
a half-dozen cancer cell types have already been associated
with at least one unique protein that targeting dendrimers
could use to identify the cell as cancerous, and as the
genomic revolution progresses it is likely that proteins
unique to each kind of cancer will be identified, thus
allowing the design of recognition dendrimers for each type
of cancer, although practical clinical therapeutics are
probably at least 3 to 5 years away. The same cell-surface
protein recognition–targeting strategy could be applied
against virus-infected cells and parasites.

Radio-controlled biomolecules

Jacobson's [65] group has attached tiny radiofrequency
(RF) antennas—1.4-nm gold nanocrystals of <100 atoms—

321 to DNA. When a ~1-GHz RF magnetic field is transmitted
 322 into the tiny antennas, alternating eddy currents induced in
 323 the nanocrystals produce highly localized inductive heating,
 324 in seconds causing the double-stranded DNA to separate into
 325 2 strands in a fully reversible dehybridization process that
 326 leaves neighboring molecules untouched. The long-term
 327 goal is to apply the antennas to living systems and control
 328 gene expression via remote electronic switching. This
 329 requires attaching gold nanoparticles to specific oligonu-
 330 cleotides that, when added to a sample of DNA, would bind
 331 to complementary gene sequences, blocking the activity of
 332 those genes and effectively turning them off. Applying the
 333 RF magnetic field would then heat the gold particles, causing
 334 their attached DNA fragments to detach, turning the genes
 335 back on. One observer noted [66]: “You can even start to
 336 think of differential receivers—different radio receivers that
 337 respond differently to different frequencies. By dialing in the
 338 right frequency, you can turn on tags on one part of DNA but
 339 not other tags.” The gold nanocrystals can also be attached to
 340 proteins, opening up the possibility of electronically
 341 controlling more complex biologic processes such as protein
 342 folding and enzymatic activity. In one case [67], an RNA-
 343 hydrolyzing enzyme called ribonuclease S was separated
 344 into 2 pieces: a large segment made up of 104 amino acids
 345 and a small 18-amino-acid strand called the S-peptide. The
 346 ribonuclease (RNAase) enzyme is inactive unless the small
 347 strand sits in the mouth of the protein. Gold nanoparticles
 348 were linked to the end of S-peptide strands and served as a
 349 switch to turn the enzyme on and off—in the absence of the
 350 RF field, the S-peptides adopted their usual conformation
 351 and the RNAase remained active, but with the external RF
 352 field switched on, the rapidly spinning nanoparticles
 353 prevented the S-peptide from assembling with the larger
 354 protein, thereby inactivating the enzyme.

355 *Biologic robots*

356 Engineered bacterial “biorobots” may be constructed
 357 from as few as 300 highly conserved genes (~150,000
 358 nucleotide bases) that constitute the minimum possible
 359 genome for a functional microbe [68]. Used in medicine,
 360 these synthetic microbes could be designed to produce
 361 useful vitamins, hormones, enzymes, or cytokines in which
 362 a patient’s body was deficient or to selectively absorb and
 363 metabolize into harmless end products harmful substances
 364 such as poisons, toxins, or indigestible intracellular detritus
 365 or even to perform useful mechanical tasks. In 2003, Egea
 366 Biosciences (www.egeabiosciences.com) received “the first
 367 [patent] [69] to include broad claims for the chemical
 368 synthesis of entire genes and networks of genes comprising
 369 a genome, the ‘operating system’ of living organisms.”
 370 Egea’s proprietary GeneWriter and Protein Programming
 371 technology have assembled libraries of >1 million
 372 programmed proteins, produced more than 200 synthetic
 373 genes and proteins, and synthesized the largest gene ever
 374 chemically synthesized (>16,000 bases). Egea’s software
 375 allows researchers to author new DNA sequences that the

company’s hardware can then manufacture to specification 376
 with a base-placement error of only $\sim 10^{-4}$, which Egea calls 377
 “word processing for DNA” [70]. The goal is the synthesis 378
 of “a gene of 100,000 bp . . . from one thousand 100-mers. 379
 The overlap between ‘pairs’ of plus and minus oligonucleo- 380
 tides is 75 bases, leaving a 25 base-pair overhang. In this 381
 method, a combinatorial approach is used where 382
 corresponding pairs of partially complementary oligonucleo- 383
 tides are hybridized in the first step. A second round of 384
 hybridization then is undertaken with appropriately comple- 385
 mentary pairs of products from the first round. This process 386
 is repeated a total of 10 times, each round of hybridization 387
 reducing the number of products by half. Ligation of the 388
 products then is performed.” The result would be a strand of 389
 DNA 100,000 bp in length, long enough to make a very 390
 simple bacterial genome [70]. The Institute for Biological 391
 Energy Alternatives (www.bioenergyalts.org) also has a \$3 392
 million, 3-year grant from the US Department of Energy to 393
 create a related minimalist organism, starting with the 394
Mycoplasma genitalium microorganism [71]. Scientists from 395
 the Institute for Biological Energy Alternatives (Rockville, 396
 Md) are removing all genetic material from the organism, 397
 then synthesizing an artificial string of genetic material 398
 resembling a naturally occurring chromosome that they hope 399
 will contain the minimum number of *M genitalium* genes 400
 needed to sustain life. The artificial chromosome will be 401
 inserted into the hollowed-out cell, which will then be tested 402
 for its ability to survive and reproduce. To ensure safety, the 403
 cell will be deliberately hobbled to render it incapable of 404
 infecting people, and will be strictly confined and designed 405
 to die if it does manage to escape into the environment. 406
 Development of biologic robots seems inevitable, with 407
 clinical trials likely in the 3- to 5-year time frame. 408

409 **Medical nanorobotics of tomorrow**

410 In the longer term, perhaps 10 to 20 years from today, 410
 the earliest molecular machine systems and nanorobots may 411
 join the medical armamentarium, finally giving physicians 412
 the most potent tools imaginable to conquer human disease, 413
 ill health, and aging. Organic building materials (eg, pro- 414
 teins, polynucleotides) are very good at self-assembly, but 415
 the most reliable and high-performance molecular machines 416
 may be constructed out of diamondoid materials, the 417
 strongest substances known. Many technical challenges 418
 must be surmounted before medical nanorobots can become 419
 a reality. Building diamondoid nanorobots—the most 420
 aggressive objective—will require both massive parallelism 421
 in molecular fabrication and assembly processes [72] and 422
 programmable positional assembly including molecularly 423
 precise manufacture of diamond structures using molecular 424
 feedstock [73-75]. Positionally controlled single-atom 425
 covalent bonding (mechanosynthesis) has been achieved 426
 experimentally for hydrogen [76] and silicon [77] atoms, 427
 but at present only computational simulations support the 428
 same expectation for carbon atoms and diamond structures. 429

430 As a result, the prospect for diamond nanorobotics remains
 431 controversial, although considerably less so for other
 432 approaches to medical nanorobotics that might use biologic
 433 components [72,78]. Yet if it can be done, the ability to
 434 build diamond-based molecular machine systems in large
 435 numbers leads, ultimately, to the most powerful kinds of
 436 medical nanorobots.

437 *Respirocytes*

438 One example of such a future device is the artificial
 439 mechanical red blood cell or “respirocyte” [79], a blood-
 440 borne, spherical, 1- μm diamondoid, 1000-atm–pressure
 441 vessel with active pumping powered by endogenous serum
 442 glucose, able to deliver 236 times more oxygen to the
 443 tissues per unit volume than natural red blood cells and to
 444 manage carbonic acidity. The nanorobot is made of 18
 445 billion atoms precisely arranged in a diamondoid pressure
 446 tank that can be pumped full of up to 3 billion oxygen (O_2)
 447 and carbon dioxide (CO_2) molecules. Later on, these gases
 448 can be released from the tank in a controlled manner using
 449 the same molecular pumps. Respirocytes mimic the action
 450 of the natural hemoglobin-filled red blood cells. Gas
 451 concentration sensors on the outside of each device let
 452 the nanorobot know when it is time to load O_2 and unload
 453 CO_2 (at the lungs), or vice versa (at the tissues). An
 454 onboard nanocomputer and numerous chemical and pres-
 455 sure sensors enable complex device behaviors remotely
 456 reprogrammable by the physician via externally applied
 457 acoustic signals. The injection of a 5-mL therapeutic dose
 458 of 50% respirocyte saline suspension, a total of 5 trillion
 459 individual nanorobots, into the human bloodstream would
 460 exactly duplicate the gas-carrying capacity of the patient’s
 461 entire 5.4 L of blood. Primary medical applications of
 462 respirocytes would include transfusable blood substitution;
 463 partial treatment for anemia, perinatal/neonatal, and lung
 464 disorders; enhancement of cardiovascular/neurovascular
 465 procedures, tumor therapies and diagnostics; prevention of
 466 asphyxia; artificial breathing; and a variety of sports,
 467 veterinary, battlefield, and other uses.

468 *Microbivores*

469 An artificial mechanical white blood cell of micro-
 470 scopic size, called a “microbivore,” has as its primary
 471 function to destroy microbiologic pathogens found in the
 472 human bloodstream using a digest and discharge protocol
 473 [80]. The benchmark microbivore nanorobot design is an
 474 oblate spheroidal 200-pW device measuring 3.4 μm in
 475 diameter along its major axis and 2.0 μm in diameter along
 476 its minor axis. During each cycle of nanorobot operation,
 477 the target bacterium is bound to the surface of the blood-
 478 borne microbivore like a fly on flypaper, via species-
 479 specific reversible-binding sites [5]. Telescoping robotic
 480 grapples emerge from silos in the device surface, establish
 481 secure anchorage to the microbe’s plasma membrane, then
 482 transport the pathogen to the ingestion port at the front of

the device where the pathogen cell is internalized into a 2- 483
 μm^3 morcellation chamber. After mechanical mincing, the 484
 remains of the cell are pistoned into a separate 2- μm^3 485
 digestion chamber where a preprogrammed sequence of 40 486
 engineered enzymes are successively injected and extracted 487
 6 times, progressively reducing the morcellate ultimately to 488
 monoresidue amino acids, mononucleotides, glycerol, free 489
 fatty acids, and simple sugars. These simple molecules are 490
 then harmlessly discharged back into the bloodstream 491
 through an exhaust port at the rear of the device, completing 492
 the 30-second digestion cycle. The nanorobots would be 493
 ~80 times more efficient as phagocytic agents than macro- 494
 phages in terms of volume/second digested per unit volume 495
 of phagocytic agent and would have far larger maximum 496
 lifetime capacity for phagocytosis than natural white blood 497
 cells. An infusion of a few milliliters of microbivores would 498
 fully eliminate septicemic infections in minutes to hours, 499
 whereas natural phagocytic defenses—even when aided by 500
 antibiotics—can often require weeks or months to achieve 501
 complete clearance of target bacteria from the bloodstream. 502
 Hence, microbivores look to be up to ~1000 times faster 503
 acting than either unaided natural or antibiotic-assisted 504
 biologic phagocytic defenses and able to extend the 505
 therapeutic competence of the physician to the entire range 506
 of potential bacterial threats, including locally dense 507
 infections. The microbivores would be removed from the 508
 body once their mission was completed. 509

Chromosome replacement therapy

510
 511 Medical nanorobots may also be able to intervene at the
 512 cellular level, performing in vivo cytosurgery. The most
 513 likely site of pathologic function in the cell is the nucleus—
 514 more specifically, the chromosomes. In one simple cytosur-
 515 gical procedure called “chromosome replacement therapy,” a
 516 nanorobot controlled by a physician would extract existing
 517 chromosomes from a particular diseased cell and insert new
 518 ones in their place, in that same cell [9,81]. The replacement
 519 chromosomes will be manufactured to order, outside of the
 520 patient’s body, in a laboratory bench-top production device
 521 that includes a molecular assembly line, using the patient’s
 522 individual genome as the blueprint. The replacement
 523 chromosomes are appropriately demethylated, thus express-
 524 ing only the appropriate exons that are active in the cell type
 525 to which the nanorobot has been targeted. If the patient
 526 chooses, inherited defective genes could be replaced with
 527 nondefective base-pair sequences, permanently curing a
 528 genetic disease.

Conclusion

529
 530 Our near-term ability to structure materials and devices
 531 at the molecular scale brings enormous immediate benefits
 532 and will revolutionize the research and practice of
 533 medicine. Early theoretical and experimental studies of
 534 the biocompatibility of nanomaterials and advanced nano-
 535 devices have begun [7]. Taking Feynman’s long-term vision

536 of medical nanorobots to heart, our present knowledge tells
 537 us that these things violate no known laws of physics,
 538 chemistry, biology, or engineering. Complex issues relating
 539 to future US Food and Drug Administration approval of
 540 nanomedical materials, devices, and even the possibility of
 541 medical nanorobots are already being addressed in main-
 542 stream legal journals [82,83]. One hopes that our society
 543 will be able to muster the collective financial and moral
 544 courage to allow such extraordinarily powerful medicine to
 545 be deployed for human betterment, with due regard to
 546 essential ethical considerations.

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551 References

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