Nanomedicine

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- Ethical and societal issues

NanoBio-RAISE

The aim of this briefing paper is to provide concise, correct and balanced information to advance public debate among consumers, media, policy makers, producers and researchers as part of the European Commission-funded Nanobio-RAISE project.[1] It results from the combined contributions of natural and social scientists, industrialists, and governmental and public interest organisations across Europe. It is intended to provide information and does not represent the views or policy of the European Commission or any other body.

Introduction

A broad array of present and future research developments are generally lumped together as "nanotechnology." A common feature is only that they are concerned with large and small things where at least some relevant measures are in the nanometre range (10^{-9} to 10^{-7} metres) and thus in the size-range of DNA-molecules or viruses. More stringent definitions require that nanotechnological research be restricted to the scientific investigation and technical exploitation of novel properties that appear discontinuously at the nanoscale: a ton of gold has the same chemical properties as a milligram, but a gold nanoparticle shows interesting and initially surprising new behaviours. This more stringent definition of nanotechnological research remains quite unspecific regarding technological applications: nanotechnology is all that these newly discovered properties and processes might be good for. And here, the imagination runs wild, challenging us to identify and support promising, feasible as well as beneficial short- and medium-term developments.

On first sight, ***nanomedicine*** is the rather more well-defined application of nanotechnology in the areas of healthcare and disease diagnosis and treatment. But here, too, one encounters a bewildering array of programmes and projects. Artificial bone implants already benefit from nanotechnologically improved materials. Nanostructured surfaces can serve as scaffolding for controlled tissue-growth. Of course, all kinds of medical devices profit from the miniaturisation of electronic components as they move beyond micro to nano. This affects diagnostic tools, pace-makers, "cameras in a pill," etc. Nanoparticulate pharmaceutical agents can penetrate cells more effectively as well as being able to cross the blood-brain-barrier. After injecting nanoparticles into tumours, these can be stimulated electromagnetically from outside the body – by emitting heat, the stimulated particles can then destroy the tumour cells. Antibacterial surfaces incorporating photocatalytic or biocidal nanoparticles reduce the risk of infection in doctors' offices and public buildings. Portable testing kits allow for self-monitoring and speedy diagnosis. New contrast agents and visualisation tools provide a closer look at cellular processes. But this, too, is nanotechnology in action: nanoparticulate steroids are introduced into the body's own red blood cells; as the cells die their natural deaths, the steroids are released to the body in very small doses, thus minimising, if not excluding the side-effects of many steroid treatments.[2]

Nanomedical sectors

- Drug delivery
- Biomaterials
- *In vivo* imaging
- *In vitro* diagnostics
- Active implants
- Drugs & therapy

These examples and many more of ongoing developments can be found in various reports on the prospects and promises of nanomedicine. But though these examples are nothing to frown at, nanomedicine has been conceived as a far more ambitious enterprise: "*Nanomedicine comes into being where a molecular understanding of cellular processes is strategically combined with capabilities to produce nanoscale materials in a controlled manner.*"[3] With these greater ambitions comes the formidable challenge to assess more visionary programmes not only for their

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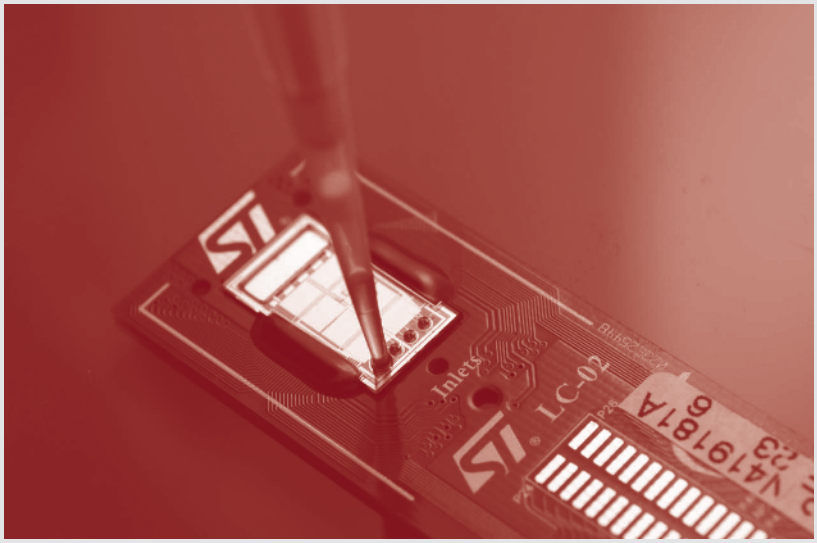


feasibility, but also for the proper balancing of public investment and societal need, and, thus for their likely benefits. These ambitions revolve mainly around the concepts "***theranostics*** (i.e. the combination of diagnosis and therapeutic functionality in one device, enabling pre-symptomatic treatment)", "***polymer therapeutics*** (rational design of nanomedicines)", "***targeted drug-delivery*** (individualised medicine)", "***regenerative medicine*** (cell repair)." The promise associated with these terms is that of therapeutically more effective, individualised, dose reduced and more affordable medicine. Before considering these ambitions and promises one by one, it helps to place them in the larger historical context of the development of nanomedicine.

A Brief History of Nanomedicine

Nanomedicine has been an important part of nanotechnology from the very beginning. And since nanotechnology began as a visionary enterprise, nanomedicine started by applying mainly nanomechanical concepts to the body. In his 1999 book on *Nanomedicine*, Robert Freitas assembled an impressive array of ingenious ideas that derive from ongoing developments and inevitably lead to extravagant speculations.[4] Freitas's conflation of the short-term with the long-term and even with technical impossibilities remains characteristic even of the far more restrained technical papers of today. The 2004 presentation of the cancer nanotechnology initiative in the United States revolves around the goal of *"eliminating death and suffering from cancer by 2015"*.[5] The 2006 European Technology Platform on Nanomedicine is more subtle than this. It speaks of a *"revolution in molecular imaging in the foreseeable future, leading to the detection of a single molecule or a single cell in a complex biological environment."*[6] This statement elegantly glosses over the fact that the problems of detecting molecules and cells are magnitudes apart: Cells are a hundred to a thousand times larger than molecules and it is certainly much easier to imagine a contrast agent or marker attached to or inside a cell. In the same report, the speculative spirit of Eric Drexler and Robert Freitas informs a vision of cell-monitoring and repair: The detection of disease will happen as early as possible and *"ultimately this will occur at the level of a single cell, combined with monitoring the effectiveness of therapy.[7]"*

The most balanced overview of nanomedicine to date is the European Science Foundation's 2006 *Forward Look on Nanomedicine*.[8] It is firmly grounded in current research. As it distances itself from speculation and hype, it seeks to give shape to a nanomedical research agenda that is clearly set apart from the grab-bag of nanotechnologies.[9] In effect, the report drives a wedge between ***scientific nanomedicine*** and something lesser that might be called ***medical nanotechnology***. Nanomedicine is based on molecular knowledge of the human body and it involves molecular tools for the diagnosis and treatment of disease. Medical nanotechnology encompasses all the other ways in which nanotechnology affects health care, especially all that comes from the miniaturisation of devices and the integration of information and communication technologies in diagnostic tools and health monitoring – including a radical transformation of the present day hospital with its traditional doctor-patient relationships.

Nanomedicine, in other words, is disease-centred, trying to do better and on a molecular level what physiology, pathology, and the various specialised medical sciences have been doing so far. Because it is disease-centred, nanomedicine leaves to medical nanotechnologies the more general and perhaps more profound transformations of health care: these concern public health monitoring, the integration of medical practices into daily patterns of work and leisure, the redefinition of the physiological body as a body of data, and the reorganisation of the therapeutic context with its medical experts, insurance companies, state interests, and health-care institutions. By the same token, nanomedicine inherits its focus on certain diseases from ongoing medical research. Accordingly, it is primarily concerned to reduce mortality from non-infectious disease, especially cancer. That is, it aims to incrementally reduce mortality where it is already low, namely in the highly developed world where cancer and coronary disease have become the most prominent physiological causes of death.

Another potential limitation of the narrowly defined nanomedical focus is brought to light by the European Technology Platform: it is explicitly addressed to an increasingly sedentary ageing population and its medical problems. Through the lens of disease-centred nanomedicine, this translates to the treatment of painfully arthritic joints. In a wider perspective, of course, the health of joints involves questions of nutrition, mobility, and an integrated approach to the problem of obesity. The strictly nanomedical alleviation of chronic pain in the joints should be a small part, indeed, of a "treatment package" that includes medical nanotechnologies for monitoring and feedback, along with physical therapy, geriatric and socio-psychological approaches, together with even economic or political incentives for increased exercise, nanotechnologically improved footwear and surfaces.

Theranostics

As distinct from medical nanotechnologies, scientific nanomedicine concentrates on four areas of research and development: theranostics, a new class of pharmaceuticals, targeted drug-delivery, and

regenerative medicine.[10] The prospects and problems of each warrant a brief review.

As indicated by the term "theranostics," its promise consists in the fusion of therapy and diagnostics. As diagnostic capabilities improve, one might come up with treatments well before a disease manifests itself symptomatically. Ideally, diagnosis and treatment could be performed in a single step through a monitoring process that automatically introduces appropriate corrections (e.g., plaque detection and removal for the prevention of cardiovascular diseases). The benefit of beginning treatment before there is a disease depends on the quality of diagnostic information. Here, the lengthy history of gene therapy offers a sobering lesson with its initial, but as yet only partially fulfilled, promise of repairing specific genes that are responsible for specific diseases.

Rather than looking for genetic causes of disease, nanomedical expectations rest on vast improvements in imaging and measuring techniques. Indeed, considerable progress is made on the road towards *in vivo* imaging as well as lab-on-a-chip technologies that simultaneously determine thousands of parameters in a tiny drop of blood. But access to vast amounts of information does not translate automatically into diagnostic capabilities. As with gene therapy, this will happen only in a piecemeal manner and in conjunction with research in bioinformatics or systems biology. Indeed, before we can know whether all the additional physiological information has any diagnostic use, it will have to be obtained in order for bioinformatics and systems biology to construct sufficiently robust models of the highly complex dynamics at the origins of disease – in the hope that these models can one day be operationalised for the diagnosis and treatment of individual patients. Like all basic scientific research, therefore, nanomedicine requires long-term funding strategies. It is only in the long run that one might realise the promised healthcare savings that would result from earlier intervention into the disease process.

Targeted Drug-Delivery

The idea that pharmaceutical agents should be delivered specifically to diseased cells holds the promise of a variety of benefits. Especially if, in addition, the pharmaceutical agent were to be adapted to the cell's genome, these benefits would be grouped under the heading "personalised medicine." However, "individualised medicine" is the more appropriate term since this form of treatment is addressed at a specific disease-process, perhaps an individual genome, but disregards the biographic, cultural, and legal particulars that define a person.

The promise of individualised medicine is that it is efficient. Targeted drug-delivery allows doctors and patients to benefit from small dosages at just the right place and thus from fewer side-effects. Even without having to understand the cause of the disease, medical researchers expect to deal with it just as things start going wrong with the molecular machinery inside the cell. Smaller dosages, early and efficient treatment are finally said to translate into lower health care costs. Of course, as closely as they appear to hang together, it is important to evaluate these various claims for the efficiency of nanomedicine one at a time.[11] Especially the promise of cost-efficiency might send a wrong signal: like all of nanomedicine, this is basic research with an uncertain, though potentially profound impact. It needs public support on its merits and not on the promise of a short- or medium-term return.

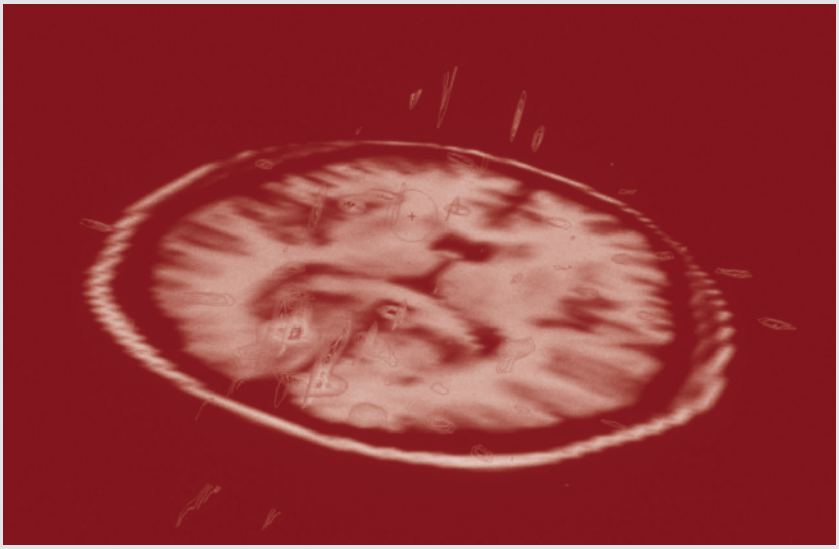
Polymer Therapeutics

The programme of targeted drug delivery requires new nanomedicines which consist of at least two components: one of them the active ingredient, the other a transport device or conjugate that attaches its cargo at the right place.[12] It is this construction of a technical system that combines different functionalities which bring liposomes, polymer-protein conjugates, dendrimers, and other nanoparticles into the realm of nanotechnology proper, as opposed to traditional pharmacology or supramolecular chemistry.[13] Also, it is this modularity which answers nanomedicine's call for "*design on a disease-specific basis.*"

While EU and US reports on nanomedicine emphasise the notion of design, the European Technology Platform takes pains to point out that the relevant design features can be achieved by "*rational design or by high throughput screening or even by a combination of the two.*"[14] Indeed, the ambition to construct nanomedicines is reminiscent of previous programmes of "rational drug design," such as attempts to prevent disease by inhibiting RNA expression and protein formation. If nanomedicine seeks to keep a cautious distance to these programmes, this is because they send a sobering message, having proved unable to compete with randomised high-throughput screening as the far more successful approach to drug development.[15] Similarly, the constructive design ambitions of scientific nanomedicine face a tremendous challenge to master physiological complexity. Under the best of circumstances, it is a matter "only" of packaging an active ingredient with a successful targeting agent. Though their origins predate the advent of "nanotechnology," some nanomedicines have already been approved for routine use and now have to prove themselves in competition with sometimes less expensive alternatives.[16]

If only because of the length of the multi-stage approval process, only time will tell the success-story of nanomedicines. Their definition as designed two-component systems suggests a short-cut, namely to consider them medical devices rather than pharmacological substances, especially

when the active ingredient is already known. Since the approval of medical devices proceeds at a considerably faster pace, this could speed up nanomedical development. In one instance, at least, this route has been chosen successfully. By creating iron oxide nanoparticles that are accumulated by cancer cells and then applying to them an external magnetic field, tumours can be destroyed very effectively. The coated nanoparticles are here taken to be components of a technical device, as parts of the machine that creates the magnetic field and thus induces a vibratory motion in those particles which then leads to the heating and destruction of the tumour. Since the particles are not introduced for their chemical properties or as pharmacologically active agents, they do not need to be regulated as drugs. It is largely because of this that the procedure moved swiftly "From Science to Business in 15 Years."[17]

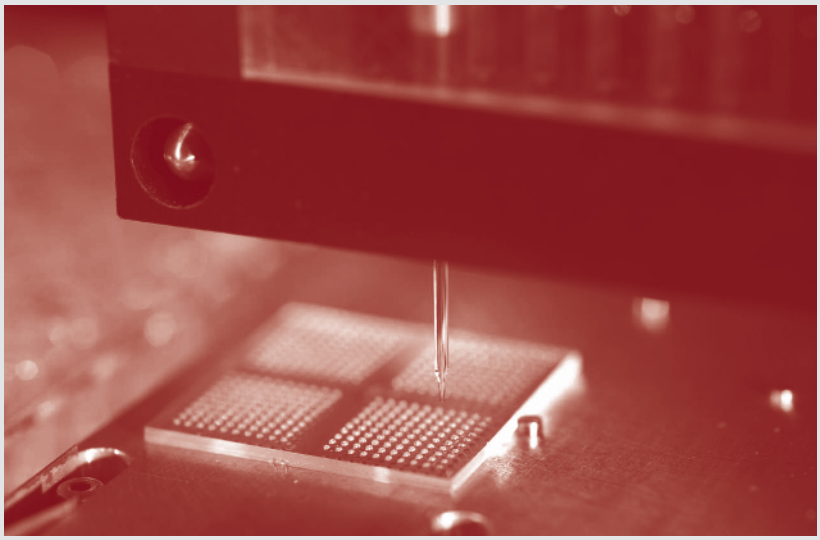


On the other hand, nanoparticulate iron oxide may well pose risks to the patient's health or, after secretion, to the environment. While this risk may be acceptable in the treatment of an otherwise deadly disease, the approval of these iron oxides as drugs may still be called for. The difficulty of this dilemma is illustrated by the recommendation of the European Group on Ethics in its opinion on nanomedicine: "*The mechanism of action is a key factor in deciding whether a product should be regulated as a medicinal product or a medical device.*"[18] In the case at issue, the regulatory question cannot be decided by referring to a matter of fact. It will be contested, after all, what the mechanism of action is: is it the action of the iron oxide particles as components of the device or is it their action in and beyond the human body after destruction of the cancer cells? In its published reports, the nanomedical community generally urges caution and close ethical as well as regulatory review.

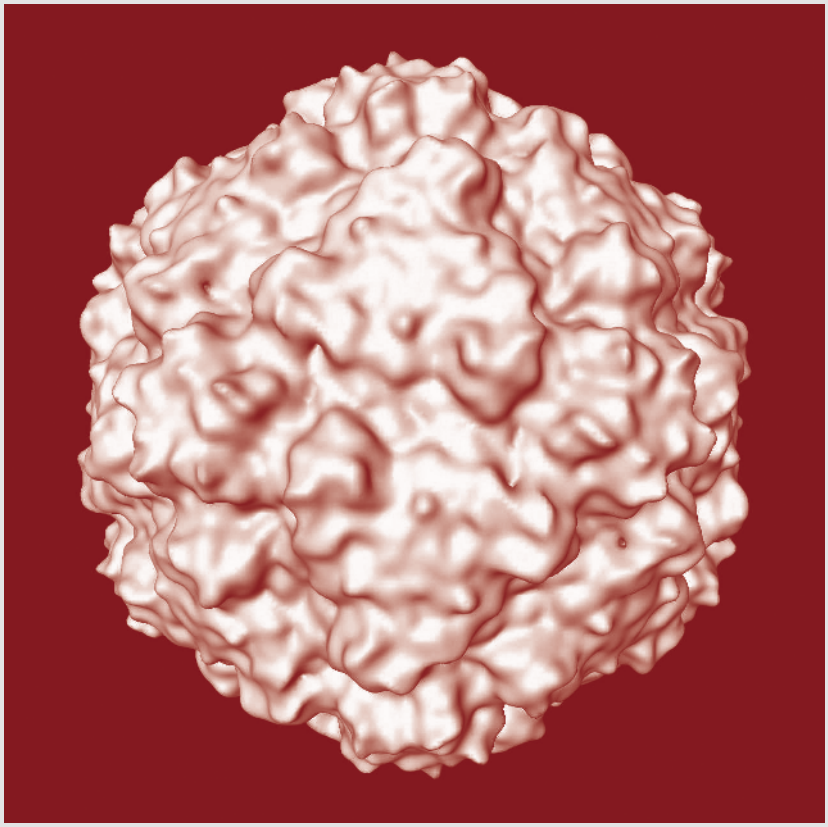
Regenerative Medicine

After diagnostics and theranostics, individualised medicine and the nanomedicines required for it, regenerative medicine remains as the last of nanomedicine's core interests. To be sure, regenerative medicine is not a single discipline but draws together a variety of medium- and long-term technical approaches, ranging from tissue engineering and wound repair all the way to various visions of cell therapy. Since these approaches predate and do not rely on nanotechnology, regenerative medicine should not be subsumed under nanomedicine and one should rather speak of nanomedical contributions to it.[19]

Regenerative medicine aims to strengthen the self-healing processes of the human body either by stimulating or emulating them. In the case of tissue engineering, for example, this might take the form of growing tissue on an external scaffold such that the patient's body recognises it as its own, thus avoiding the need to suppress an immune response. Diabetes patients could be helped by restoring insulin production within the body. Among the most ambitious goals of regenerative medicine is to stimulate the growth and to reconnect severed nerves or to restore neural function in neurodegenerative diseases such as Alzheimer's or Parkinson's. In the words of the European Technology Platform, "*The challenge is to convert this to a reality.*"[20]



To be sure, some would posit even more ambitious goals for regenerative medicine, namely a kind of cell-repair that might prevent, even reverse ageing. Though this idea attracts much attention in popular discourse,[21] it does not occur in the reports of nanomedical working groups. It is important to note this clear demarcation of nanomedical ambitions from speculative visions. However, the more modest aim to understand and treat degenerative disease processes requires a further demarcation: Support of medical research, in general, and nanomedical research, in particular, should be dedicated to the advance of public health and quality of life but not the increase of longevity as an end in itself. Increased average life-expectancies should be considered as nothing but welcome side-effects of improved access to health care and better health maintenance overall. Indeed, some proponents of nanomedicine prematurely anticipate just this side-effect. One of the earliest public documents to acquaint a general audience with nanotechnology singles out as a societal issue that "*longer average lifetimes will*



mean more people on Earth. But how many more people can the Earth sustain?"[22] In a similar vein, the European Technology Platform notes that one large impact of nanomedicine will be "*increased costs of social security systems due to ageing of population.*"[23]

It is important to be clear about the achievable goals of nanomedicine that are in the public interest. Popular fascination with envisioned technologies of life extension does not render longevity a public good. Conversely, before worrying about increased life-expectancy as one of the potential impacts of nanomedicine, one should ensure that nanomedicine gets off the ground and meets the formidable challenge to convert even its more modest ambitions into reality.

As it is converted from vision to reality, the notion of cell repair will be a testing ground for the very idea that cellular processes involve a nanotechnological machinery that can break down and that can also be repaired. This metaphor of nanomachinery has proven productive for understanding cellular mechanisms but it is unclear as of yet how far this metaphor carries when it comes to the precision control of highly complex biological realities.[24] It also leads to the ethical question of whether we may mechanically reduce the human being to a sum of physical traits.[25]

Ethical and societal issues

Traditionally, medical ethics is patient- and treatment-centred rather than research- and disease-centred. In other words, most medical ethics is focused on doctor-patient relations, on end-of-life decisions, on resource-allocation, on treatment choices, informed consent, and the like. Biomedical research becomes significant only as it enters clinical trials. Accordingly, medical ethics has been rather indifferent to the level of medical intervention. While the removal of the causes of disease is generally preferable to symptomatic treatments, it does not appear to matter much whether diseases are addressed at a molecular or cellular or whole-organ level.

As the previous sections indicated, however, the nanomedical research programme raises issues that serve to expand the scope of medical ethics. This concerns, for example, the distinction between drug and device and its regulatory implications. It also concerns the recognition and acknowledgment of limits of knowledge and control, in other words, care to avoid hype and to state achievable goals credibly and responsibly. Regenerative medicine in the service of public health and quality of life should be distinguished from the notion that life-extension is a public good. Finally, nanomedical research raises questions of distributive justice and global equity as major public investments are directed at cancer treatments and thus at attempts further to reduce mortality in developed societies where it is already comparatively low.

Nanomedical ethics should not serve to validate an uncertain future, for example, by assuming too readily an increase of diagnostic powers or an impact on life-expectancy. Instead, it might contribute to public deliberation on the research agenda for nanomedicine. Once one starts questioning its primary focus on cancer and cardiovascular diseases, one might have to consider the very definitions of illness and health and the medicalisation of society. Similarly, one might consider the metaphors we use to describe the human being or the changing boundaries of human bodies as the body's own tissue or insulin, for example, might be generated outside the body or by way of an implanted device.

Conclusion

A 2007 nanomedical bulletin offered the following news item: "*Working with an organic semiconductor, researchers at the University of Arkansas have fabricated and tested two similar but slightly different biosensors that can measure physiological signs. Integrated into 'smart' fabrics – garments with wireless technology – the sensors will be able to monitor a patient's respiration rate and body temperature in real time.*"[26] In many ways, this appears to be nanotechnology at its best and is therefore not at all unique to the University of Arkansas. It is an example of highly interdisciplinary research that integrates functionalities at the nanoscale, namely the otherwise separate nanotechnological fields of point-of-care diagnostics and 'smart' fabrics. This kind of ***medical nanotechnology*** may enable a profound reconfiguration of the relations between doctors, patients, and hospitals. It can also promote the further medicalisation of society, that is, of bringing social behaviours (risk taking, dietary practices, stress and anger) into the realm of medical supervision. These developments are likely to be contested and call for the debate of their ethical and societal implications.

It is unlikely that ***nanomedicine*** will be as transformative. It defines itself as basic medical research, and is application-oriented like all medical research. As such, nanomedicine can realise its promises

only in the longer term. While it makes a compelling case for these promises, it also asks for our patience. And as with all basic research, something is bound to come of it, though not perhaps the full mastery of physiological complexities that is envisioned in the name of theranostics, individualised medicine, and cell repair. Some of its most important contributions will consist of progress in instrumentation and analytic methods that is now considered primarily a stepping-stone towards bigger and better things.

One should therefore not expect nanomedicine to revolutionise medicine. It is one promising avenue by which medicine can advance. At the end of the day, it will have contributed new treatment-options for certain diseases, some new nanomedicines, better imaging-techniques and other diagnostic tools. These will add significantly to the currently available arsenal of therapies and medicines, raising similar ethical and societal concerns as did the medical advances of the past. Demonstrations of efficacy have to be considered together with physiological and environmental side-effects and general quality-of-life issues, comparing all of these to alternative treatment options. And like all disease-oriented research, it requires public deliberation on which diseases should be prioritised in the context of global health care.

References

1 Nanobiotechnology: Responsible Action on Issues in Society and Ethics: http://nanobio-raise.org/
2 Mauro Magnani *Eythrocyte Engineering for Drug Delivery and Targeting*. New York: Kluwer, 2003.
3 Volker Wagner and Axel Zweck Nanomedizin: *Innovationspotenziale in Hessen für Medizintechnik und Pharmazeutische Industrie* Wiesbaden: Hessisches Ministerium für Wirtschaft, 2006.
4 Robert A. Freitas (1999): *Nanomedicine, Volume I: Basic Capabilities*, Georgetown, TX: Landes Bioscience.
5 *Cancer NANOTECHNOLOGY: Going Small for Big Advances – Using Nanotechnology to Advance Cancer Diagnosis, Prevention and Treatment*. Washington, DC: U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, National Cancer Institute, 2004.
6 *Nanomedicine: Nanotechnology for Health – European Technology Platform*. Brussels: European Commission, Research DG, 2006, p. 12.
7 Ibid., p. 10, see also p. 6 and especially p. 12.
8 *Nanomedicine: An ESF – European Medical Research Councils (EMRC) Forward Look report*. Strasbourg: European Science Foundation, 2006.
9 Like synthetic biology, nanomedicine is thus poised to become an off-shoot of nanotechnology that claims its own, at least partly separate identity and integrity. – Two of the authors of the ESF-report reflect on this quite explicitly, see Ringsdorf and Duncan "nanogames gaining ground" 2006.
10 The European Technology Platform subsumes new pharmaceuticals under "targeted delivery": "Seamlessly connecting Diagnostics, Targeted Delivery and Regenerative Medicine: Diagnostics, targeted delivery and regenerative medicine constitute the core disciplines of nanomedicine. The EuropeanTechnology Platform on NanoMedicine acknowledges and wishes to actively support research at the interface between its three science areas." This research at the interface can establish theranostics (p. 9).
11 Alfred Nordmann "Knots and Strands: An Argument for Productive Disillusionment," *Journal of Medicine and Philosophy*, 32:3, 2007, pp. 217-236.
12 ESF-report, p. 11.
13 This constructive principle also distinguishes nanomedicine (as a kind of nanotechnology) from biotechnology which is developing and deploying proteins as active agents.
14 ETP, p. 16.
15 Matthias Adam "What to expect from rational drug design,"*Expert Opinion on Drug Discovery* 2 (6), 2007, 773-776.
16 Joachim Schummer "The Impact of Nanotechnologies on Developing Countries," in Fritz Allhoff, Patrick Lin,, James Moor, John Weckert, eds., *Nanoethics: The Ethical and Social Implications of Nanotechnology*, Wiley, 2007.
17 Andreas Jordan "From Science to Business in 15 Years" in the Proceedings of *EuroNanoForum 2005: Nanotechnology and the Health of the EU Citizen in 2020*, edited by Michael Mason, Sophia Fantechi, Renzo Tomellini, Brussels: EC DG Research, 2006, p. 16.
18 The European Group on Ethics in Science and New Technologies to the European Commission "Opinion on the ethical aspects of Nanomedicine (Opinion N° 21)," January 17, 2007, section 5.5.1, p. 57.
19 While the European Technology Platform considers regenerative medicine one of nanomedicine's three core disciplines, the ESF's Forward Look treats it only under the heading of new materials (in particular, scaffolding for tissue growth and repair). The US-report on Cancer Nanotechnology does not refer to it at all.
20 ETP, p. 6.
21 Paul Miller and James Wilsdon "The man who wants to live forever" in Paul Miller and James Wilsdon (eds.) *Better Humans? The Politics of Human Enhancement and Life Extension*, London: DEMOS, 2006, pp. 51-58.
22 Ivan Amato *Nanotechnology - Shaping the World Atom by Atom*, Washington: National Science and Technology Council, Interagency Working Group on Nanoscience, Engineering and Technology, 1999, p. 8.
23 ETP, p. 24.
24 Richard Jones *Soft Machines* Oxford: Oxford University Press, 2004.
25 Jean-Pierre Dupuy in *Journal of Medicine and Philosophy*, 32:3, 2007.
26 NanoMedicine News (www.euronanotechnews.com), #71, July 20, 2007.

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