The convergence of biotechnology and nanotechnology: Why here, why now?

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Abstract

Nanotechnology offers a promise to revolutionise the life sciences because it equips biologists with tools and materials that can interact directly with the biomolecules that they study on a daily basis. Both biotechnology and nanotechnology have matured to the point that their convergence offers opportunities for novel solutions to unmet needs in biology. This paper explores the developments that have led to this convergence.

In 1985, chemists and physicists studying the behaviour of carbon in the atmosphere of N type stars discovered that pure carbon could be manipulated to form a perfectly symmetrical 60-atom sphere that resembled a geodesic dome. These now famous 'bucky balls' were the first of many carbon structures that brought nanotechnology from theory to reality. Researchers subsequently realised that this new 'nanotechnology' could play a large role in transforming existing industries. Early applications of nanotechnology included coatings, sensors and other tool-related applications. Nanotechnology also began to be explored in the semiconductor industry as a way to address some of the barriers to the continuing extension of Moore's Law. Although researchers were also exploring the application of nanotechnology to the biological sciences, until recently the convergence of these technologies was not living up to its early promise.

THE EARLY PROMISE FOR BIOLOGICAL APPLICATIONS

Using nanotechnology to further developments in biotechnology has always made fundamental sense: the arrangement of atoms differentiates a human from a bird and a protein from a fat molecule. 'The benefit of getting nano-small means that chemists and biochemists can meet nature at its own interface,' says Laura Mazzola, CEO of Excellin Life Sciences and Chair of *NanoBioConvergence*, a Silicon Valley-based non-profit organisation. She notes that 'most of the biological recognition that drives biological processes occurs because of interactions in molecular structure', making nanoscale devices and materials a perfect partner for biology. Nanotechnology and biotechnology are a good match for several reasons.

First, nanomaterials and devices can be built at the same size as cell components, making them ideal for interacting with individual molecules. Steve Edwards, Principal of S. A. Edwards & Associates and author of the forthcoming book 'Nanotechnology Pioneers', states that there is a 'natural synergy between nanotechnology and biotechnology because nanomaterials such as dendrimers and quantum dots can be made at the same diameter as proteins and ribozomes. Thus, their small size allows them to pass through cell membranes and interact with biomolecules.' Although traditional biochemistry takes advantage of this scale of interaction, its use of naturally occurring tools and processes is hard to control and often shifts in unpredictable ways. In contrast, nanotechnology holds the promise of allowing us to build tools from the ground up, making them more reliable and predictable than biochemical molecules.

Second, nanotechnology will allow biological scientists to recognise, measure and interact with single biological events, changing the dynamics of diagnosis and treatment. For example, most types of cancer can be spotted only when the tumour arises, making early detection almost impossible. Charles Craik, Director of Bay Area Labs Integrating Nanotechnology and Cancer (Bay-LINC: a UCSF, UC Berkeley, Lawrence Berkeley National Labs and San Francisco State University collaboration), is working to modify highly sensitive nanomaterials to bind protein receptors thought to be over-expressed in cancer cells. The binding would occur throughout the body, allowing early detection because physical visualisation of a mass of cancer cells is no longer necessary. Treatment would therefore be more effective because each abnormal cell could be identified and targeted during treatment.

Nanomaterials can be built at the same size as cell components

Nanomaterials are more reliable and predictable than biochemical molecules

Increasing maturity of biotechnology and nanotechnology is accelerating the convergence of these technologies

Third, therapeutic nanomaterials can be developed in a manner that allows them to be highly specific, resulting in fewer negative consequences. Traditional therapeutics and diagnostics typically interact with molecules at a bulk level, using brute force on the cells and tissues of the body to effect desired changes non-specifically. Nowhere is this more prominent than in cancer therapy, where the best method of treating cancer is to physically remove it from the surrounding healthy tissue. Therapeutic nanomaterials on the other hand hold the promise of being delivered when and where they will be most effective, refining the methodology of pharmaceutical transport. If lower doses of pharmaceuticals are localised to the diseased area, drug efficacy can be improved while side-effects can be reduced.

Although nanotechnology has always held great promise as a platform for biotechnology applications, this convergence has taken longer than many had anticipated. Nevertheless, the pace of this convergence is accelerating.

WHY HERE, WHY NOW?

The accelerating pace of this convergence leads to the question: why here, why now? Although there are a number of factors that have probably catalysed this convergence, the primary ones relate to the increasing maturity of biotechnology and nanotechnology, greater opportunities for public funding and collaborations, and increasing interest and funding from the private sector.

Advances in biotechnology

The maturation of genomics as a field of study has accelerated research pinpointing the molecular basis of biological processes. The science of genomics measures biological activity across the genome, studying the entire genetic composition of an organism to determine each gene's function.

The Human Genome Project was the first step in the process. Researchers were able to determine the molecular base pair sequence of the entire human genetic code.[1] This created a road map that details the physical structure of our genetic composition, but it does not tell us how that map causes the body to function. Now that the map is laid out, researchers seek to determine how that map directs the body to function by discovering what every single gene in an organism's repertoire is doing.

The development of DNA microarray technology allowed researchers to identify the key genes in any given process. Microarrays use the genome sequence as a blueprint to construct a chip that allows researchers to determine whether a gene in the genome is turned on or turned off.[2] These snapshots of gene activity have enabled scientists to get a molecular handle on how cells respond to certain conditions, such as the introduction of pharmaceuticals, and how cell types differ from one another, for example, by distinguishing a healthy cell from a cancerous cell. By knowing which genes are active during a biological process, researchers can pinpoint which gene or combination of genes may be important to the studied process.

Determining what specific function each gene has to a process, or how disease affects that process, is a step that cannot yet be done rapidly and painlessly. Researchers use traditional biological methods such as knocking genes out to determine the function that each gene has in a studied process. However, this is a laborious and time-intensive procedure. If nanotechnology can help label and survey what is happening in a process, it will be able to speed up the determination of molecular processes tremendously. Once a given molecular process is elucidated, nanotechnology will be one step closer to being able to manipulate molecular processes for therapy.

Advances in identifying gene function brings nanotechnology one step closer to being able to manipulate molecular processes

Advances in nanotechnology

Several advances in nanomaterials and investigational tools have ripened nanotechnology to the point where engineers can work with biologists in elucidating molecular processes.

Advances in nanomaterials and investigational tools allows greater visualisation and manupulation at the nano level

The invention of scanning probe microscopes (SPMs) catalysed the maturation of practical nanotechnology by allowing visualisation and manipulation at the nano level. One of the earliest SPMs, a scanning tunnelling microscope, has a tip that sweeps over a surface like a phonograph needle and uses the data to create enlarged visual images.[3] This tip can also be used to position individual atoms very precisely.[4] The atomic force microscope (AFM) is one type of scanning probe microscope used in biology. In biophysics, researchers are using the AFM to probe the physical properties of biological molecules.[5] For example, the AFM can be used to pull on atoms of a molecule and determine how elastic the molecule is. By elucidating the mechanical properties of biological molecules, researchers can understand how to design a device or material so it interacts with the molecule in the desired manner.

Nanomaterials have also been maturing to a level where they are ripe for adoption by biological science researchers. Because nanomaterials are artificially built or synthesised, their use in biological systems may be more predictable than the biologically based molecules traditionally used by researchers. Thanks to advances in manufacturing techniques, nanomaterials are now being produced more consistently, in larger quantities and at lower cost.

Quantum dots are one example of a maturing nanomaterial. Quantum dots are being produced at a low enough cost and high enough quantity that they are already being used in commercial applications. These nanocrystal semiconductor compounds are used as fluorescent tags to label cells and macromolecules.[6] Quantum dots are an improvement over standard fluorophores because the dots are able to fluoresce for several months, allowing scientists to observe processes over a longer and more biologically meaningful timeframe. Moreover, the absorption spectrum for quantum dots is broad, giving them more unique signatures than those of standard fluorophores. This allows researchers to distinguish between different concentration amounts or target substances in a single sample.

Dendrimers are another example of a maturing nanomaterial. Dendrimers may now be produced consistently enough to meet the Food and Drug Administration's biomedical application standards in terms of precision, scalability and reproducibility.[7] These tree-like branched macromolecules may be used to selectively deliver complex therapeutics because the different branches of the dendrimer can be modified to hold a labelling agent, targeting agent or chemotherapeutic. Dendrimers are an improvement over biologically derived macromolecules because they do not activate the body's immune system and are more consistent in size and surface characteristics than biologically based macromolecules.

Public funding and collaboration

Increased public funding and the creation of collaboration centres have been key elements in the accelerating convergence of nanotechnology and biotechnology.

Public funding for nanotechnology has increased worlwide

In the USA, the federal National Nanotechnology Initiative has seen funding increase from US$116m in 1997 to US$847m in 2004.[8] Although only about one-eighth of this is directed specifically towards the life sciences, research in areas involving the Department of Defense and NASA may also lead to advances in biosensors, biological weapon defence and other life science-related research. State and local governments have also increased their support of nanotechnology initiatives, a portion of which has been directed towards life sciences. In a recent Lux research report, Massachusetts, California, Colorado, Virginia and New Mexico were the top five states that supported economic development in nanotechnology.[9] New York, which in 2004 was the top state with US$150m in funding available, was ranked tenth in this recent report.

Worldwide government funding has also grown. Western European government funding for nanotechnology increased from US$126m in 1997 to about US$650m in 2003. The Japanese government boosted nanotechnology funding from US$120m in 1997 to about US$800m in 2003.

A number of centres have sprung up to facilitate collaboration between the public and private sector

In addition to increases in funding, a number of nanotechnology and nanobiotechnology centres have sprung up in the last five years that have helped facilitate collaboration between the private and public sectors in the development of nanotechnology, and this collaboration has allowed researchers to leverage these technologies more effectively. These centres range from government funded multidisciplinary efforts that fuel primarily academic research to academic–industry collaborations that build on academia's ability to pursue risky ideas with an eye toward commercialisation.

In the USA, the National Institutes of Health (NIH) has taken the lead by identifying nanomedicine as one of the six priorities established by the NIH Roadmap. The NIH hopes to '1) obtain a comprehensive set of measurements on molecules and assemblies of molecules, and use those measurements to understand molecular pathways and networks, and 2) use that knowledge to drive the design and development of new nanomachines and technologies to improve human health.'[10] To achieve these goals, the NIH is creating multidisciplinary development centres that focus on advancing nanomedicine and fund nanomedicine-related projects.

The Nanobiotechnology Center (NBTC), funded by the US National Science Foundation, is one example of a centre that seeks to use nanofabrication to study biosystems in a multidisciplinary environment.[11] The centre is a collaboration between Cornell University, the Wadsworth Center (New York State Health Department in Albany), Princeton University, Oregon Health & Science University, Clark Atlanta University, Howard University, and representatives from industry and government. In addition to promoting collaborative research in nanotechnology and biotechnology, the centre also sponsors a graduate level course in nanobiotechnology that fosters interdisciplinary communication and project solving by requiring biologists and engineers to complete a team design project.

In Asia, the Asia Pacific Nanotechnology Forum is a platform that allows industry, governments and venture capitalists to collaborate and develop nanotechnology on a region-wide basis.[12] The forum publishes a quarterly journal, hosts an annual conference, and supports networking events across the region.

Private funding for nano-bio ventures has been slow in coming

Private funding appears to be increasing as nanotechnology begins to be applied more to therapeutic applications

In the European Union, the European Commission has identified nanobiotechnology as a major research focus in its FP6 community-wide research programme. Nano2Life is the implementation of that research focus, a European Union network for collaboration that includes integration of member research activities, member access to research facilities, technology transfer and education.[13] CEA Grenoble, a French public research organisation, pursues innovative research in the nanobiotechnology area, bringing together multidisciplinary teams to perform both fundamental and applied research.

Collaboration opportunities have been an important factor in early stage nano-bio research and development. Charles Craik, director of Bay-LINC, noted that close relationships between industry and academia were vital in a recent grant proposal he submitted to the NCI. Craik stated that collaboration between universities and industry brought great benefits, yet the potential was still largely untapped because of differences in perception. 'Both industries and universities must have realistic expectations about the desired outcomes. Because nanotechnology is such a young science, we have to keep in mind that 90 per cent of our proposals are not going to work, as in much of basic science.' Because funding is not dependent upon the value a technology can bring to market, an industry–university collaboration is ideal for these kinds of riskier early-stage projects.

Private funding

Private funding for nano-bio ventures has been slow in coming. Nevertheless, it appears that the level of interest and, more importantly, funding for these types of ventures is beginning to pick up. Although it is difficult to assess with certainty the actual proportion of nanotech funding that is devoted to nano-bio applications, it is probably safe to assume that changes in the levels of funding in this area have generally mirrored those for nanotech applications generally. In this regard, although there was a drop in funding for nanotech ventures following the burst of the technology bubble, since that time, funding for this sector has been increasing. In 2004 funding for all nanotech ventures was US$196.4m.[14] Although this represented a decrease in dollar amount from 2003, it represented an increase in the number of funding rounds. In addition, almost 40 per cent of the nanotech funding in 2004 took place in the fourth quarter, suggesting that investment in nanotech is on the upswing.

Venture capitalists (VC) that traditionally invest in biotechnology tend to focus the majority of their resources on drug discovery and other therapeutic applications, which generate significantly higher valuations and returns. Chen Yu, a principal at Vivo Ventures, notes that nanotechnology is in its infancy when applied to therapeutic applications and to date has been applied more to tool, device and platform applications. It has therefore been less attractive to traditional biotechnology VCs. However, as nanotechnology begins to be applied more to therapeutic applications, VC interest and funding appear to be increasing. Nanobiotechnology also appears to be benefiting from the desire on the part of pharmaceutical companies to use new technologies in an effort to reduce costs, accelerate research programmes, clear up clinical trial bottlenecks and generate more effective data.

CONCLUSION

The early promise of nanotechnology's application to biology is starting to be fulfilled. Continued advances in biotechnology and nanotechnology are accelerating this process and new collaboration opportunities and increased public and private funding are helping to convert these advances into commercial applications.

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