

2nd Annual National Academies Keck *Futures Initiative* Conference

Designing Nanostructures at the Interface between Biomedical and Physical Systems

Arnold & Mabel Beckman Center, Irvine, California
November 18-21, 2004

An In Vivo Nanofactory: the Medicine of the Future **Focus Group Summary**

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Summary:

Tiny solutions for big problems

When great minds in modern science convene to identify and solve the big problems facing the world, it is impossible for them to disregard flaws in human health. Disease comes in many forms, but consistently confers pain and suffering on individuals. Some of the greatest challenges in science and engineering today involve understanding diseases at a fundamental level and developing innovative solutions for battling them.

This grand challenge was the inspiration for a group of 13 researchers—biologists, chemists, physicists, and engineers; the best in their respective fields—to propose the construction of a biological *nanofactory* that could be broadly applied to prevent or remedy diseases ranging from mental retardation to prostate cancer.

The nanofactory was a solution to a problem posed to these researchers at the Second Annual National Academies Keck *Futures Initiative* Conference, “Designing Nanostructures at the Interface between Biomedical and Physical Systems.” Charged with “building a factory to synthesize products,” utilizing biological systems as starting materials, the group pooled their broad and varied areas of expertise to design a prototype for an artificial *pseudo-cell* that will have the ability to manufacture and deliver a biological product to an appropriate region of the body to correct an existing biological condition. Such a nanofactory would be therapeutic in a number of diseases including diabetes, thyroid disorder, and cancer.

A nano-“mobile defense force”

Before delving into the specific aspects of disease chemistry, the group used their engineering prowess to describe a prototype for their powerful nanofactory, a weapons factory a billion times smaller than a single bullet, that could single-handedly wage war against human disease.

A sketch of the nanofactory highlights six basic components. These key features are comparable to those required in a more conventional factory.

Just as pharmaceutical or car manufacturers must carefully select their location site to market their product to consumers, the nanofactory must have a mechanism for targeting the region for which it will manufacture its products. A delivery sensor—manifested as a cell-specific antibody or another recognition molecule—can be chemically attracted to the body tissue that would benefit from the factory’s product.

A second, and somewhat self-evident, requirement of the factory is its walls. A car company will construct a building that will be suitable for the conditions necessary for its purpose; and the nanofactory, likewise, needs a compartment that can contain its inner workings. It must thus be like a human cell, which is compartmentalized inside a vesicle. The pseudo-cell’s walls can be built out of a variety of materials that will suit its purpose of containing the inner workings without being rejected by the body. Both a lipid bi-layer and a polymer structure would serve to sequester the chemical assembly line, while allowing the flow of water through its pores to survive the strict osmotic regulations that the human body requires.

Next, there must be a front door, or input gate for the raw materials—chemical precursors, cofactors, and energy molecules—to flow in. In the most sophisticated incarnation of the nanofactory, the door will be locked and will only open when the product the factory creates is needed in the body. The key to opening the door will be a sensor that will detect chemical levels near the factory site.

Once the door is open, reactants, cofactors, and energy molecules can flow into the factory where they will move through an assembly line of enzymes each with a specific job to modify the raw materials into the desired product. The enzymatic assembly would be specific to the metabolic pathways necessary to produce the output of each nanofactory.

After the product is created it must exit the factory to be distributed where it is needed. An output gate can also be regulated with a key that will detect the presence of product inside the cell and open only when there is material to exit.

Finally, there must be damage control. What if the factory malfunctions or the patient reacts badly to its insertion? As it cannot be withdrawn, it must have a self-destruct mechanism that could be initiated by an external electric or magnetic field—something like an MRI—that would trigger the factory walls to decompose so that its inner workings could diffuse safely through the body.

A model for moderating PKU

The features described here must undergo significant engineering analysis to determine the best solutions to remedy or prevent a particular disease. A simple prototype can be built to provide an

important proof-of-principle that the strategy will work.

A prototype nanofactory can be built to contain phenylalanine hydroxylase (PAH), the naturally occurring enzyme that is absent in sufferers of phenylketonuria (PKU) who experience severe mental retardation because the phenylalanine they consume in their diet cannot be properly converted to tyrosine. This disorder results from a common genetic mutation that affects 1 in 10,000 individuals. There is no cure; and the only remedy is a simple dietary measure that urges individuals genetically predisposed to PKU to avoid eating foods high in phenylalanine or its precursors, such as diet soda due to the product aspartame.

An anti-PKU nanofactory would include only one enzyme, PAH, in a simple assembly line that would convert phenylalanine, entering through the input gate, into tyrosine, which would exit through the output gate and diffuse through the patient's blood, remedying the natural deficiency. The factory could be dissolved in a solution and administered through injection. It would be targeted to the liver, where PAH is normally produced, via chemical receptors. Intelligent design may mitigate the need for such receptors. Since all mid-size objects put into the body tend to congregate in the liver, an appropriately sized nanofactory—about 100 nanometers in diameter—will be drawn to the right place without any sensors. The tyrosine product would exit into the patient's blood stream, preventing a profound irreversible mental disease.

This pared down factory, proposed by the group, may require input and output sensors to serve as door-keys, but a molecular understanding of the nature of the disorder must be mastered for their design. While this gap in knowledge is not a general scientific failure, it was, unfortunately, not available within the expertise in the group. It points to a larger gap, though, for the expansion of this technology for other diseases: the metabolic pathways and basic biochemistry of the problem must be understood before a factory can be built to fill in for the body's malfunction.

Miniaturized pharmaceuticals

The design for the nanofactory laid out by the group can be modified for the production of hormones like thyroxine to manage thyroid disorder; growth factors, such as tumor necrosis factor- α (TNF α), to specifically target and kill cancerous tumors; and insulin precursors that could be produced and self regulated to relieve diabetes sufferers of daily injections. Nanofactories could also be used to withdraw unwanted materials from a biological environment—toxic chemicals resulting from a drug overdose or excess LDLs (low density lipoproteins), famous for their link to heart disease. Each of these conditions would require a complex multi-enzyme assembly line to produce the biomedically useful product.

The nanofactory blueprints developed by the group have the potential to revolutionize individualized medicine. Instead of taking daily doses of drugs, which are mostly excreted before they are absorbed and can cause nasty side effects, injections of medicinal nanofactories have the potential to offer selective, regulated, time-sensitive therapy to produce and deliver the medicine your body needs exactly when and where your body needs it.

While the factory blueprints can be drawn up without much further effort, as the biochemistry and engineering knowledge already exists, there are some gaps that must be bridged before the nanofactories can be mobilized to treat disease. The most difficult challenges to overcome will be disease specific, as the construction of the nanofactory will vary based on its desired function. Designing a vesicle to safely contain particular enzymes will, of course, vary with the nature of those enzymes. The size and durability of the cell may also change, depending on its ultimate desired lifetime. A PKU sufferer, for instance, would require injections throughout his life, so a very stable pseudo-cell would maximize the factory's lifetime so that the patient would need to receive an injection only, say, once a month.

Unknown unknowns

Science fiction writers have conjured up images of nanomachines that can self-assemble into macroscale objects with powerful functions. Even on the nanoscale, a self-sustained and self-

regulated factory inserted into a human body could potentially wreak biomedical havoc instead of providing therapeutic assistance to its host. Is such a concern menacing enough to impede research into their construction?

On the other hand, therapeutic nanofactories could be considered to be “politically correct” stem-cells, as they can be created to provide distinct therapy to various parts of the body selectively, without dealing with the matter of using discarded embryos. In addition, while the mechanism of stem cells is not yet well understood, the nanofactories present an intelligent alternative because they will be able to regulate and correct metabolic processes in a planned and organized way.

There are, as always, ethical concerns that must be considered along side the scientific details of the new technology. Overall, if further development of the in vivo nanofactory is approached with biochemical acumen and levelheaded caution, the gaps that exist in the current scientific wisdom can and should be resolved. The in vivo nanofactory holds a world of promise in treating a range of human diseases.

Postscript:

To further explore this topic, a focus group member recommends the following publication:
Noireaux, V. and Libchaber, A., *A vesicle bioreactor as a step toward an artificial cell assembly*, PNAS, | **December 21, 2004**, vol. 101, no. 51, **17669-17674**. **(Published online before print December 10, 2004)**