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NANOTECHNOLOGY REVOLUTION

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DEDICATED TO MY TEACHER DOCTOR EDWARD R. RAUPP

Tbilisi, Georgia

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PREFACE

Nanotechnology powers enormous resources to impact at various field of science and industry. All aspect of involvement of NT is hard to cover at the same moment.

Opportunities of NT often outpace our imaginations and resemble science fiction. However even more incredible accomplishment are achieved, due to outstanding inventions in physics, chemistry and material sciences. From contemporary vision NT represents not only single discipline, but outreaches abilities of each fields of S&T and overlapped utilities enable NanoS&T more versatile. We should distinguish extent of hype, accompanying this novel sphere of technology on it's way of maturation. In the chapter one is revised attitudes towards this intriguing discipline and discovered what is realistic versus fanciful.

Realistic landscape will be uncovered if we'll delve in the search of indicators and denominators of research activities in the field of NanoS&T. By proper selection of the exact type for investigational method at the starting stage of our research, will give the tool to determine the extent of interest into nano innovation. In the chapter two then suggested sources to determine "leading indicators" that can be helpful and that might provide early hints of change. To highlight the certain type of innovation it is important to choose appropriate type of evaluation method. In the case of nanotechnology bibliometric and patent application analysis will be helpful, as these are the most indicative methods for pursuance the scale of implication of nanotechnology in science, technology and industry.

In the chapter three are represented some assumptions about technology assessment of nanotechnology, as emerging technology, to highlight present goals for socio-economic and ethical implications of nanotechnology.

Finally, overview of nano medical applications is presented, focused on novel drag delivery systems, which reside on their inceptive stages of development. Most of drugs are at preclinical or starting phases of clinical investigations.

NANOTECHNOLOGY – BRIDGE TO THE FUTURE

• 'Nano" is a term creeping into our vocabulary and our culture these days, and it's likely to be one of the buzzwords of the future, the way "cyber" was in the '90s.[1]

•Nanotechnology is widely expected to be one of the most important industrial innovations of the 21st century. U.S. Senator Ron Wyden, Democrat from Oregon, said, "My own judgment is that the nanotechnology revolution has the potential to change the world on a scale equal to, if not greater than, the computer revolution.

• Nanotechnology is the science of building things or devices at the molecular and atomic level - at the nanometer scale, usually 100 nanometers or less in size. For example, a single data bit might be represented by only one atom some time in the future.
National Nanotechnology Initiative (NNI)

• The term "nano" refers to the measurement of a nanometer - one nanometer equals one thousandth of a micrometer, or one millionth of a millimeter, or one billionth of a meter.
source: CERN http://microcosm.web.cern.ch/microcosm

• Nanotechnology is expected to produce an immense new wave of novel products and improved versions of what we have now. Scientists envision materials with several times the strength of steel but a fraction of its weight. Developments in data storage could put nearly all the world's information on a single tiny chip.
A swatch of NanoCare fabric, for example, resists stains and liquids because it is layered with billions of microscopic hairs that

[1] Chapman, G., (2005) Nanotechnology looks like the next big thing. Nanotech.

act like the fur on a seal. But these hairs are so small that NanoCare fabric looks no different than plain cotton.

• Nanotechnology is providing a critical bridge between the physical sciences and engineering, on the one hand, and modern molecular biology on the other. Materials scientists are learning the principles of the nanoscale world by studying the behavior of biomolecules and biomolecular assemblies.
In return, engineers are creating a host of nanoscale tools that are required to develop the systems biology models of malignancy needed to better diagnose, treat, and ultimately prevent cancer.
Going Small for Big Advances
Using Nanotechnology to Advance
Cancer Diagnosis, Prevention
and Treatment
U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute
July 2004

• There should be major advances in medical technology. Beyond being used in computers and communications devices, nanotechnology could be used extensively in biotechnology to build devices, fight disease, and change the properties of materials. There should be major advances in medical technology.

CHAPTER ONE

FINE LINE BETWEEN REALITY AND SCIENCE FICTION

Science fiction has played a powerful role in creating excitement and fascination for nanotechnology in society. It envisions fictitious scenarios of both the meritorious and the dark side of nanotechnology. The public perception of the power of nanotechnology in medicine is still dominated by scenarios described in movies and science fiction literature. In the movie "Fantastic Voyage" from the 1960s, for example, macroscopic design principles were scaled down to the nanoscale to create nanobots — nanoscale robots — that travel through the blood stream equipped with intelligently controlled arms and sensors. In Star Trek, the blind wear goggles that transmit visual images directly to the brain; and with the command "Energize" people are transported across space, disassembled and reassembled in an instant. Robots are often indistinguishable from humans, able to rationalize, argue and perform intelligent tasks. And the endless dream of immortality is portrayed by some to become reality once society fully exploits its new nanotech toys. In fact, scientists must play a vital role in drawing the line between realistic predictions and futuristic dreams, to prevent the public podium from remaining occupied by scientifically unsubstantiated optimists or worriers (Vogel, 2001).

It no longer seems a question of whether nanotechnology will become a reality. No one knows how much of nanotechnology's promise will prove out. Technology prediction has never been too reliable. "Nanotechnology is the builder's final frontier," remarked Nobel laureate Richard Smalley (Amato, 1999).

Richard Smalley, in the introductory part of a public speech about his very specific work on the use of carbon nanotubes for energy storage, claims: '*The list of things you could do with such a*

technology [nanotechnology] reads like much of the Christmas Wish List of our civilization' (Smalley, 1995).

The prefix "nano" has begun diffusing into popular culture. It's getting into screenplays and scripts for TV shows like the Xfiles and Star Trek: The Next Generation. Companies are using it in their names. It's a favorite topic of science fiction writers. For many years futurists steeped in the culture of science fiction and prone to thinking in time frames that reach decades ahead have been dreaming up a fantastic future built using nanotechnologies. (Amato, 1999).

Organization and process professionals like those from ITRI and the Institute for Alternative Futures can coordinate experts who would typically not relate to each other. Technology assessment professionals like those with Coates & Jarratt, Inc. can apply time-tested tools to estimate a range of possible circumstances and assess the secondary and tertiary effects of incremental and radical changes (Smith, 2001). Joe Coates is a world-renowned thinker, writer, and speaker on the future. After leading Coates & Jarratt, Inc. through more than two decades of designing and delivering studies on the future of technology, business and government. In the course of his pioneering future studies, Joe has consulted with 45 of the Fortune 500 companies and numerous smaller firms, scores of professional, trade and public interest groups, and with all levels of government.

The history of predictions about the societal and economic impacts of promising new technologies is replete with predictions that incipient advances will amount to little, only to have them substantially transform daily life, and those about major advances that subsequently fizzle. Here are some brief examples from The Experts Speak, compiled by Cerf and Navasky (1984)[2]:

[2] Cerf, C. and Navasky, V. (1984), The Experts Speak. New York: Pantheon Books.

Failing to See the Future:

"When the Paris Exhibition closes, the electric light will close with it and no more will be heard of it." (Erasmus Wilson, Oxford University, 1878)

"I think there is a world market for about five computers." (Attributed to Thomas Watson, 1943)

"There is no reason for any individual to have a computer in their home." (Ken Olson, 1977)

Seeing a Future that Wasn't:

"(A) few decades hence, energy may be free — just like the unmetered air." (John von Neuman, 1956)

"(I)t can be taken for granted that before 1980 ships, aircraft, locomotives and even automobiles will be atomically fueled." (General David Sarnoff, 1955).

These quotes point to fundamental difficulties in predicting the what, where, when, and how of asserted major scientific and technological advances, however carefully and thoughtfully crafted the projections (Feller, 2001).

Technology pessimists can probe areas of risk that might escape a less vigorous review. *Technology optimists* from organizations like the Foresight Institute can provide insights into the kinds of systems that seem to be within the realm of the possible if assemblers can be made to work. Public education may be needed to balance the views expressed by anti-technology writers and press (Smith, 2001).

NANOVISION THROUGH THE SOCIETY

Types of attitudes to nanotechnology among different groups of society are dividing in three main groups, which may consist several subgroups.

A least three categories of public presented[3] (Wilsdon, J. & Willis, R. 2005):

» NANO-RADICALS see nanotechnology as profoundly disruptive of economies and societies. In his 1986 book Engines of Creation, Eric Drexler, the so-called "father of nanotechnology", predicted a world in which nanoscale machines – "molecular assemblers" - would be capable of arranging atoms to build almost anything from the bottom up. Because it would take millions of these assemblers to build anything, Drexler argued that assemblers would also need to be capable of replicating themselves, hence his famous - and now disowned - scenario of self-replicating nanobots smothering the world in "grey goo".

» NANO-REALISTS emphasize the incremental innovations and commercial returns that the technology will provide in sectors such as manufacturing, IT and healthcare. They aren't interested in the hypothetical possibilities of bottom-up molecular manufacture. Theirs is a venture-capitalized, research-council approved version of nanotechnology, focused on practical applications and economic returns. It is this vision that has excited policymakers and unleashed a cascade of government funding across the industrialized world.

» NANO- SKEPTICS count Prince Charles and Michael Crichton amongst their number, but their most active and articulate representatives are the ETC Group, a small Canadian NGO. It's not grey goo that worries them, so much as the immediate risks posed by nanoparticles to human health and the environment. They also have some pretty serious questions about who is controlling the technology and whose interests it will ultimately serve. (Wilsdon, J. & Willis, R. 2005)

The vision of few intelligent nanometer robots mentioned in science fiction literature (for example, the novel Prey by Michel

[3] Wilsdon, J. & Willis, R. (2004). See-Through Science: Why Public Engagement Needs to Move Upstream. London: Demos.

Crichton) leads to immediate criticism by some groups that are concerned that such robots would take over the world and damage the environment. This criticism ignores input from researchers who note that basic laws of mass and energy conservation may not lead to infinitely multiplying material objects, and that only a complex systems of presumably already known living systems may be able to multiply and be intelligent (Roco, 2003). [4]

Nanobots are often on top of the list of nanotechnological creations that cause deep concern to the public. Eric Drexler and followers postulate that it will soon be possible to create nanoscale, addressable robots that have the ability to move in space, recognize the environment and self-replicate. Will it indeed be possible to create another form of life at the nanoscale? When it comes to the engineering of nanoscale machinery, nature is still far superior in its ability to integrate synergistically operating nanoscale systems of high complexity. Yet, even nature has not been able to engineer nanoscale creatures that combine all of the above-mentioned attributes of nanobots. Viruses are amazing nanoscale systems, but even they do not have the finesse of the hypothetical nanobots. Viruses are not capable of self-replication. Future man-made nanosystems will certainly be able to perform a variety of functions, but a robot that is proficient in all three functions — movement in space, recognition of a chemically complex environment and self-replication - *will remain the fabric of dreams* (Vogel, 2001).

NANOTECHNOLOGY INSPIRATION FROM RICHARD FEYNMAN'S 1959 TALK

Usually, though, the credit for inspiring nanotechnology goes to a lecture by *Richard Phillips Feynman*, a brilliant Caltech

[4] Roco M.C. (2003), NNI after three years (2001-2003): Setting new targets for responsible nanotechnology, in the Report of the NNI Workshop.

physicist who later won a Nobel Prize for "fundamental work in quantum electrodynamics." (Toumey, 2005).[5]

He is best remembered today for his clear and quirky classroom lectures and for his critical role on the presidential commission that investigated the Challenger accident. On the evening of December 29, 1959, Feynman delivered an after-dinner lecture at the annual meeting of the American Physical Society; in that talk, called "There's Plenty of Room at the Bottom," Feynman proposed work in a field "in which little has been done, but in which an enormous amount can be done in principle." (Keiper, 2003).

In his speech he predicted that physicists would eventually be able to manipulate matter at the molecular or even atomic scale, and would thus usher in a new technological revolution. "It doesn't cost anything for materials, you see. So I want to build a billion tiny factories, models of each other, which are manufacturing simultaneously, stamping parts, and so on. As we go down in size, there are a number of interesting problems that arise. . . . But I am not afraid to consider the final question as to whether, ultimately—in the great future—we can arrange the atoms the way we want; the very atoms, all the way down!" (Feynman, 1960). The tools to begin to pursue Feynman's playful predictions started to come on line in the coming decades. In 1980, IBM scientists used a scanning tunneling microscope to directly image individual atoms for the first time (Binnig & Rohrer 1982). The development of the atomic force microscope in the mid 1980s further advanced imaging capabilities, and in 1990, again at IBM, scientists actually manipulated individual Xenon atoms to write their company logo (Eigler & Schweitzer, NSTC,1990; 2000). A giant step had been taken toward confirming Feynman's assertion that it should be

[5] Toumey, C. (2005), Does nanotechnology descend from Richard Feynman's 1959 talk? J. Engineering & Science No. 1/2, P.16-23.

possible to print the entire *Encyclopedia Britannica* on the head of a pin.[6]

"What I want to talk about," Feynman said, "is the problem of manipulating and controlling things on a small scale. As soon as I mention this, people tell me about miniaturization, and how far it has progressed today … But that's nothing; that's the most primitive, halting step in the direction I intend to discuss." (Feynman, 1960).

He was talking about nanotechnology before the word existed. Feynman regaled his audience with a technological vision of extreme miniaturization in 1959, several years before the word "chip" became part of the lexicon. Extrapolating from known physical laws, Feynman argued it was possible (with, say, an electron beam that could form lines in materials) to write all 25,000 pages of the 1959 edition of the Encyclopedia Britannica in an area the size of a pin head! He calculated that a million such pinheads would amount to an area of about a 35 page pamphlet. Said Feynman: "All of the information which all of mankind has ever recorded in books can be carried in a pamphlet in your hand– and not written in code, but a simple reproduction of the original pictures, engravings and everything else on a small scale without loss of resolution." (Amato, 1999).

Feynman himself didn't use the word "nanotechnology" in his lecture; in fact, the word didn't exist until 15 years later in 1974, when Japanese engineer *Norio Taniguchi* of the Tokyo University of Science suggested it to describe technology that strives for precision at the level of about one nanometer (Klaes, 2004)[7]. In his lecture, Feynman pointed out several avenues for research that would later come to define nanotechnology, such as

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[6] Bennett, I. and Sarewitz, D. (2005), Too Little, Too Late?: Research Policies on the Societal Implications of Nanotechnology in the United States, Consortium for science, Policy, and Outcomes, Arizona State University.

[7] Klaes, L. (2004) What is Nanotechnology? Well, It's Very, Very, Very Small. The Ithaca Journal, No 4.

making computers much smaller and therefore faster, and making "mechanical surgeons" that could travel to trouble spots inside the body. Feynman admitted that he didn't have a clear conception of how such tiny machines might be used or created, but to help get things going, he offered two prizes: $1,000 to the first person to make a working electric motor that was no bigger than one sixty-fourth of an inch on any side, and another $1,000 to the first person to shrink a page of text to 1/25,000 its size—the dimension necessary to fit the Encyclopedia Britannica on the head of a pin. (He awarded the former prize in 1960, the latter in 1985.) (Keiper, 2003).

And that's just how his talk began. He outlined how, with proper coding, all the world's books at the time actually could be stored in something the size of a dust speck, with each of the million billion bits in those books requiring a mere 100 atoms to store. How about building computers using wires, transistors, and other components that were that small? "They could make judgements," Feynman predicted. He spoke about using big tools to make smaller tools suitable for making yet smaller tools, and so on, until researchers had tools sized just right for directly manipulating atoms and molecules. (Amato, 1999).

"And what might that mean?," asked Feynman. Chemistry would become a matter of literally placing atoms one by one in exactly the arrangement you want. "Up to now," he added, "we have been content to dig in the ground to find minerals. We heat them and we do things on a large scale with them, and we hope to get a pure substance with just so much impurity, and so on. But we must always accept some atomic arrangement that nature gives us...I can hardly doubt that when we have some control of the arrangement of things on a small scale we will get an enormously greater range of possible properties that substances can have, and of different things that we can do." Repeatedly, during this famous lecture, Feynman reminded his audience that he wasn't joking. "I am not inventing anti-gravity, which is possible someday only if

the laws are not what we think," he said. "I am telling you what could be done if the laws are what we think; we are not doing it simply because we haven't yet gotten around to it." (Feynman, 1960).

SCIENCE FICTION AUTHORS IN NANOTECHNOLOGY

Within the genre of science fiction, nano-science fiction is certainly one of the most flourishing fields nowadays. An online bibliography on Nanotechnology in Science Fiction lists 189 books, novels and anthologies, published between the mid-1980s and November 2003 in the English language only (Napier 2004). Milburn has identified many nano-science fiction stories in the 1940s and 1950s and argues that these stories already inspired Richard Feynman's 1959 visionary speech "There is plenty of room at the bottom", which later became the posthumous founding myth of nanotechnology (Milburn 2002)[8]. Invisibly small devices or the manipulation of the "ultimate building blocks of nature" have been a favorite topic ever since the genre of science fiction emerged and appear throughout the works of Jules Verne and H.G. Wells. In addition, 'manipulating-nature' was the pivotal theme in all the 19th-century 'mad scientist' stories, which in turn go back to medieval and early modern satires of alchemy (Schummer, 2006). Thus, the vagueness of nanotechnology definitions is passed on to the vagueness of what is nano-science fiction. (Schummer, 2005).[9]

Although the primary goal of science fiction is entertainment, the genre is frequently divided up according to different moral messages expressed by optimistic or pessimistic prospects of technology for society. Many of the stories that are

[8] Milburn, C.: 2002 'Nanotechnology in the Age of Posthuman Engineering: Science Fiction as Science', Configurations, 10, 261-295.

[9] Schummer, J. (2005), "Societal and Ethical Implications of nanotechnology": Meanings, Interest Groups, and Social Dynamics, Techné: Journal of the Society for Philosophy and Technology, Vol. 8, No 2.

today called nano-science fiction, including for instance Neal Stephenson's *The Diamond Age* (1995), also run under the insider labels of 'Cyberpunk' and 'Postcyberpunk', depending on whether they focus on a radically computerized society or additionally employ fictional biotechnology. “Now nanotechnology had made nearly anything possible, and so the cultural role in deciding what should be done with it had become far more important than imaging what could be done with it.” Instead of conveying a simple moral message, it is rather up to readers to make their own positive or negative judgment on the fictional technology's impacts on society. While many readers might feel uncomfortable with such visions, Cyberpunk has, as a matter of fact, inspired many, if not all, visions of transhumanist utopia. (Schummer, 2005).

Few nano-science fiction stories directly prompt moral questions about technology. An example is Michael Flynn's *Nanotech Chronicles* (1991). There are exceptional cases, however, like Michael Crichton's nanotechcatastrophe book *Prey* (2002) that employs Drexler's gray goo fiction. In the tradition of 19th-century mad scientist horror stories, Crichton retells the old fable of scientists (here, software engineers) who loose control over their work to the extent that they are threatened and finally controlled by their own creations. (Schummer, 2005).

For the majority of nano-science fiction authors, "societal and ethical implications of nanotechnology" is an experimental field of composing social contexts with visionary technologies (mostly computer technology) that more or less radically change humans and society, from using new tools to achieving a state of transcendence. Apart from making a living and from entertaining readers, their major interest seems to be to make readers think about general social and moral issues, about the place of technology in society, and about radical change, without providing simple answers or moral messages. Many have taken visionary ideas from SF authors, e.g. on the release of the movie version of Michel Crichton’s novel, Prey. (Schummer, 2005).

DEALING WITH THE LANDSCAPES OF NANOHYPERBOLE

Nano-radical like K. Eric Drexler, whose 1986 book, *Engines of Creation*, popularized the vivid and exciting possibilities of "the coming era of nanotechnology" as his subtitle put it (Drexler 1986). Subsequently he institutionalized his enthusiasm in the form of the Foresight Institute in Palo Alto, California. In his book and elsewhere, Drexler has emphasized one form of nanotech more than any other, namely, nano-size machines, commonly called nanobots. It is generally agreed that if these devices are to be realized, they must be preceded by some kind of machines which can reliably manufacture nanobots in very large quantities. Thus the controversy that surrounds Drexler's vision is centered not on the desirability of nanobots *per se*, but rather on the feasibility of the process of producing them. Extremely nanophilic hyperbole includes excitement about nanobots and the assemblers that make them, as anticipated by Eric Drexler and his supporters, and it also comprises a pair of contradictory theories about the interface of technology with human anatomy. One is the expectation that medical nanotechnology will cure diseases and repair human anatomy so quickly and successfully that the normal human lifespan will be extended indefinitely. The other is the hope that all human consciousness can be uploaded into machines, thus making human anatomy unnecessary. So our bodies can stay healthy for enormous lengths of time; but, our bodies are irrelevant to knowledge, thought, or spirituality. Extreme nanophilia is also represented in some works of science fiction, especially the novels of Kathleen Ann Goonan (1994; 1997; 2000). (Toumey, 2004). [10]

Nano-realistic approach is characteristic for the U.S. government's optimism, which is much more concerned with

[10] Toumey, C. (2004), Narratives for Nanotech: Anticipating Public Reactions to Nanotechnology, Techné 8:2, Narratives for Nanotech, pp. 88-116.

immediate and near-future events, especially in materials science, medicine, information technology, and other areas in which commercial products can be delivered fairly soon. It distances itself from Drexler's agenda of nanobots and assemblers (Roco & Bainbridge 2001, p. 14). In 1998, the U.S. government organized the Interagency Working Group on Nanotechnology (IWGN). Two years later, starting funded at $270 million, president Clinton's Clinton administration gathered its various nanotech projects under the umbrella of the National Nanotechnology Initiative (Amato, 1999).[11] In the January 2000 President Clinton's program speech at Caltech unveiled the initiative, saying "Caltech is no stranger to the idea of nanotechnology. . . . Over forty years ago, Caltech's own Richard Feynman asked, 'What would happen if we could arrange the atoms, one by one, the way we want them?' The National Nanotechnology Initiative's brochure reminds us that "one of the first to articulate a future rife with nanotechnology was Richard Feynman." (Toumey, 2005).

In the detailed blueprint for the NNI, it was said that "developments in…(nanotechnology) are likely to change the way almost everything - from vaccines to computers to automobile tires to objects not yet imagined—is designed and made" (NSTC 2000, p. 13). The next major NNI text told us that "The effect of nanotechnology on the health, wealth, and standard of living for people in this century could be at least as significant as the combined influences of microelectronics, medical imaging, computer-aided engineering, and man-made polymers developed in the past century" (Roco & Bainbridge 2001, p. 2.).

My next category is that of *measured skepticism*. This genre comes from a group of science writers who recognize that important work is being done at the nanoscale, and that this work will generate profound consequences for science and society. But

[11] Amato, I. (1999), Nanotechnology: Shaping The World Atom By Atom, National Science & Technology Council, Washington, D.C.

they also express disdain, almost contempt, for the hyperbole of extreme nanophilia. *Scientific American* is their principal venue, and the epitome of this kind of writing is Gary Stix's 1996 profile of Eric Drexler, wherein Drexler and his followers are comic eccentrics (Stix 1996)[12]. Stix's next article on nanotech was slightly kinder to Drexler, but still found ways to diminish him (Stix 2001). When *Scientific American* reported on carbon nanotubes (Minsky 2000) and molecular computing (Reed & Tour 2000), it found it necessary to suggest that stories of "microscopic robots rearranging atoms on command" might be "moonshine." "The hype," said John Rennie, "outruns the reality" (Rennie 2000). The September 2001 special issue on nanotechnology gave Drexler a chance to present his vision of nanobots (Drexler 2001), but the following article by Richard E. Smalley explained why nanobots were preposterous (Smalley 2001). And a facetious opinion piece in the same issue by Michael Shermer (Shermer, 2001) ridiculed the idea that "nanocryonics" will banish death (Toumey, 2004).

The genre of *measured skepticism* is continued by other authors as well. Peter Vettiger & Gerd Binnig clearly aspire to create nanoscale computers, but they emphasize how difficult it will be do so (Vettiger & Binnig 2003). Adam Keiper writes a lucid introduction to nanotech which bifurcates all the talk of a "nanotechnology revolution." On the one hand there are solid advances, incrementally achieved by hard-working scientists, and on the other there are the vivid fantasies of Drexler and such (Keiper 2003). Military applications from nanotech will be remarkable, says Jurgen Altmann, but they involve so many risks that we need a series of preventive measures to prevent them from creating disasters (Altmann, 2004).

[12] Stix, G. (1996), Trends in Nanotechnology: Waiting for Breakthroughs, Scientific American, 274(4), 94-99.

Measured skepticism final stance is an *extreme nanophobic counter-hyperbole,* approximately as intense as that of the *visionary nanophiles or nano-radicalism.*

The most sustained commentary in this genre comes from the ETC Group of Winnipeg, Manitoba, an activist organization that during the 1980s and 90s played a central role in opposition to genetically modified foods, especially to Monsanto's "terminator" technologies. Following several angry denunciations of the dangers of nanotech (ETC Group 2002; 2003a; 2003b), this organization called for a moratorium on commercial development of nanotech (ETC Group 2003c; 2003d; 2003e; see also Brown 2003), after which it published additional denunciations of nanotech (ETC Group 2003f; 2003g; see also Thomas 2003). The Big Down, an extended polemic on the potential evils of nanotechnology, published at the start of this year by an organization called ETC, a pressure group based in Canada. The ETC perspective focused on a combination of equity issues (who would benefit socially and economically from nanotechnology?) and a more traditional risk framework (what are the environmental and health risks associated with nanotechnology?) (Bennett and Sarewitz, 2005).

Lord May, president of the Royal Society and former government chief scientist, said that advances in science and technology have made life better in both the developed and developing worlds. Lifespan have increased, from a global life expectancy at birth 50 years ago of 46 years, to 64 years today, he said. World food production has doubled over the past 35 years, using only 10 per cent more land (Highfield, 2003).

The Greenpeace report on nanotech (Arnall 2003) relied very heavily on the ETC Group's position papers but, after briefly flirting with the idea of a moratorium, it recommended instead a balance of industrial self-restraint and government oversight (Arnall 2003,40-41). The Chemical Market Reporter expressed a sense of alarm in the business community that popular hostility to nanotech, regardless whether it had its basis in fact or in fiction,

could poison the future of this kind of research (Lerner 2003). The dark view of nanotech is also represented in a recent series of science fiction films, particularly *The Hulk*, *Agent Cody Banks*, *Jason X* and *Cowboy BeBop*. A group of novels, the best known of which is Michael Crichton's *Prey* (Crichton 2002), present visions of a world radically altered for the worse by nanotechnology. (For recent commentaries on nano in science fiction, see Collins 2001; Hayles 2004; Miksanek 2001; Milburn 2002, Johnston, 2001). Another form of dramatic nanophobia comes from Bill Joy (2000; 2001) and Bill McKibben (2003). This subgenre indicates that nanotech is the centerpiece of a so-called convergence of technologies which will diminish human nature so much, in relation to high-performance machines, that our human qualities will become irrelevant: the end of humanity, so to speak. Vicki Colvin and others have instigated good questions about nanorisk (Rotman 2003; Tenner 2001), while Doug Brown, Barnaby J. Feder and Candace Stuart have chronicled these discourses (Brown 2001; 2002a; 2002b; 2002c; Feder 2003a; 2003b; Stuart 2002; 2003a; 2003b).

Fears by the Prince of Wales that armies of microscopic robots could turn the face of the planet into an uninhabitable wasteland have prompted the nation's top scientists and engineers to launch an inquiry. Having attacked GM foods in the past, Prince Charles has more recently turned his attention to nanotechnology, the ability to manipulate matter at scales of billionths of a metre. Concerned by claims by environmentalists that swarms of rogue "nanomachines" could one day reduce all in their path to "grey goo", the prince has asked the Royal Society to help him to weigh up the risks. (Highfield, R. 2003).[13]

[13] Highfield, R. (2003), Prince asks scientists to look into 'grey goo', in online magazine Telegraph, http://www.telegraph.co.uk/

Table 1. Two opposite (political) visions on nano-bio-info-cogno technologies (NBIC) convergence (based on Garreau 2004, Hughes 2004).

Scenarios - Political ideology	**Optimistic**	**Pessimistic - BioLuddism**
Development technology	Technology develops exponentially	
Determining factor	Technology determines history (technological determinism)	
Outcome technological development	Progress	Disasters and catastrophes
Development humankind	Human nature is 'under construction' Intelligent machines (Übermensch) win the evolutionary struggle with humans	Technology changes the principle characteristics of human nature Humans as a species are threatened by technology
People and parties	Eric Drexler (1986) Ray Kurzweil (1999) Gregory Stock (2002) Roco & Bainbridge (2002(a)) -NSF-workshop Transhumanists, such as James Hughes (2004) and Nick Bostrom (2006)	Bill Joy (2000) Francis Fukuyama (2002) Bill McKibben (2003) President´s Council on Bioethics (2003) Susan Greenfield (2003) ETC Group (2003) Martin Rees (2003)

Lord May at the Cheltenham Festival of Science announced that the Society and the Royal Academy of Engineering are to launch a study into nanotechnology. But Lord May stressed: "There is nothing inherently sinister about nanoscience or nanotechnology, it just refers to the study of things on the scale of one-millionth of a millimetre." He said the prince should be reassured that the "grey goo" scenario, which is raised by various sources, notably Michael Crichton's book Prey, is even less likely to come true than cloning dinosaurs. "The nightmare scenario of self-replicating nanobots destroying everything is about as likely to come true as Jurassic Park, another product of Michael Crichton's fertile imagination," said Lord May. Compared with the real threat from nuclear weapons, Sir Martin said that the "grey goo" scenario "might become a concern 50 years from now but is science fiction for the moment". (Highfield, 2003).

Polarizes discussions of nanotech between extreme nanophilic and extreme nanophobic hyperbole thereby erases the more nuanced ideologies in between. *The Economist has noted that, unfortunately, common images of nanotech tend to arrange themselves into a bipolar division of love-nano-or-hate-nano positions* (Economist 2002).

SCIENCE FICTION RATHER THAN REALITY

By sketching extreme future versions the political discussion about the present and future of our information society gains meaning and new demarcation lines for politics in the 21st century appear. On the one side of this new political dimension transhumanism (quasi religious organization) sees itself as a progressive emancipation movement which fights for the right of people to improve themselves (via technology), and which tries to enthuse the present-day culture for their utopian vision. On the other side, the bioLuddites accept the cultural analysis of the transhumanists, but oppose the utopia that they sketch because they

experience this as a dystopia. (European Parliament's Department of Economic and Scientific Policy, 2005).[14] The popular press has often aired heated discussions by the author Ray Kurzweil and others about the idea that it will soon be possible to scan the human brain and essentially transfer its neural activity to a computer designed to simulate billions and billions of human neurons (Kurzweil 1999).[15] *Raymond Kurzweil* is the author of several books on health, artificial intelligence, transhumanism, technological singularity, and futurism.

This fantastic thought is based on a series of assumptions, some of which are reasonable extrapolations of future technological abilities. If Moore's law can be extrapolated, computers will achieve the memory capacity and computing speed of the human brain by around the year 2020. Computer experts claim, it will be possible to simulate the brain and its function and eventually the state of the human mind, complete with its memories, emotions and creativity (Vogel, 2001).

Two pioneers in molecular electronics, Mark A. Reed and James M. Tour (2000), pose the question: "Will it be possible someday to create artificial 'brains' that have intellectual capabilities comparable - or even superior - to those of human beings?" - which they answer in a review of their *own* research as follows: "…scientists have achieved revolutionary advances that may very well radically change the future of computing. And although the road from here to intelligent machines is still rather long and might turn out to have unbridgeable gaps, the fact that there is a potential path at all is something of a triumph. The recent advances were in molecular-scale electronics…By pushing Moore's Law past the limits of the tremendously powerful

[14] European Parliament's Department of Economic and Scientific Policy (2005), Technology Assessment on Converging Technologies, Report of European Parliament.

[15] Kurzweil, R. 1999. The Age of Spiritual Machines. Penguin Books.

technology we already have, these researchers will take electronics into vast, uncharted terrain. If we can get to that region, we will almost certainly find some wondrous things - maybe even the circuitry that will give rise to our intellectual successor."

Bill Joy's recent article, "Why the Future Doesn't Need Us" in Wired is a widely read example. His article, though intriguing, misses a most critical point. Virtually every "millennium survey" of the future poses some social, ethical, or legal questions about nanotechnology. But there is little so far in the way of serious study (Smith, 2001).

Expanding on scenarios already published by Drexler, as well as the ideas of the inventor technological visionary Ray Kurzweil (1998), Joy wrote: "robotics, genetic engineering, and nanotechnology . . . pose a different threat than the technologies that have come before. Specifically, robots, engineered organisms, and nanobots share a dangerous amplifying factor: They can self-replicate. A bomb is blown up only once - but one bot can become many, and quickly get out of control." While Drexler had devoted a chapter to the possible dangers of self-replication, he had also considered it to be a manageable problem. Joy saw it as intrinsically uncontrollable. His solution?: "relinquishment: to limit development of the technologies that are too dangerous, by limiting our pursuit of certain kinds of knowledge." Joy's position as one of the chief architects of the world's high technology information infrastructure meant that he could not be dismissed as a fringe voice or Luddite. Advocates of the benefits of nanotechnology thus sought from the outset to discredit the plausibility of Joy's ideas on either the scientific grounds that self-replicating "nanobots," as originally described by Drexler, were impossible (e.g., Armstrong, 2001; also see discussion in Sarewitz and Woodhouse, 2003), so there was nothing to worry about (Bennett and Sarewitz, 2005).

PROFESSIONAL FUTURISTS – REALISTIC VISIONARIES

As early as 1990 the popular journal 'The Futurist' published an article entitled "Nanotechnology and Human Values" (Wrubleski, 1991); during the 1990s business magazines such as 'Forbes' and 'Futures' also featured occasional coverage of the implications of nanotechnology, and academic journals such as 'Scientometrics' and 'Research Policy' began to track scientific and technical trends (Bennett and Sarewitz, 2005).

Futurists is a term used to describe management science consultants who practice systems thinking to advise private and public organizations on diverse global trends, risk management and emerging market opportunities. Some countries call these interdisciplinary practitioners *Futurologists*. A key element of all management is being able to anticipate what competitors, employees and customers are likely to do next, in the context of a rapidly changing wider world. Thus it is true that to some extent all effective leaders are futurists. All serious futurists have demonstrated their professionalism in the field of future studies and the application of trends knowledge and insights.

To meet the challenges of the future, we need to find out about what we can plausibly expect in the years ahead so we can understand what our options are. We can then set reasonable goals and develop effective strategies for achieving them. A key part of futuring is managing uncertainty and risk. Every crisis should be a reminder to us of the importance of thinking now about the future. A crisis almost always results from earlier failures to deal with an emerging problem or to anticipate a likely eventuality. In retrospect, we often recognize that the crisis was perfectly preventable. The importance of thinking ahead is growing rapidly because the pace of change is accelerating. New technologies are producing a cascade of economic and social changes in our lives

and raising serious questions for politicians and ethicists (World Future Society, 2002).[16]

In 1999 the Institute for Global Futures deployed a privately funded study to assess the general awareness and readiness of the business community regarding the economic and business impact of nanotechnology. A series of interviews with a broad range of business executives in health care, manufacturing, medicine, real estate, information technology, consumer goods, entertainment and financial services was conducted, and is still being conducted at this time. The Institute for Global Futures, a ten-year-old San Francisco organization advises the Fortune 1000 and government on the impact of leading-edge technology on markets, society, customers and the economy. The Institute covers telecommunications, robotics, computers, life sciences, the Internet, software, artificial intelligence and a host of other technologies and forecasts trends.(Canton, J., 2001, *Institute for Global Futures).*

Governments rely to a considerable extent on technology foresight studies in their long-term science and technology policy planning. These exercises provide governments with estimates about future technological developments and the implications they might have for society. Some of these studies also addressed NST. We shall have a closer look at them in the following section (Meyer.M., 2001, Technopolis Ltd.).

[16] World Future Society, (2002), The Future: An Owner's Manual.

SOCIETAL INNOVATION REGARDING NANOINNOVATION

THEORETICAL INTERFACE OF SOCIO-ECONOMIC IMPLICATIONS IN NANOINNOVATION

Nanotechnology, if even partially realized, over the next few decades has the potential to realign society, change business and affect economics at the structural level. New business models, design tools and manufacturing strategies may emerge at price points much reduced and highly efficient.

Nanotechnology will touch all aspects of economics: wages, employment, purchasing, pricing, capital, exchange rates, currencies, markets, supply and demand. Nanotechnology may well drive economic prosperity or at the least be an enabling factor in shaping productivity and global competitiveness (Canton, 2001). Social scientists and economists should be encouraged to address six main research questions, in support of the NanoInitiative (Darby and Newlon, 2003).

- ***First***, what policies increase or determine the transfer of nanoscale science and engineering knowledge from academe to industry? Issues to be examined include licensing intellectual property to inventor-affiliated companies under the Bayh-Dole Act* and concerns about conflict of interest or commitment. The issues could be framed in terms of the optimal assignment of property rights for university research, developing ideas of Aghion and Tirole (1994)* and Jensen and Thursby (2001)*.

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* The Bayh-Dole Act is one of the most important 20th century pieces of legislation in the field of intellectual property in the US, along with the creation in 1982 of the Court of Appeals for the Federal Circuit. Perhaps the most important contribution of Bayh-Dole is that it reversed the presumption of title. Bayh-Dole permits a university, small business, or non-profit institution to elect to retain title first.

∗ P. Aghion. J. Tirole. The management of innovation. The Quarterly Journal of Economics, 109,1185-l209 (1994).

- ***Second,*** what are the returns from nanotechnology investment? This question addresses why government should be investing in nanotechnology. An interesting alternative question is: How much should government and industry invest, given a reference rate of return?
- ***Third*** research question, with both economic and social dimensions, concerns how longer, healthier lives will change work patterns. If people are able to work far into their seventies, will they and the labor market around them become segmented by age? How will the activity of older people be distributed across entertainment, paid labor and volunteer contributions to the well-being of others?
- ***Fourth***, what skill biases are associated with major nanotechnology applications and what do they imply for wages and returns to education?
- ***Fifth***, should there be a research exemption for patents? At present, there is much debate about the conditions under which scientists should have a free license to employ patented inventions in non-profit research for example, in their instrumentation and other research tools. Traditionally. technological inventions can be patented, whereas scientific discoveries cannot. Yet, the line between nanotechnology and nanoscience is unclear, and the economic benefits of progress be diminished if intellectual properly rights prevent rather that stimulate innovation.
- ***Finally,*** what are the most efficient and effective forms of government-industry cooperation? NSI's Grant Opportunities for Academic Liaison with Industry (GOALI) and the Microelectronics Advanced Research Corporation/Department of Defense Focus Center Research Program are examples that deserve considerations.

∗ R. Jensen, M. Thursby, Proofs and prototypes for sale: The tale of university licensing. American Economic Review; 91.240-259 (200l).

The research methods that are most likely to result in usable, credible answers to these questions are; major data collection (firms, products, people); Nanobank.org and studies of NNI grant awardees; Center for Economic Studies/Research Data Series: case studies (e.g.. industry, cross-cutting tech); surveys (e.g., technology transfer job skills, Delphi*) economic models, dynamic adjustment); and input-output analysis of impact on sectoral productivity (Darby & Newlon).

EMPIRICAL INTERFACE OF SOCIO-ECONOMIC IMPLICATIONS IN NANOINNOVATION

As nanotechnology moves from the theoretical, through the empirical, to the practical, as many of us believe it shall do faster than is expected, then the possible impact on business, society and the economy will become evident over time. But we have a new opportunity today. Given the recent history of digital technology and access to better models of socio-economic analysis, we must

* Most NSF (nanoscale science and technology) supported work on the public understanding of sciences focuses on attitudes toward science and knowledge about science rather than the ends to which science could or should be put. Several modes of identifying social needs on which to base justifications for advances in S&T have been outlined. These include Foresight and Delphi techniques, Charettes in city planning, as well as public discussion models from the philosophy of science. The identification of technology goals could also process from social science research on human needs, e.g. Maslow's hierarchy of goals. Foresight studies attempt to depict an image of a possible future using a variety of techniques. An important foresight method is the Delphi survey. A Delphi survey basically is a tool to create consensus and detect areas of conflicting expert opinions. In a first round, experts are confronted with a number of topics they have to evaluate with respect to time of realization, implication on wealth creation, quality of life, and similar issues. In another round the results of the previous round are introduced to the experts who then have a chance to re-evaluate the topic.

consider growing readiness a social responsibility. We must consider readiness as part of our social policy (Canton, 2001).

1. Nanoscience and nanotechnology provide an excellent testbed case to study the speed at which new scientific findings are transformed into commercially important technological innovations? (Feller, 2001).
2. Current developments at the frontiers of research in these domains also provide a natural experiment to assess alternative models (e.g., linear, pipeline models; chain-link models; Pasteur's Quadrants, soccer games) of relationships between scientific and technological advances. (Feller, 2001).
3. Why is the potential economic impact of nanotechnology so important to consider? The risks in not preparing for and examining the economic and business impact are too large to ignore (Canton, 2001).
4. There would be a dramatic impact on lifestyles, jobs, and economics. Most value chains, supportive linkages, alliances and channels of distribution will be altered. Institutions of learning, financial services and certainly manufacturing will be reshaped. What if the fabrication lines for making computers are reduced in costs by 50%? What if drug development and manufacturing costs are reduced by 70%? What if energy sources were not dependent upon fossil fuels? What then might the impact be if nanotechnology were applied to real cost reductions for essential goods and services that affect quality of life, health, habitat and transportation? (Canton, 2001).
5. We must learn to ask the questions now about how nanotechnology may change our choices, affect our lifestyles, shape our careers, influence our communities — we must ask now and prepare so we may examine the implications that may shape the future we will live in together. Readiness is always a wise choice. Though one

could question at this time, when nanotechnology is still in its infancy, largely theoretical, why should anyone care and why would we even expect readiness? (Canton, 2001).

6. Must we interested in readiness and awareness prior to the accelerated changes that may lie ahead, not so far ahead as we might think? (Canton, 2001).
7. The issues that remain are to consider in what timeline what actions might be taken. How might we prepare as a society for these changes? Will there be radical dislocations or a smooth coordinated adaptation? (Canton, 2001).
8. Is there any reason to expect that nanotechnology would impact a wide range of industries—creating entirely new industries, increasing demand for some goods and lowering demand for others? (Darby and Newlon, 2003).
9. What might the economic impact on the computer industry be overnight? (Canton, 2001).
10. Imagine a super-strong and inexpensive material to be used for construction and manufacturing that would eliminate the market for steel and plastics. How might that influence the economy? (Canton, 2001).
11. In an era of prosperity it is difficult to consider the lack of global leadership that might occur with a nation such as the United States. How might the United Kingdom have better prepared for its 19th century challenges if it had known what was to come at the height of its global leadership in the last century? We might well ask the same questions today. (Canton, 2001).
12. If NT would develop in the way it ought, might or not poor and sick in the developing world equally benefit from advances in NT? Furthermore, if developing countries were to see the potential of NT and became early players in the field (China increase expenditure on NT R&D), NT might have an impact on their economic development and obviate the need quite soon for these countries to become net

importers of NT. This is similar to what is happening in biotechnology, a field in which countries such as India, China, Brazil, and Cuba have already begun to invest in. (Maclurcan, 2005).

APPLICATION INTERFACE OF SOCIO-ECONOMIC IMPLICATIONS IN NANOINNOVATION

In addressing future economic and societal effects, researchers need to take a number of different but ultimately complementary viewpoints.

One point of view addresses the macroeconomic effects in terms of effects of economic growth, productivity, real wages, and the standard of living.

Another industrial organization approach focuses on the particular industries that will be most directly affected by nanotechnology and attempts to assess how they will be transformed.

Labor economists take a similar point of departure, but instead focus on the movement of labor among industries, the acquisition by some workers of new skills, the obsolescence of other skills, and the necessary wage signals to accomplish both labor movement and training.

We must plan for multiple scenarios. The value of these scenarios may be viewed as a catalyst for mapping future impact on an economy and society (Darby and Newlon, 2003).

1. For each of these viewpoints, the first step is framing the "counter-factual question"- what is the effect of the nanotechnology we are going to see compared to what alternative? (Darby and Newlon, 2003). Nanotechnology provides a stimulating and somewhat awesome challenge to meet. If we had the knowledge in the 1960s and 1970s to prepare for the impact of computers or telecom in the 1990s, how might we have prepared the nation? Today we have real-time examples and a history of rapid accelerated economic

change due to new technology to learn from, in preparing for the future (Canton, 2001).

2. What might the potential scenarios be, given the contrasting readiness factors of a society? Many of the necessary factors are in place to drive this scenario: widespread potential cross-industry applications; fast track R&D; government investment (Canton, 2001).
3. The evolution of a nano-economy, as contrasted with the petro-economy of today, is an intriguing idea. How might an economy not dependent on oil realign itself? More study will be need to be conducted in order to understand and map these scenarios. Fundamental nanotechnology innovations yet to come will set the timeline for this economic transformation. Or, nanotechnology may just become integrated into industries such as health care, manufacturing and energy much like artificial intelligence became an embedded component of new products (Canton, 2001).
4. A nanotechnology revolution would have implications for education and infrastructure. Real wages and the standard of living are closely tied to growth in labor productivity resulting from both increasing levels of education and from innovations. The first point is that the top scholars and doctoral students are the scarce resource around which industries will be formed and transformed (Darby and Newlon, 2003).
5. Business schools should offer courses to familiarize both MBA students and mid-career executives with the basic ideas and the potential of nanotechnology. Promote NT education in secondary schools and universities. To emphasize that this multidisciplinary subject is gaining priority. Schools and universities could discuss the issue in depth: as well, could include exhibits on NT; Conversely, there is an important niche in facilitating the aspirations of scientists attempting to

become or work with entrepreneurs in order to bring their discoveries to market (Darby and Newlon, 2003).

6. In conclusion, the readiness of a nation to prepare for large-scale socio-economic change is a challenging task. Nevertheless, the future wealth of nations, certainly the economic sustainability of nations, will be shaped by the preparations we make today. Coordinated large-systems strategic planning efforts may well shape our ability to adapt. Strategically important decisions will need to be made. Vastly important national security and economic issues lay yet unexamined. Huge cultural issues related to managing large-scale change will need to be better understood and plans formulated (Canton, 2001).

ACTION RECOMMENDATIONS

The research questions in theoretical part listed above depicted the important role that socio-economic research can play in resolving major issues in how much government should invest in nanoscale research and how to make those investment have the greatest return to the national welfare.

The accumulated research to date makes a strong and clear case for one recommendation that is most important for maximizing the benefits from investment in nanoscale science and engineering:

- research should be broadly funded primarily based on peer-reviewed investigator-initiated proposals: research grants, career awards, increased funding, etc;
- benefits of nanoscale science and engineering are so broad that funding should not be driven by a few specific top-down priorities*;

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* Nanotechnology is often represented by two fundamentally different approaches: 'top-down' and 'bottom-up'. 'Top-down' refers to making nanoscale structures by machining, templating and lithographic techniques,

- short-term and long-term priorities should be indicated;
- global opinion-leaders network for socio-economic and ethical implications ought to be established so that third world countries may be involved (Darby and Newlon, 2003).

It is too trite to state no one can know the future. The future may indeed be unpredictable. But we do know that without asking the hard questions, without speculating on the possibilities, without preparing the nation by building readiness, we may do ourselves a disservice that will be difficult to repair. We might well consider the possible futures that will result from our collective actions. We must have the courage to speculate on the possible nanotech futures we may shape as a nation (Canton, 2001).

whereas 'bottom-up', or molecular nanotechnology, applies to building organic and inorganic materials into defined structures, atom-by-atom or molecule-by-molecule, often by self-assembly or self-organisation. Biologists/chemists are involved in the synthesis of inorganic, organic and hybrid nanomaterials for the use in nanodevices, the development of novel nanoanalytical techniques, and the manipulation of biological molecules such as DNA and the evolution of molecular machines.

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CHAPTER TWO

ESSENTIAL INDICATORS OF R&D EXCELLENCE IN NANOS&T: PUBLICATIONS AND PATENTS ANALYSIS

NANOTECHNOLOGY PATENTS ON THE INCREASE

Main quantifiable indicators of scientific and technological excellence are patents and publications (Hullmann, 2006).

Statistics produced by Thomson Derwent show that whilst there was a sudden rise in journal papers on nanotechnology beginning in the mid-1990s, patent applications did not start to accelerate until 1998. From that time, however, huge yearly jumps have been recorded, from around 500 in 1998 to nearly 1,300 in 2000. All of which is putting patent offices under strain. Nowhere more so than the United States Patent and Trademark Office (USPTO), which has to deal with the majority of applications (Wild, 2002).

PATENT APPLICATIONS AS AN INDICATOR OF NANOTECHNOLOGY EXCELLENCE

Patents are generally regarded as output indicator of technology development (Schmoch, 1999). They represent intellectual property rights and are thus legal documents. A patent application has to fulfill various criteria to be granted:

1) The described invention has to be new on a worldwide level.
2) The new product or process must be distinctly different compared to the state-of-the art; it must imply an inventive step.

3) The invention has to be exploitable in commercial terms. Scientific discoveries without a practical purpose are not patentable.

The third criterion implies that most patent applicants are industrial companies. This is reinforced by the fact that patent applications are expensive so that their issuance is only reasonable if a commercial exploitation is aimed at. With North American universities increasingly filing patents (mainly as a result of the Bayh-Dole Act 1980) in the last two decades, such an approach allows the identification of patenting activity of public research organizations. However, the situation in Europe is different. A recent study of the Organization for Economic Cooperation and Development ("OECD") concludes that public research organizations are presently not active patent applicants (Org. for Econ. Cooperation & Dev., 2003). Traditionally, the ownership has remained in the hands of individual employees (mainly university professors). Although several countries, among them Germany and Austria, transferred the property rights to the universities by modifying their patent law in the last couple of years, until recently universities did not frequently file patents. An inventor law, valid in the past period, which allowed university professors to exploit their intellectual property on their private account; whereas the universities did not appear as applicants in the patent documents (Heinze, 2004).

An assessment of 2003 figures from the U.S. Patent and Trademark Office (USPTO) highlighted the commanding lead held by the U.S. in nanoscale science and engineering patenting, with 42% of the overall share. Germany followed with 15.3%, and Japan was placed 3rd, with 12.6%. Fast growth was said to be occurring in South Korea, the Netherlands, Ireland and China (Huang et al, 2003). A report later that year claimed China was ranked 3rd in general nanotechnology patents behind the U.S. and Japan (Xinhua News Agency, 2003).

Furthermore, of all the U.S. patent applications in nanotechnology, about 90% of the applications came from private corporations, while universities filed roughly 7%, and about 3% were filed by government agencies and collaborative research centers. The number of issued patents involving nanotechnology has increased by more than *600%* in the last five year period, from 370 in 1997 to 2,650 in 2002. While only 2% of all patents issued in 2002 involved nanotechnology, that was much higher than the 0.3% in 1997. Nanotechnology-related patent applications are evenly split between process and product inventions. Most of the inventions are refinements to known technology, but a significant number can be considered "revolutionary" or pioneering in nature (Heines, 2003).

A BIBLIOMETRIC ANALYSIS OF ON-GOING R&D ACTIVITIES IN NANOSCIENCE AND TECHNOLOGY

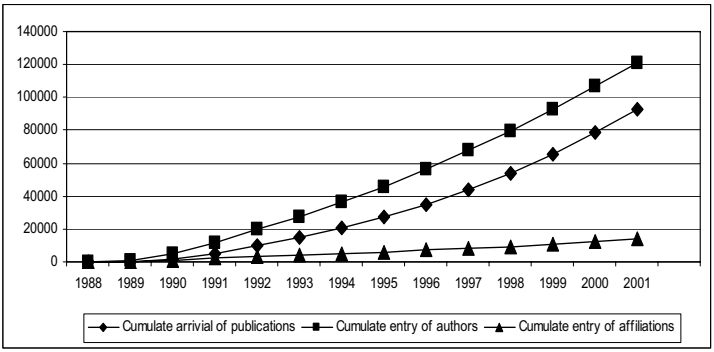
The scientific publications and citations represent scientific basis of nanotechnology. Scientific publications are the most appropriate indicator for measuring scientific excellence by quantifying the output (Hullmann, 2006).

Heinze (2004) pointed out, that worldwide rise both in nanopublications and nanopatents is remarkable. Since the discovery and development of the Scanning Tunnel Microscope ("STM") in the early 1980s and later Atomic Force Microscope ("ATM"), research on nanoscale phenomena has burgeoned, particularly since the early 1990s, only when the expensive STM and ATM become available at reasonable prices. The stark increase in publications in the year 1991 has continued ever since and has led to a lagged but similar development in patenting activity. The number of SCI publications (Science Citation Index ("SCI"), the world's largest publication and citation database in the natural and medical sciences) in 2002 is six times the number it

was 1992. Over the whole 20-year period, an annual growth rate of 37% in the number of publications.

The results are consistent with other bibliometric studies on nanoscience and nanotechnology published since the late 1990s. In the most recent study, however, Meyer (2001) reports far fewer worldwide nano patent applications because he used the official EPO database instead of DWPI. Derwent World Patents Index ("DWPI") is the database. Searching with DWPI titles and abstracts proves to be a major advantage for the proper identification of nanotechnology patents. The staff of Thomson Derwent prepares new titles and abstracts that describe the technological content of each patent application in more detail and depth. A search of "nano" with right-hand truncation in DWPI titles and abstracts yields about three to four times as many documents as a search in official databases of the U.S. Patent and Trademark Office or the European Patent Office (Heinze, 2004).

Figure 1. Evidence from Nanopublications. Source: Bonaccorsi and Thoma (2005).



IDENTIFYING CREATIVE RESEARCH ACCOMPLISHMENTS IN NANOS&T

Whenever a new product or process emerges, patent offices are under pressure to ensure that they understand the parameters

within which development work is taking place. It is crucial to be able to differentiate between what is already established knowledge and what is new when assessing a patent application for novelty and non-obviousness. The problem is that when you are dealing with something that has not been around for very long, it is not easy to find examiners who have experience of working in the field or to track down all references to prior art. The risk is that the granting of patents can be too broad and give the successful applicant a stranglehold on huge areas within the technology, so making it far harder for other companies to operate in that field (Wild, 2002).

Nanotechnology first gained recognition after Nobel Laureate, Richard Feynman, presented his talk, "There's Plenty of Room at the Bottom" to the American Physical Society in 1959 (Coleman, 2003).

Heinze et al (2006) had examined the relationships between nominated creative researchers (obtained through their expert survey and prize winner data bases) and bibliometric assessments of highly cited researchers. They found that combining two data sources – the nominations of creative research and the databases of scientific prizewinners – was complementary and offered additional validation, particularly in identifying researchers who were recognized for their creativity through multiple nominations and prizes. Authors delineated types of scientific research creativity: e.g. Invention of novel instruments that opened up new search perspectives and research domains, e.g. Scanning tunneling microscopy (STM), a powerful research instrument (Hessenbruch 2004) by physicists Gerd Binnig and Heinrich Rohrer (Binnig & Rohrer 1982). Binnig and Rohrer were awardees of the 1986 Nobel Prize in Physics “for their design of the scanning tunneling microscope”. STM opened up new research avenues in semiconductor physics, microelectronics, and surface chemistry. Most significantly, STM is recognized as an important tool in the emergence of nanotechnology (mid-1980s to present), giving rise

to the promise of assembling materials, structures, and systems at atomic and molecular scales.

Donald Eigler of IBM's Alden Research Center remembers the day in 1990 when he and Erhard K. Schweitzer, who was visiting from the Fritz-Haber Institute in Berlin, moved individual atoms for the first time. Using one of the most precise measuring and manipulating tools the world had ever seen, the researchers slowly finessed thirty-five xenon atoms to spell out the three-letter IBM logo atop a crystal of nickel. To be sure, it only worked in a vacuum chamber kept at a temperature that makes the North Pole seem tropical (Sarewitz and Woodhouse, 2003).

In 1988, Eric Drexler taught the first course on NanoTechnology. In that program, he suggested the possibility of nanosized objects that were self-replicating. The next major milestone was when Rice University Professor Richard Smalley won the 1996 Nobel Prize for discovering a new form of carbon: a molecule of sixty carbon atoms (referred to as C60).Today C60 has become one of a growing number of building blocks for a new class of nanosized materials. The advancements in NanoTechnology really began to accelerate in the late 1990s (Coleman, 2003).

NANOSCIENCE AND NANOTECHNOLOGY LINKAGES

Nanoscience and nanotechnology provide an excellent testbed case to study increasingly commonplace statements about the blurring of distinctions between science and technology and the speed at which new scientific findings are transformed into commercially important technological innovations. Current developments at the frontiers of research in these domains also provide a natural experiment to assess alternative models (e.g., linear, pipeline models; chain-link models; Pasteur's Quadrants, soccer games) of relationships between scientific and technological advances (Feller, 2001).

Mehta, M. D. (2002). denotes that developments in nanoscience and nanotechnology will provide social scientists with a unique opportunity to examine how different models of innovation may explain how the knowledge-based economy is being shaped by radically new approaches to science. Nanoscience and developments in nanotechnology are expensive and require cooperation between universities, governments and industry. Not too long ago, the ***linear model*** of innovation dominated. Traditionally, knowledge transfer within innovation processes is considered a one-way flow of scientific or technological knowledge from academic research (university) to industrial development. Several other actors play important roles in innovation processes, such as government (Leydesdorff & Etzkowitz, 1996), investors (Coehoorn, 1995), and end users (Bobrowski, 2000; Bunders, Broerse, & Zweekhorst, 1999; von Hippel, (1988); Kline and Rosenberg, (1986)), criticized the linear model and launched the so-called ***chain-linked model*** of innovation processes. In this model, the "central chain of innovation" begins with design and moves toward development and production to marketing. *Each step is linked together via feedback loops and all are side-linked to research.* It is assumed that scientific research is not a source of inventive ideas but is used to solve problems along the chain of innovation.

Stokes (1997) introduced an alternative innovation model in his book ***Pasteur's Quadrant***. This model rejects the traditional distinction made between basic and applied research. Stokes outlines how basic science could be oriented toward improving simultaneously an understanding of fundamental principles and stimulating improvements in technology by formalizing the links between science and technology. Another innovation model is the ***"triple helix"*** of Leydesdorff (2000) and Leydesdorff and Etzkowitz (1996). This model focuses on the overlay of communications and interactions between the three institutional spheres (three helices) of *industry, university and government.*

Each sphere produces its own knowledge, engages in marketplace activity and attempts to control external influences. Through information exchange and shared expertise, internal transformations in each of the helices facilitate the generation of new ideas and stimulate innovation.

The last type of innovation model the author of this article would like to mention is called ***"national systems of innovation"*** (Niosi, 2000) and has been defined by Lundvall (1992) as "the elements and relationships which interact in the production, diffusion and use of new, and economically useful, knowledge either located within or rooted inside the borders of a nation state". Such a system creates, stores and transfers information, knowledge, skills and artifacts related to technologies and innovations. Although scholars and policymakers apply different definitions and perspectives to this concept, in general the basic premise is that understanding the linkages between actors involved in innovation is central to improving technology performance (Organization for Economic Cooperation and Development, 1996).

Understanding the roles and relations between academia, government, and industry could be the basis for assessing and anticipating the likely trajectories of technology-induced social change and help answer the following question: *What model or models of innovation best explain the changes being ushered in by the revolution in nanotechnology?*

Darby, M. R. and Newlon, D. H., (2003) stated several research and evaluation methodologies which are encouraged economists to address several main research questions, in support of the National Nanotechnology Initiative. ***One question is,*** what policies increase or determine the transfer of nanoscale science and engineering knowledge from academe to industry? Issues to be examined include licensing intellectual property to inventor-

affiliated companies under the Bayh-Dole Act[18] and concerns about conflict of interest or commitment. The issues could be framed in terms of the optimal assignment of property rights for university research, developing ideas of Aghion and Tirole (1994) and Jensen and Thursby (2001).

Other issue is, should there be a research *exemption* for patents? At present, there is much debate about the conditions under which scientists should have a free license to employ patented inventions in non-profit research for example, in their instrumentation and other research tools. Traditionally. technological inventions can be patented, whereas scientific discoveries cannot. Yet, the line between nanotechnology and nanoscience is unclear, and the economic benefits of progress be diminished if intellectual properly rights prevent rather that stimulate innovation. The fear lies where potentially devastating effects of being excluded from a market because of a rival's over-broad patent means extra expense for companies who could do without it. It is not cheap to challenge an examiner's decision within the USPTO, let alone through the courts, whilst delays in obtaining protection could make the difference between securing funding and going out of business. When Todd Dickinson former Commissioner of the USPTO was made aware of difficulties in handling business method patent applications, he undertook a period of extensive consultation with industry. As a result new examination guidelines were drawn up. Companies and investors, who are pouring billions of dollars into the nascent nanotechnology industry, are expectant of a similar approach (Wild, 2002).

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[18] The Bayh-Dole Act is one of the most important 20th century pieces of legislation in the field of intellectual property in the US, along with the creation in 1982 of the Court of Appeals for the Federal Circuit. Perhaps the most important contribution of Bayh-Dole is that it reversed the presumption of title. Bayh-Dole permits a university, small business, or non-profit institution to elect to retain title first.

BAYH-DOLE'S ACT IMPLIED DUTY TO COMMERCIALIZE

The Bayh-Dole Act can be seen to impose a duty on the part of all researchers who contract with the government, referred to as grantees or contractors, to pursue the commercialization of government-funded scientific inventions. Recognizing an implied duty to commercialize under Bayh-Dole begins with the Act's enumerated objectives, contained in Section 200. Directly implicating utilization of the patent system for the purpose of effectuating its goals, Congress identifies seven objectives which form the basis of its policy promoting commercialization, three of which are of particular importance in outlining a duty to commercialize. The first of these relevant objectives, "to promote the utilization of inventions arising from federally-supported research or development," indicates the intent of Congress to ensure that promising research results are put to productive use.

The second objective, "to protect the public against nonuse or unreasonable use of inventions," supports the first objective and further demonstrates Congress's intent to ensure that publicly-funded inventions reach the public. Furthermore, it reflects the government's right to enforce the commercialization provisions of Bayh-Dole. The third key objective, "to promote collaboration between commercial concerns and nonprofit organizations, including universities," explicitly partners academia and industry, providing a pathway for academic interests to comply with the Act's duty and ultimately effectuate the Act's goals. (Henderson et al 2002).

CATEGORIZATION OF NANOTECHNOLOGY ACTIVITY AT MULTINATIONAL LEVELS

Denominating national engagement in NanoS&T development by means of assessment of country participation in innovation, Barker et al. suggest that "most government

investments are aimed at improving national corporate competitiveness in nanotechnology". Roco believes some governments are focussing efforts towards nanotechnology because they have recognised lost opportunities at the dawn of earlier technologies such as the Human Genome Project, ICT and biotechnology.

Whilst global government spending on nanotechnology is relatively evenly split between North America (inclusive of Canada) ($1.6 billion), Asia ($1.6 billion) and Europe ($1.3 billion) (President's Council of Advisors on S&T, 2005).

Categorization of general level on NT activity of the country is performed according to the degree of government support for NT, as well as on level of industry involvement and the amount of internet accessible NT research from academic institutions and research groups (Court et al 2004).

Category	Requirements To Fulfil The Category
National Activities or Funding	Either: 1. A national strategy for nanotechnology; 2. Nationally co-ordinated nanotechnology activities; 3. Government funding for nanotechnology research
Individual or Group Research Project	At least one individual or group currently conducting work identified as 'nanotechnology research'
Country Interest	An expression of interest from country governments, representatives or delegates

Table 1. Denomination by categorization of country activity in NanoS&T.

The Lux Research data included U.S. State funding in the total for North America and incorporated figures from associated and acceding EU countries in the European estimate. The

remaining governments, not covered above, contributed $133 million. Funding among nations varies greatly. In Russian Federation 2007 year was nominated under the hallmark of nanotechnology innovation. 20 billion is spent each year. By the year 2015 is launched federal program for the development of nano-industry. For example, whilst both the U.S. and Thailand have national nanotechnology programs, established in 2000 and 2003, respectively, Thailand's program receives approximately $2 million per year (Changsorn, 2004) compared with 2005 annual funding for the U.S. National Nanotechnology Initiative (NNI), set at $982 million (Office of S&T Policy, Executive Office of the President, 2005). At 25th of November 2006 Arab News reports, that the King of Saudi Arabia is putting the equivalent of about US$9.6 million into nanotechnology at Saudi universities.

U.S. CURRENTLY LEADS THE WORLD IN GOVERNMENT R&D INVESTMENT, WITH A LITTLE OVER 25% OF THE TOTAL[19]

National Nanotechnology Initiative supported by U.S. government holds *Worldwide Leadership in Nanotechnology Research.* At the White House, at the 3rd of December, 2003, the President George W. Bush signed into law the "21st Century Nanotechnology Research and Development Act". This legislation puts into law programs and activities supported by the National Nanotechnology Initiative (NNI), one of the President's highest multi-agency R&D priorities. The Act aims to cement U.S. economic and technical leadership by assuring stable, long-term support for nanotechnology research.

The U.S. is the world leader in generating knowledge and performing creative interdisciplinary research.

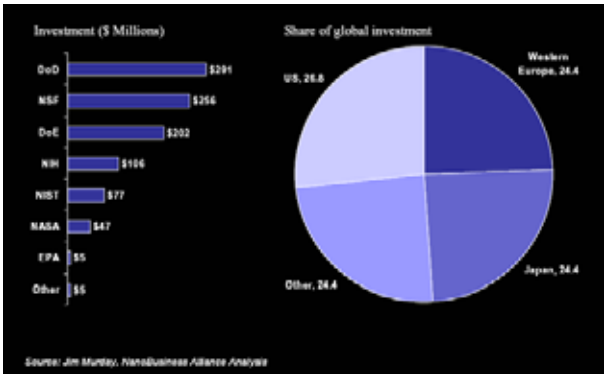
[19] Source: Jim Murday. NanoBusibess Aliance Analysis, in "Nanotechnology and Energy. Be a Scientist –Save the World!" by Adams, W., Jaffe, A., Smalley, R. (2005). In memoriam of R. Smalley.

Funding for the National Nanotechnology R&D Program is one of the Administration's top multi-agency priorities.

The National Nanotechnology R&D Program involves 10 federal agencies and continues to be a high priority of both the Administration and the Science Committee. Between FY 2001 and FY 2005, spending on federal nanotechnology R&D more than doubled, rising from $464 million in FY01 to $982 million in FY05. The FY06 budget requests an estimated $1.05 billion for the program in FY06, an decrease of $27 million, or 2.5 percent, over the estimated FY05 level. Requested funding for the five agencies authorized in the 21st Century Nanotechnology Research and Development Act (P.L. 108-153) is $665 million, and remains significantly below the $890 million authorized for these agencies for FY06 in the Act.

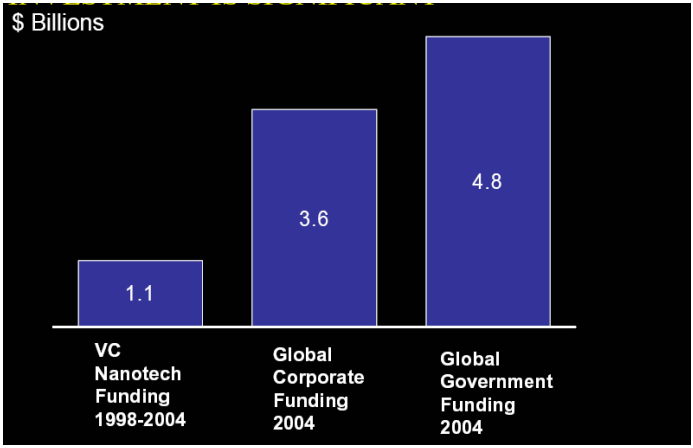
Nanotechnology promises to be both evolutionary and revolutionary-improving and creating entirely new products and processes in areas from electronics to health care. Nanotechnology can help provide clean energy. Nanotechnology is expected to have a broad and fundamental impact on many sectors of the economy, leading to new products, new businesses, new jobs, and even new industries (Rejeski, 2006).

Figure 2. Share of Global Investment in NanoS&T by Leading Countries.



Lux Research, Inc., expects sales of products that incorporate emerging nanotechnology to rise from less than 0.1% of global manufacturing output today to 15% in 2014, for a total of $2.6 trillion annually - a value that approaches the size of the information technology and telecom industries combined and is 10 times larger than biotechnology revenues.

Figure 3. More good newa: U.S. corporate investment is significant ($ Billions).



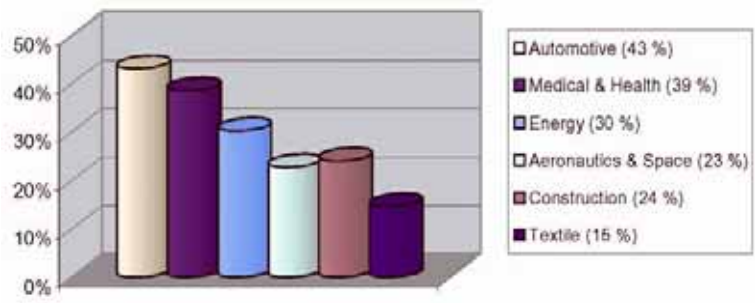
THE SIXTH FRAMEWORK PROGRAMME OF THE EUROPEAN COMMISSION

Nanotechnology initially was the priority of material sciences and began it's start-up mainly in materials production industry. Nanotechnology is providing a critical bridge between the physical sciences and engineering, on the one hand, and modern molecular biology on the other. Materials scientists are learning the principles of the nanoscale world by studying the behavior of biomolecules and biomolecular assemblies. In return, engineers are creating a host of nanoscale tools that are required to develop the systems biology models of malignancy needed to

better diagnose, treat, and ultimately prevent cancer (NIH Publication, 2004).

The Sixth Framework Programme of European Community predominantly covers activities in the field of NT research, technological development and demonstration (RTD) for the period 2002 to 2006. The data collected are gathered in a knowledge database, which gives the possibility to obtain specific technology roadmaps depending from the branches and the industrial applications. The results have been published in different reports, one of them is "European survey on success factors, barriers and needs for the industrial uptake of nanomaterials in SMEs" (Small and Medium Sized Enterprises survey). SMEs account for around two-thirds of employment in Europe, it is evident that more effort is needed to encourage the creation of new and innovative enterprises (Commission of the European Communities, 2004).

Figure 4. Sector specific distribution of application field of companies' products.



In order to remain competitive on these markets, companies have to integrate these new results in their commercial vision for future products. Within the survey the situation for companies working in the branches medical & health, energy, automotive and aeronautics has been examined in detail. 39% of the enterprises (not mainly pharmaceutical) specified "Medical & Health" as

main application field of their products and/or parallel among their basic productions.

HEALTH-RELATED NANOTECHNOLOGY PATENT ACTIVITY AND RELEVANCE OF INDUSTRIAL IMPLICATION

The U.S. National Institutes of Health counts nanomedicine as one of its top five priorities, the National Cancer Institute committed $144 million to nanotechnology research in October 2004. Yet major pharmaceutical companies are committing almost no money or people to nanotechnology research – exposing them to strategic risks (Lux Research, 2005).

Between 1996 and 2001 among all of NT patents medical applications were filed most often, both in United States and Europe according to comparison of nanopublications and nanopatents, seems that specialization in pharmaceutics tends to be reflected in a relatively high share of patents for medical purposes (Heinze, 2004).

However, as of mid-2006, 130 nanotech-based drugs and delivery systems and 125 devices or diagnostic tests are in preclinical, clinical or commercial development. The combined market for nanoenabled medicine (drug delivery, therapeutics and diagnostics) will jump from just over $1 billion in 2005 to almost $10 billion in 2010 and the US National Science Foundation predicts that nanotechnology will produce half of the pharmaceutical industry product line by 2015. Nanomedicine will help big pharma extend its exclusive monopoly patents on existing drug compounds and on older, under-performing drugs. Analysts suggest that nanotech-enabled medicine will increase profitability and discourage competition. (The ETC Group, 2006)

Despite the promise of nanotechnology, experts of Lux Research, Inc., mention, that the big pharmaceutical companies are 'flat-footed' in their nanotech initiatives, while medical device firms are more advanced in their race to develop nanotechnologies,

with major players such as Baxter International Inc., Medtronic Inc., and Guidant Corporation all pursuing nanobiotech R&D," says Lynn Yoffee, associate publisher of NanoBiotech News, which produced the 2005 Nanomedicine, Device & Diagnostic Report.

It is tentative for belief, that transfer from S&T sector to industry is somehow delayed. When matching performed for revealing confluence of publications and patents, in order to reflect flow rate of science to technology, Meyer observed, that knowledge transfer from science to technology is most prominent within the academic sector, rather than from academe to industry (Meyer, 2001).

Coleman (2003) brings suggestions, that medical and healthcare sectors takes only *8%* in whole nanotechnology industry (Fig. 5.). Opposite data are proposed according to US National Nanotechnology Initiative report nanotechnology involvement by 20% of companies focused on medical applications.

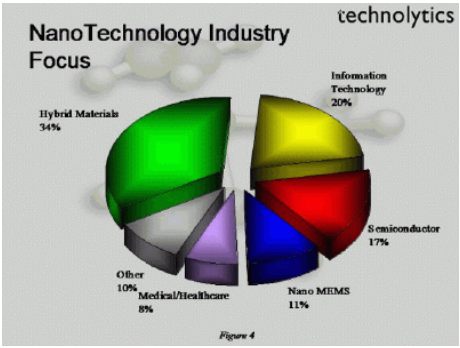
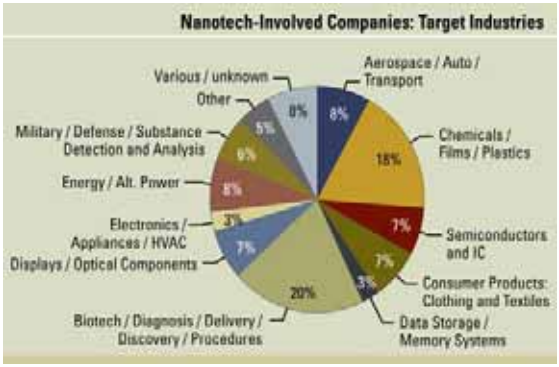


Figure 4

It's noteworthy to mention the case study (Borreguaro et al, 1994) from marketing manual, which is depicted, that one of the Hispanic homeland medium-sized textile enterprise "Industrias Beltran" was considered as market leader with ownership of only 7% share of total textile market in the country. The total market share of materials' production and informational technologies are much more prevailing, compared with medical & healthcare industrial market in general. So even in case of merely 8% involvement for NT investment in medical & healthcare sector could be accepted as substantial impact for advance in innovative technology implication.

"Nanotech presents many opportunities to pharmaceutical giants, ranging from better delivery of existing drugs to entirely new therapies based on nanomaterials," said Lux Research Vice President of Research Matthew M. Nordan. "But big pharma is not investing in nanotech today. If this trend continues, nanotech will play out in pharmaceuticals just as biotechnology did, with major pharmaceutical companies leaving money on the table and allowing new competitors to take root." Lux Research bases its conclusions on in-depth interviews conducted with individuals accountable for nanotechnology at 33 global corporations with annual revenues exceeding $5 billion. The interview data reveals that:



- No life sciences interviewee rates NT as a high corporate priority, as opposed to 78% of interviewees in electronics and materials;

- Only one out of six life sciences respondents claims to have an explicit strategy for nanotechnology, compared with two-thirds of those in other electronics and materials;

- Big pharma companies on average commit 16 people and less than half of one percent of R&D spending to nanotechnology research, whereas like-sized electronics and materials firms commit more than 100 people and more than 8% of R&D.

Lux Research's analysis finds that large drug manufacturers pay little attention to nanotechnology for three reasons: organization, history, and hubris. *First,* big pharma companies typically entrust accountability for nanotechnology to

an executive responsible for drug discovery, pharma's biggest cost driver – but nanotech's big near-term impact is in drug delivery.

Second, big pharma companies learned during the biotech revolution that they could avoid their own investment and instead in-license drugs from start-ups at a late stage – but greater pressure on big pharma's drug pipelines today gives nanotech start-ups a negotiating advantage. *Finally*, many big pharma executives claim they've been "doing nanotech" for years by developing small-molecule drugs or engineering proteins – however, few can claim the materials science expertise that truly novel nanotech innovations depend on. Pharmaceutical companies' laissez-faire attitude towards nanotech will have consequences. "Big pharma will have to contend with a new wave of superbranded generics that will erode market share. This trend began with the approval of American Pharmaceutical Partners' nano-enabled ABRAXANE cancer therapy this February, 2005" said Nordan. "On the other hand, opportunity exists for a forward-thinking drug manufacturer to go on the offensive and acquire competitive capabilities by picking up a nanoscale reformulation specialist, as mid-cap pharma manufacturer Elan and medical devices leader Baxter already have." Even with big pharma companies largely sitting on the sidelines, start-up companies are surviving and even thriving and new start-ups emerging nearly every month (Powers, 2006). Welland challenges the contemporary belief that drug research has to be capital intensive, claiming that pocket-sized, drug factories "could theoretically end the control of large companies over manufacturing" (Mantell, 2003).

PATENT PROTECTION BECOMES INCREASINGLY CRITICAL FOR INVESTMENT

Successful researchers are frequently turning into entrepreneurs by launching start-up companies. Out of the hundreds of such companies founded in recent years, one-half are

located in the USA compared with one-quarter in the EU (De Francesco, 2003).

"For start-ups especially patents are absolutely critical," says Leon Radomsky, a patent attorney with US law firm Foley & Lardner. "Their assets are based on their intellectual property and this is what they are selling to the venture capitalists (VCs) and to the larger companies when they are planning their exit routes." He says that for investors, who were hit badly by the dotcom meltdown, patents covering technologies with applications in potentially huge markets are just the kind of tangible asset they are looking for. And companies clearly realize this. According to the 2001 Business of Nanotechnology Survey, the smaller nanotech businesses are attracting record levels of venture capital interest with 53 funds in the US now actively investing in the sector. For 2002, the total amount invested by venture and private equity is forecast to come in at $1 billion, with a growth rate of 20% per year for both 2003 and 2004 as technologies and products begin to have an impact in various market places. Between them, the three strands of the nanotech revolution are expected to spend $2 billion to $3 billion on research and development over the next 12 months. And as more and more money is poured into R&D activities, so the importance of patents is on the increase.

Banks and venture capitalists are very selective when offering risk capital, in particular, for areas that are perceived by them to have a high technical risk, uncertain time-to-market, or could have negative ethical, health or environmental consequences. Patents are normally needed to prove ownership of the knowledge and new entrepreneurs need not only to be at the forefront of nanotechnology but to combine this with management and business strategy acumen. New entrepreneurs often complain that they are offered credit (instead of risk capital) and that they receive no support in management - this increases their exposure and perception of risk. Despite technological success, start-ups may fail due to lack of financial breakeven – the so-called “death valley”.

This problem can be acute for nanotechnology, where the R&D process necessitates a long-term commitment. In this context, the European Investment Bank (EIB) can play an important role in providing loans and strengthening the capital base for nanotechnology enterprises (Commission of the European Communities, 2004).

FOCUSED RECOMMENDATIONS FOR NT COMMERCIALIZATION

National Science Foundation (NSF) predicts that the world market for goods and services using nanotechnologies will grow to $1 trillion by 2015. Lux Research calculates that in 2004 there was $13 billion worth of products in the global marketplace incorporating nanotechnology (Lux Research, 2004)*. Worldwide about $9 billion annually is being spent by governments and the private sector on nanotechnology research and development. Any government program, policy, or strategy must work for our small businesses; they are the heart of the nanotech revolution and will remain so into the foreseeable future. According to the 2003 Small Tech Census™ research, nearly 72% of 300,000 manufacturing entities in the United States have less than 20 employees and 92% of manufacturing companies have less than 100 employees. Additionally, the Small Business Administration estimates that there were approximately 22.9 million small businesses in the U.S. in 2002 and that small businesses provide approximately 75% of the net new jobs added to the economy, represent 99.7% of all employers, and represent 97% of all U.S. exporters (Small Business Administration 2006).

Nanotechnology is no longer just a large government science research project. In the long run, key social and economic benefits will only occur if we succeed in bringing innovations to

* http://www.luxcapital.com/nanotech_report_b.htm (June 30, 2004).

market. To do that, we need to place new people, resources, and ideas behind an expanded national nanotechnology initiative.

NANO T&S PATENT OWNERSHIP BY MEDICAL & HEALTHCARE SECTOR

With respect to medical-healthcare sectoral ownership, 77% of patents are held privately, 16% by universities, 5% by government and 2% by independent, not-for-profit organizations. The U.S. remains the leader in terms of the shear number (75%) of nano-based medical products in development, and of the 25% of drug and device candidates being developed outside of the U.S., Canada, Australia and Israel are working on 43% of the total 63 drugs and devices in the works around the world.

Sector	Share (%)
Private	
Company	54
Individual	23
University	16
Government	5
Independent, Not-For-Profit	2

Table 2. Distribution of health-related nanotechnology patent activity by sectors for 2004. Source: Maclurcan, D.,C. (2005).

U.S. government added financial muscle to nanobiotech development in 2005, with major capital infusions through the National Cancer Institute's Alliance for Nanotechnology in Cancer and the National Institutes of Health's Program of Excellence in Nanotechnology.

Nanomedicine started out with a bang in 2005, with the U.S. Food and Drug Administration's (FDA) approval of ABRAXANE in February, considered a seminal event by industry experts. And experts predict 2006 will be another good year for nanomedicine. In fact, this year may bring several new nano-based

drug approvals and the continued rapid evolution of tools and enabling technologies that are propelling the development of drugs, delivery vehicles, diagnostics, and medical devices. According to data compiled by NarwBiotech News in the 2006 Nanomedicine, Device & Diagnostic Report, more than 130 nano-based drugs and delivery systems and 125 devices or diagnostic tests have entered preclinical, clinical, or commercial development - up from 61 drugs and 91 devices and diagnostics the previous year, meaning the clinical pipeline has grown 68% since last year at this time (Powers, 2006).

CONCLUSIONS

1. Activity in nanoscience is determined by increase of publications and patent applications. So patent submission data and bibliometric analysis are the most useful investigational tools for assessing global engagement with nanotechnology.
2. Identifying research creativity by means of counting top scientists, who are prize winners and owners of awards, gained for high level NT discoveries.
3. Flexible and smart interaction and collaboration within Academia-Industry-Government nexus is essential contributor for faster advance in NanoS&T developments.
4. One of the marker and indicator of strength in NT development of the country is government's involvement in investment.
5. The U.S. is the world leader in generating knowledge and performing creative interdisciplinary NanoS&T researches.
6. However both in United States and Europe according to comparison of nanopublications and nanopatents, pharmaceutics tends to be reflected in a relatively high share of patents for medical purposes, medical and healthcare sector takes less than IT in whole nanotechnology industry.
7. In medical-healthcare sector 77% of patents are held privately, 16% by universities, 5% by government, and 2% by independent not-for-profit organizations .

8. Advancement of NT involvements in pharmaceutical industry is more expected to be promoted by privately held small and medium sized companies rather, then by government. So focus group for implementation of strategic plan for new drug promotion will be private sector.
9. It's essential to raise stakeholders interest in emerging and fast racing field of NT, convincing them to make steps for NT commercialization of their companies' propriety products.

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CHAPTER THREE

SOCIAL SCIENCE RESEARCH METHODS FOR TECHNOLOGY ASSESSMENT IMPLICATING SOCIETAL DIMENSIONS OF NANOS&T

INTRODUCTION

Research into nanotechnology's impact on any societal implication, as ethical, environmental, economic, legal aspects, must try to keep pace with the technological progress that has been made. Otherwise, the technological progress will slow down (Mnyusiwalla et al, 2003). *This will be one of the first times in history that social scientists have such a participatory role in nanotechnology's development.* Research methods in the economic, social, and behavior science will allow social sciences to evaluate nanotechnology developments, as well as government funding for research provides input toward the improvement of potential applications. To have such a role, social scientists need to proceed beyond the data in econometric studies in order to get inside the research and development processes as they occur. The techniques of interpretive social research (e.g. interviews and focus groups), as well as original data collection with surveys will enhance our ability to understand societal and economic effects much more than archival data (Mihail Roco and Marie Thursby, 2003)[20].

Technology and society evolve together. Nuclear weapons joined with U.S. and Soviet hegemonies to constitute a prime determinant of geopolitical evolution after World War II. Cars, television, air conditioning, and birth control likewise arose in

[20] Ten Research and Policy Themes, in the report of NNI workshop: 'Nanotechnology – Societal Implications – Maximizing Benefits for Humanity. Edited by Roco, M.C., Bainbridge W. S.

particular social contexts and contributed to the remaking of everyday life (Daniel Sarewitz and Edward Woodhouse, 2003).

No one can fully understand the long-term implications of such advances, emerging under the heading of nanotechnology - "the art and science of building complex, practical devices with atomic precision," with components measured in nanometers, billionths of a meter. The essence of the nanotechnology story is the continuation of a fifty-year trend of machine miniaturization culminating in the rise of design control at the molecular level. Nanotechnology is not confined to a single area of innovation; "smallness" is its unifying attribute. Researchers in a number of technical fields are keenly interested in manipulation of matter at the nanoscale, and funding is assured because many of the research forefronts hold promise for business and military applications. (Sarewitz, D. and Woodhouse, E. 2003).

In an ideal world, scientists would communicate scientific knowledge clearly and effectively to laypersons, who would then understand the knowledge and use it to make sound judgments about science policy. After Hiroshima and Nagasaki, scientists made a great effort to explain the atom to the public, thereby preparing the public to accept nuclear plants to generate electricity. During the 1950s and '60s, NASA and the media presented the basics of space science in a friendly way which enabled millions to understand it, at least at a rudimentary level. Currently the Human Genome Project devotes at least 3% of its budget to ethical, legal and social issues, including public understanding. In these three examples, scientists and science teachers have aspired to an ideal model of communication and understanding. In many other cases, however, the world is far from ideal. Certain cultural values, including strong hopes and deep fears, are likely to shape public understanding of nanotechnology. To paraphrase Rosenberg, nanotechnology will be appreciated or feared, not because of its scientific merits, but because of pre-existing extrascientific values. Nanophilic hopes and nanophobic fears will not wait until after

scientific work is completed, assessed and disseminated. The tangible results of nanotech will be selectively appreciated and interpreted in accordance with those hopes and fears (Toumey, 2004).

Nanotechnology must be developed in a safe and responsible manner. Ethical principles must be adhered to and potential health, safety or environmental risks scientifically studied, also in order to prepare for possible regulation. Societal impacts need to be examined and taken into account. Dialogue with the public is essential to focus attention on issues of real concern rather than "science fiction" scenarios (Commission of the European Communities, 2004).

EXPLORING IMPORTANCE OF TECHNOLOGY ASSESSMENT

Scientific and technological innovation continually remakes society. *Technology Assessment* (TA) can significantly enhance the societal value of research-based innovation.

A half-century ago, philosopher and skeptics critic of technology, Jacques Ellul (1967) argued that the rise of technology leads to the decline of traditional spirituality, as man transfers "his sense of the sacred … to technique itself." We develop a "worship of technique," Ellul said, and we associate our technology with a "feeling of the sacred."

According to skeptics point of view Jacques Ellul, technology perhaps is the most pervasive and potentially dehumanizing product of modern life (1967, 1980).

Selected questions adapted from the Jacques Ellul Society's Seventy-Six Reasonable Questions to Ask About Any Technology (International Center for Technology Assessment, 2002) were used specifically to stimulate debate and analysis in the ethics seminars. The following questions were used:

Ecological: Does it preserve or reduce ecosystem integrity? How much, and what kind of waste, does it generate? Does it incorporate the principles of ecological design?

Social: How does it affect our way of seeing and experiencing the world? Does it serve to commodify knowledge or relationships? To what extent does it redefine reality?

Moral: What values does its use foster? What is gained by its use? What are its effects on the least advantaged in society?

Ethical: What does it allow us to ignore? Can we assume personal or communal responsibility for its effects? Can its effects be directly apprehended? What behavior might it make possible in the future? What other technologies might it make possible?

Political: Does it concentrate or equalize power? Does it require or institute a knowledge elite? Does it require military defense? Does it enhance or serve military purposes? How does it affect warfare? Is it consistent with the creation of a global economy? Does it empower transnational corporations? What kind of capital does it require?

According to Ellul, technology ultimately acts to isolate people from each other and from the natural environment, and despite the (usual) benignity of its intended consequences, there always are unforeseen negative consequences. Most provokingly, Ellul (1980) also suggested that technological development will soon reach a point at which direct human control will no longer be necessary or possible.[21] (Sweeney et al. 2003).

Eric Drexler's the author of "Machines of Creation" and who was awarded an interdisciplinary degree, the world's first doctorate in nanotechnology, noted that nanotechnology is

[21] Sweeney A.E., Seal, S. (2003), The Promises and Perils of Nanoscience and Nanotechnology: Exploring Emerging Social and Ethical Issues, Nanoscience and nanotechnology, bulletin of science, technology & socienty .No 8, pp. 236-245.

perfectly suited to arouse religious enthusiasm, it involves incredible, invisible powers (Keiper, 2003).

Richard Smalley, Nobel Prize winner, claims in the introductory part of a public speech about his very specific work on the use of carbon nanotubes for energy storage, that, the list of things you could do with such a technology [nanotechnology] reads like much of the Christmas Wish List of our civilization (Smalley, 1995).

The starting points with the development of nanotechnology needs to develop approaches and methodologies that can address doubly "fictional" character of *technology assessment* of nanotechnology. Many of the envisaged uses of nanotechnology are still science fiction, and the study of possible impacts is therefore social science fiction (Rip, 2005).

Headlines about e.g. self-replicating nano-robots (M. Crichton, Prey), that are well beyond our present capability but are often presented as an immediate risk, demonstrate that there is an urgent need to provide information about present-day nanotechnology research and its possible applications (Commission of the European Communities, 2004).

"Real time" TA has been proposed by Sarewitz and Guston (now at Arizona State University). Further development of such approaches and methods is important, including ways of 'public engagement' as it is now called in the UK (Report of the Royal Society, 2004). However, methods development should be embedded in understanding of innovation dynamics and the embedding of technology in society (Rip, 2005).

Public reactions to nanotechnology in the U.S. are more difficult to envision this way because there has been practically no history of public awareness, let alone public *reaction*_(!) to it. In lieu of such information, we need to turn to past episodes of the arrival of new forms of science and technology, and public reactions to them: atomic energy, space science, cold fusion, stem cell research, remediation of environmental disasters, genetically

modified foods, and so on. American society has had many experiences with the arrival of new technologies, and perhaps comparisons and analogies with some of them will help us anticipate public reactions to nanotechnology. The following general statements describe numerous episodes of the arrival of new technologies presented here as the these and anti-these (Toumey, 2004).

NEW TECHNOLOGIES PERCEPTION BY SOCIETY	
THESE	ANTI-THESE
1A. When a new technology arrives, it will be so expensive that only the very wealthy can afford it, thereby exaggerating class differences. [Think of the initial days of cell phones, hand-held calculators, and air bags in cars, for example.]	1B. Shortly after a new technology arrives, mass production will great reduce the cost, thereby democratizing its availability. [Think of the second phase of cell phones, hand-held calculators, and air bags in cars.]
2A. If a new technology involves profound changes in health or medicine, some people will object that scientists and doctors are playing god. [Here one might recall organ transplants, tissue transplants and technology-assisted reproduction.]	2B. If a new technology involves profound changes in health or medicine, some people [including patients, their doctors, and their families, plus administrators, investors and manufacturers] will fervently advocate for its use, on the grounds that patients should not suffer or die needlessly. [Here one might recall organ transplants, tissue transplants and technology-assisted reproduction.]
3A. The best way to nurture an expensive new technology is to consign it to	3B. The best way to nurture an expensive new technology is through public

processes of proprietary capitalism, centered on patents and copyrights, because no one else besides proprietors and their investors will have the will or the resources to develop it, and because this will protect it from political interference. [Currently this argument is made on behalf of pharmaceutical research.]	funding and government regulation, so that potential dangers can be closely monitored, and the benefits of the new technology will become available to the largest possible number of people. [Here a good example is the Human Genome Project.]
4A. As Dorothy Nelkin pointed out, the media usually embrace a new technology enthusiastically and emphasize its promises and supposed advantages (Nelkin 1987). [Perhaps you can recall the initial accounts of cold fusion from 1988.]	4B. As Dorothy Nelkin pointed out, the media often denounce a new technology when it is seen to be imperfect, that is, when it fails to fulfill utopian expectations, even though the exact same media may have previously exaggerated its promises and supposed advantages (1987). [No doubt you can recall the later accounts of cold fusion.]

SURVEY REVEALS PUBLIC ATTITUDES TO NANOS&T

Recent (Jan/Feb 2005) survey on Europeans' experience and perception of science and technology includes some questions regarding nanotechnology:

- ca. 20% not at all interested in general S&T (U.S. ca. 10%);

- Among those interested, NT receives by far the lowest rate of interest;

- Developments in *medicine* are by far the field in which respondents are the most interested in (W 73%, M 50%), and *the second most mentioned item is the environment.*

High interest in medicine and environment can be explained: Both areas are linked to health issues – public health issues S&T area with highest interest (also in the U.S.) Positive effect on our way of life in the next 20 years are especially expected from new medical and energy technologies, though people are not interested in NT so far (lowest numbers 8% and high 'no-response' rate).[22]

Scientific literacy for nanotechnology is practically nonexistent and general scientific literacy in this country is very poor. Trends seem to be similar in U.S. and Europe.

General public does not know very much about nanotechnology:

- GB 2004: 29% have heard about NT, 19% can give some kind of definition;

- D 2004: 30% have heard about NT, 15% can link it to specific developments;

- USA 2004: >80 % had heard "little" or "nothing" about NT, most could not correctly answer factual questions about it.

- Majority (~90%) is not interested in NT (or does not care);

- Nanotechnology is perceived as a 'fuzzy' concept;

- Positive expectations prevail over negative;

- The higher the (subjective) level of information and the level of education, the lower the 'fear of risk'.

[22] Data: Special Eurobarometer 224 & 225 / Wave 63.1 2005; NSF Science& Engineering Indicators, (2004).

To summarize attained results of this survey that reveals 'no attitudes'. Since qualitative judgments about NT mainly similar to general attitudes to S&T.

CONCEPTUAL FOCUS OF TECHNOLOGY ASSESSMENT

Technology assessment (TA) developed as a scientific and societal reaction to the problem of how to deal with complex side effects and uncertainties in science and technology.(Grunwald et al, 2004 – 2006).

The main questions defined to be answered by TA:

- whether and how knowledge of side-effects can already be integrated into decision-making processe;
- the problem of dealing with the inevitable uncertainties of knowledge.
- the unintended side-effects of science, technology and technological advance can be experienced in modern age.

The respective concepts offered by TA to society and politics are strongly dependent on the context – and require continued modernization if these contexts are subject to rapid changes in a dynamically developing global society (Grunwald et al, 2004-6).

Technology assessment is dedicated to help business, government and the public anticipate and manage possible health and environmental implications of nanotechnology (Rejeski D. 2006).

It is therefore important that, in parallel with technological development, appropriate R&D is undertaken to provide quantitative data on toxicology and ecotoxicology (including human and environmental dose response and exposure data) to perform risk assessments and, where necessary, to enable risk assessment procedures to be adjusted. Scientific investigation and assessment of possible health or environmental risks associated with nanotechnology need to accompany the R&D and

technological progress. Addressing the potential risks of nanotechnologies to public health, the environment and consumers will require evaluating the possible re-use of existing data and generating new, nanotechnology-specific data on toxicology and ecotoxicology (including dose response and exposure data). This also calls for examining and, if required, adjusting risk assessment methods. In practice, addressing the potential risks associated with nanotechnologies necessitates that risk assessment be integrated into every step of the life cycle of nanotechnology-based products (Commission of the European Communities).

Nanotechnologies present new challenges also for the assessment and the management of risks. We need formal risk analysis because risk is one of the most important ethical and social issues we could imagine (Smith, 2001).

PUBLIC UNCERTAINTY OF NT BENEFITS V. RISKS PERCEPTIONS ON HEALTH AND ENVIRONMENT

Nanotechnology could ultimately turn out to be risky, but the prudent way to assess the risks is not the abandonment of the field. Society needs formal risk analysis because risk is one of the most important ethical and social issues. Just as fear of cloning could slow efforts in biomedicine and fear of genetically modified foods could contribute to hunger, fear of futuristic nanobots running amok could delay the benefits offered by nanotechnology. When discourse is founded on emotional prejudices, its unreasonableness discredits the legitimate need to identify and assess risks (Smith, 2001).

Health risks of nanoparticles may link NT to areas of greater public attention. Proven health risks, or uncertainties, may link NT debates with historical technology debates (hazardous chemicals, GMO). (Fleischer, 2005).

Science & Engineering typically assume probabilities and consequences of adverse events, and hence the “risks,” as to be

objectively quantified by *risk assessment*. Social Science analysis rejects this notion. It focuses instead on the effects that risky outcome distributions have on the people who experience them. Risk is seen as inherently subjective (Paul Slovic and Elke Weber).

TWO ASPECTS OF RISK:

Characterisation of risk has both *quantitative* and *qualitative* components:

a) Risk can be *technically* defined, e.g.:

Risk = Hazard x Exposure (health risk)

Risk = Damage x Probability of Occurrence (insurance)

b) Risk can be *culturally* defined:

"A thread to that which we value";

"The probability of loss of that which we value" risk.

"Perceptions of risk play a prominent role in the decisions people make, in the sense that differences in risk perception lie at the heart of disagreements about the best course of action" (P. Slovic).

"It is not the things themselves that disturb us but our views of them." (Epiktet).

THE RISK DEBATE (Fleischer et al, 2005):

- Risks of visions: Visions show real consequences regardless of their seriousness;
- Risks of unknown material properties at the nanoscale;
- Risks of (failed) communication and of public engagement.

TA could include a 'vision assessment' that aims to achieve transparent, knowledge-based discussion about imaginations of the future. Vision assessment within a TA process could prevent 'fear of fears' and help to avoid damages for the development of S&T and for the culture of democratic decisions.

Visions (positive and negative) are an important topic in the public communication of NT ('Bill Joy-Debate', visualizations in magazines, popular culture: 'Prey', 'Matrix', …). Visions may shape acceptance and further development of this field. Visions are ambivalent: high potentials often include high risks.

Challenging issues that may arise associated with the risks of new material properties:

- New (surprising and partially still unknown) properties of materials at the nanoscale. (E.g. Behaviour of nanoparticles in the human body and the environment needs extensive research, though already on the market);
- NanoToxicology – first results, knowledge still insufficient, challenges for conventional methods of toxicological research;
- „New forms of known chemicals“ or „new chemicals because of different chemistry“?

Recommendations for policymakers for public involvement in dialogue and risk evaluation: to incorporate views from the general public in decision-making; improve the knowledge base and quality of decisions establish trust and legitimacy; identify issues, mediate and resolve conflicts, reduce risk of rejection; educate and inform.

TA provides procedural knowledge on risk communication and experiences from public and political debates about other ‘risk technologies’ (nuclear, genetic, …). TA as a process contributes to societal opinion forming, addresses public concerns, supports public understanding of science and technology. TA provides knowledge and methods to avoid mistakes, to reduce uncertainties and support diffusion of NT (Fleischer et al, 2005).

In light of this perception of potential danger, the Foresight Institute (nonprofit educational organization established to help society prepare for advanced technologies) has drafted a set of guidelines for the ethical development of nanotechnology. These include the banning of free-foraging self-replicating pseudoorganisms on the Earth's surface, at least, and possibly in other places.

A fear exists that nanomechanical robots, if achieved, and if designed to self-replicate using naturally occurring materials (a difficult task), could consume the entire planet in their hunger for

raw materials, or simply crowd out natural life, out-competing it for energy. Some commentators have referred to this situation as the "grey goo" or "ecophagy" scenario. K. Eric Drexler considers an accidental "grey goo" scenario extremely unlikely and says so in later editions of Engines of Creation. The "grey goo" scenario begs the Tree Sap Answer: what chances exist that one's car could spontaneously mutate into a wild car, run off road and live in the forest off tree sap?

ENFORCEMENT VISIONS OF NANOTECHNOLOGY - STRENGTH IN SCIENCE, SOUND ETHICS

> *"The best defense against nanotech misuse is good nanotechnology.".*
> *"Any powerful technology can be abused." (G. Reynolds, 2001)*

It would be difficult to deny the potential benefits of nanotechnology and stop development of research related to it since it has already begun to penetrate many different fields of research. However, nanotechnology can be developed using guidelines to insure that the technology does not become too potentially harmful. *Technology assessment* recognizes the fact that scientists normally are not trained ethicists themselves and accordingly ought to be very careful when passing ethical judgment on their own, or their colleagues´, new findings, projects, or work in progress.

As with any new technology, it is impossible to stop every well funded organization who may seek to develop the technology for harmful purposes. However, if the researchers in this field put together an ethical set of guidelines (e.g., Molecular Nanotechnology Guidelines, Foresight Institute, 2000) and follow them, then we should be able to develop nanotechnology safely

while still gathering its promised benefits. Recent technical proposals for Molecular Nanotechnology (MNT) nanofactories do not include self-replicating nanobots, and recent ethical guidelines prohibit self-replication. MNT nanofacturing is popularly linked with the idea of swarms of coordinated nanoscale robots working together, as proposed by Drexler in his 1986 popular discussions of the subject in the “Engines of Creation”. It is proposed that sufficiently capable nanobots could construct more nanobots.

New scientific discoveries and the ensuing technologies are often accompanied or followed by utopian or dystopian visions about the future of humankind under their new dominance. These visions can be found in science communication, literature ('high' and 'low' level), in popular science, in newspaper articles, books, cinema and TV series, Internet and also in more or less arcane religious sects. This especially holds for current themes around nanotechnology. What effects do such visions have on society and back on the further development of nanoscience? (Stefan et al. 2005).

What are the chances and what are the risks of the fictionalisation of nanotechnology? Nanoscience and nanotechnology are among today's most promising fields of research. As NT quickly develops, the ethical evaluation of such a development has yet to begin. If their full potential is to be realized, we need to attend along the way to key ethical issues. But ethics should not be grounded in exaggerations, either positive or negative; hyperbole just obscures important issues (Stefan et al. 2005).

To what extent does this already influence the interpretation of facts and the visions of future development? "The need for special ethical principles in a scientific society is the same as the need for ethical principles in society as a whole. They are mutually beneficial. We must become competent in dealing with moral concerns related to all new technologies. And remember that a code of ethics will not solve all ethical problems. "We must

remember that good laws, if they are not obeyed, do not constitute good government. Hence there are two parts of good government; one is the actual obedience of citizens to the laws, the other part is the goodness of the laws which they obey..." (Aristotle, Politics 1294a3-6).

In 1980s, when nanotech pioneer and Foresight Institute's founder and Chairman up to 2003, K. Eric Drexler considered keeping his thoughts quiet, rather than risk opening a Pandora's box of new technology with threats that could include a range of microscopic terrors. But in the end Drexler and his colleagues reached a simple conclusion: "If you don't discuss it, someone else would come along and develop it. And their intentions might not be as good".(Caroll, 2001).

K. Eric Drexler, author of Engines of Creation, has begun to develop guidelines for the use of NT, particularly concerning self-replication, but also issues such as wealth distribution and environmental protection (Mnyusiwalla et al, 2003). (see. Foresight Guidelines for Responsible Nanotechnology Development.)

The ethical issues associated with NT fall into a variety of categories including:

1) **Equity**: NT does not stand to help developed countries only, but also (and perhaps mainly) developing countries. For example, third world countries suffer most from things that can be improved upon from advancements made in NT. For instance, providing cleaner water, developing cheaper energy, and also the enormous health benefits to be reaped from NT are all aspects of NT that could have a dramatic impact on third world countries. A global opinion-leaders network for social and ethical implications ought to be established so that third world countries may be involved.

2) **Privacy and security:** While NT could dramatically improve surveillance systems and would undoubtedly have numerous military applications, some are left wondering how

personal privacy would be affected. Questions concerning the regulation of this new technology are arising without many answers being offered. As nanotechnology begins to deliver new and improved weapons, secrecy will eventually mask important research work.

The first round of nanotech-inspired materials, for example, is likely to find an active suitor within the U.S. defense industry – particularly for radar-resistant, lighter and much more durable materials. And as the first weapons to use nanotechnology go into development, secrecy is likely to follow.

For now nanotechnology doesn't have any applications in the war on terrorism because it's still too young. Nanotechnology lurks between five and ten years into the future.

3) **Environment**: The effects of NT materials on the environment. The funding have to increased to study the effects of NT on the environment.

4) **Human or machine?** How far are humans willing to go with replacement of human parts with replacement robot parts? Some avenues of research in NT include the incorporation of artificial materials or machines into human systems, as is beginning to happen with implanted computer chips. The modification of living systems is met with great skepticism by much of society. How acceptable will technologies such as implantable cells and sensors be for the general population? What are its implications and what are our limits? (Mnyusiwalla et al, 2003).

ROLE OF TECHNOLOGY ASSESSMENT FOR RESPONSIBLE DEVELOPMENT OF NT

Ethical principles must be respected and, where appropriate, enforced through regulation. These principles are

embodied in the European Charter of Fundamental Rights[23] and other European and other international documents[24]. The opinion of the European Group of Ethics (EGE)[25], who are examining the ethical aspects of medical applications related to nanotechnologies, should also be taken into account. (Commission of the European Communities, 2004).

If it is difficult to predict the future direction of nanoscience and nanotechnologies and the timescale over which particular developments will occur, it is even harder to predict what will trigger social and ethical concerns. In the short to medium term concerns are expected to focus on two basic questions: 'Who controls uses of nanotechnologies?' and 'Who benefits from uses of nanotechnologies?' These questions are not unique to nanotechnologies but past experience with other technologies demonstrates that they will need to be addressed (Report of the Royal Society).

Apart from denying society the possible benefits, it may lead to the constitution of "technological paradises", i.e. where research is carried out in zones without regulatory frameworks and is open to possible misuse. Our consequent inability to follow developments and intervene under such circumstances could lead to even worse consequences. The Precautionary Principle, as used up to now, could be applied in the event that realistic and serious risks are identified. (Commission of the European Communities, "Communication from the Commission on the Precautionary Principle" COM(2000) 1.).

Given the huge uncertainties about the future social impacts of nanotechnology, we ought to think of the unfolding revolution as a grand experiment—a clinical trial—that technologists are

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[23] See http://www.europarl.eu.int/charter/default_en.htm

[24] See http://europa.eu.int/comm/research/science-society/ethics/legislation_en.html

[25] See http://europa.eu.int/comm/european_group_ethics/index_en.htm

conducting on society. From this perspective, we can reflect upon the robust societal consensus that demands prior *informed consent* as a basis for participation in scientific experiments. This consensus is formally codified in the World Medical Association's Helsinki Declaration, strengthened most recently in 2000, and reinforced in the public consciousness by the memory of, for example, the Tuskegee experiments, where African American males with syphilis were left untreated as part of a "control group," despite the existence of treatments known to be efficacious. In the United States, every publicly funded research project involving human subjects is monitored by an institutional review board (IRB) that must approve the research before it can be conducted. Every university, independent laboratory, and private-sector lab receiving federal funding for human subjects research has an IRB; there are thousands of boards operating in the United States, nearly 800 in California alone. These boards demonstrate that comprehensive governance is a reasonable goal, and while IRBs certainly impose a cost in terms of the efficiency of conducting research, they are an accepted element of a scientific infrastructure that respects human dignity. Similar commitments of the entire research enterprise to larger democratic strictures occur in experiments with animals and in compliance with environmental health and safety regulations. Comprehensiveness, in other words, is possible, when the stakes are high and societal intent is clear. (Daniel Sarewitz and Edward Woodhouse, 2003).

Some of the basic ethical values include: the principle of respect for dignity; the principle of individual autonomy; the principle of justice and of beneficence; the principle of freedom of research; and the principle of proportionality. The relevance of such principles towards human and non-human applications of nanotechnology should be understood. In addition, certain applications, e.g. miniaturised sensors, may have specific implications for the protection of privacy and personal data (Commission of the European Communities, 2004).

POTENTIAL ANALYSIS FOR TECHNOLOGY ASSESSMENT

Since NanoTA deals with emerging enabling technologies, novel methodical approaches are needed as a tool to link R&D activities with visions for applications and as a 'support layer' for the technological interpretation of (political) scenarios including future technology options.

Science & Technology Roadmapping methodology can be adapted for TA for emerging enabling technologies. When integrated into a TA process, roadmapping may serve as a powerful tool to provide empirical and structural knowledge and to produce consensus on strategies. Traditionally used to gather, structure and communicate information about technologies and products, and to link them to options for the future in companies and industries. More recently used as decision aids to design public policies related to research and development (de Laat 2004). For NT, a number of roadmaps exists - produced by small groups of experts with a "technology push" perspective - most remain unnoticed or ignored in R&D policies. On June 21, 2005 press release was announced in Menlo Park, CA, that Foresight Nanotech Institute launched Nanotechnology Roadmap for productive nanosystems.

In 2005-6 series of the Roadmap Reports was made in connection with the European project "Development of Advanced Technology Roadmaps in Nanomaterial Sciences and Industrial Adaptation to Small and Medium sized Enterprizes" ("NanoroadSME") by authorship of *René de Groot* (Syntens – Stiching Syntens, Innovation Network for Entrepreneur, Netherland) and *Dr. Jonathan Loeffler* (Steinbeis-Europa-Zentrum, Germany). The project was funded by the European Community under the "Sixth Framework" Programme. Expert of technology assessment and roadmapping, *Ineke Malsch,* founder and director of *Malsch TechnoValuation* (Netherland), made contributions to reports produced in this EU funded projects (2006).

Method of *hypothesis* used for the acceptance and the relevance of a roadmap, process aspects (design, participants, modes of communication) are as important as the technical product (the roadmap) itself. Variety of technology forecasts, foresight reports, market studies – general or sectoral are available (Fleischer, 2005).

FORECASTING, SCENARIO-BUILDING AND OTHER TOOLS OF FUTURE RESEARCH

Forecasting, scenario-building and other futures research tools will help tease out the possible landscapes of the world to come.

Research need to talk directly to and listen to business leaders, nanotechnology researchers and nano-product development personnel. With respect to studying the possible impacts of disruptive technologies on public perceptions, new research methodologies are needed (such as "preview" represent communities) that can provide prospective information on social impacts prior to the mass deployment of the new technology. Most NSF (national science Foundation) supported work on the public understanding of sciences focuses on attitudes toward science and knowledge about science rather than the ends to which science could or should be put. Several modes of identifying social needs on which to base justifications for advances in S&T have been outlined. These include Foresight and Delphi techniques, Charettes in city planning, as well as public discussion models from the philosophy of science. The identification of technology goals could also process from social science research on human needs, e.g. Maslow's hierarchy of goals. Foresight studies attempt to depict an image of a possible future using a variety of techniques. An important foresight method is the Delphi survey. A Delphi survey basically is a tool to create consensus and detect areas of conflicting expert opinions. In a first round, experts are confronted

with a number of topics they have to evaluate with respect to time of realization, implication on wealth creation, quality of life, and similar issues. In another round the results of the previous round are introduced to the experts who then have a chance to re-evaluate the topic (Etzkowitz, 2001).

FUTURE SOCIAL SCENARIOS

Bainbridge and Kasperson, (2003) performed future social scenario analysis, which, can help identify issues and hypotheses, and thus is a useful tool of theoretical analysis. This panel puts forth two very different scenarios for the coming 10 to 20 years, in order to help clarify both the issues related to nanotechnology that policy makers will face, and the knowledge that needs to be gained through research. *In one scenario, the transition will he smooth and benign, whereas in the other scenario the transition will be rough and marked by many different kinds of harm and conflicts with social values and institutions.*

Smooth transition: In this optimistic scenario nanotechnology produces clear, demonstrable benefits and solutions for real-world problems, and management strategies for threats. For example, it will enable low-cost energy production with minimal impact on the environment, as well as achieving greater efficiency in energy use. It will help prevent and cure disease, and will provide many rewarding jobs. It will contribute to applications that strengthen the nation's defense capabilities without unduly burdening the privacy of citizens, while also reducing the incidence of terrorist activity and strengthening the cause of peace worldwide. In this scenario, early applications stress positive effects on publicly valued areas, such as health, energy and food development, pollution abatement, and environmental protection.

Importantly, the smooth transition scenario assumes that nanotechnology development will benefit from strong public involvement.

Rough Transition: This scenario could lead eventually to a happy situation Like that described in the smooth scenario, hut only after a longer period of delay and with very substantial human costs. Clearly unmanaged or unanticipated risks become evident with this scenario. At the extreme, it could lead to the near-permanent abandonment of some forms of nanotechnology and thus to a failure to take advantage of their benefits.

Societal institutions and the general public would not he effectively involved in the policy-setting process. Perhaps nanotechnology-enabled weaponry would be used in such a way as to increase rather than decrease fatalities, ultimately leading to reduced security. The public would perceive that industry and scientists are concerned only with their own profits and careers, causing widespread apprehension and mistrust. There could be irrational fads leading to government regulation that was either too rigid or too lax, and a tremendous loss of investment coupled with tragic failures to realize the greatest benefits of nanotechnology.

There are parallels in previous technology revolutions or evolutions that can inform us about the future of nanotechnology. Genetically modified organisms, stem cells, and nuclear power exemplify the rough transition scenario. Indeed, one of the more disturbing possibilities is that policy makers and leaders of social movements may respond to nanotechnology not as it actually is, but in terms of false analogies.

Research and Evaluation Methodologies

Scenario analysis, as mentioned earlier, can help identify issues and hypotheses, and thus is a useful tool of theoretical analysis. A worthwhile variant of scenario analysis is backcasting, the mirror image of forecasting, which specifies an outcome and tries to identify the steps that might lead to it. Scenarios are an art form, akin to brainstorming, but there are ways to render them

more rigorous. For example, acknowledged experts can be asked to write the scenarios, and their output can he harmonized with known facts (such as demographic data or statistics on availability of natural resources). Even when they are not fully rigorous, scenarios can help policy makers and ordinary citizens alike to imagine possible futures, both to prepare responses to anticipated problems and to set goals for positive accomplishments. Ideas generated through scenarios can become the focus of more rigorous methods of empirical research.

Multi-agent modeling is akin to scenarios, but is carried out through computer simulation. An agent is a dynamic computer representation of an individual person, organization (such as a corporation), sector of the economy, or other social unit. Among the most intellectually influential examples is a study by political scientist Robert Axelrod (1984), in which a computer modeled the interaction of a number of individual people, who followed various strategies in their economic dealings with each other. The point of the study was to see if these agents could learn to cooperate, despite the fact that each was programmed to seek his or her own best selfish interests, and indeed they could. The relevance to real people was that the study showed that cooperation between humans was logically possible even without shared social values, religion, or any of the other sophisticated cultural factors that are often assumed to help humans he reliable partners. For 30 years, agent-based and other computer simulations have contributed to a greater understanding of issues, such as the ways a society may affect the natural environment and the ways social movements may organize around a variety of issues (Bainbridge, 1987, Forrester, 1971, Meadows et al. 1974).

Axelrod's simulations employed game theory; it is also possible to use pure mathematical methods in this way of conceptualizing human relations in terms of strategic interactions for personal gain.

The case study method is an important qualitative research approach that can be practiced somewhat rigorously, either with historical or ethnographic data. Given that nanotechnology is quite recent, historical studies will have to rely upon carefully drawn analogies with earlier technologies. For example, an extensive literature already exists on the often-rocky adoption of new medical technologies, as some excellent therapies and diagnostic tools are ignored while others spread rapidly throughout the medical community despite lack of evidence for their value (Bunker et al. 1977, Howell, 1995) . The challenge is how to identify close analogies between past cases and particular nanotechnology applications. The ethnographic approach avoids this problem through direct observation of a specific emerging nanotechnology in the laboratory or in the wider organization of which it is a part. Ethnography is not well suited for prognostication, however, because it focuses on the present and very recent past. Potentially, the combination of history (to get the time perspective that reveals outcomes) and ethnography (to determine the nature of an innovation to support appropriate analogies) could he more powerful than either alone.

New technologies do not merely have an *impact upon* society. Rather, they *interact with* society and their impact is a result of technical facts with social factors. Thus, public opinion surveys and methods like market testing are important ways to chart the changing meaning of nanotechnology. *Focus groups* can provide insights in to how to intervene and how to get information across. The research method must be tailored to the particular population under study. For example, young people may not respond well to formalized *questionnaires*, so it may he best to conduct listening tours in high schools to examine youth culture and understanding. *Content analysis* (obtained by looking at media, popular culture, and Hollywood) could be integrated with surveys of audiences for analysis of the social values that nanotechnology may affect.

Finally, it will be important to collect solid facts about the institutions and individuals that are most involved in the development and application of nanotechnology. An inventory should be undertaken of existing institutions and assessment of how they cope with change and uncertainty. Also valuable would he research to develop a future nanotechnology-skills inventory for identifying best-of-breed competencies that will enable jobs, career development and competitiveness.

THE RESPONSIBLE DEVELOPMENT OF NANOTECHNOLOGY

While the phrase 'responsible innovation' occurred occasionally, it is now becoming more common, especially in nanotechnology. Examples are the USA Centre for Responsible Nanotechnology (with links to the Drexlerian "social world"), and the International Dialogue on Responsible Research and Development of Nanotechnology, recently started up by Mihael Roco (US National Nanotechnology Initiative), include attempts at interactive TA from CSPO at Columbia University (Rip, 2005).

If still unformed, however, there is reason to believe that public debate about nanotech is about to take off - with two just founded new nanotech organizations. The Center for Responsible Nanotechnology, run by a social activist and a nanosystems theorist, *Chris Phoenix*, one of the Center's founders says, "What we want, is to see molecular nanotechnology policy developed and implemented with a care appropriate to its powerful and probably transformative nature." And two Washingtonians—a futurist, Eric Drexler and an antitrust lawyer, Chris Phoenix —are in the process of launching the Nanotechnology Policy Forum to improve the quality of public discourse about nanotech. They intend to host events every few months, and to stay scrupulously evenhanded: the advisory panel planned for the organization will include both friends and foes of nanotech - as well as present and former congressmen (Keiper, 2003).

TECHNOLOGY ASSESSMENT FOR THE EUROPEAN PARLIAMENT EUROPEAN TECHNOLOGY ASSESSMENT GROUP (ETAG)

Since October 2005 a group of five European scientific institutes - with the Institute of Technology Assessment and Systems Analysis (ITAS), Research Centre Karlsruhe, Germany as the leading partner - has been providing scientific services for the European Parliament on social, environmental and economic aspects of new technological developments (Chatzimarkakis, 2006).

Initially for a period of three years, the European Technology Assessment Group (ETAG; www.itas.fzk.de/etag) will carry out TA studies on behalf of the STOA Panel. Apart from being leading institutions in the field of Technology Assessment (TA) in their home countries all members of the group have long-term experience in policy consulting for parliamentary bodies. The group is made up of the following organizations:

1 Institute of Technology Assessment and Systems Analysis (www.itas.fzk.de), which operates the Office of Technology Assessment at the German Parliament,
2 Danish Board of Technology, which provides consultancy services for the national parliament (www.tekno.dk),
3 Flemish Institute for Science and Technology Assessment (viwTA), the TA-institution of the Flemish parliament (www.viwta.be),
4 Parliamentary Office of Science and Technology (POST) of the British Parliament (www.parliament.uk/post/home.htm),
5 Rathenau Institute, the central TA institution in the Netherlands working for the Dutch parliament (www.rathenau.nl). The ongoing work programme funded from the 2005 STOA budget consists of a set of 10 projects dealing with a broad range of subjects from various sectors

of policy making, such as R&D, ICT, environment, health and energy.

6 Institute of Technology Assessment of the Austrian Academy of Sciences in Vienna.

ESSENTIAL QUESTIONS CONCERNING ETHICAL, ENVIRONMENTAL, ECONOMIC, LEGAL AND SOCIAL IMPLICATIONS OF NT

1. Main task of nanotechnology assessment (TA) is to foster principles of ethical governance, maintenance balance of fundamental human rights and responsibilities of government regarding to emerging enabling nanotechnology.
2. What are linked with the new opportunities of NT: possible technological, ethical, environmental, societal, economic and health risks? What are the actual barriers to be overcome these risks in the corresponding sectors? To what uncertainties may lead illiteracy of public in NT?
3. The main purpose is not only defining opportunities or threats, but perform sound comparisons balancing supposed benefits and risks of NT. If 'threats' and 'risks' overwhelm the 'strengths' and 'opportunities', societal attitude obviously may be rejection.
4. Investigate and study environmental, health and socio-economic impact of NT: Where do nanomaterials go when they enter the environment and what are their effects? There are always possibilities for environmental or health harms. Address forecasting and roadmapping for future implications and determining the role of NT in economical development.
5. Create code of ethics concerning NT utilization in country. Design principles to discourage unethical or accidental misuses of nanotechnology, versus, encourage and advocate friendly 'green' NT; As the science of NT leaps ahead, so the ethics lags behind; Either the ethics of NT will catch up, or the

science will slow down. NT may have devastating consequences, including public fear and rejection of NT without adequate study of its ethical and social implications.

6. Public engagement, involvement of NGO and promote decision making activities at governmental and international levels. Mass media need to be involved in the early stages of NT since they have an important influence on public perceptions.
7. Increase awareness and ferry appropriate overview information (chemo/bio – nano threats and defense) to concerning authorities about national security issues. As said Glenn Reynolds, a law professor and longtime nanotech expert at the University of Tennessee: "Any powerful technology can be abused." NT is capable of dramatically improving surveillance devices, and producing new weapons. Will these new technologies increase security or add to the arsenal of bio- and techno- or even nano-terrorism? Who will regulate the direction of research in defensive and offensive military NT? How much transparency will be necessary in government and non-governmental NT initiatives to avoid misuses?
8. Promote NT education in secondary schools and universities. To emphasize that this multidisciplinary subject is gaining priority. Schools and universities could discuss the issue in depth, as well, could include exhibits on NT…

CONCLUSIONS

The aim of Technology Assessment is to measure benefit to risk ratio. The purpose of TA is to study ethical controversies in societal prism. Technology Assessment determines public perception. TA establishes visionary attitude.

Technology Assessment Alleviates:

- to highlight creativity of field (Nobel Prize winners, different awards and grants);
- to define unequivocal ethical and legislative statements;

- to find out readiness for investments by venture capitalists (VC);
- to recognize stakeholders willingness to benefit from technology;
- to involve equally all layers of society: government-academy-society-industry;
- to maintain balance between benefits & risks of technology.
- to match convergence with simultaneously emerging enabling technologies (cogno-nano-info-bio).

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CHAPTER FOUR

REVIEW OF NANOTECHNOLOGY APPLICATIONS IN PHARMACEUTICAL INDUSTRY*

NANOTECHNOLOGY - A POWERFUL RESEARCH ENABLER

Nanotechnology is providing a critical bridge between the physical and chemical sciences and engineering, on the one hand, and modern molecular biology on the other. Materials scientists are learning the principles of the nanoscale world by studying the behavior of biomolecules and biomolecular assemblies.

In return, engineers are creating a host of nanoscale tools that are required to develop the systems biology models of malignancy needed to better diagnose, treat, and ultimately prevent cancer.

Nanotechnology is the science of building devices at the molecular and atomic level. For example, a single data bit might be represented by only one atom some time in the future.

Beyond being used in computers and communications devices, nanotechnology could be used extensively in biotechnology to build devices, fight disease, and change the properties of materials.

Nanotechnology will serve as a versatile development platform that will be able to quickly turn biological insights into clinically useful products.

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* Presented summary is performed mainly based on SWOT analysis of Concerning the Use of Nanomaterials in the Medical and Health Sector, 6th FP of European Committee (courtesy of authors René de Groot and Dr. Jonathan Loeffler); Cancer Nanotechnology Plan of NCI and NSF of U.S., and press releases of interrelated information from pharmaceutical drug manufacturers, compiled together.

FIGHTING CANCER WITH NANOTECHNOLOGY

By the year 2015 National Cancer Institute plan to meet the goal of eliminating death and suffering from cancer.

The National Cancer Institute is engaged in efforts to utilize the power of nanotechnology to radically change the way we diagnose, image, and treat cancer.

The US National Science Foundation (NSF) expects nanotechnology to account for around half of all pharmaceutical industry sales by 2010.

As part of NCI mission to accelerate the application of nanotechnology to the major challenges in clinical oncology and basic cancer research, the NCI Alliance for Nanotechnology in Cancer is dedicating $144.3 million as part of a 5-year initiative for nanotechnology in cancer research. Main goal is to foster the development of nanoscale devices that can identify the early molecular signatures of cancer and deliver therapeutic or preventive agents that can intervene in the cancer process at this early stage.

NANOTECHNOLOGY - STRATEGIC IMPLICATION IN ONCOLOGY

Thirty years ago, cancer was a poorly understood and usually deadly disease. This is no longer the case.

Eliminating suffering and death from cancer requires an unprecedented collaborative effort that leverages resources from government, industry, and academia.

Nanotechnology will revolutionize the very foundations of cancer treatment, prevention and diagnosis.

Nanoscale devices have the potential to radically change cancer therapy for the better and dramatically increase the number of highly effective therapeutic agents. Nanoscale constructs can serve as customizable, targeted drug delivery vehicles capable of ferrying large doses of chemotherapeutic agents or therapeutic

genes into malignant cells while sparing healthy cells, greatly reducing or eliminating the often unpalatable side effects that accompany many current cancer therapies.

Nanoscale particles and devices are similar in size to biomolecules and can easily enter most cells. Our ability to manipulate the physical, chemical, and biological properties of these particles affords researchers the ability to engineer and use nanoparticles for drug delivery, as image contrast agents, and for diagnostic purposes.

Nanotechnology refers to the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology. Such nanoscale objects—typically, though not exclusively, with dimensions smaller than 100 nanometers—can be useful by themselves or as part of larger devices containing multiple nanoscale objects.

Nanotechnology is the development and engineering of devices so small that they are measured on a molecular scale. This emerging field involves scientists from many different disciplines, including physicists, chemists, engineers, information technologists, and material scientists, as well as biologists. Nanotechnology is being applied to almost every field imaginable, including electronics, magnetics, optics, information technology, materials development, and biomedicine.

At the nanoscale, the physical, chemical, and biological properties of materials differ fundamentally and often unexpectedly from those of the corresponding bulk material because the quantum mechanical properties of atomic interactions are influenced by material variations on the nanometer scale. In fact, by creating nanometer scale structures, it is possible to control fundamental characteristics of a material, including its melting point, magnetic properties, and even color, without changing the material's chemical composition. For instance, opaque substances become transparent (copper); inert materials become catalysts

(platinum); stable materials turn combustible (aluminum); insulators become conductors (silicon). Much of the fascination with nanotechnology stems from these unique quantum and surface phenomena that matter exhibits at the nanoscale. A material such as gold, which is chemically inert at normal scales, can serve as a potent chemical catalyst at nanoscales. One hundred and fifty years after one of the founders of chemistry Michael Faraday in 1850s (Thomas & Kulkarni 2003) first created gold nanoparticles and observed that these nanoparticles absorbed light, researchers have created a 21st century version that absorbs light so efficiently that a mere flash of light can cause the particles to melt. This ability to efficiently turn light into extreme heat could prove useful for creating nanoscale thermal scalpels capable of killing cancer cells.

Used in manufacturing for many years, nanotechnology enables scientists to build devices and materials one atom or molecule at a time, creating tightly packed structures that take on new properties by virtue of their miniature size.

EXPLORING NANOTECHNOLOGY IN CANCER

NANOTECHNOLOGY PLATFORMS FOR CANCER RESEARCH

A nanometer is one-billionth of a meter(10^{-9}), or about 100,000 times smaller than the width of a human hair. Most animal cells are 10,000- 20,000 nanometers in diameter, so nanoscale devices are tiny enough to enter cells and analyze DNA and proteins, potentially identifying and treating cancerous cells at much earlier stages than currently possible.

They are smaller than human cells and organelles and similar in size to large biological macromolecules ("biomolecules") such as enzymes and receptors— hemoglobin, for example, is approximately 5 nm in diameter, while the lipid bilayer surrounding cells is on the order of 6 nm thick. Nanoscale devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can move out of blood

vessels as they circulate through the body. As a result, nanoscale devices can readily interact with biomolecules on both the cell surface and within the cell, often in ways that do not alter the behavior and biochemical properties of those molecules. From a scientific viewpoint, the actual construction and characterization of nanoscale devices may contribute to understanding carcinogenesis.

Because of their small size, nanoscale devices by gaining access to so many areas of the body, they have the potential to detect disease and deliver treatment in ways unimagined before now. Since biological processes-including events that lead to cancer-occur at the nanoscale at and inside cells, nanotechnology offers a wealth of tools that are providing cancer researchers with new and innovative ways to diagnose and treat cancer.

PRIMARY ASPECTS OF NANOTECHNOLOGY IN MEDICINE

Today, cancer-related nanotechnology is proceeding on two main fronts: laboratory-based diagnostics and in vivo diagnostics and therapeutics.

Work is currently being done to find ways to safely move these new research tools into clinical practice. But there are already examples in clinical use that show the promise of nanotechnology.

- Nanotechnology has been used to create new and improved imaging techniques to find small tumors. Researchers have shown that incredibly small iron oxide particles (nanoparticulates) can be used with magnetic resonance imaging (MRI) to accurately detect cancers that have spread to lymph nodes, without requiring surgery.
- Nanoscale drug delivery devices are being developed to deliver anticancer therapeutics specifically to tumors. Liposomes are one such "first generation" nanoscale

device. Liposomal doxorubicin[26] is used to treat specific forms of cancer, while liposomal amphotericin B treats fungal infections often associated with aggressive anticancer treatment. Recently, a nanoparticulate formulation of the well-known anticancer compound taxol was submitted as a new treatment for advanced stage breast cancer.

- In the near future, nanoscale devices may lead to detection of the earliest stages of cancer while simultaneously delivering anticancer agents to the tumor. Early research has shown that nanoparticulate sensors can detect the cell death that occurs when a cancer cell succumbs to the effects of an anticancer drug. As a highly sensitive means of determining if a therapy is working, this application of nanotechnology could save a patient from months of ineffective medication and debilitating side effects, allowing a switch to a potentially more effective course of treatment. In addition, such a sensor could greatly accelerate clinical trials of new anticancer agents, again by demonstrating very early signals of the effectiveness of a drug.

The NCI envisions over the next five years that nanotechnology will result in significant advances in early detection, molecular imaging, assessment of therapeutic efficacy, targeted and multifunctional therapeutics, and the prevention and control of cancer.

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[26] ALZA Corporation's STEALTH® liposomal technology, developed for state-of-the-art intravenous drug delivery, is the basis for the anticancer agent Doxil® (doxorubicin HCl liposome injection). The proprietary STEALTH® liposomes evade recognition by the immune system because of their unique polyethylene glycol (PEG) coating.

RELEVANT NANOTECHNOLOGY EFFECTS FOR APPLICATIONS IN THE MEDICAL & HEALTH SECTOR[27]

Nanoparticles are especially relevant for the Medical & Health sector, because they are in the same range of dimension than biomaterials (Table 1).

Table 1. Dimensions of biomaterials

Biomaterials	Size (about)
Atoms	- 0,1 nm
Nitrogenbases DNA molecules (A,G,T,C)	0,1 nm
Genes	0,1 nm
DNA molecules	1 – 2 nm
Small molecules	1 nm
Peptides (part of enzymes)	1 – 4 nm
Proteins	2 – 8 nm
Enzymes (proteins)	2 – 8 nm
Hormones (proteins)	2 – 8 nm
Lipids (cholesterol, part of cell membrane)	10 nm
Nucleus of cell	40 nm
Viruses	50 – 100 nm
Vaccines	50 – 1000 nm (0,005 – 1 μm)
Cell (human, animal)	2000 – 10000 nm (2 – 10 μm)
Antibody	2000 – 10000 nm (2 – 10 μm)
Bacteria	5000 – 1000 nm (0,5 – 1 μm)

[27] Groot de, R., Loeffler, J., (2006). Roadmap Report Conserning the Use of Nanomaterials in the Medical and Health Sector. The Sixth Framework Programme of European Community.

Nanotechnology is already impacting drug delivery. The use of nanostructured materials for drug delivery is an area with a great deal of activity that could have a major impact on the medical and pharmaceutical industry. Nanotechnologies dedicated to biology are called nanobiotechnologies. Nanobiotechnology refers to the ability to create and manipulate biological and biochemical materials, devices and systems at atomic and molecular levels.

A key area of research is **targeted drug delivery**. Nanotechnology offers the promise of delivery of the right drug in the right place at the right time. Some approaches use nanoparticles or nanocapsules to deliver drugs through the skin, lungs, stomach and eyes already. These approaches offer numerous advantages such as increased solubility, resistance to gastric enzymes, controlled release or the ability to direct the drug through various means to the very place where it is needed.

The nanostructured materials for drug delivery are presented by different methods:

- Oral delivery.
- Pulmonary / inhaling systems.
- Implantable / injectable polymer systems.
- Transdermal systems.
- Liposome delivery systems.
- Needle free injection systems.

Formulating drugs with nanoparticles can also improve their solubility (because many drugs are not water-soluble).

A key area of research is targeted drug delivery to individual cells within the body. Nanotechnology offers the promises of:

- New formulations and routes for drug delivery to previously inaccessible sites in the body.
- The delivery of the right drug in the right place at the right time.
- Personalized drugs.

Also some approaches talk about nano pumps and valves, nano MEMS devices (NEMS), nano needles and stents to deliver nano-litres or nano-quantities of chemical substances.

Nanomaterials presently used in clinical or pre-clinical trials are for example:

- Nanoparticles.
- Nanocapsules (inclusive liposomes).
- Nanoshells.
- Fullerenes.
- Nanotubes.
- Nanoporous materials.
- Nanocrystals (quantum dots).
- Dendrimers.
- Nanomagnets.
- Calcium Phosphate (CAP) Vaccins.
- CAP nanoporous particles.

For drug delivery, these nanomaterials combine the advantages of high surface area, improved interfacial properties and size confinement to deliver drugs that have increased efficacy, offer more convenient dosing of regimens and have improved toxicity profiles compared to their micron-sized predecessors. With nanoparticles, it is possible that drugs may be given better solubility, leading to a better absorption. Also, drugs may be contained within a molecular carrier, either to protect them from stomach acids or to control the release of the drug to a specific targeted area, reducing the likelihood of side effects. These nanoparticles could also contain a slowly-released drug payload, be radioactive, or enhance the heating effects of a laser shone through the flesh to destroy tissue.

For example, inhalation of sub-micrometer diameter particles may offer an efficient route for the administration of therapeutic substances: these particles can be deposited deep within the lungs, whence, with a thin blood-gas barrier and copious

blood supply, they can be absorbed rapidly into the body. Ultra fine particles individually contain very little mass, but if present in extremely large numbers can disperse significant amounts of material deep in the lung. Once there, their very large cumulative surface area may assist their dissolution.

It is hypothesized that engineering inhaled drug particle sized down to ultra fine particle levels will produce effective "vectors" for respiratory and other drugs, by virtue of their large numbers (and hence potential area coverage) and their penetrative and deposition properties. In order to prove that, a size-controlled ultra fine aerosol delivery system has been developed for human volunteer studies and will be used to determine the clinical efficacy of a given dose of drug administered in a variety of particle sizes. An added benefit would be a reduction in deposition to the mouth and throat, reducing some of the adverse side effects seen with current inhaled drug delivery systems. Such drugs are already beginning pre-clinical or clinical trials, adhering to the strict regulatory requirements for new pharmaceuticals.

Regarding oral drug delivery, factors that affect the efficacy of a drug include the solubility, bioavailability, biological half-life, dose and dosing regimen and shelf-life.

Technologies that can improve oral delivery of drugs by controlling the release and absorption in the gastro-intestinal tract are in great demand and improved powder processing is one strategy that can overcome these obstacles. Indeed, in vivo studies have shown sustained-release and improved bioavailability of pressed powders for improved tablet processing of next generation pharmaceuticals. For example, the company Nanotherapeutics has developed a system based on nanoparticles that enables oral delivery of macromolecules (peptide/protein) and improves the oral bioavailability of insoluble and poorly absorbed drugs that require injection (e.g. antibiotics, antivirals, anti-inflammatories).

Nanoparticle suspensions also offer an advanced approach in the delivery of insoluble drugs for injectable delivery. Indeed,

nanoparticles for injectable delivery offer several advantages including low excipient loads/smaller dose volumes, better control of particle size and dispersion efficiency, controlled release-rates, increased efficacy and systemic bioavailability.

As has been described nanotechnology is already impacting drug delivery, however this will continue apace. In the future, nanoparticles will contain far more intelligence than the entire current system of drug delivery. These will be able to target and deliver therapeutics to specific tissues and cells with no side effects. For example a nanoparticle taken orally, that passes undisturbed through the stomach and small intestine and into the colon, where it homes in directly on the tumour cells and releases a powerful anticancer drug that destroys just the cancerous cells, could soon be a reality. In this respect antibodies that bind exclusively to cancerous cells could be attached to nanoshells and injected into patients.

Following infrared irradiation of the nanoshell-targeted tumour the resultant heat would destroy the cancer cells (Virginia Commonwealth University). The same directions are conducted by French company Nanobiotix. Clinical tests are starting within 2 years.

Another possible targeted drug delivery system involves the use of nanomagnets that can be directed to specific sites within the body using external magnetic fields. These magnets could be attached to drugs, modulated field could release drug from particles, that treat specific cellular structures. (Biophan Technologies, Inc.)

A drug payload is not even necessary: the material could just produce high temperature under heat or light to destroy the targeted cells. The advantage of such a system is that it allows very focused and intense treatment of diseased cells without harming cellular structures of non-interest. Nanotubes may one day be used in transdermal drug delivery patches as nanoscale needles that can inject substances into the body. In fact, developing nanotubes as

nanoscale, intravenous or intradermal, drug delivery devices is medically significant because

a) it increases the mechanical and sensing functionality of the resultant nanoneedle, which makes it precise.

b) it is a less invasive and less painful drug administration. Nanotubes offer the potential of targeted drug delivery, for example to muscles, with molecular amounts of material, which maximizes efficiency by permitting lower doses, thereby minimizing possible toxicity and harmful side effects.

The following examples of potential applications can be given.

Nanotubes could even be used as nanoneedles that inject drugs directly into individual cells, as developed at Purdue University. Indeed, many drugs destroy infectious bacteria by poking holes in their cellular membranes and leaking out their nutrients, just like pricking a hole in a balloon. The nanotubes developed by Purdue University could also act in this manner, but in addition, they can be targeted and thus lure bacteria with "a bait" that guides the nanotubes to the bacterial cell membrane where they can start destroying the cell.

Nanoparticles such as fullerenes[28] (molecules based on a 60 carbon atom cage) and quantum dots (complexes of semi-conductor material that have unique fluorescent properties) are being exploited in many areas including imaging (e.g. enhancement of magnetic resonance imaging [MRI] and

[28] Fullerenes, which are made of 60 linked carbon atoms, or C60 made a splash in the scientific world when they were unveiled in 1985 by chemists Robert Curl and Richard Smalley (1943-2005) at Rice University and Sir Harry Kroto at the University of Sussex. The trio won the Nobel Prize in chemistry in 1996 for their discovery. They proved that fullerenes were a third form of carbon, after graphite and diamond, and named the molecules buckminsterfullerenes because they resembled the geodesic dome invented by Buckminster Fuller. Buckyballs and another form of fullerene called carbon nanotubes are expected to become key ingredients in some nanotech products.

ultrasound) and drug delivery (e.g. a modified fullerene is entering clinical trials as an anti-HIV agent).

Other nano-devices will allow the continuous monitoring of the level of various biochemicals in the bloodstream and in response could release appropriate drugs. For example, an insulin-dependent diabetic could use such a device to continuously monitor and adjust insulin levels autonomously.

On the other hand drugs can be inhaled in a foggy form instead of applied by injection.

Nektar Therapeutics at the 8th of September, 2005, reported that Pfizer Inc and the Sanofi-Aventis Group said that a U.S. Food and Drug Administration (FDA) advisory committee panel has recommended the approval of Exubera®, rapid-acting, insulin [rDNA origin]),dry powder for oral inhalation for the treatment of adults with type 1 and type 2 diabetes. Companies leading technology is advanced PEGylation.

Nanocrystalline sun blocker (protection) cream that possess zinc-oxide, offer the best protection against skin cancer because it stops both UVA-beams (cause of sun burn) andUVB-beams (penetrate deeper in the skin). BASF developed a very pure nanocrystalline zinc-oxide what makes the sun cream colourless and silk-soft. The nanocrystalline zinc-oxide is used in the SunSense SPF 30 suncream of NuCelle.

NanoCrystal™ Technology has developed for poorly water soluble compounds, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. The NanoCrystal technology can be incorporated into all dosage forms both parenteral and oral, including solid, liquid, fast-melt, pulsed release and controlled release dosage forms.[29]

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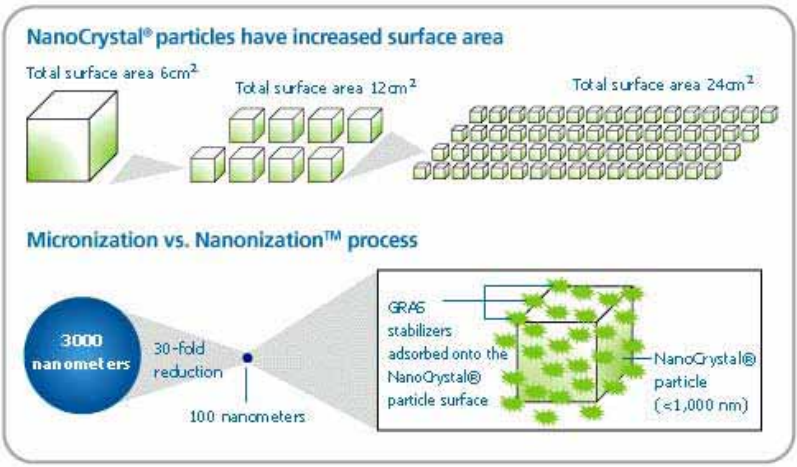
[29] In July,2006 Elan Corp. filed a lawsuit against Abraxis BioScinece Inc. alleging patent infringement in relation to ABRAXANE and asserting that ABRAXANE uses technology protected by two Elan-owned patents. Abraxis is

A surgical intracavitary application of **paclitaxel** and **carboplatin** encapsulated by liquid crystalline cubic phases are examined in a pilot study. Cubic phases consist of curved biocontinuous lipid bilayers, separating two congruent networks of water channels. Used as a host for cytotoxic drugs, the gel-like matrix can easily be applied to the walls of a surgical resection cavity. The authors have an intracavitary developed Nanocarrier system of biodegradable liquid crystalline cubic phases encapsulating **carboplatin** and **paclitaxel**.[30]



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confident in the integrity of its patents and believes that ABRAXANE does not infringe on the patent rights of Elan. The company intends to vigorously defend against this lawsuit to protect its patent rights. (Press Release of Abraxis BioScience Inc. from Aug. 3, 2006, (NASDAQ:ABBI)).

[30] von. Eckardstein, K. L., Reszka, R., Kiwit, J. C. W. (2005). Intracavitary Chemotherapy (Paclitaxel/Carboplatin Liquid Crystalline Cubic Phases) for Recurrent Glioblastoma – Clinical Observations. J. Neuro-Oncology. 305 - 309 . von. Eckardstein, K. L., Patt, S., Kratzel, C., Kiwit, J. C. W., Reszka, R. (2005). Local chemotherapy of F98 rat glioblastoma with paclitaxel and carboplatin embedded in liquid crystalline cubic phases. J. Neuro-Oncology. 209 - 215.

Medical coatings are also an area of application where much is expected. On this moment you can see much effort in the research and development of coatings with nanomaterials with depending on the specific application properties and characteristics like anti-bacterial, non toxic, stimulation of tissue growth, biocompatibility, good attachment to surfaces and sustainability.

Nanocomposites of titanium alloys, for example, can be used to improve the biocompatibility and longevity of surgical devices and implants.

Nanostructuring surfaces can improve cellular attachment (e.g. etching surfaces with nanoscale grooves or using instruments such as an AFM to imprint surfaces with cell attachment molecules), and direct cells to grow into defined structures. By incorporating biodegradable polymers to act as a scaffolding, these structures can be assembled into dimensional "tissues". Nanostructuring can also be used to provide an anti-microbial coating on implants.

Another area of application with high expectations is the imaging of molecules. It is expected that the application of nanoparticles (for example with gold, iron, fluorine, manganese quantum dots) could be extremely important for the development of contrast agents for almost all imaging techniques (magnetic resonance, ultrasound, optical, nuclear).

Quantum dots, nanometer sized crystals of a semiconductor material such as cadmium selenide, (CdSe), cadmium sulfide (CdS) or cadmium telluride (CdTe) with an inert polymer coating, are another promising nanoscale tool for laboratory diagnostics. The color of a quantum dot depends on its size. These quantum dots emit across the entire visible spectrum even though all are irradiated with white light.

The semiconductor material used for the core is chosen based upon the emission wavelength range being targeted: CdS for UV-blue, CdSe for the bulk of the visible spectrum, CdTe for the far red and near-infrared, with the particle's size determining the

exact color of a given quantum dot. Because of the multitude of colors with which they can emit light, quantum dots can be combined to create assays capable of detecting multiple substances simultaneously. Due to their tiny size they are traced in dividing cells versus other fluorescent dyes. The polymer coating safeguards cells from cadmium toxicity but also affords the opportunity to attach any variety targeting molecules, including monoclonal antibodies directed to tumor-specific biomarkers. In one demonstration, researchers were able to simultaneously measure levels of the breast cancer marker Her-2, actin, microfibril proteins, and nuclear antigens.

Because of their small size, quantum dots can function as cell- and even molecule-specific markers that will not interfere with the normal workings of a cell. In addition, the availability of quantum dots of different colors provides a powerful tool for following the actions of multiple cells and molecules simultaneously.

In August 2004, researchers announced the successful preparation of water-soluble gold quantum dots that can also be constructed to emit light at a variety of wavelengths. These polymer-coated quantum dots may prove to be more suitable for use in human clinical applications.

BIO-NANOTECHNOLOGY BREAKTHROUGH: RNA COULD FORM BUILDING BLOCKS FOR NANOMACHINES

Eventually, it should be possible to mix and match anticancer drugs with any one of a number of nanotechnology-based delivery vehicles and targeting agents, giving researchers the opportunity to fine-tune therapeutic properties without needing to discover new bioactive molecules. A good example from the biological world is a virus capsule, made from a limited set of proteins, each with a specific chemical functionality, that comes together to create a multifunctional nanodelivery vehicle for

genetic material. In fact, at least one research group is using the empty RNA virus capsules from cowpea mosaic virus and flockhouse virus as potential nanodevices.

Purdue Universitie's researchers developed some of their RNA-manipulation techniques in 2003 by building an RNA nanomotor.

Peixuan Guo, professor of molecular virology at Purdue University, has found that a virus known as Bacteriophage Phi 29 uses six RNAs strung together in the shape of a hexagon to create a motor that transports DNA in the virus.

Guo's findings represent the first example of a hexagonal-shaped RNA complex. It is also the first example of transportation vehicles using RNA as building blocks.

The motor measures about 25 nanometers long, which is less than one hundredth the size of a red blood cell. It is made from six strands of RNA surrounding a center strand of DNA. In the presence of ATP, the RNA strands push the DNA axle in succession, spinning it around. This produces 50 to 60 piconewtons, or trillionths of a newton of force. A falling apple exerts about one newton of force.

Professor Guo's team created their nanoparticles by linking together different kinds of RNA, sorted through a variety of RNA forms that have shown promise for disease treatment and found three that could perform each of the desired tasks. One is "small interfering RNA," or siRNA, which deactivates certain genes in cells. The anothers are RNA aptamers, which bind to cancer cell surface markers, and the last are ribozymes, which can be designed to degrade specific RNA in cancer cells or viruses.

The successful use of small RNA for therapeutic purposes requires a safe and efficient delivery system capable of targeting specific cells. These protein-free 25-nm nanoparticles will allow for repeated and longterm administration escaping immunoresponse and avoid the short retention time of smaller molecules and the undeliverability of larger molecules.

The nanoparticles have already proven effective against cancer growth in living mice as well as lab-grown human nasopharlyngeal carcinoma and breast cancer cells. [Shu, D., Moll, W.-D., Deng, Z., Mao, C., and Guo, P. (2004). Nano Lett. 4:1717–1724]

"This is an incredible accomplishment that points to the versatility and potential medical value of these nanoparticles." said Jean Chin, a scientist at the National Institute of General Medical Sciences, which is part of the National Institutes of Health.

UTILIZATION OF BIODEGRADABLE POLYMERS FOR CONTROLLABLE DRUG RELEASE

While such work with naturally existing nanostructures is promising, chemists and engineers have already made substantial progress turning synthetic materials into multifunctional nanodevices.

Over the past decade for development of nano and microparticles are investigated biodegradable polymers, as effective drug delivery systems (DDSs) for the most urgent areas of medicine, particularly for chemotherapy, vaccines, and anti-infectious agents.

Life is polymeric in its essence, as the most important components of living cells (proteins, carbohydrates and nucleic acids) are polymers. Polymers are natural and synthetic in origin.

Most essential polymers could possess such important features as biodegradability, biocompatibility and capability of sustained intracellular delivery of multiple classes of cargoes, so to be a suitable system for intracytoplasmic delivery of drugs, proteins, or genes.

Already, some dendrimer-based constructs are making their way toward clinical trials for treating a variety of cancers. Dendrimers are of particular interest for cancer applications because of their defined and reproducible size, but more

importantly, because it is easy to attach a variety of other molecules to the surface of a dendrimer.

Dendrimers are 1- to 10-nanometer spherical polymers of uniform molecular weight made from branched monomers, are proving particularly adept at providing multifunctional modularity.

A dendrimer is a tree-like highly branched polymer molecule (Greek dendra = tree). Dendrimers are synthesized from monomers with new branches added in discrete steps ("generation") to form a tree-like architecture. A high level of synthetic control is achieved through step-wise reactions and purifications at each step to control the size, architecture, functionality and monodispersity. Several different kinds of dendrimers have been synthesized utilizing different monomers and some are commercially available. This picture shows a "3rd generation" polyamidoamine (PAMAM) dendrimer.

The guest molecules, which are hydrophobic when trapped into the suitable sites of dendrimers, are becoming soluble in aqueous solution. Such molecules could include tumor-targeting agents (including but not restricted to monoclonal antibodies), imaging contrast agents to pinpoint tumors, drug molecules for delivery to a tumor, and reporter molecules that might detect if an anticancer drug is working. In one elegant demonstration, investigators attached the anticancer drugs methotrexate or paclitaxel to a single dendrimer.

ANTICANCER DRUG DELIVERY BY POLYMER -BASED NANO/MICROSPHERES

Although, the drug delivery system (DDS) concept is not new, great progress has recently been made in the treatment of a variety of diseases. Targeting delivery of drugs to the diseased lesions is one of the most important aspects of DDS. To convey a sufficient dose of drug to the lesion, suitable carriers of drugs are needed. Nano/microspheres carriers have important potential

applications for the administration of therapeutic molecules. The research in this area is being carried out all over the world at a great pace. Research areas cover novel properties that have been developed increased efficiency of drug delivery, improved release profiles and drug targeting.

Nano and microspheres for their attractive properties occupy unique position in drug delivery technology. Nano/micro-particles and spheres attained much importance, as the different dosage forms reported. One of the current trends in this area will be discussed, particularly PGLA nano/microspheres utilization as DDS.

The term nano/microcapsules and nano/microspheres are defined, as a spherical particles with the size varying in between 50 nm to 2 mm containing a core substance. Due to attractive properties and wider applications of nano/microcapsules and nano/microspheres, a survey of the applications in controlled drug release formulations is appropriate.

One way to overcome side effects of anticancer drags and resolve these problems is to encapsulate the drug in polymer matrix. Commercially available best known class of biodegradable materials for controlled release are the poly L lactide (PLA), poly(D,L-lactide-co-glycolide)s (PLGAs), poly ethylene glycol (PEG) and etc. Various drug release profiles can be achieved by varying the molecular weight, copolymer ratio, drug loading, microspheres size and porosity, and the fabrication conditions. The fabrication technique chosen should be based on the nature of the polymer, the drug, its intended use and the duration of the therapy.

The research report from Singapore National University[31] describes the in vitro release of Paclitaxel from PLA-based

[31] Reports are presented by the group of authors, from the Department of Chemical and Biomolecular Engineering, National University of Singapore:
[1] Lee, LY., Smith, K. A., Wang, CH., (2005). Fabrication of micro and nanoparticles of paclitaxel-loaded Poly L Lactide for controlled release using supercritical antisolvent method: Effects of Thermodynamics and Hydrodynamics.

nano/microspheres fabricated using the modified SASEM process was further evaluated for their suitability for controlled release applications. The encapsulation and sustained release of a hydrophobic anticancer drug, paclitaxel, was employed to characterize the properties and release from PLA micro and nanoparticles. Paclitaxel is a promising anticancer drug with efficacy against a wide variety of carcinomas. However, its clinical application has been limited due to its hydrophobic nature. One method to overcome the problems brought about by Cremophor® EL is to encapsulate paclitaxel in biodegradable polymers such PLA or poly (DL lactic-co-glycolic acid) (PLGA) in micro and nanoparticles. These biodegradable polymeric particles also have the advantage of providing sustained release of paclitaxel for chemotherapy.[32, 33.]

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APPLIED NANOTECHNOLOGY FOR PACLITAXEL DRUG DELIVERY COULD BE THE SOLUTION

As terrible as cancer can be, chemotherapy treatments can make one think that the disease might be the lesser of two evils. The basic premise behind chemotherapy is to poison the patient's system with a cocktail of drugs. Not only does the cancer get attacked but so too does the entire body.

If the drugs aren't water soluble the need to be dissolved in another solvent so they can be injected. Often this solvent is highly toxic and causes strong side effects. American Pharmaceutical Partners have announced that its cancer-fighting drug ABRAXANE™ (consisting of 130-nanometer spheres of protein and paclitaxel) has demonstrated greater tumour reduction and fewer side effects when compared to a solvent-dissolved equivalent.

For the first time, the anticancer drug Paclitaxel can now be delivered using the body's transport protein, *human serum albumin* rather than a chemical solvent. As a solvent-free chemotherapy agent, ABRAXANE™ increases the convenience of administration.

ABRAXANE™ (Paclitaxel) was approved in February 2005 by the FDA. ABRAXANE™ launched by Abraxis Oncology, the proprietary drug division of (APP) American Pharmaceutical Partners, Inc. Abraxane™ is trademark of BioScience, Inc.(USA).

ABRAXANE™ - for Injectable Suspension is the first and only approved taxane for the treatment of metastatic breast cancer in a new class of albumin-bound nanotechnology that is free of solvents. As a solvent-free chemotherapy agent, ABRAXANE™ increases the convenience of administration.

ABRAXANE™ - FINANCIAL PERFORMANCE OVERVIEW OF MARKETING FOR 2005-2006[34]

> "This has been an exciting year of growth for the company. We have exceeded, for the first time, half a billion in net sales supported by the approval and successful launch of ABRAXANE™ and the stability of the base business," said, Patrick Soon-Shiong, APP's president and chief executive officer.

Current overview is made based on press releases of APP and Abraxis Inc. Assuming that unless marked as Company Confidential, all information has been made punlic. This presentation provides an overview of financial performance American Pharmaceutical Partners, Inc. is a specialty drug company that develops, manufactures and markets injectable pharmaceutical products, focusing on the oncology, anti-infective and critical care markets. Abraxis Oncology, the proprietary division of APP, is devoted entirely to developing and promoting innovative, next-generation cancer therapies such as ABRAXANE™.

AMERICAN PHARMACEUTICAL PARTNERS REPORT RECORD FOR 2005 SALES AND NET INCOME

Full year net sales increased 28% to $518.8 million and net income increased 52% to $86.4 million;
ABRAXANE™ brings of 11 months net sales following launch to $133.7 Million;
For the full year, gross margin was 56.5%, versus 53.3% in 2004.

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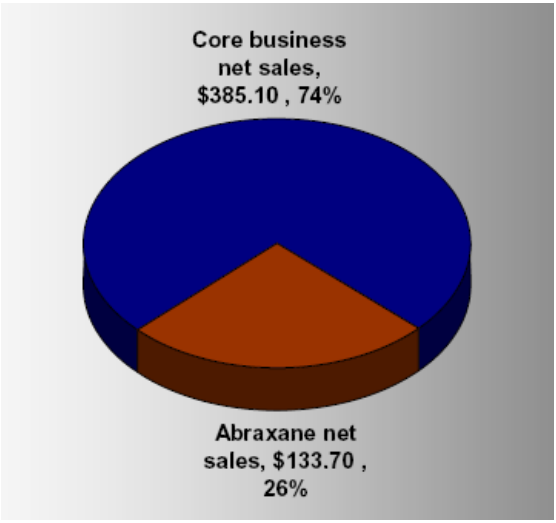
[34] ABTAXIS BIOSCIENCE, INC.
AMERICAN PHARMACEUTICAL PARTNERS

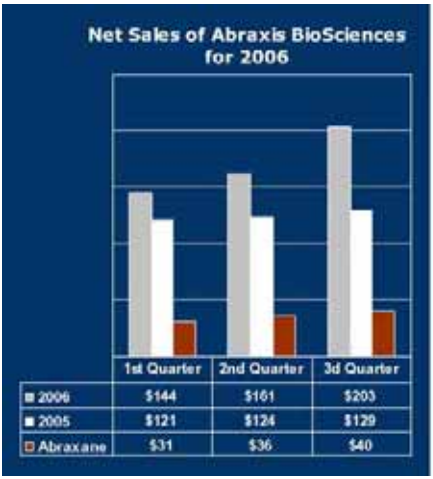
ABRAXANE™ revenue for the 3rd quarter 2006 increased to $52.3 million, which includes $40.2 million of net sales, versus net sales of $32.1 million in the same period last year. Net sales in the third quarter of 2006 represent a 25% increase.

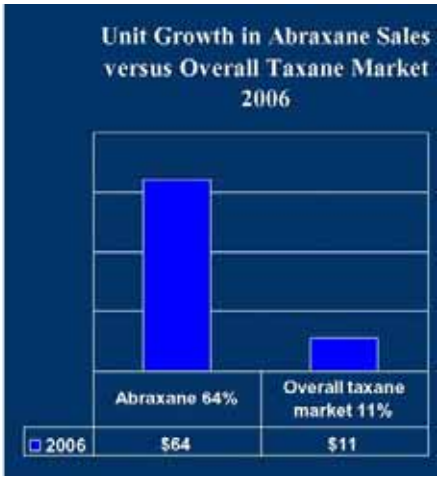
- ABRAXANE™ shows a *positive trend* in market penetration for metastatic breast cancer. According to IMS data, for the period between February 2006 and September 2006 versus the same period last year, there was a 64% unit growth in ABRAXANE™ versus an 11% increase in the overall *taxane market*. At the beginning of the *third quarter*, an expanded team of 172 oncology specialists began selling ABRAXANE™ throughout the U.S. This



team now consists of the original ABRAXANE™ sales force as well as the added AstraZeneca oncology specialists.

- It's five and a half year U.S. co-promotion of ABRAXANE™. This agreement effectively *doubles* the *sales force* and *promotional investment* in ABRAXANE™.

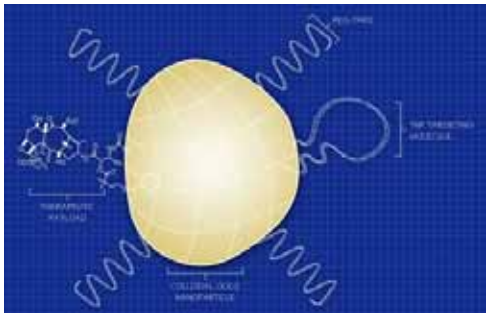




CytImmune - PEGilated gold nanoparticals - A Novel Vector for Tumor Directed Drug Delivery

In 2000, CytImmune discovered that pegylated colloidal gold nanoparticles bind anti-cancer therapeutics on their surface and carry these drugs safely through the blood stream.

Thiolated forms of small molecule therapeutics, such as paclitaxel, TNF, bind directly to the surface of colloidal gold nanoparticles.



With tumor targeting resulting in increased drug levels in the tumor and reduced drug uptake by healthy organs, the technology improves efficacy and reduces toxicity. Polyethylene glycol (PEG) masks particles from immune recognition preventing uptake by liver and spleen. Nanoparticles exit circulatory system only at the tumor neovasculature due to leakiness of blood vessels

Particles too large to exit circulation elsewhere TNF targeting molecule on particle's surface binds to receptors causing rapid absorption of drug in and around tumor.

ACUSPHERE Inc.

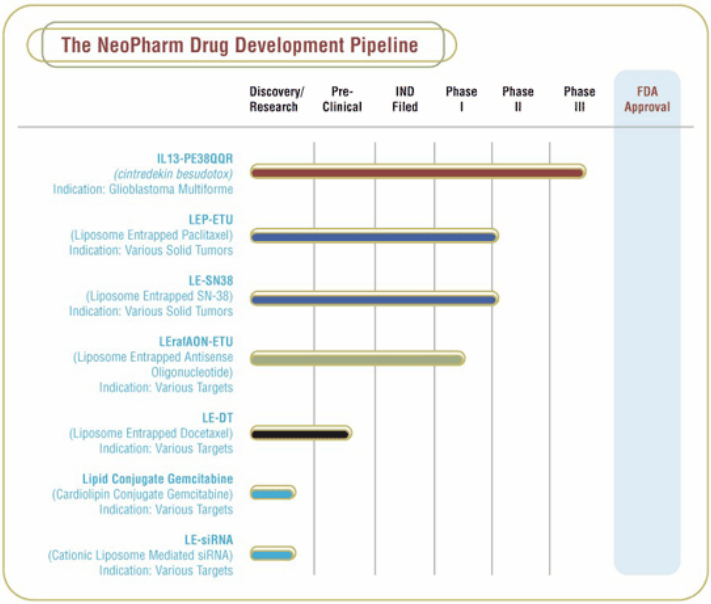
ACUSPHERE Inc. is a specialty pharmaceutical company that develops new drugs and improved formulations of existing drugs using its proprietary porous microparticle technology.

AI-850, our initial product candidate utilizing our HDDS technology, is a readily dissolving formulation of the hydrophobic drug, paclitaxel, the active ingredient in the cancer drug, Taxol. To dissolve paclitaxel, Taxol contains Cremophor, which is believed to cause severe hypersensitivity reactions, such as an extreme allergic reaction called anaphylaxis. Therefore, Taxol is typically administered using pre-medications and by long infusions to patients with cancer. By putting nanoparticles of paclitaxel into sponge-like microparticles, is created a paclitaxel formulation that is free of Cremophor and consists of paclitaxel nanoparticles in a porous, hydrophilic matrix, composed primarily of a sugar that has been proven to be innocuous in other injectable drugs.

NEOPHARM - DRUG DELIVERY PLATFORM - NEOLIPID®

NeoPharm is a biopharmaceutical company dedicated to the research, discovery, and commercialization of new and innovative cancer drugs for therapeutic applications. NeoPharm has built its drug portfolio based on its two novel proprietary technology platforms: a tumor-targeting platform and the NeoLipid® drug delivery system.

NeoLipid® technology entraps anticancer agents inside liposomes, which are microscopic membrane-like structures created from lipids. Because tumor cells need to consume large amounts of fats to sustain their rapid growth, they eat the liposome, while at the same time absorbing the anticancer agents. LEP-ETU embedded paclitaxel enters II phase of clinical trials.



BIODELIVERY SCIENCES INTERNATIONAL, INC.

BDSI Technology is patented and proprietary drug delivery technologies: Bioral® and BEMA™ technologies.

The Bioral® drug delivery technology encapsulates the selected drug in a nanocrystalline structure termed a “cochleate” cylinder. All of the components of the cochleate cylinder are naturally occurring substances. Cochleate cylinder provides an

effective delivery mechanism without forming a chemical bond, or otherwise chemically altering, the selected drug.

The BEMA™ drug delivery technology consists of a dissolvable, dime-sized polymer disc for application to mucosal (inner lining of cheek) membranes. BEMA™ discs deliver a rapid, reliable dose of drug across mucous membranes for time-critical conditions like breakthrough cancer pain, or trauma cases where intravenous lines or injections are unavailable or not practical. Bioral paclitaxel is available for licensing.

Drug	Indication	Status
Emezine	Nausea/Vomiting	Partnered
BEMA Fentanyl	Breakthrough pain	Proprietary
Bioral Amphotericin B	Fungal infections	Proprietary
Bioral NSAID	Pain	Licensed
Bioral paclitaxel	Oncology	Avail. for Licensing
Bionasal Amphotericin B	Chronic rhinosinusitis	Partnered
Biorazyme	Gauchers Disease	Avail. for Licensing
Bioral siRNA	Infectious disease/cancer	Avail. For Licensing

APHIOS CORPORATION

Aphios Corporation is developing enhanced therapeutics for health maintenance and the treatment of human diseases with a focus on infectious diseases, cancer and quality-of-life medicines

Aphios has utilized its patented SuperFluids™CFN technology to form nanosomes (small, uniform liposomes) of

paclitaxel. Liposomes are microscopic vesicles of phospholipid bilayers comprised of single or multiple lipid bilayers. Most liposomes are non-toxic, non-antigenic and biodegradable in character since they have the molecular characteristics of mammalian cell membranes. Hydrophobic compounds are trapped inside the lipid bilayers, masking the toxic nature paclitaxel and permitting a biocompatible formulation to be administered.

Aphios has developed and patented a nanosomal formulation of Paclitaxel, Taxosomes.™ The formulation is Cremophor-free and produced by Aphios' patented phospholipid nanosomes technology [U.S. and European Patents, 1995, 1997, 1998 and 2002]. Harvard Medical School researchers have demonstrated that Taxosomes™ is much less toxic in vitro than Taxol,® while being twice as effective in the in vivo treatment of nude mice with breast cancer xenografts.

NANOMED PHARMACEUTICALS, INC.

NanoMed has developed a scaleable nanoparticle manufacturing technology (Nanotemplate Engineering) to deliver small molecules, peptides, proteins, plasmid DNA, and diagnostic agents.

NanoMed has developed a scaleable nanoparticle manufacturing technology (Nanotemplate Engineering) to deliver small molecules, peptides, proteins, plasmid DNA, and diagnostic agents. The company is utilizing this novel platform technology to develop new and improved formulations for two approved chemotherapeutic drugs -- paclitaxel (Paclitaxel NP™) and doxorubicin (Doxorubicin NP™) -- and a new indication for a third approved therapeutic agent for use as a novel anti-cancer drug (NAC NP). The therapeutic focus is breast, lung, and colorectal cancer.

SONUS PHARMACEUTICALS

The Company's lead product candidate is TOCOSOL® Paclitaxel, an injectable, ready-to-use formulation of the widely prescribed anti-cancer drug paclitaxel.

The product is administered to patients in a short 15-minute infusion compared to the prolonged three-hour infusion required with Taxol. TOCOSOL Paclitaxel has been designed to overcome the limitations associated with Taxol® and generic paclitaxel-based chemotherapy, including time consuming and expensive preparation of the products prior to administration, long infusion times and undesirable or treatment-limiting side effects.

Sonus has completed patient enrollment in Phase 2a studies of TOCOSOL Paclitaxel in non-small cell lung, bladder and ovarian cancers, and Phase 2b studies are ongoing in bladder and breast cancers. In addition, the U.S. Food and Drug Administration has completed a Special Protocol Assessment (SPA) for the pivotal Phase 3 trial of TOCOSOL Paclitaxel, which Sonus expects to initiate in 2005.

The TOCOSOL® technology uses vitamin E and vitamin E derivatives to solubilize, stabilize and formulate drugs with the goal of enhancing their delivery, safety and efficacy. The Company's development strategy is:

Develop proprietary formulations of therapeutic drugs utilizing the TOCOSOL technology platform; and identify and acquire additional therapies and technologies in oncology and related fields in order to expand product pipeline and corporate capabilities.

SPHERICS, INC – FEASIBILITY STUDY OF ORAL NANOPARTICLE FORMULATION PACLITAXEL

Paclitaxel exists in several states, e.g., semicrystalline, dehydrate and amorphous and is generally supplied in the semi-

crystalline state. A micronization method that could reduce particle size and reduce crystallinity of paclitaxel would increase absorption of both particulate and soluble drug.

The paclitaxel nanoparticle formulations in the present study were prepared using a proprietary phase-inversion precipitation technique, to produce discrete particles of amorphous paclitaxel in the size range of 300 nm. The oral pharmacokinetics of the PNF were evaluated after single and repeat dosing in fasted mice. Paclitaxel nanoparticles were fabricated via a phase inversion technique.

NANOTECHNOLOGY FORECASTING

PIRIBO provides informational databases and performs information about products, including market research, covering the Drug Delivery Industry, including latest technologies, company profiles, biopharmaceuticals, market data and information covering Europe, the UK, North America and Asia. PIRIBO performs "Drug Delivery Market Research, Intelligence and Forecasts." There are presented 183 biotechnology and 164 drug delivery companies.

GREYSTONE ASSOCIATES is a medical technology consulting firm and offers forecasts and projections cover the period from 2004 to 2008. "Nanoparticle Drug Delivery, Technology, Therapies, and Prospects".

Nanotechnology first successfully developed in chemical and material production industry. Later some major companies commercialize their developments and start to sale production mostly to leading pharmaceutical companies, such as Jonson & Jonson, Bristol Mayerr Squibb, Roche, Sanofi-Aventis and so on. For example - Nektar Therapeutics (UK) is a leader drug delivery company. They have partner collaborations with more than 25 pharmaceutical and biotechnology companies, including Pfizer, Roche, Amgen, Bristol-Myers Squibb, Scherig-Plough, UCB

Pharma, Chiron, InterMune, Serono. This technologies are essential to six drugs approved in the United States and/or Europe.

The combination of technology leadership and development expertise allows Netar to capitalize on the rapidly expanding market for drug delivery solutions, which is estimated to grow from $50 billion in 2000 to more than $100 billion by 2005.

Recently, a nanoparticulate formulation of the well-known anticancer compound taxol was submitted by as a new treatment for advanced stage breast cancer.

Pharmaceutical market is partially traversed by nanotechnology based medications. However, most clinical reports in the nanotechnology are of phase 1 and phase 2 trials.

To conclude, nanotechnologies have already begun to change the scale and methods of drug delivery. Nanotechnology can provide new formulations and routes for drug delivery that broaden their therapeutic potential enormously by effecting delivery of new types of medicine to previously inaccessible sites in the body.

The use of nanocapsules and nanoparticles for drug delivery is an area with a great deal of activity that could have a major impact on the medical and pharmaceutical industry. Some of the technologies are relatively developed but will be affected by the notoriously long timescales needed for clinical testing. The eventual success of nanotechnology in areas of medicine will require patient acceptance and careful consideration of the social and economic consequences of genetic testing and therapy. [35]

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CHAPTER FIVE

INVENTION OF NOVEL DRUG DELIVERY SYSTEMS FOR IMPROVEMENT AND ENHANCEMENT OF CHEMOTHERAPY

NANOPARTICLES OF BIODEGRADABLE POLYMERS FOR NEW-CONCEPT CHEMOTHERAPY[36]

Clinical trials are the most important step for any medical product to be approved for clinical use. Pharmacology of experimental animals could be very different from that of humans, and interpatient and intrapatient differences also exist. *Few reports of clinical trials can be found from the literature for nanoparticles of biodegradable polymers for chemotherapy, although some preclinical guidelines have been provided.* Chemotherapy plays an important role especially when surgery and radiotherapy fail to cure the patients, who have only a 10% chance of cure by other therapies.

While the effort to find medical solution should be continued, new hope will most likely come from emerging technology, especially nanobiotechnology, which can be defined as chemotherapeutic engineering[37]. The situation for the emerging chemotherapeutic engineering looks similar to that for tissue engineering 30 years ago. Chemotherapeutic engineering will be well defined and begin to play a necessary and important role in the fight against cancer and other fatal diseases in the next 5 years.

It has been shown by the marvelous progress in the past decades in molecular biology, materials science and nanoparticle technology, that nanoparticles of biodegradable polymers have

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[36] Feng S. S. (2004). Nanoparticles of Biodegradable polymers for new-concept chemotherapy. Expert Rev. Medical Devices 1 (1), pp.115-125.

[37] Feng SS, Chien S. (2003), Chemotherapeutic engineering: application and further development of chemical engineering principles for chemotherapy of cancer and other diseases. Invited review. Chem. Engr. Sci. 58, 4087-4114.

great potential to provide an ideal solution for most of the major problems encountered in chemotherapy and with further development, to promote a new concept of chemotherapy, which may include sustained chemotherapy controlled and targeted chemotherapy, personalized chemotherapy, chemotherapy across various physiological drug barriers such as the GI barrier for oral chemotherapy and the BBB for treatment of brain tumors and other CNS diseases, and eventually, chemotherapy at home. Chemotherapy will become safer, more efficient and eventually under full control. The quality of life of the patents can then be greatly improved. While tissue engineering is thought to be likely to change the traditional concept of surgery, chemotherapeutic engineering should be of potential to substantially change the current practice of internal medicine.

Development of effective carriers for both existing and newly developed anticancer drugs may be as important as the discovery of new anticancer drugs.

There has been intense research over the past decade into the development of nanoparticles of biodegradable polymers as effective drug delivery systems for chemotherapy. Progress in nanoparticle technology, material science and engineering, and cellular and molecular physiology and pathology has contributed to the advancement in nanopsrticle technology for chemotherapy. The polymers used are biocompatible and biodegradable, either synthesized or natural, which are subject to FDA approval. The drug can either be dispersed in the polymeric matrix, or conjugated/attached to the polymer molecules. Following administration, the drug can be released from the nanoparticles. The drug release mechanism can be diffusion, polymer matrix swelling, polymer erosion and degradation. For most FDA-approved biodegradable polymers, which have bulk erosion properties, drug diffusion and polymer matrix swelling play a major rule since the degradation of these polymers is relatively slow, often occurring over a year or so. However, more and better

polymers of surface erosion properties or hydrophilic components are being developed, where polymer erosion/degradation can play a primary role. No other adjuvant is required. The drug encapsulated in the nanoparticles will gradually be released from the polymer matrix, which will eventually be degraded into harmless molecules such as hydrogen, nitrogen and water. Nanoparticles of biodegradable polymers can be made adequately small to allow intracapillary or transcapillary passage and can be appropriately coated to escape elimination by the reticuloendothelial system, as well as to promote adhesion to and uptake by cancer cells. Nanoparticles for cancer chemotherapy have been extensively investigated in the past decade, including, but not limited to, paclitaxel, doxorubicin and 5-FU.

In addition to drug formulation, nanoparticles of biodegradable polymers can be employed to solve other problems in chemotherapy such as pharmacokinetics, drug toxicity and drug resistance.

Polymeric nanoparticles can be prepared either by dispersion of the polymers or by polymerization of monomers; both approaches involve the use of chemical engineering techniques. Various FDA-approved biodegradable and biocompatible polymers such as polylactic acid (PLA), polylactic-co-glycolic acid (PLGA) and polyepsilon-caprolactone (PCL) are available for this purpose.

NEW DRUG DISCOVERY - BIRTH OF A DRUG*

From the time it leaves the discovery laboratory until it is cleared by the U.S. Food and Drug Administration, a new drug typically follows a series of well-defined steps. Here is an

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* Roche Pharmaceuticals in U. S. (2002). Innovative Research and Development - Birth of a Drug.
Elan Corporation, (2001- 2004). Benefits of Drug Delivery. Dublin, Ireland.

overview of the process that all pharmaceutical companies must follow to file a new compound in the United States.

Development of new treatments in medicine is made possible by the design, conduct and reporting of prospective clinical trials. There are number of early stage and internal development projects for each of the technology platforms which are shown below:

- **Feasibility** – In vitro (laboratory) feasibility study to determine whether, under laboratory conditions, the formulation of the product candidate can be achieved. Laboratory and animal studies are conducted to evaluate the safety and efficacy of the new compound in lower animals, to determine its toxicity and clinical effects.
- **Investigational New Drug Application (IND) –** to receive permission in the U.S. to test the drug on humans, companies, show the results of previous series of animal testing. Further pharmacological and pharmacokinetic experiments then attempt to elucidate the method of action of the drug and suggest appropriate doses for administration to humans.
- **Phase I** - Also called *pre-clinical*, where batches are manufactured for in vivo studies (in humans) in healthy volunteers. This phase involves testing on 20 to 80 normal, healthy volunteers to determine a safe dosage and how the drug is absorbed and metabolized in the human body. Some preliminary dose proportionality data may be obtained. At this phase, the drug development group may set about developing an appropriate dosage form for administration to humans.
- **Phase II** – Also called pre-pivotal trials. Additional in vivo testing my be performed involving in small patient population. In phase II clinical trials, patients, affected by the disease for which the therapeutic indication is being sought, are recruited to gain information on the dose proportionality of the drug, and preliminary efficacy data. It is at this phase that a dosing schedule is usually determined.

- **Phase III** – Also called pivotal trials. Phase III clinical trials are larger programs in which the product is administered to an expanded patient population typically at dispersed sites. All of the improved outcome or new products under development require a phase III trial. To assess the drug's effectiveness, studies are conducted with 1,000 to 3,000 patients, with the disease that the drug has been designed to treat. Physicians monitor patients closely to confirm the drug's efficacy and identify adverse reactions. The purpose is to determine the safety and effectiveness of the drug when compared with a placebo or an established product on the market.
- **Commercial Manufacturing -** In parallel with Phase II and Phase III trials, development work is usually undertaken to scale up the production of the prototype dosage forms developed in the laboratories.
- **New drug Application (NDA) – Filed.** Data from all phases are analyzed and findings (if positive) are compiled and filed with the FDA. Company (which initially develops original production) file for regulatory approval in jurisdiction in which it is intended that the product will be marketed. For example, in USA, this will require filing with the FDA.
- **FDA Advisory Review -** An independent panel of experts appointed by the FDA reviews the NDA, considers presentations by company representatives and FDA reviewers, then makes a recommendation to the FDA. The FDA may or may not follow that recommendation.
- **Labeling Discussions -**Companies work with the FDA on the specific wording for the product label, which provides the essential information needed by a physician to prescribe a drug properly.
- **Registration -** Information collected throughout the discovery and development process is forwarded to a government regulatory agency (FDA, in the United States) for a complete review. The agency determines, sometimes with the help of a

committee of experts, whether the company submitting the file has made a case for use of the drug in patients for specific diseases. In particular, the FDA will look for statistical and clinical evidence that the drug is effective, often compared to drugs currently used in the market, and most importantly, that it is safe for use in the indication which has been studied. If the company has shown this convincingly, the drug will then be approved.

- **Approval**– Approved by the relevant regulatory authority.
- **Phase IV – Marketed.** Product is available in the market. Once a drug has been cleared for marketing, the new medicine is made available to physicians to prescribe. Once marketed, further clinical studies may be undertaken to compare the market potential or cost-effectiveness of the new drug with established market leaders, or in other therapeutic areas for which marketing claims are not sought. These studies are usually termed "Phase IV trials," and they are used to position the product in the marketplace and facilitate acceptance of the new drug among the medical community. Phase IV studies are often undertaken to answer questions posed by regulatory authorities and thought leaders. The company must continue to submit periodic reports to FDA, including any cases of adverse reactions.

DRUG DELIVERY SYSTEMS

Devices capable of bypassing biological barriers to deliver therapeutic agents with accurate timing and at locally high concentrations directly to cancer cells will play a critical role in the development of novel therapeutics.

Drug delivery and targeting systems under development aim to minimize drug degradation and loss, prevent harmful side effects and increase the availability of the drug at the disease site. Drug carriers include micro and nanoparticles, micro and

nanocapsules, lipoproteins, liposomes, and micelles, which can be engineered to slowly degrade, react to stimuli and be site-specific. Targeting mechanisms can also be either passive or active. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumors as a result of the differences in the vascularization of the tumor tissue compared with healthy tissue. Active targeting involves the chemical 'decorating' of the surface of drug carriers with molecules enabling them to be selectively attached to diseased cells.

The controlled release of drugs is also important for therapeutic success. Controlled release can be sustained or pulsatile. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate, by diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often preferred, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g. exposure to light, changes in pH or temperature).

Other nano-based approaches to drug delivery are focused on crossing a particular physical barrier, such as the blood-brain barrier; or on finding alternative and acceptable routes for the delivery of a new generation of protein-based drugs other than via the gastro-intestinal tract, where degradation can occur. Nanoscience and nanotechnology are thus the basis of innovative delivery techniques that offer great potential benefits to patients and new markets to pharmaceutical and drug delivery companies.

For over 20 years, researchers in Europe have used nanoscale technology as the basis of vast improvements in drug delivery and targeting, and Europe is now well placed to build on this body of knowledge[38].

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[38] European Technology Platform on NanoMedicine. Nanotechnology for Health. Vision Paper and Basis for Strategic Research Agenda for NanoMedicine. European Commission. September 2005.

BENEFITS OF DRUG DELIVERY

There is enormous potential for nanotechnology to be applied to gene and drug delivery. The vehicle might be a functionalized nanoparticle capable of targeting specific diseased cells, which contains both therapeutic agents that are released into the cell and an on-board sensor that regulates the release. Different stages of this approach have already been demonstrated, but the combined targeting and controlled release have yet to be accomplished. In this event the way will be opened up for initial trials, and the eventual approval of such techniques will be fully regulated as for any new pharmaceutical.

A related approach already in use is that of polymer-based drug therapies: they include polymeric drugs, polymer–drug conjugates, polymer–protein conjugates, polymeric micelles to which the drug is covalently bound, and multi-component complexes being developed as non-viral vectors for gene therapy. Many of these materials are now undergoing clinical trials for a variety of disease states[39].

Polymeric nanoparticle have advantages over liposomes and micelles and the polymer-based drug delivery systemss (DDS) have relatively shorter history . It is thus clear that more and better results for polymer synthesis nanoparticle formulation and characterization and *in vitro* and *in vivo* experiments, are needed for nanoparticles of *biodegradable polymers to be approved for clinical trials as a DDS* for chemotherapy of cancer and other diseases such as cardiovascular restenosis. It is most likely that clinical trials of nanoparticles for chemotherapy could be approved and would be under intensive investigation if and only if close collaborations between oncologists and biomedical engineers have

[39] The Royal Society & The Royal Academy of Engineering (2004), Nanoscience and nanotechnologies: opportunities and uncertainties, Bulletin: Nanoscience and nanotechnologies.

been established. It is probable that nanoparticles of biodegradable polymers will become commercially available as a medical device in the next 5-10 years[40].

HISTORICAL PERSPECTIVE OF DRUG DELIVERY SYSTEMS[41]

The concept of polymeric DDS was first introduced in the early 1960s by Folkman and Long[42]. In the 1970s, the long-term controlled release of contraceptive steroids, narcotic antagonists, local anesthetics, antimalarial and anticancer agents were mainly investigated to attain potentiation of the pharmacological activities and elimination of the inconvenience of repeated injections. Thereafter, in the late 1980s, biodegradable polymers were investigated intensively for those peptides and proteins to both achieve satisfactory efficiency and increase patient compliance. Primarilyin vitro studies DDS investigated for various applications. Brem et al.[43] reported the delivery of nitrosourea carmustine (BCNU) from biodegradable polyanhydride disks. The DDS can be either biodegradable by using degradable polymers such as poly(lactide-co-glycolide) (PLGA),[44, 45, 46, 47, 48] fibrin,[49] and

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[40] Feng S. S. (2004). Nanoparticles of Biodegradable polymers for new-concept chemotherapy. Expert Rev. Medical Devices 1 (1), pp.115-125.

[41] Cao, X. (1997). Delivery of Neuroactive Molecules from Biodegradable Microsperes. M.A. Sc. Degree thesis. University of Toronto.

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[45] Yamakawa, I., Tsushima, T., Machida, R., Watanabe, S. (1992). In vitro and in vivo release of poly (DL-lactic acid) microspheres containing neurotensin

bovine serum albumin; or biostable by using non-biodegradable polymers such as poly(ethylene oxide) (PEO) and ethylene-vinyl acetate copolymer (EVAc). Injectable and biodegradable microspheres appear to be a particularly ideal delivery systems because they are small and they degrade, obviating the necessity to remove the device after the drug supply is exhausted.

Microspheres and microcapsules

Microspheres are fine spherical particles that contain drugs that can be divided into two categories: (i) homogeneous or monolithic microspheres in which the drug is dissolved or dispersed throughout the polymer matrix and (ii) reservoir-type microspheres in which the drug is surrounded by the polymer matrix in a mononuclear state. Particles belonging to (i) and (ii) are referred to as microspheres and microcapsules, respectively. There is, however, no clear-cut between these two, because the morphological structures are sometimes mixed. For example, in some systems, most of the drug core is surrounded by the polymer but some drug molecules are dispersed separately or adsorbed on the surface of the polymer.

Types of Copolymers - Poly (lactide/glycolide). Linear polyesters of lactide (PLA) and glycolide (PGA) have been used

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analogue prepared by novel oil-in-water solvent evaporation method, J. Pham. Sci., 81, 808-811.

[46] Gupta, P.K., Johnson, H., Allexon, C. (1993). In vitro and in vivo evaluation of clarithromycin/poly(1actic acid) microspheres for intramuscular drug delivery, J. Controled Release, 26, 229-238.

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Polyactides and related polyesters, J. Controlled Release, 17, 1-22.

[48] Arshady, R. (1990). Biodegradable microcapsular drug delivery systems: manufacturing methodology, release control and targeting prospects, J. Bioactive Compatible Polymers, 5, 315-342.

[49] Ho, HO., Hsiao, CC., Sokoloski, T. D., Chen, CY., Sheu, MT. (1995). Fibrin-based drug delivery systems, the evaluation of the release of macromolecules from microbeads, J. Controlled Release, 34, 65-70.

for more than three decades for a variety of medical applications[50]. They were among the first synthetic degradable polymers to find application as surgical suture materials, controlled drug release devices, as well as orthopedic and reconstructive implants[51]. Low molecular weight PLA and PGA are prepared by the direct condensation of lactic acid and glycolic acid, respectively, whereas poly(lactide-co-gtycolide) (PLGA) is obtained by the condensation of both lactic and glycolic acids with or without catalysts. High molecular weigh polymers are produced by the ring opening method with a catalyst such as dialkyl zinc. Having an asymmetric carbon atom, lactic acid has two optical isomers. Therefore, its polymer consists of L-, D- and D, L- lactic acid in which the L- or D-polymers have a crystalline form and D, L- polymers are amorphous and more rapidly degraded.

Degradation of PLA, PGA, PLGA copolymers has been studied extensively both *in vitro* and *in vivo*. Degradation can be followed by changes in mass, molecular weight, morphology, mechanical strength. It has been shown that the degradation of PLA, PGA, PLGA is due to the hydrolysis of the ester bonds along the backbone of the polymer chains, and the degradation products are carboxylic acids and alcohols.

Once a polymer device is immersed into water, the first event that happens is water uptake. This results in the bulk water penetration throughout the polymer's amorphous domains whereas crystalline domains remain intact because they are less accessible to water. Due to the hydrolysis of the ester bonds along the polymer chain, the molecular weight of the degrading polymer decreases. As the degradation time increases, some of the degraded

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[50] Domb, A. J. (1994). Implantable biodegradable polymers for site-specific drug delivery in "polymeric site-specific pharmacotherapy" (A.J. Domb, Ed.), John Wiley & Sons Ltd.

[51] Menei, P., Benoit, J. P., Boisdron-Celle, M., Fournier, D., Mercier, P., Guy, G. (1994). Drug targeting into the central nervous system by stereotactic implantation of biodegradable microspheres, Neurosurgery, 34, 1058-1064.

polymers are cleaved so small that they eventually become water soluble and leach out of the polymer matrix, resulting in the mass loss of the degrading device. Random scission of the ester bonds also results in a mechanical strength decay. The water impermeable domains, however, degrade much more slowly, giving rise to a multimodal molecular weight distribution as observed by gel permeation chromatography (GPC) for a degrading semi-crystalline polymer.

In general, factors that affect water uptake and hydrolysis reaction of the ester bond will affect the degradation of polymers, *i.e.* chemical structures, degree of crystailinity, molecular weight, degradation conditions *(e.g.* pH and temperature) and the size of degrading device.

Furthermore, two phenomena are of critical importance in considering the degradation of PLGA. First, degradation causes an increase in the number of carboxylic acid chain ends that are known to autocatalyse the ester bond hydrolysis. Second, only oligomers which are water soluble in the surrounding aqueous medium can escape from the matrix. It therefore can be predicted that during degradation, soluble oligomers that are close to the surface can leach out once they are produced, whereas those which are located well inside the matrix may remain entrapped and contribute to the autocatalytic effect. The autocatalytic effect, in turn, results from the production of the carboxylic acid groups, resulting in faster degradation. This ultimately results in a steep mass loss observed in the PLGA degradation profile. A subsequent sudden release of degradation products *in vivo,* can render a sudden local environment acidic and induce an inflammatory reaction or even tissue necrosis. Recum et al. successfully employed a blend of different molecular weight PLAs to address this problem.

Biocompatibiliiy

PLA, PGA, PLGA have good biocompatibility and now are being used clinically in human therapy, such as sutures and bone

fracture devices. Visscher et al. studied the tissue reaction to PLGA (50:50) microspheres by injecting the microspheres intramuscularly. There was no inflammatory reaction to the microspheres after 56 days of injection when microspheres were completely absorbed, although a few foreign body cells and the encapsulation of microspheres by immature fibrous connective tissue were observed in the first several days after injection. It was concluded that PLGA (50:50) is a biocompatible material. Another experiment was conducted by Menei et al. in an attempt to extend the application of degradable PLGA polymers into neurosurgery. The brain tissue's reaction to the injected PLGA (50:50) microspheres was investigated. PLGA (50:50) microspheres were stereotactically injected into the rat brain. An astrocytic proliferation, which is typically found following damage to the CNS was observed, and some foreign-body giant cells were also found. However the inflammatory and macrophagous reaction decreased dramatically after 2 month and almost disappeared after 2 months when the microspheres were totally degraded. They concluded that PLGA (50:50) is a biocompatible material for implantation in the brain.

CHEMICAL SYNTHESES OF BIODEGRADABLE POLYMERS [52]

One of the strategies to solve problems of global environmental pollution with fossil resources wasted products is thorough recycling of polymeric materials. In such cases it would be indispensable to use biodegradable polymers, one way of their recycled is by microorganisms without consumption of thermal energy.

[52] Okada, M. (2002). Chemical syntheses of biodegradable polymers. Progress in Polymer Science N 27, p. 87-133.

Biodegradable polymers are defined as polymers that are degraded and catabolized, eventually to carbon dioxide and water, by microorganisms (bacteria, fungi, etc.) under natural environment. These polymers, when they are degraded, should not generate any substances that are harmful to the natural environment. Biodegradable polymers are classified into three major categories: (1) polyesters produced by microorganisms, (2) polysaccharides and other biopolymers, (3) synthetic polymers, particularly aliphatic polyesters. Synthetic biodegradable polymers have a great advantage, since recent advances in polymer science and technology have made it possible to design and synthesize at will a great variety of polymers with desirable properties. Furthermore, they are adaptable for mass production. As to synthetic biodegradable polymers, aliphatic polyesters are the representatives. Nowadays, aliphatic polyesters such as poly(epsilon caprolactone), poly(L-lactide), poly(butylene succinate) are commercially produced, and their output continues to increase.

Polyesters from lactides

Polylactides are widely used for medical purposes such as sutures, fracture fixation, oral implant, and drug delivery microspheres. Polylactides including polyglycolide are hydrolyzed at a relatively high rate even at room temperature and neutral pH without any help of enzymes if moisture is present, are hydrolyzed in our body to the respective monomers and oligomers that are soluble in aqueous media, and hence they are often called bioabsorbeble polymers rather than biodegradable polymers. Poly(lactic acid) (PLA) and its copolymer with glycolic acid (PLG) have increasing importance also as materials for the preparation of microspheres. The knowledge of their degradation process is important to prepare microparticulate delivery systems with suitable drug release rates. Giunchedi et al.[53] studied the

[53] Giunchedi P, Coni B, Scalia S, Conte U. J. (1998). Controlled Release; 56:53.

degradation of a poly(D,L-lactide-co-glycolide) (50:50) (PLGA). They showed that the preparation methods play an important role in determining the degradation behavior of microspheres: the unloaded spray-dried particles were characterized by a higher monomer release rate than the microspheres obtained by solvent evaporation.

MARKET VIEW OF COMMERCIALLY AVAILABLE BIODEGRADABLE POLYMERS [54]

The Roadmap Report was made in connection with the European project "Development of Advanced Technology Roadmaps in Nanomaterial Sciences and Industrial Adaptation to Small and Medium sized Enterprizes" ("NanoroadSME") by authorship of *René de Groot* (Syntens – Stiching Syntens, Innovation Network for Entrepreneur, Netherland) and *Dr. Jonathan Loeffler* (Steinbeis-Europa-Zentrum, Germany). The project was funded by the European Community under the "Sixth Framework" Programme (Contract No MP4-CT-2004-505857).

In this Roadmap the focus is on the actual State of the Art and the future use of nanomaterials in the Health & Medical Systems sector. It will give to small and medium sized enterprises (SMEs) a good tool to have a concise description of the development in this sector and to make choices for their strategy. This roadmap report has the main purpose to help SMEs which are in the process of looking for new materials with improved properties to be integrated in their new products and to give them a first list of relevant nanomaterials they should consider depending on the industrial applications foreseen, the time to market and the R&D capacity of the company.

[54] Groot, de R., Loeffler, J., Sutter. S., (2006). Roadmap Report Concerning the Use of Nanomaterials in the *Medical and Health Sector.* The Sixth Framework Programme of European Community.

The results of the roadmap are based on a database with information about more than 100 nanomaterials, which was developed in the frame of the EC-funded project NanoRoadSME. The database and the linked roadmapping tool were structured taking into account the results of a European Survey on more than 300 European SMEs, the results of several R&D surveys and industrial SWOT analysis as well as workshops and experts' interviews.

The report is structured in domains of applications in which nanomaterials have the potential to play an important role in the future in the Medical&Health sector.

Presentation of relevant nanomaterials are presented by drawing 4 tables, which represent the nanomaterial roadmap for the specific domain of application and which give the following information: the level of development of the nanomaterials and a prognosis of its evolution in the next 15 years; the timeframe of possible industrial applications in this domain at short (0-2 years), middle (3-5 years) and long term (6-10 years); the nanomaterial costs and its possible evolution at short, middle and long term (when available); the market size of the nanomaterials (when available).

For each relevant nanomaterial, detailed information like a short material description, improved properties, advantages/disadvantages of the nanomaterial, barriers for the development as well as specific applications for each category are given. Finally a list about companies and organisations (if available) active in the specific areas is presented.

In order to have a quick overview of the development stage of the different nanomaterials and its evolution, five different levels of development were defined:

1. Scientific result / technology invention ;
2. Laboratory prototype;
3. Industrial demonstrator;
4. Industrialization;

5. Market entry (ME) – the final stage in the development process. The material is now ready available for the end consumer, probably still not everywhere and at a rather higher price.

These stages of development have different order of importance for SMEs depending to their position in the supply chain of nanomaterials. Three main categories can be defined: developer of nanomaterials; producer of nanomaterials; user of nanomaterials.

Marketing description of poly-lactic-co-glycolic acid (PLGA) nanofibers

Polymer nanofibers, nanocapsules and nanofilms with good chemical and mechanical properties, used for tissue engineering and drug delivery.

Description of material properties which have been improved:

The morphology of the electrospun nanofibers can change with the spinning conditions, forming droplets when the concentration of the polymer solution is low.

Advantages: biodegradable; biocompatible; flexibility for nanofibers and nanofilms, nanostructured PLGA enhances cell proliferation and adhesion.

Disadvantages: high collagen type I proliferation but not so high with collagen type II or III; fabrication of PLGA complexes is needed in these cases.

Barriers for the development:

1. Technology - PLGA based materials should be further developed for specific tissues to enhance its properties.

2. Market - Many other new materials with similar applications.

3. Regulatory - Investigation in different mammals must be done before using any products in humans, although many other PLGA experiments have already been done.

4. Environmental impacts - Effects of small nanoparticles entering the human body and accumulating in the cells of the respiratory or other organ systems are yet unknown.

Table 1. Level of development of the PLGA and a prognosis of its evolution in the next 15 years in the drug delivery and tissue engineering sectors.

	Short term 2006-2012	Middle term 2013	Long term 2014-2020
poly-lactic-co-glycolic acid (PLGA) nanofibers		**Market Entry**	

Table 2. Possible industrial applications of the PLGA in the drug delivery and tissue engineering sectors in dependence of a short (0-2 years), mid (3-5 years) and long term (5-10 years) view.

	Unspecified	0 -2 years	3 -5 years	6 -10 years
poly-lactic-co-glycolic acid (PLGA) nanofibers		**drug delivery nanocapsules and nanospheres, nanofibers scaffold**	**nanofibers hoses**	

Table 3. Expected market size and material costs until poly-lactic-co-glycolic acid (PLGA) nanofibers 2015.

	Short term			Middle term			Long term		
	2006	2007	2008	2009	2010	2011	2012	2013	2014
Market size poly-lactic-co-glycolic acid (PLGA) nanofibers	**~250 tons/year**			**~500 tons/year**			**~2500 tons/year**		
Material costs poly-lactic-co-glycolic acid (PLGA) nanofibers	**~37000 Euro per Kg**			**~33000 Euro per Kg**			**~29000 Euro per Kg**		

NANO- AND MICROPARTICLES AS CONTROLLED DRUG DELIVERY SYSTEMS [55]

Nano- and micro- particles and microspheres for their attractive properties occupy unique position in drug delivery technology. Some of the current trends in this area will be discussed.

The solvent evaporation process is commonly used to encapsulate drugs into poly(lactide-co-glycolide) microparticles (PLGA) [56]. It is well known that the candidate drugs must be soluble in the organic phase. In the case, where the active ingredient is not oil soluble, other alternative can be considered. The W/O/W-multiple emulsion method is particularly suitable for the encapsulation of highly hydrophilic drugs. For drugs which are slightly water soluble, like IdUrd (2mg/ml), other approaches must be investigated to achieve significant encapsulation: dissolution of the drug in the organic phase through the use of a cosolvent or dispersion of drug crystals in the dispersed phase. In the latter case, it is often admitted that the suspension of crystals in the organic phase can lead to an initial drug release, which is difficult control [57, 58]. To reduce IdUrd particle size, two-grinding processes

[55] Ravi Kumar, M. N. V. (2000). Nano and Microparticles as Controlled Drug Delivery Devices, J Pharm. Pharmaceut. Sci, 3(2):234-258.

[56] Benoit, J. P., Marchais, H., Rolland, H. and Van de Velde, V. (1996). Biodegradable microspheres: advances in production technology. In: Benoit, S. (Ed.), Microencapsulation methods and industrial applications, Marcel Dekker, New York, pp. 35-72.

[57] Bodmeir, R., Chen, H., Davidson, R. G. W. and Hardee, G. E. (1997). Microencapsulation of antimicrobial ceftiofur drugs. Pharm. Dev. Technol., 2: 323-334.

[58] Shenderova, A., Burke, T. G. and Schwendeman, S. P. (1997). Stabilization of 10-hydroxycampto- thecin in poly(lactide-co-glycolide) microsphere delivery vehicles. Pharm. Res., 14: 1406-1414.

were used, spray-drying and planetary ball milling [59, 60, 61]. The optimal conditions of grinding were studied through experimental design and the impact on in vitro drug release from PLGA microspheres was then examined. More recently, Geze et al [62], studied IdUrd loaded poly(D,L-lactide-co-glycolide) (PLGA) microspheres with a reduced initial burst in the in vitro release profile, by modifying the drug grinding conditions. IdUrd particle size reduction has been performed using spray drying or ball milling. Spray drying significantly reduced drug particle size with a change of the initial crystalline form to an amorphous one and lead to a high initial burst. Conversely, ball milling did not affect the initial Id Urd crystallinity. Therefore, the grinding process was optimized to emphasize the initial burst reduction. The first step was to set qualitative parameters such as ball number, and cooling with liquid nitrogen to obtain a mean size reduction and a narrow distribution. In the second step, three parameters including milling speed, drug amount and time were studied by a response surface analysis. The interrelationship between drug amount and milling speed was the most significant factor. To reduce particle size, moderate speed associated with a sufficient amount of drug (400-500 mg) was used. IdUrd release from microparticles prepared by the O/W emulsion/extraction solvent evaporation process with the lowest crystalline particle size (15.3 μm) was studied to overcome

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[62] Geze, A., Verier-Julienne, M. C., et al. (1999). Development of 5-iodo-2'-deoxyuridine milling process to reduce initial burst release from PLGA microparticles. Int. J. Pharm., 178: 257-268.

burst effect. In the first phase of drug release, the burst was 8.7% for 15.3 mm compared to 19% for 19.5 μm milled drug particles (Geze et al).

In the other procedure, Rojas et al.[63] optimized the encapsulation of β-lactoglobulin (BLG) within PLGA microcaparticles prepared by the multiple emulsion solvent evaporation method. The role of the pH of the external phase and the introduction of the surfactant Tween 20, in the modulation of the entrapment and release of BLG from microparticles, was studied. Better encapsulation of BLG was noticed on decreasing the pH of external phase to a value close to the PI of BLG, however, a larger burst release effect. In contrast, the addition of Tween 20 increased the encapsulation efficiency of BLG and considerably reduces in the burst release effect. In addition, Tween 20 reduced the number of aqueous channels between the internal aqueous droplets as well as those communicating with the external medium. Inventors claimed that these results constitute a step ahead in the improvement of an existing technology in controlling protein encapsulation and delivery from microspheres prepared by the multiple solvent evaporation method (Rojas et al).

Blanco-Prieto et al.[64] studied the in vitro release kinetics of peptides from PLGA microspheres, optimizing the test conditions for a given formulation, which is customary to determine in vitro/in vivo correlation. The somatostatin analogue vapreotide pamoate, an octapeptide, was microencapsulated into PLGA 50:50 by spray drying. The solubility of this peptide and its in vitro release kinetics from the microspheres were studied in various test media. The solubility of vapreotide pamoate was approximately

[63] Rojas, J., Pinto-Alphandary, H., et al, Optimization of the encapsulation and release of β-lactoglobulin entrapped poly(D,L-lactide-co-glycolide) microspheres. Int. J. Pharm., 183: 67-71, 1999.

[64] Blanco-Prieto, M. J., Bewsseghir, K., et al. (1999). Importance of the test medium for the release kinetics of a somatostatin analogue from poly(D,L-lactide-co-glycolide) microspheres. Int. J. Pharm., 184: 243.

20-40 μg/ml in 67 mM phosphate buffer saline (PBS) at pH 7.4, but increased to 500-1000 μg/ml at a pH of 3.5. At low pH, the solubility increased with the buffer concentration (1-66 mM). Very importantly, proteins (aqueous bovine serum albumin (BSA) solution or human serum) appeared to solubilize the peptide pamoate, resulting in solubilities ranging from 900 to 6100 μg/ml. The release rate was also greatly affected by the medium composition. The other results are, m PBS of pH 7.4 only 33+1% of the peptide was released within 4 days, whereas, 53+2 and 61+0.95 were released in 1% BSA solution and serum respectively. The type of medium was found critical for the estimation of the in vivo release. From their investigations, it was concluded that the in vivo release kinetics of vapreotide pamoate form PLGA microspheres following administration to rats were qualitatively in good agreement with those obtained in vitro using serum as release medium and sterilization by γ-irradiation had only a minor effect on the in vivo pharmacokinetics (Blanco-Prieto et al).

In a recent study from England, methods used to microencapsulate human serum albumin (HSA) in a biodegradable polymer were compared for their effects on the physicochemical characteristics of HSA-loaded microparticles and on the release and integrity of encapsulated HSA. Postemulsification spray-drying enables efficient preparation of high-quality PLGA microparticles for protein drug delivery [65].

"The polymer used was poly(D,L-lactide-co-glycolide) (75:25) (PLGA) (Boehringer Ingelheim, Resomer RG 752, MW 20,900)," noted M.E. Lane et al. at the University of London. "Microparticles were formulated by (i) w/o/w emulsification and

[65] Lane, M.E. et al. (2006). Influence of postemulsification drying processes on the microencapsulation of Human Serum Albumin. International Journal of Pharmaceutics; 307(1):16-22.

freeze-drying (EFD) or (ii) w/o/w emulsification and spray-drying (ESD)."

In the Department of Chemical and Biomolecular Engineering, National University of Singapore, was conducted other study: Fabrication of controlled release devices using supercritical antisolvent method[66]. Supercritical antisolvent with enhanced mass transfer (SASEM) method is used to process biodegradable and biocompatible polymer PLGA (poly DL lactic co glycolic acid) in an attempt to fabricate micro or nano sized particles for encapsulation of drugs for purposes of controlled release. In this process, an ultrasonic vibrating surface provides the liquid atomization in the supercritical fluid medium. The ultrasonic vibration also creates turbulence in the supercritical phase and enhances the mixing and mass transfer between the organic solvent and supercritical antisolvent. The setup has been designed for visualization of the liquid atomization and antisolvent process in the high pressure vessel. PLGA particles obtained from this process are further analyzed using SEM (Scanning Electron Microscopy). Experiments were also carried out to study the droplet size distribution from ultrasonic liquid atomization using a Phase Doppler Particle Analyzer (PDPA).

DRUG DELIVERY TO THE CNS

Due to poor transport across the BBB, when administered by an implantable drug delivery system (DDS) can be delivered directly to the CNS. Moreover, the DDS maintained the drug dosage within a desired therapeutic range for a pre-determined time via a controlled release mechanism. The treatment of infiltrating brain tumors, particularly oligodendrogliomas, requires

[66] Lee, L. Y., Smith, K. A., Wang, C. H., (2005). Fabrication of controlled release devices using supercritical antisolvent method.

radiotherapy, which provides a median survival of 3.5-11 years[67]. Since 5-iodo-21-deoxyuridine (IdUrd) is a powerful radio sensitizer[68], the intracarnial implantation of IdUrd loaded microparticles within the tumor might increase the lethal effects of γ-radiations of malignant cells having incorporated IdUrd. The particles can be administered by stereotactic injection, a precise surgical injection technique[69]. This approach requires microparticles of 40-50 μm in size releasing in vivo their content over 6 weeks, the standard period during which a radiotherapy course must be applied.

IN VITRO STUDY AT C6 GLIOMA CELLS OF ANTICANCER DRUG DOXORUBICIN IN PLGA-BASED MICROPARTICLES[70]

Doxorubicin (DOX), also known as adriamycin, is an anthracycline drug commonly used in cancer chemotherapy. Unfortunately, its therapeutic potential has been restricted by its dose limited cardiotoxicity and the resistance developed by the tumor cells to the molecule after some time of treatment. Like many other drugs used to treat cancer, DOX is a potent vesicant that may cause extravasations and necrosis at the injection site or any site that the skin is exposed to. One way to overcome these problems is to encapsulate the drug in poly (D,L-lactide-*co*-

[67] Daumas-Duport, C., Tucker, M. L., Kolles, J. H., Cervera, P., Beuvon, F. and Varlet, P., Oligodendrogliomas. Part II: a new grading system based on morphological and imaging criteria. J. Neuro-Oncol., 34: 61-78, 1997.

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[70] Lin, R. Ng, LS., Wang, CH., (2005). In vitro study of anticancer drug doxorubicin in PLGA-based microparticles. Biomaterials 26, 4476-4485.

glycolide) (PLGA) microparticles. This paper investigates the release characteristics of DOX from polymeric carriers fabricated using the spray-drying technique. Finally, a cytotoxicity test was performed using Glioma C6 cancer cells to investigate the cytotoxicity of DOX delivered from PLGA microparticles.

PLGAs have different properties according to the variation of lactide and glycolide ratio. Accordingly, an increase in the lactide/glycolide ratio makes the polymer more hydrophobic thus reducing degradation rate. This can be verified by the release curve where the initial burst and release rate decreased by approximately 10% when the lactide/glycolide ratio was increased. Despite the slight improvement in the initial burst and release rate, 70% of the drug was released within the first day.

Particle size also affects the initial burst of the drug. When particle size increases, the initial burst reduces. This is because a smaller particle size has a larger volume-to-surface area. Hence, during particles formation, the low solubility of DOX in EA resulted in the easy exclusion of the drug from the polymer matrix, which resulted in drug accumulation on the particle surface.

Hence, for a smaller particle, more drug accumulates on a smaller surface area hence resulting in a greater initial burst. The biconcave morphology was observed to accelerate the drug release. The morphology change can certainly affect the surface area/volume ratio. Presumably, an increase of this ratio results in the observed acceleration of drug release rate.

CONCLUSIONS

In the study performed in Singapore National University, nano/micro-particulate drug delivery devices were developed for DOX using spray drying. These devices were fabricated using various polymers, namely, PLGA, pluronic and PLLA in the form of polymer blends and composite nano/microparticles. The polymers were used in different combination with the aim of obtaining a device with improved drug release characteristics and enhanced cytotoxicity against cancer cells.

It has been found that the cytotoxicity of DOX to Glioma C6 cancer cells is enhanced when DOX is delivered from PLGA polymeric carrier. The use of a biodegradable polymer matrix, whith encapsulated DOX, reduces the toxic effects against normal cells whilst increasing its therapeutic activity.

RESULTS OF PHASE II CLINICAL TRIALS WITH USE OF IMPLANTABLE 5-FU-BIO-MICROPARTICLES [71,72,73]

The group of French scientist (Faisant, N., Benoit, J. P., Menei, P.) received patent in May, 2006. Title is: "Use of Biodegradable Microspheres That Release an Anticancer Agent for Treating Gliobastoma". United States Patent No 7,041,241. United States Patent and Trade Mark Office. This is successful achievement after conducting of series of experiments during more then decade.

The present invention relates to the use of biodegradable microspheres that release a radiosensitizing anticancer agent for producing a medicament to be used simultaneously with, separately from or spread over time with a radiotherapy, for treating glioblastoma. The use of said biodegradable microspheres according to the invention results in a patient survival time of at

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[71] Menei, P., Venier, M. C., Gamelin, E., Saint-André, J. P., Hayek, G., Jadaud, E., Fournier, D., Mercier, P., Guy, G., Benoit, J. P. (2000). Local and sustained delivery of 5-fluorouracil from biodegradable microspheres for the radiosensitization of glioblastoma. A pilot study. Cancer V. 86, 2 , P. 325 – 330.

[72] Menei, P., Jadaud, E., Faisant, N., Boisdron-Celle, M., Michalak, S., Fournier, D., Delhaye, M., Benoit, J. P., (2003). Stereotaxic implantation of 5-fluorouracil-releasing microspheres in malignant glioma. A Phase I study. Cancer, V. 100, 2 , P. 405 – 410.

[73] Menei, P., Capelle, L., Guyotat, J., Fuentes, S., Assaker, R., Bataille, B., Francois, P., Dorwling-Carter, D. Paquis, P., Bauchet, L., Parker, F., Sabatier, J., Faisant, N., Benoit, J. P. (2005). Local and Sustained Delivery of 5-Fluorouracil from Biodegradable Microspheres for the Radiosensitization of Malignant Glioma: A Randomized Phase II Trial. Neurosurgery. 56(2):242-248.

least 90 weeks, a therapeutically effective concentration being maintained in the parenchymatous area throughout this time. The microspheres used preferably contain 5-fluorouracil of the tumor, by intratissular injection. The radiotherapy targeting the tumorous mass is dosed at 60 Gy over approximately 6 weeks. The invention also relates to a method for producing the biodegradable microspheres by emulsion-extraction, and to a suspension containing the biodegradable microspheres obtained using this method (Boisdron-Celle, M., Menei, P., Benoit, J. P. (1995). "Preparation and Characterization of 5-Fluorouracil-loaded Microparticles as Biodegradable Anticancer Drug Carriers," J. Pharm. Pharmacol., 47:108-114.).

The polymer is preferably poly(D,L-lactic acid-co-glycolic acid), or PLGA, which is a biodegradable polymer permitted in the formulation of sustained-release galenic preparations. The poly(D,L-lactic acid-co-glycolic acid) is preferably 50:50 PLGA (i.e. containing an equal amount of lactic acid and of glycolic acid).

This study was a phase I/II open pilot clinical trial comparing the effect of perioperative implantation of 5-fluorouracil-releasing microspheres followed by radiotherapy in patients with gross total resection of high-grade glioma.

RESULTS

The preliminary results regarding survival could not be interpreted statistically due to the small number of patients. They were, however, very encouraging. At the final assessment, in the first group treated (70 mg), the three patients died at 61, 114 and 125 weeks. It should be noted that the patient who died at 114 weeks died of pulmonary metastases of the glioblastoma. In the second group treated (132 mg), three patients died at 31, 59 and 82 weeks and two were still in remission at 159 and 172 weeks, at the date of drafting of these preliminary results.

The survival median for the patients is 98 weeks (it is 50.6 weeks in the literature for patients satisfying the same criteria

(Devaux et al, 1993)[74]. Five out of eight patients, i.e. 62%, were alive at 18 months, whereas, in the literature, for patients satisfying the inclusion criteria of this study, the survival at 18 months is 20% (Devaux et al, 1993).

CONCLUSIONS

1. Nanotechnology provides wide opportunities to modify basic chemotherapeutic drugs, some of them are under investigation at different stages of pre-clinical and clinical trials.
2. The thorough survey of the appropriate literature revealed, that recently has been finished 2nd phase clinical trials in neurooncology with the use of 5-FU embedded in PLGA microsperes and entering 3rd phase of clinical trials. Scientist from France received patent in May 2006 by USPTMO (United States Patent and Trade Mark Office).

GUIDELINES FOR NEURO-ONCOLOGY - STANDARDS FOR INVESTIGATIONAL STUDIES - REPORTING OF CLINICAL TRIALS

Most comprehensive and upgrade guidelines for conduction of 1 and 2 phase clinical trials in neuro-oncology are presented by Chang S. et al (2005)[75]. Authors present guidelines to standardize the reporting of phase 1 and phase 2 neuro-oncology trials. The guidelines are also intended to assist with accurate interpretation of results from these trials, to facilitate the peer-review process, and to expedite the publication of important and accurate manuscripts. Our guidelines are summarized in a checklist format that can be used as a framework from which to construct a phase 1 or 2 clinical trial. Development of new treatments in oncology is made possible by the design, conduct, and reporting of prospective

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[74] Devaux, B. C., O'Fallon, J. R., Kelly, P. J. (1993). Resection, biopsy and survival in malignant glial neoplasms, J. Neurosurg, 78: 767 -775.

[75] Chang, S. M., Reynolds, S. L., Butowski, N., Lamborn, K.R., Buckner, J. C., Kaplan, R. S. and Bigner D.D., (2005): GNOSIS: Guidelines for neuro-oncology: Standards for investigational studies - reporting of phase 1 and phase 2 clinical trials. J. Neuro-Oncology, N 7, pp. 425–434.

clinical trials. The phase 3 randomized, controlled clinical trial is considered to be the "gold standard" of clinical research, providing the most reliable method for comparing standard with experimental therapies. However, most clinical reports in the neurooncology literature are of phase 1 and phase 2 trials, which are required for testing the safety and efficacy of a proposed drug before the initiation of a phase 3 study. Incomplete, unclear, or inaccurate design, interpretation, and reporting of the results from these vital early phase trials can hamper timely drug development and lead to erroneous conclusions as to efficacy (Mariani and Marubini, 2000[76]). Recently, there has been a trend in the scientific community toward the creation of guidelines for increasing the transparency of clinical study results. Some examples of these guidelines include the STARD, or Standards for Reporting of Diagnostic Accuracy, statement for reporting studies of diagnostic accuracy (Bossuyt et al. 2003[77]), the TREND, or Transparent Reporting of Evaluations with Nonrandomized Designs, statement for reporting nonrandomized public health interventions (Des Jarlais et al., 2004[78]), and most familiar, the CONSORT, or Consolidated Standards of Reporting Trials, statement for the reporting of randomized, controlled clinical trials (Altman et al., 2001[79]). The CONSORT statement has particular relevance to neuro-oncology. However, as it deals exclusively with phase 3

[76] Mariani, L., and Marubini, E. (2000) Content and quality of currently published phase II cancer trials. J. Clin. Oncol. 18, 429–436.

[77] Bossuyt, P.M., Reitsma, J.B., Bruns, D.E., Gatsonis, C.A., Glasziou, P.P., Irwig, L.M., Moher, D., Rennie, D., de Vet, H.C., and Lijmer, J.G. (2003). The STARD statement for reporting studies of diagnostic accuracy: Explanation and elaboration. Clin. Chem. 49, 7–18.

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[79] Altman, D.G., Schulz, K.F., Moher, D., Egger, M., Davidoff, F., Elbourne, D., Gotzsche, P.C., and Lang, T. (2001) The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. Ann. Intern. Med. 134, 663–694.

trials, it does not address many important issues that arise in the reporting of phase 1 and phase 2 neuro-oncology trials.

CONSORT, or Consolidated Standards of Reporting Trials, statement is an important research tool that takes an evidence-based approach to improve the quality of reports of randomized controlled clinical trials. Its critical value to researchers, health care providers, peer reviewers, and journal editors, and health policy makers is the guarantee of integrity in the reported results of research. CONSORT comprises a checklist and flow diagram to help improve the quality of reports of randomized controlled trials. It offers a standard way for researchers to report trials. The intent is to make the experimental process more clear, flawed or not, so that users of the data can more appropriately evaluate its validity for their purposes.

CONSORT: **Checklist of items to include when reporting a randomized trial (RCT)**

PAPER SECTION And topic	ITEM	DESCRIPTION
TITLE & ABSTRACT	1	How participants were allocated to interventions (*e.g.*, "random allocation", "randomized", or "randomly assigned").
INTRODUCTION Background	2	Scientific background and explanation of rationale.
METHODS Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.
Objectives	5	Specific objectives and hypotheses.
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors).
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.
Randomization --Sequence generation	8	Method used to generate the random allocation sequence, including details of any restrictions (*e.g.*, blocking, stratification)

Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Randomization implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.
RESULTS Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline data	15	Baseline demographic and clinical characteristics of each group.
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat". State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%).
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval).
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.
Adverse events	19	All important adverse events or side effects in each intervention group.
DISCUSSION Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.
Generalizability	21	Generalizability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

ANNOTATED BIBLIOGRAPHY - CHAPTER FIVE

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Shelf Life: The NSTC book program is a service to our members and the books are available whenever they are needed. All books, with the exception of proceedings, remain in print until replaced by an updated version.

Quality Control: Many publishers place the burden of proofreading on the author. Although we request that our authors proofread carefully, we also proof read all manuscripts except those for proceedings (which come to NSTC in camera-ready form). We have full-time copy editors in house who are familiar with nanotechnology and its applications.

Support of the Profession: When a book is purchased from a consortium like us, the revenue is used to foster new programs and products for consortium members. Same we are doing for the development of Nanotechnology community.

Flexibility: Our staff works with authors and editors to accommodate special needs such as modified typesetting systems and unusual formatting.

Distribution: All books are shipped directly from the NSTC office. This means that fulfillment of orders takes place within 48 hours of receipt. The orders do not have to be sent to another location to be filled.

Special Assistance: Because we intend to publish a modest number of books each year, each volume receives the special attention that is often not possible in a large corporation that publishes several hundred books each year. Our publications staff is always available to answer questions and provide specific guidelines.

Rapid Publication: Because we work with authors from an early stage, we are often able to publish books in a relatively short period of time.

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