FORESIGHT INSTITUTE'S

WORKSHOP ON ATOMIC PRECISION FOR MEDICAL APPLICATIONS

May 29-31, 2015 | Palo Alto, CA

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ABSTRACT

The workshop on Atomic Precision for Medical Applications aimed to promote the development and use of atomically precise tools for medicine. About 50 people attended, with a range of experience (from senior researchers to graduate students), institutions (universities, government and industry) and expertise (medicine, nanoscale tools, and computation).

The workshop identified potential interdisciplinary collaborations among the researchers at the workshop. It also developed several near-term research projects that illustrate how precise tools can significantly improve medicine.

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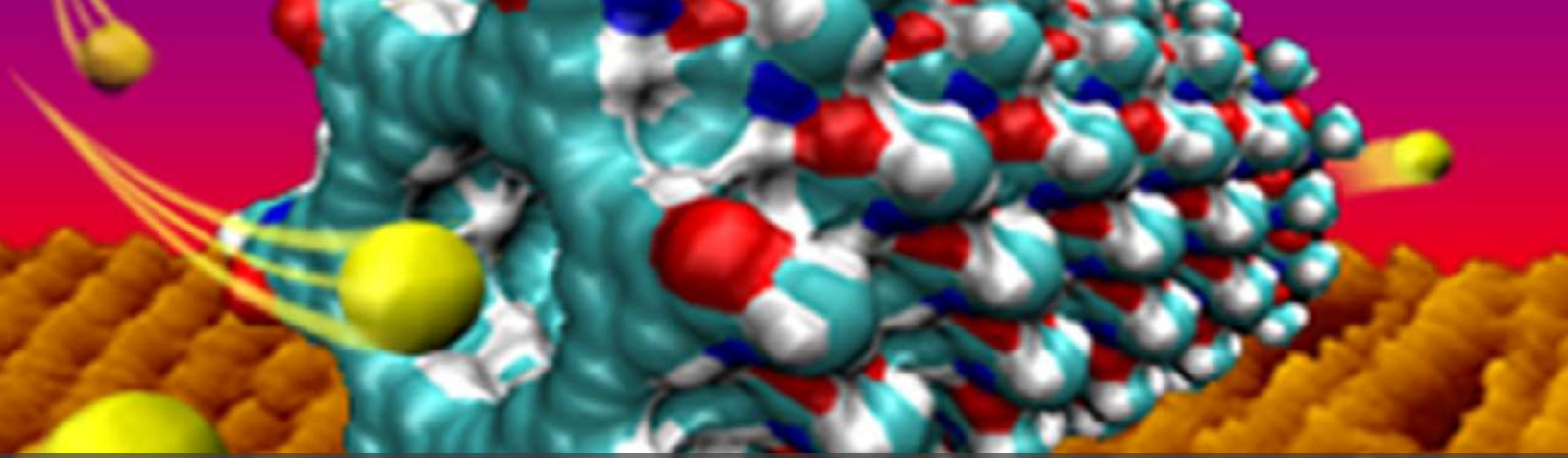


Self-assembling subnanometer pores with unusual mass-transport properties; X-Therma, Inc., Biomemetic Nanotech Nature Communications 2012, 3, 949

INTRODUCTION

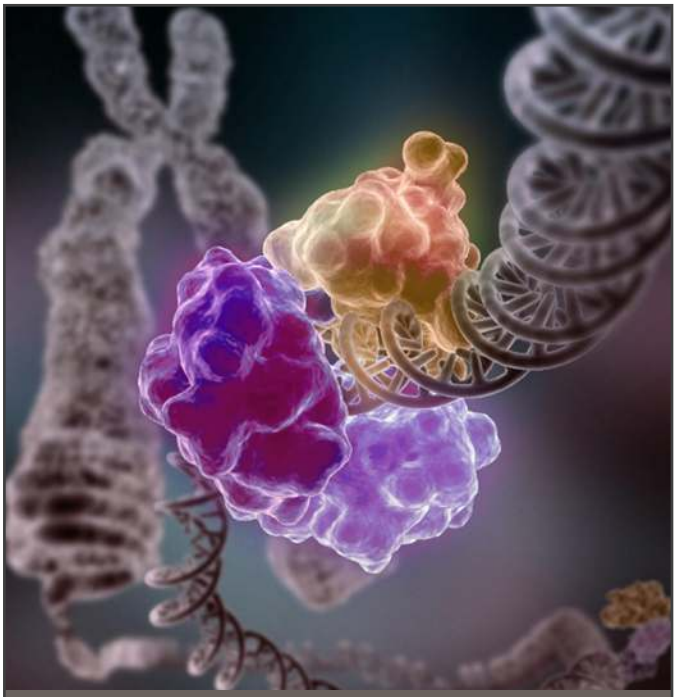
An opportunity to significantly improve medicine

Medicine has progressed significantly in the last century, particularly for preventing and treating infectious diseases. However, there remains an ever-increasing burden of chronic diseases associated with an aging population, as well as emerging infectious diseases. Current approaches to these medical problems have limited effectiveness, significant side effects and high cost.

To address this problem, significant resources are devoted to developing better ways to treat diseases such as cancer. This is leading to incrementally better treatments, deeper understanding of the biology underlying disease, and increased personalization of medical treatments to the biology of individual patients [Collins and Varmus 2015]. However, even if these approaches are successful to one disease, they lead to only modest improvement in life expectancy and quality of life, due to the consequent increased incidence of other diseases without effective treatments (e.g., Alzheimer's). There thus remains a need for broadly effective and affordable prevention, diagnosis and treatment of all diseases, and the ability to rapidly detect and respond to emerging diseases.

Opportunity

Two recent developments could lead to significant improvement in medical care. These are the identification of a relatively small number of fundamental causes of diseases and the fabrication of increasingly precise tools for sensing and manipulating biological organisms, tissues, cells and their molecular components.



Enzyme repairing DNA - A special enzyme encircling the double helix to repair a broken strand of DNA. Image from Tom Ellenberger, Washington Univ. School of Medicine in St. Louis, and Dave Gohara, Saint Louis Univ. School of Medicine.

Treating fundamental causes of disease could not only cure currently intractable diseases, but also lead to rejuvenation and halting damage that accumulates during aging [de Grey 2007].

These causes include:

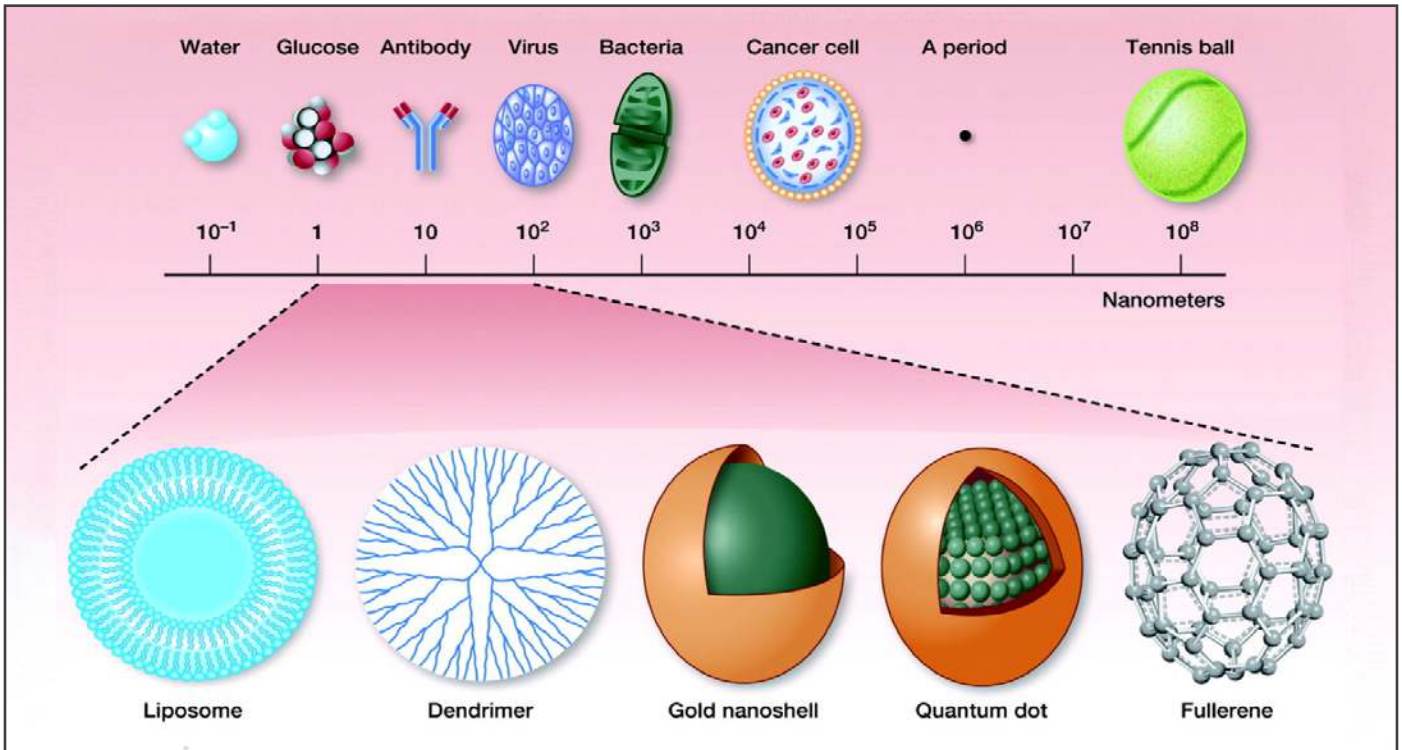
- Advanced glycation end products (AGEs)
- Aging clocks — e.g, accumulated damage and epigenetic changes
- Auto-immune problems
- Autophagy and "garbage collection"
- DNA mutations (environmental and inherited)
- Infections
- Inflammation
- Mitochondrial defects

Fully addressing these causes requires improved understanding of their molecular basis and tools that can sense and alter processes on that scale.

Large scale manufacturing of tools created and operating with atomic precision could significantly improve diagnosis and treatment of these fundamental causes, without significant side effects [Freitas 1999]. Such precise tools have been discussed theoretically for many years. Recent developments have now produced a variety of demonstrated tools with precision at or close to atomic scales [Kim et al. 2015].

An example is DNA self-assembly producing complex structures through suitable choice of base pair sequence and their selective binding. These developments show the way toward a large range of new high-precision tools. Learning how to exploit these new tools for applications, such as medicine, requires significant study beyond just learning how to make the tools in laboratory settings. Since research plans and funding cycles take years to mature, there's an opportunity now to identify high-value areas for precise tools. Medicine is one such high-value area.

Moreover, identifying clear applications will guide tool development in directions most likely to have major impacts, and have applications 'ready to go' as soon as tools become available. This will reduce the time between new tools achieving laboratory demonstration and their use to help patients in the clinic.



Examples of nanotechnology platforms used in drug development. Image from William C. Zamboni et al. Clin Cancer Res 2012; 18:3229-3241 © 2012 American Association for Cancer Research

Challenge

Exploiting this opportunity requires close long-term collaboration among different research communities, with different terminologies, interests and funding sources. Moreover, there are significant technical obstacles to developing atomically precise tools and identifying how to apply them to fundamental causes of disease.

These obstacles involve two major limitations in current science and technology. First, for some diseases we lack sufficient knowledge of the underlying biological mechanisms to identify effective, curative treatments. Alzheimer's disease is an example. Second, we often lack sufficiently precise tools to apply our knowledge to treat the disease without also causing harm to healthy tissues.

For example, an inability to precisely target drugs to every cancer cell without also affecting many healthy cells. We also face challenges arising from the complexity of planning, controlling and testing treatments with available tools, particularly treatments that require customization based on large numbers of patient-specific diagnostics.

Purpose

This Foresight workshop aimed to address the scientific aspects of this challenge by bringing together about 50 researchers from diverse research communities to identify promising medical opportunities as the precision of available tools increases toward the atomic scale.

Procedure

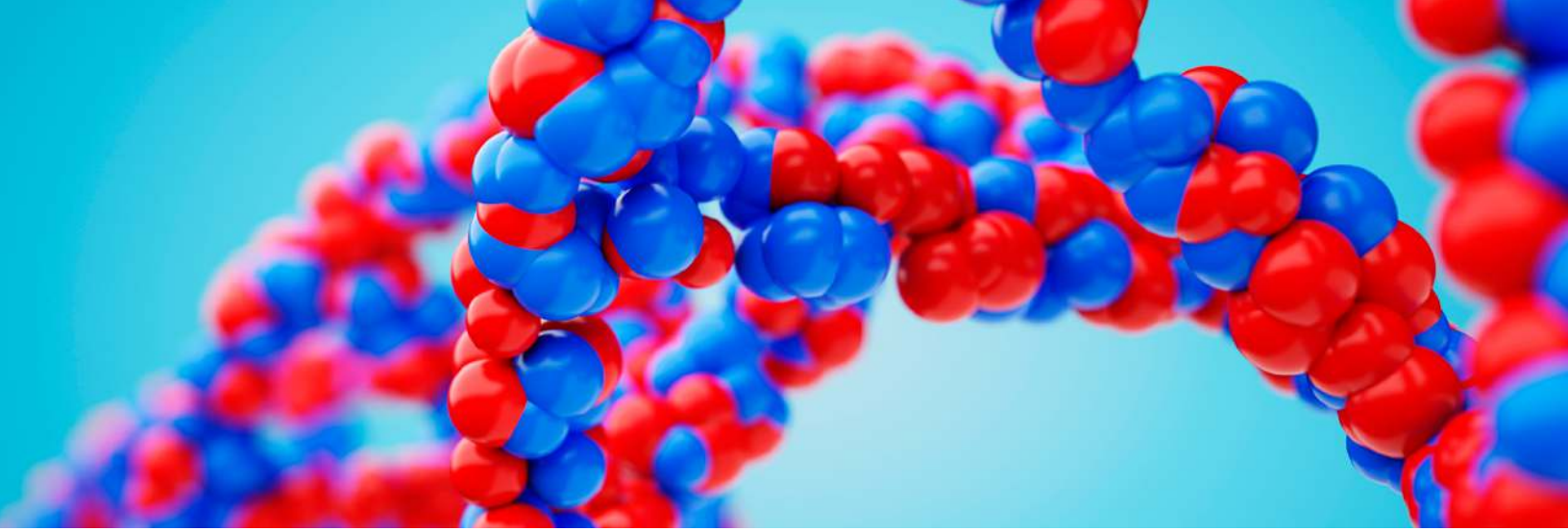
The workshop consisted of a series of sessions to explore and develop medical applications for atomic precision.

These sessions involved:

- Listing medical benefits of specified precise tools
- Evaluating recent and likely future progress in developing high-precision tools
- Identifying tools and supporting infrastructure needed for various medical applications
- Discussing criteria for selecting research projects
- Developing research projects

The workshop aimed to characterize the opportunity for improving medicine and suggest feasible next steps with a few representative research projects. The workshop focus was mainly on improving treatment for individual patients. In addition, the technologies discussed here could improve public health, e.g., by quickly and precisely tracking outbreaks of infections with harmless chemical tags or widespread environmental sensing. The workshop was not a comprehensive survey of the development of atomically precise tools or the full range of their possible medical applications.

This report describes the outcome of these sessions, with particular focus on the research projects developed during the workshop.



MEDICAL BENEFITS OF ATOMIC PRECISION

Increasingly precise tools could provide a wide range of medical benefits. To understand these potential benefits, this section describes applications of several hypothetical tools that could act within the body much more precisely and over a larger range of cells than current technologies. In addition to physical precision of the tools' actions, effective use requires knowing how to use the tools effectively. High precision tools would also be useful as research techniques to obtain the necessary knowledge. For the purpose of this discussion, the hypothetical tools were assumed to be widely available, affordable, and safe to use. The primary focus of discussion for medical application of precise tools is on treating or preventing diseases, or using the tools to learn more of the underlying disease biology. Beyond these applications, precise tools could enhance human performance and longevity. These tools could also have cosmetic applications.

DNA repair

Many medical problems arise from errors in DNA. These include heritable diseases as well as cancer forming from successive mutations to DNA that natural mechanisms are unable to repair. A tool to repair or replace the DNA in cells throughout the body could address these problems. These tools could be created based on each patient's genome sequence.

Applying DNA repair tools requires an ability to deploy many tools throughout the body, that these tools can enter cell nuclei to make precise changes to DNA, and then the tools either harmlessly degrade or can be removed from the body. Making these changes requires that the tool can access and unravel the highly coiled DNA in the nucleus, make the specific required changes and return the DNA to its coiled state. In addition, effective use of the tool requires sufficient knowledge of which edits to make for individual patients.

This level of DNA repair would be powerful, by effectively and precisely altering biochemical processes within cells throughout the body. For instance, DNA repair could eliminate fully or partially inherited genetic diseases, such as Huntington's, cystic fibrosis, Parkinson's and sickle cell anemia. The repair could also address diseases arising from genetic mutations such as cancer.

Moreover, in addition to treating existing diseases, DNA repair could proactively repair pre-cancer cells. That is, repair cells that have accumulated some mutations on the path toward cancer but not yet all the changes required to become cancerous.

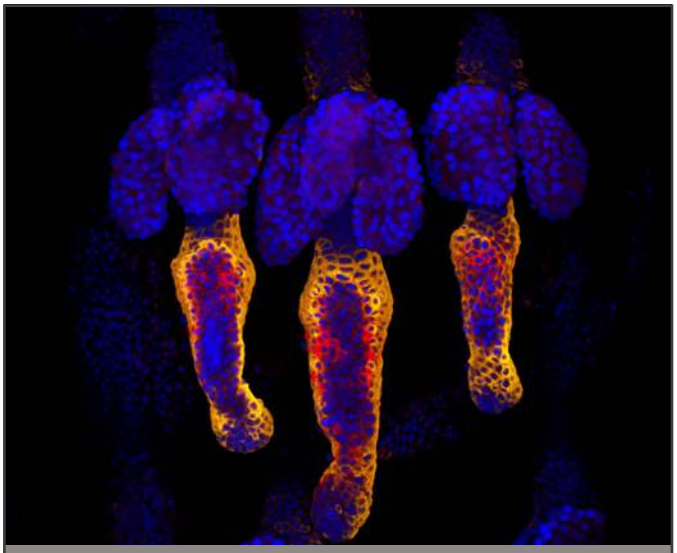
Precise DNA edits could also address some aspects of aging. One example is repairing telomeres that normally shorten as cells divide. Such repairs often raise the concern of possibly promoting cancer growth since shortening telomeres provide one check on indefinite cell growth. However, with precise DNA edits, telomere repair would only apply to normal cells, or be combined with repair to pre-cancer cells. Alternatively, the edits could selectively enhance telomere shortening in cancer cells.

DNA repair could not only alter genes, and hence the resulting proteins, but also change regulatory regions on DNA, thereby changing expression patterns. This would allow altering interactions among many genes. If these hypothetical DNA editing tools operate quickly enough, these changes could apply only when the cell is in particular states, e.g., due to environmental stress or at specific points during the cell cycle.

Tools able to precisely edit DNA in many cells throughout the body could be useful to repair radiation damage. This could be useful, for example, in aiding recovery from radiation medical treatments and supporting space travel to other planets, which can involve long-term exposure to higher levels of radiation than on the earth.

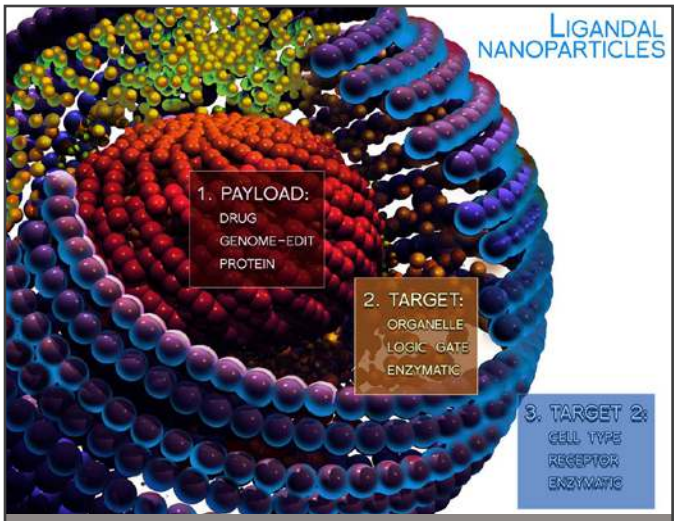
Stem cell repair

Organs sufficiently damaged by disease or injury eventually fail. Transplants are a current treatment for organ failure, but are limited by a lack of compatible donors and require ongoing immunological management to avoid organ rejection. Stem cells offer an alternative therapy to augment or replace failing organs, by using cells from the patient to ensure immune compatibility. By assumption, such therapies can accurately identify and extract appropriate stem cells, and deliver them into the body with microenvironments that encourage proper differentiation and growth. The techniques also prevent any of the implanted stem cells from forming uncontrolled secondary growths. Instead of repairing damaged cells, as DNA repair does, this stem cell therapy would replace those cells with new, healthy ones as the stem cells differentiate and grow.



This confocal microscopy image from a mouse lacking the Sept2/ARTS gene shows a tail wound in the process of healing. Cell nuclei are in blue. Red and orange mark hair follicle stem cells that cause hair regrowth, indicating healing. Image from Yaron Fuchs and Samara Brown, National Institutes of Health.

This level of precise control of stem cell behavior would provide a range of benefits. For instance, stem cells could aid the regeneration of injured spinal cords and regrow limbs. This technology could also grow new tissue in vivo for whole organ replacement, and to reconstruct the patient's immune system.



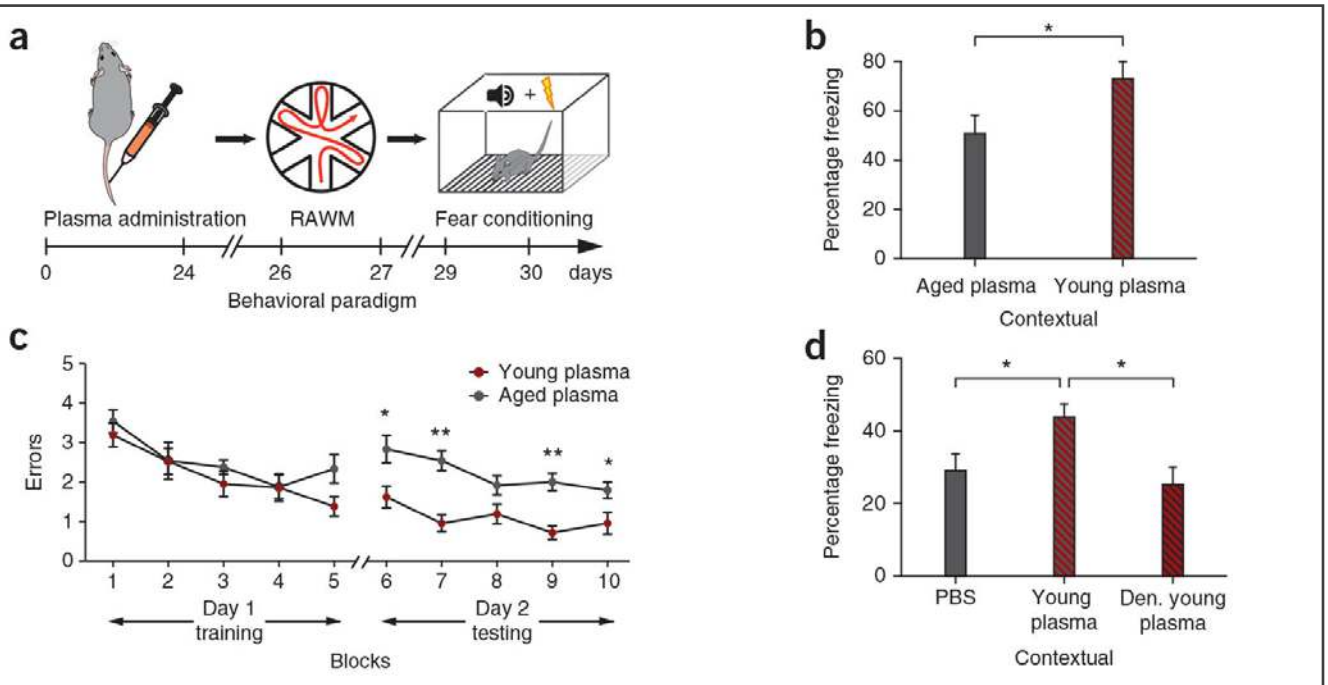
Advanced multistage synthetic assembly. Image from Ligandal, Inc. www.ligandal.com/technology.html

Growing stem cells with repaired DNA in tissue could replace cells with damaged DNA. This use of stem cells could achieve results similar to that of DNA repair of those damaged cells.

Precise Control of Blood Composition

The circulatory system delivers nutrients and removes waste from throughout the body. Thus high-precision tools that act only in the bloodstream could have significant benefits, and such tools may be easier to develop than those discussed above that involve modifying cells throughout an organ or the entire body. An example of the potential benefit of altering blood contents comes from studies of supplying blood from young animals to older ones. These benefits include improved cognitive function [Villeda et al. 2014].

High-precision tools include filters that could remove specific chemicals or cells from the blood, and delivery vehicles to add chemicals or cells under precisely defined conditions. These tools contain sensors and controls to determine if, when and how much to modify blood composition on an ongoing basis with rapid reaction to changes in the body. These devices could act as artificial blood cells, replacing the functions of nutrient delivery, injury response and immune surveillance. In general, combinations of circulating and stationary devices may perform these functions. This precise control includes making different modifications to blood composition in different parts of the body.



Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Image from Nature Medicine 20, 659–663 (2014) doi:10.1038/nm.3569; Received 08 February 2014 Accepted 16 April 2014 Published online 04 May 2014

Selective removal of chemicals and cells from blood could treat a variety of medical problems. While the liver and kidneys alter blood composition, new functions could be added.

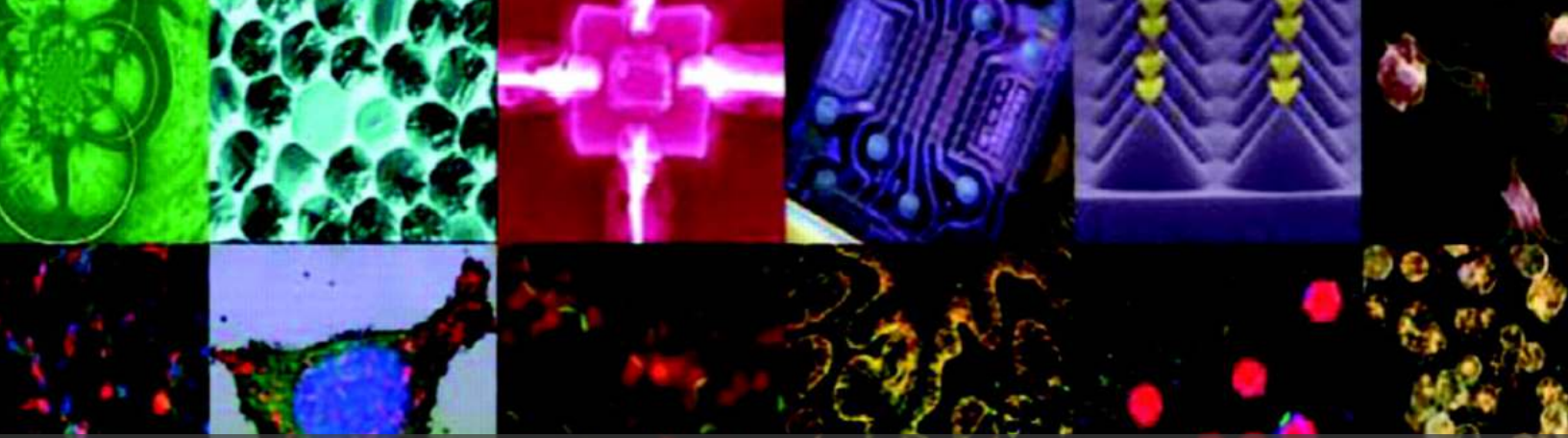
These included:

- Remove inflammatory cytokines to reduce inflammation injury.
- Remove cholesterol to reduce cardiovascular disease.
- Remove bacteria, viruses and parasites in blood, thereby eliminating some infections and improving the efficacy of the immune system.
- Remove toxins, including overdoses of alcohol and other drugs.
- Remove circulating tumor cells to prevent metastasis.

In addition, altering clotting and thrombosis could eliminate vessel blockages underlying stroke and heart attacks. Precise control over blood chemistry could correct hormonal imbalances, possibly leading to rejuvenation. Applied to chemicals introduced into the body, this capability could improve drug delivery, including drug delivery across the blood-brain barrier. Similarly, precise control over cells in the blood could deliver stem cells to specific parts of body as part of a procedure to rejuvenate organs.

More generally, the ability to precisely control blood composition could substitute for or augment the function of organs that support the blood, e.g., the kidney, liver and pancreas. Similarly, the tools could supply nutrients directly into the blood, replacing the function of the digestive system. Hence, precise control of blood chemistry could substitute for organ failure for long periods of time, perhaps indefinitely. This capability could delay or avoid organ transplant or repair. This is especially notable if the tools could operate autonomously for long periods of time within the body, providing the function of organs without the inconvenience and infection risk of current procedures, such as dialysis to support failing kidneys.

Beyond addressing existing diseases, control of blood composition could enhance performance. For instance, increasing oxygen carrying capacity of the blood could allow people to function well in low-oxygen environments (e.g., at high-altitude), and enhance endurance exercise. Moreover, the sensors required for precise adjustment of blood composition could also provide ongoing, real-time sensing for diagnosis, and collect detailed person-specific normal ranges of variation in blood chemistry. This would improve diagnosis with early detection of deviation from normal ranges for that person. This use of sensory information requires that the sensors, circulating with the blood, can communicate their measurements outside the body, e.g., to a receiver a person wears on his or her skin.



Collage of nanomedical particles and devices developed by members of the NCI Alliance for Nanotechnology in Cancer. Image from William C. Zamboni et al. Clin Cancer Res 2012; 18:3229-3241 © 2012 American Association for Cancer Research

PROGRESS TOWARDS ATOMIC PRECISION

Advances in capability to create and deploy high-precision tools provide the context for improving medical treatments.

Tools and techniques undergoing significant improvements include:

- Sensors for diagnosis
- Drug delivery
- Analysis
- Membranes for filtration
- Communication: among devices, and between devices and physician
- Implantable devices

This section describes some of these recent developments and prospects for further progress.

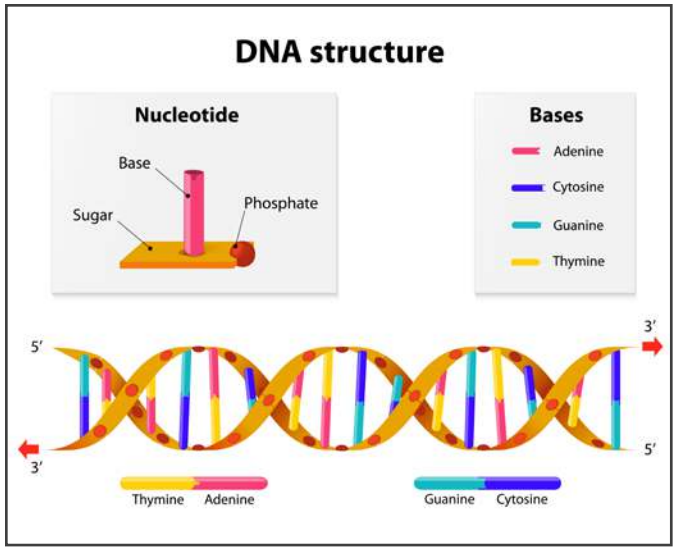
Recent Tool Development

Ongoing developments by many groups are creating increasingly precise tools. These advances illustrate the near-term potential for applying high-precision tools to medicine as the developments continue toward atomic precision. This section surveys a selection of these developments as a guide for capabilities available to near-term projects applying precise tools to medicine.

A broad area of advance is the increasing ability to combine sensing, computation and actuation on ever-smaller scales. Such tools are often referred to as "robots", although their capabilities for computation and autonomous action are severely limited compared to conventional robots. Nevertheless, such devices are potentially useful in medicine for minimally invasive surgery at small scales and in regions of the body not reachable by endoscopes [Sitti et al. 2015].

One example combining local sensing and directed motion is attaching nanoparticles to bacteria, which can move toward or away specific chemicals, light or magnetic fields [Martel et al. 2014]. In this case, the bacteria provide sensing and local navigation, while external magnetic fields can position the devices coarsely, e.g., in a particular organ. These hybrid nano-biological devices deliver particles to locally-defined environments, e.g., for drug delivery or building aggregates. Another approach to hybrid devices is modifying signals biological organisms use to coordinate their behavior, thereby changing the group behavior [Halloy et al. 2007].

At a much smaller scale, DNA robots sense specific DNA or RNA sequences and combine those detections via a few logic operations to determine when they act by releasing other chemicals [Bath and Turberfield 2007].



Biologically based devices already having working systems for power, locomotion and sensing, which can be used or modified for new applications. This contrasts with the greater challenge of building small devices with all these capabilities from scratch. In particular, such devices currently lack capabilities for autonomous navigation. Instead, they can be useful when passively absorbed by cells or moved with coarse resolution by external fields. Magnetically guided devices are one example [Yesin et al 2005]. Such magnetic nanoparticles can deliver drugs to a wide range of specific targets in the body. This includes passing through blood-brain barrier by local heating of a few degrees, which reversibly opens gaps in the barrier, allowing large molecules and nanoparticles to move out of blood vessels into the brain [Tabatabaei et al. 2015].

In addition to complete functioning devices, biology provides a wide range of machines and components. Examples range in scale from molecular motors [Phillips and Quake 2006] to interlocking mechanical gears several hundred microns in size [Burrows and Sutton 2013]. These examples show that self-assembly can produce small-scale versions of machines that are manufactured by directed placement at large scales. Understanding the range of components self-assembly can produce, and how to control the process, is important for the development of atomically precise tools because self-assembly is a promising route toward making small structures [Whitesides and Grzybowski 2002]. An example is increased flexibility in automating small molecule synthesis, analogous to 3D printing but at a molecular scale [Li et al. 2015].

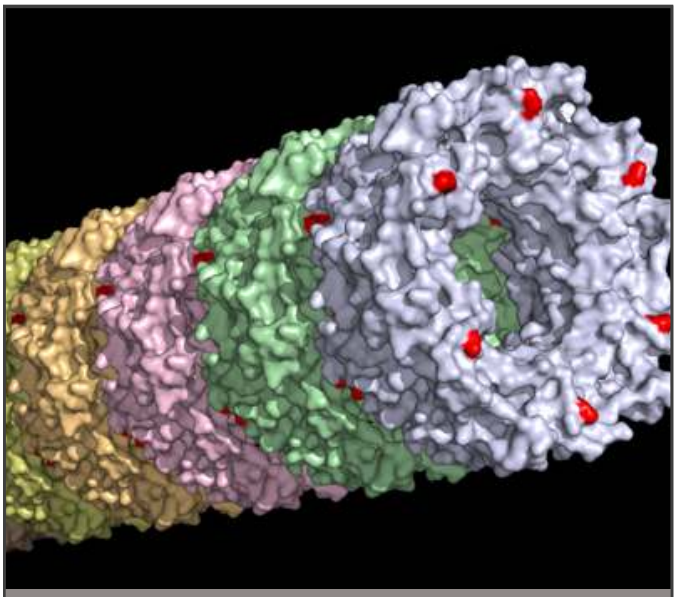
Another area of progress is modifying biological mechanisms to incorporate new molecules. One example is incorporating new nucleotides into DNA in E. coli, in effect, extending the genetic code [Malyshev et al. 2014]. Using additional nucleotides increases the range of structures DNA self-assembly could produce and highlights the long term potential for using DNA to make structures [Sanderson 2010]. For instance, this increases data storage in DNA by providing more options for each base pair. Additional nucleotides also have applications simply because they do not occur in nature.

For instance, a public health application could use additional nucleotides as identifiers for foods, e.g., to trace food-borne infections more quickly and precisely than is possible today. They could also be incorporated into drug delivery, giving the ability to remove them if not working by targeting the new nucleotides. Because these bases do not occur in normal cells, such targeting would be specific to the introduced drug.

New tools allow increasingly precise measurements of individual cells, including using and applying mechanical stress to cells [Huang et al 2004], and measuring electrical behavior in individual cells [Duan et al. 2012]. One application relies on detecting mechanical operations inside cells (e.g., the motion of protein motors). These motions produce vibrations on cell walls, which may provide a novel sensing modality for nanoscale devices investigating cell behavior and distinguishing between healthy and diseased cells [Pelling et al. 2004]. As another example, measuring mechanical properties of cells aid in identifying stem cells [W. Lee et al. 2014].

Manufacturing precise materials can improve existing medical devices. For example, nanotube coatings on stents prevent growth of unwanted cells [P. Lee et al. 2014]. Another example is

applying nanomaterials to improve drug delivery [Fox et al. 2015], such as using precisely-sized nanotubes to constrain diffusion for improved drug release kinetics (e.g., http://www.nanoprecisionmedical.com/technology/the-goldilocks-effect). In addition to creating more precise tools, the ability to evaluate biological molecules and structures more precisely helps identify fundamental causes of disease. One example involves how two meters of DNA is packed into the small volume of a cell. A recent study shows that incorrect packing (heterochromatin disorganization) can lead to disease, such as Wiener syndrome. Adding the correct protein fixes the packing and thus offers a new approach to these diseases [Zhang et al. 2015].



Hcp1 is a ring-shaped protein from Pseudomonas aeruginosa that was engineered by scientists at the Molecular Foundry at Lawrence Berkeley Lab to form covalently linked nanotubes. Image from Ronald Zuckermann.

Future Tool Development

Developing viable research projects on applying precise tools to medicine requires understanding not just currently demonstrated performance of such tools but also how the tools and associated biomedical knowledge will likely improve over the next few years. This is important so projects are not confined to capabilities of currently demonstrated tools, but instead evaluate applications for future tools. This evaluation, in turn, will motivate the development of those tools and prepare applications for them to reduce the time between tool development and their medical applications. This section describes likely improvements to available tools, though the time frames are necessarily somewhat speculative.

Sensors will decrease in size and increase in performance, i.e., increased signal-to-noise, sensitivity and selectivity. New sensors will provide this performance with label-free detection, allowing their use in a wider range of settings. Sensing will combine with real-time reporting, and allow safe, effective implants for long-term continuous monitoring of a large number of different simultaneous measurements in the body. The sensors will improve disease diagnosis. Similar improvements in medical image resolution will provide more precise overview of tissues and organs, complementing information obtained from small, embedded sensors.

Drug delivery will provide increasingly precise targeting, based on multiple measurements and some logic operations to identify appropriate release sites. As devices decrease in size, drug release will involve computation at the level of individual cells to identify targets. Delivery devices will not only move passively through the body, but can also be self-directed, extending today's capability move devices based on external fields. Beyond delivering small molecules as drugs, the devices will deliver engineered cells or viruses to cells recognized by specific chemical markers or mechanical properties.

Sensors and drug delivery devices used in the body must be safely disposed of after use. In some cases, the devices will be small enough for removal via normal body mechanisms, e.g., via the kidneys. For larger devices, improved materials should allow making implanted devices that dissolve into harmless smaller components for normal removal by the body.
Nanoscale surgery will provide precise operations on individual cells, including editing or replacing a cell's DNA. Combined with improved

sensing, precise surgery will remove diseased cells and replace with new ones, while avoiding healthy cells.

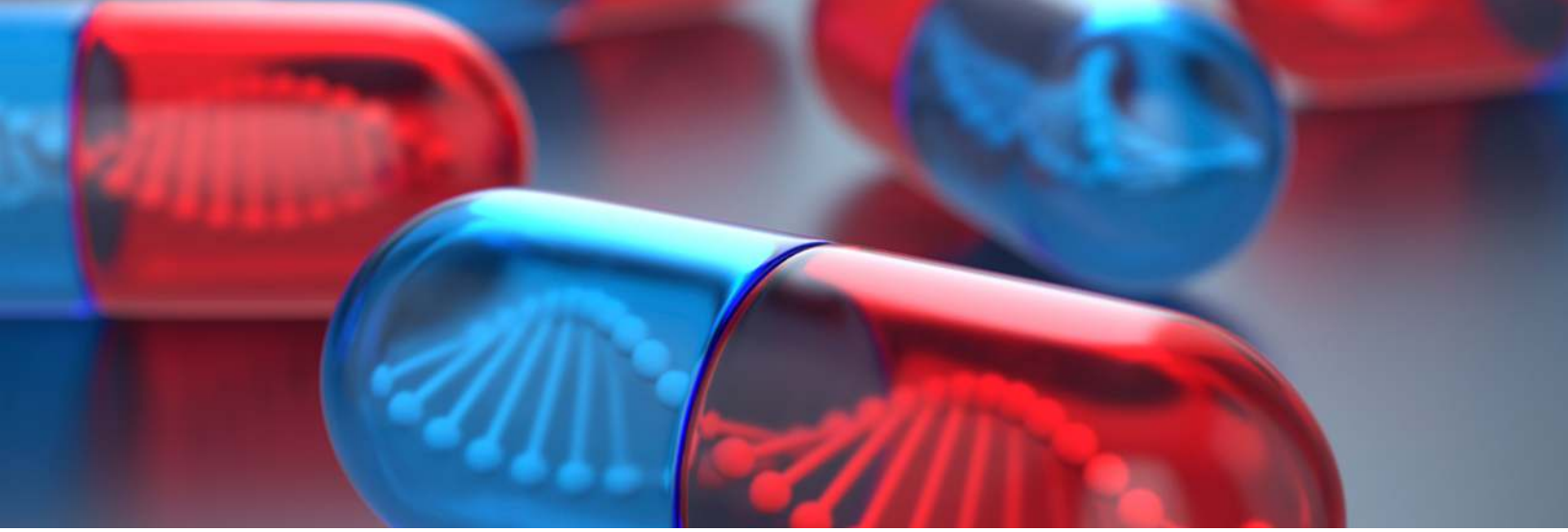
In addition to direct repairs to injured tissue, precise surgery could introduce materials in specific locations that provide guides to aid the body's own repair processes. These guides will act as scaffolds, providing both mechanical support and chemicals necessary to guide the repair, e.g., for faster and better wound healing. The scaffolds could also include patient-specific stem cells to grow specific tissues.

Improved membranes will provide precise blood filtration and other separations of specific molecules. Such membranes could be part of implantable bioreactors, which will create molecules in response to changing conditions within the body. This will be much more responsive than adjusting drug dosage based on intermittent testing, e.g., on a weekly or monthly basis.

As devices become smaller and more numerous, coordination of many devices operating simultaneously in the body will become increasingly important. This coordination can arise from external commands sent to the devices, e.g., by modulating magnetic fields the devices can sense. A longer-term development is devices communicating locally among themselves to coordinate activities. Even devices with limited computation and communication range can robustly organize activities over large scales in space and time, e.g., as swarms [Rubenstein et al. 2014]. These behaviors will lead to devices forming a communication network to relay information to and from external devices, such as the patient's cell phone.

Large numbers of precise sensors measuring many values raise a significant challenge for data analysis. This will require software for searching through and evaluating the large data sets produced by sensors operating within a single person.

Kilobot is a thousand robot swarm developed at Harvard University, Wikimedia Commons.



REALIZING THE OPPORTUNITY

Realizing the potential for precise tools to improve medicine requires matching tools to applications and identifying improvements in research infrastructure to support the projects.

Tools to Address Medical Challenges

Medicine could benefit from expanding the set of substances that can be used as precisely targeted drugs. For example, natural catalysts can have useful medical properties but are too large to deliver effectively. Two approaches are improved delivery vehicles that could accommodate larger molecules, and designing and synthesizing smaller, robust versions of the catalysis so they can get to sites too small for conventional catalysts.

Combining information from multiple sensors will improve diagnosis and drug targeting. For example, sensors for multiple binding targets on cells will allow more specific identification than a single binding site. Such sensors will need to account for variation in the spatial distribution of multiple sites on different cells. These sensors would be particularly useful for identifying cancer cells that lack single specific markers that distinguish them from other cells.

Recent studies of the body's micro-biome indicate the ecosystem of organisms living on and within the body have significant impact on some diseases. Thus precise tools to quantify and alter the micro-biome should be useful additions to medicine. In particular, detecting changes to the biome would help identify infections before they spread throughout the body. This data collection would transform the biome into a continuous medical sensor.

Many diseases involve inflammation. Better sensors as part of tools for drug delivery could help treat inflammation by identifying the precise type of inflammation and hence suitable treatment options. One approach to achieve this is for tools that mimic immune cell response such as ability to pass through vessel walls, allowing the tools to get to and interact with cells involved in inflammation response anywhere in the body.

Aging clocks underlie many of the fundamental causes of disease. In principle, tools such as DNA editors can alter these clocks. However, we currently lack sufficient knowledge of these clocks and how they operate in the body. Thus development treatments for these causes could benefit from precise sensors used as research tools to identify where clocks act. For example, developing sensors to examine the methylation status of DNA in various cell types and under various disease conditions. In particular, it would be useful to compare RNA expression patterns in young and old organs.

Interpreting RNA information accurately requires knowing which cells and tissues produce the observed RNA. The most direct approach is to use a large number of small sensors that can get next to or inside individual cells. An alternative is to measure the RNA that cells release into the blood. This could use simpler sensors, e.g., confined to blood vessels, but does not directly identify which cells in which tissues produced the observed RNA. One approach to gain this information would first use cell-specific drug delivery to target an RNA sequence of interest to specific organs, and connect to a ligand excreted by the cell. This would provide a bar code identifier with RNA sensed in blood that would tell where the RNA came from.

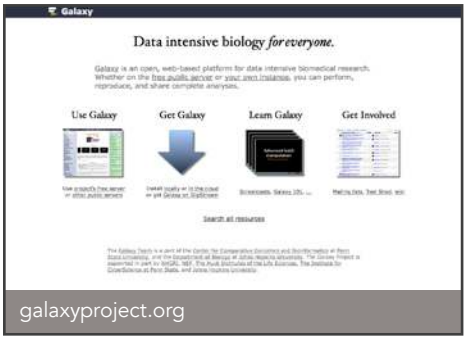
Infrastructure

A significant obstacle to progress with interdisciplinary projects discussed at the workshop is the difficulty of sharing information among diverse research communities. This arises through limited funding support for cross-disciplinary meetings and tool development. In particular, there is a lack of easily-accessible online resources that provide relevant information in a form useful for researchers in other disciplines. Moreover, potential developers of medical applications for new, precise tools need to be aware of the rapidly improving capabilities of these tools. This is gradually improving. This workshop is an example of how to engage researchers to take time from their schedules to explore potential collaborations with researchers in other fields, for projects with large potential payoff for medicine involving high-precision tools.

Web-based collaborative tools for scientific research are under development, e.g., the Galaxy Project (www.galaxyproject.org) for data-intensive biological research, the Open Science Framework (https://osf.io) for managing research projects, and the Jupyter Project (jupyter.org) to support scientific data analysis and interactive reports.

In terms of spreading awareness of new tools, one source of information on material and device capabilities to guide medical application developers is data collected by the National Nanotechnology Initiative (NNI) with indications of the quality of the data through emerging standards of data readiness levels (described at www.nano.gov/NSINKI).

Conversely, materials and computer scientists need convenient access to quantitative biological data, at many scales, to inform the engineering of tools and algorithms to exploit them. For initial evaluation of designs, even order-of-magnitude values would be helpful. Beyond expanding the range of measured values and their accuracy, a significant challenge is the large variation in biological systems: robust tools and algorithms need not only typical values but also an indication of the range of variation and how that variation depends on other measurable properties. This variation occurs among individual organisms as well as within a single individual, including stochastic variation in behavior among genetically identical cells even in identical environments.



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jupyter.org

Currently, such quantitative biological data is widely scattered in the literature, and presented as results of a variety of experimental protocols whose differences are not readily apparent to non-specialists. This makes it difficult for researchers in other fields to collect the comprehensive sets of measures relevant for designing high-precision tools for medical applications. Nevertheless, large-scale data sets are becoming more available, such as for protein and gene interactions. Another example is the Bionumbers project (at http://bionumbers.org), which provides quantitative values, and ranges, for many cellular processes.

In cases where values useful for engineering new devices are not known, higher-precision sensors could be useful tools to collect the information. This is somewhat a chicken-and-egg situation where better data is needed to inform device design, but the data is not readily measurable until higher-precision sensors are available for widespread in vivo use. This relates to the project selection criteria supporting tool development even if it is not immediately apparent whether or how those tools will be medically useful. This applies both to new sensors to collect information and better computational approaches to make the data available to non-experts, e.g., extending from keyword-based searches to natural language queries.

New tools and medical knowledge can suggest a large number of possible new applications. The number of possibilities is far too large to systematically evaluate each possibility with a detailed research project. Researcher experience and intuition can help focus on the most promising possibilities. However, the rapid development of more precise tools opens opportunities for approaches that were not feasible before, and therefore for which researchers have little prior experience. This could lead to overlooking some significant benefits of newly developed tools.

One way to help address this problem is improving accessibility and significantly reducing the cost of performing biomedical experiments. This would be especially useful at early stages of a project to evaluate potential outcome quickly and cheaply.

An example is Emerald Cloud Lab (http://www.emeraldcloudlab.com) which is attempting to improve availability of biological experiments. If successful, such approaches could significantly reduce the costs for research groups to perform initial evaluations of applications of new tools. This approach is analogous to Amazon Web Services (http://aws.amazon.com) providing scalable computing platforms, significantly reducing the upfront capital cost of compute-intensive projects.

CRITERIA FOR SELECTING RESEARCH PROJECTS

The continuing improvement in tool precision and opportunity to use them to address fundamental causes of many diseases favors relatively long-term, interdisciplinary projects, and steps to simplify those collaborations by improving infrastructure to support such projects. While such projects have large potential payoffs, they are also risky and require sustained effort from people with differing expertise. This risk, and the need for people from different fields to contribute (e.g., medicine, biology, nanoengineering, and computer science), make it difficult to identify funders willing to devote some of their budget to such projects. In particular, the tools applied to fundamental causes of disease could, if successful, help with many diseases while funders of medical research tend to focus on one or a few specific diseases, and so are less willing to devote resources to a project with a low chance of addressing their particular disease even if, aggregated over multiple diseases, it has reasonable prospects of helping with at least some of them.

Main criteria are the benefit of successful outcome vs. the risk of not achieving that outcome. As described above, high-precision tools could have significant medical benefits and address many diseases through treating fundamental causes. With this potential comes large risks of not achieving the goals due to challenges of fabricating tools, especially with atomic precision, the complexity of biological systems at the molecular scale these tools could access, and the high cost of translating laboratory demonstrations into effective and affordable clinical practice. Thus the discussion of selection criteria focused primarily on the technical questions of evaluating project outcomes and technical feasibility. Additional important practical issues involve the required resources, availability of funding and compatibility with researchers' individual goals. The remainder of this section discusses these criteria.

Outcomes

The outcome of the project, if successful, is a major criterion. This emphasizes aiming for major advances to identify and exploit the full potential of new, more precise tools for a variety of medical problems, rather than incremental improvements for individual diseases. Long term benefits (e.g., in terms of lives saved per dollar) instead of focus on incremental progress on high-profile diseases that, even if cured, would have relatively little improvement on life expectancy. This motivates focusing on fundamental causes of disease, e.g., potentially leading to a solution to aging, rather than each disease individually.

For projects advancing the use of atomic precision for medicine, the most direct focus is on medical outcomes, i.e., demonstrating the efficacy of treatment. In addition, the outcome should have reasonable potential to transfer from demonstrated efficacy in research studies to widespread clinical use. This includes affordable per-patient cost of the procedure (as opposed to research and development cost), which is particularly relevant for applications in developing countries, e.g., treating tropical infectious diseases.

Projects involving advanced applications enabled by precise tools may raise significant ethical or public policy concerns. This is especially important for outcomes that already trigger such concerns, e.g., editing germ line DNA or enhancing human performance rather than just curing recognized diseases.

Due to the high risk the project may not fully reach its goals, a good project will have secondary outcomes that will be useful whether or not the intended clinical outcome is successful. For instance, the project could be a useful learning opportunity and develop knowledge and tools useful to other researchers. Or the project could inspire additional research and train the next generation of researchers, e.g., so they are ready to move quickly if and when tools improve to the point of enabling this or similar projects to succeed in the future even if the current attempt does not reach its goals.

Another useful outcome is a project to remove a bottleneck in the technical feasibility of an approach to fundamental causes of disease, even if that result would only be part of an overall treatment that requires additional work.

Projects need not attempt complete solutions to clinical problems: a project limited to improve performance or manufacturability of high-precision tools could be useful in demonstrating practical feasibility of the tools, thereby enabling other researchers to use them for biomedical research and later clinical applications. New tools may have a variety of medical applications that are not apparent until people gain experience using the tools. One way to pursue this criterion is to view the project as creating a combinatorial platform that other research groups could use. For example, a device capable of carrying a variety of sensors in the bloodstream could be useful for other groups testing various combinations of sensors.

Finally, a useful outcome for short exploratory projects is evaluating whether a potential set of collaborators can work effectively together. This is particularly useful for interdisciplinary groups who have not previously worked on projects with researchers from those other fields. Gaining this experience from a short, low-cost project addresses this question with minimal commitment of time and funds.

Technical Feasibility

Trading off with the desirability of the project outcome is the risk of not being able to deliver that outcome. For projects involving new tools and aspects of biology that are not well-understood, technical feasibility is a major component of this risk. This includes the ability to develop the precise tools, along with their safety and efficacy in clinical use.

Another aspect of technical risk is competing approaches. That is, to what extent could incremental improvements of current methods achieve similar clinical outcomes? This requires estimating how the other techniques might develop. Moreover, existing techniques already have an established group of clinical users and acceptance in standard practice.

This comparison with existing techniques requires identifying situations where the new tool has a large, fundamental advantage over existing practice. That is, to what extent does high precision actually improve outcomes. For example, nanodevices can target specific cells, e.g., killing cancer cells.

However, when many cancer cells are close together in large tumors, surgical removal of the tumor mass all at once may be more effective than using many nanodevices that each target one cell at a time, and then require the body to dispose of a large number of necrotic cells. In this case, the best use of the new tools could be to combine surgery for large, operable tumors with nanoparticles to target small remaining cells that are too dispersed for surgical removal.

Technical feasibility is difficult to determine for projects that involve combining techniques and expertise from different fields. Furthermore, for new tools, there will not yet be prior clinical experience to guide the assessment of clinical effectiveness. The proposed tools for the project may not even yet exist. Thus evaluation is uncertain and may require interdisciplinary committees to have the range of relevant expertise. This can require substantial time commitment from members to learn enough about aspects of the project outside their field of interest and expertise.

Resources

Required resources are an important criterion for evaluating projects. This includes the number of people, their expertise, lab facilities, project duration and funding requirements. Another aspect of the resource evaluation is the availability of supporting infrastructure. This includes the extent to which required tools, techniques and relevant biological data are already available or need to be created as part of the project.

The projects discussed at the workshop are relatively small, in terms of people and funding. Such small science projects could demonstrate technical feasibility of tool development and application. However, much larger efforts and funding will be necessary to bring successful outcomes to clinical use, not least due to the cost of clinical trials. Partnering with large pharmaceutical companies is a possible approach to acquiring the resources to transition to clinical use.

Project Evaluation

It is helpful if a project has intermediate, measurable goals to monitor progress. This encourages devoting some resources to many different approaches, with the knowledge that less promising ones will be identified early. Moreover, early results could usefully inform the direction of other projects.

Funding

The feasibility of obtaining funding is a practical constraint on projects. This includes evaluating the attractiveness of the project to conventional funders (government, industry and specific disease advocacy foundations) as well as emerging ones (crowd funding and use of prediction markets to allocate funding). This requires finding a balance between pushing well beyond incremental improvements while remaining within the scope and time frame of funders.

IP Status

For potential commercial use of project outcome, a company would likely need to negotiate license agreements with others owning relevant patents. Thus an important issue is the likely cost of such licenses.

Investigators' Interest

Projects should engage the interest of the researchers involved, providing the excitement and challenge of addressing problems with innovative science and technology, and the potential for large medical benefits. The project must fit with the researchers' technical and career goals. This includes educational goals for academic groups to motivate and train new researchers. For an effective interdisciplinary collaboration, the project should have appealing scientific challenges for all the people involved.

EXAMPLE RESEARCH PROJECTS

Six projects were selected for further study during the workshop. These illustrate how interdisciplinary teams could pursue the opportunity of atomic precision for medicine over the next few years. Additional projects were briefly presented but not considered further: improved immunotherapy, enabling drugs to cross the blood-brain barrier, developing energy sources for nanoscale implanted devices and extending databases of biomarkers for various disease conditions.

This section describes the rationale and research plans for the selected projects. Each project was discussed as a proposal for academic research or a new business. Much of these discussions focused on specific diseases and new tools with high, if not atomic, precision. This focus made the projects more compatible with the interests of funders. Nevertheless, experience from projects will likely transfer to addressing fundamental causes of disease and applying atomically precise tools.

Artificial Immune System from Modular Molecules

Drugs are typically small molecules that bind to pockets of enzymes, thereby interfering with their activity. However, most proteins are not enzymes and have no pocket for a small molecule to specifically bind. Thus, small molecule drugs are not a useful technology for inhibiting or otherwise altering the biological function of most proteins. This severely limits the available targets for medical intervention in networks of protein interactions.

This project addresses this limitation by creating larger molecules that bind to a wide variety of proteins by wrapping around them instead of binding to just one small part of the protein. Such molecules will interact with the protein over a considerably larger surface area than small molecules, potentially resulting in much higher binding energies than small molecules can achieve. This is analogous to the binding achieved by antibodies.

Achieving this goal requires both the ability to make a wide variety of large molecules and the ability to design such molecules for particular targets. This project will use a set of modular molecules to exploit the rapidly improving capability to synthesize large molecules precisely with reasonably high yields.

Instead of attempting to custom design a molecule for each application, the project will create a combinatorial library of 1010 molecules, each about 5% the size of antibodies. These molecules will be tested for their binding to various proteins. Ideally, a molecule will bind specifically to a single protein. Thus the screen

process will include testing for binding to the desired target and for undesired bindings to other molecules.

The result of these tests will be a library of molecules, each of which can be readily synthesized and has known binding to particular proteins. These molecules could form the basis of drugs that target these proteins, giving a much larger range of possible drug targets than currently available with small molecules that require binding pockets. The project's estimated cost is $3 million over several years.

Artificial Organs

Many patients who could benefit from organ transplants do not get them due to lack of available donors. An alternative is to grow new organs from the patient's stem cells [Badylak et al. 2012], thereby avoiding the need for other donors and for continual suppression of immune rejection of the transplanted organ.

Kidney organoid (5.7 x 6.4 mm in size) generated from human induced pluripotent stem cells contains all renal cell types. Image from Minoru Takasato.

As a proof of concept, the project will focus on an artificial liver. The liver has several advantages as a first demonstration of this technique for growing organs.

First, the liver has a relatively simple vascular structure, organized mainly in layers that are well-suited to reproduce with 3D printers. The structure also appears to allow significant departures from its natural form without detriment to the liver's function. This degree of flexibility in structure could be useful if, for instance, the 3D printing requires additional supporting structures, such as struts, to maintain its form while the cells grow.

Second, the liver is the most structurally simple of the major organs, with only a few types of cells. Since each cell type will need to grow in the artificial structure to produce a new organ, starting with an organ having relatively few cell types reduces the research effort required to create suitable growth environments for the cells and hence increases the likelihood of producing a functional organ. At a higher level of organization, the liver consists of a set of modules which could help simplify the engineering of an artificial organ by first producing similar modules before attempting to create a full organ.

Third, the liver is primarily a venous organ. Thus its oxygen demands are far lower than for other organs. This could be important in the early stages of the growth if the initial artificial vascular structure provides less oxygen and nutrients than the normal blood supply to the liver.

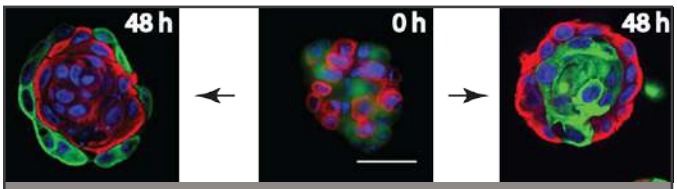
This project requires finding suitable stem cells that can differentiate into liver cells. Alternatively, with the development of sufficiently precise DNA editing tools, any cell type could be converted into suitable stem cells.

Liver cells (hepatocytes) do not divide in culture. Thus growing a liver requires a scaffold to support the distribution of cells into a fully functional organ replacement matrix. Constructing such scaffolds is difficult for vascular organs such as the liver. This project addresses this challenge by 3D printing the vessel structure first, with the vascular component filled with hydrogel to support it from inside, with sufficient branch points to strengthen the vascular network so it can, with the internal hydrogel support, stand on its own, surrounded by "empty space" (liquid medium only).

Prefabricated organizing extracellular structures are then inserted into that empty space. This

organizing structure includes binding sites to guide non-vascular cells of different types to their correct locations in the organ.

The hepatocytes and other non-vascular cells are then slowly infused into the extravascular space until they occupy most of its available volume, all the while amply supplied by nutrients and oxygen from the cell-infusing solution. Subsequently, rapidly photodegrading the hydrogel inside the vessels, perhaps using two-photon technology, allows prompt perfusion of the entire structure with nutrients and oxygen through the vascular system to maintain viability, thus avoiding the "vascular limitation" problem of current organ printing methods. Ideally, the scaffold is constructed at least in part of normal extracellular matrix molecules for the liver, which are both biodegradable and replaceable by normal liver cell mechanisms.



Human epithelial cells self-organizing in different conformations as a function of the microenvironment experienced. Red = Keratin 14; Green = Keratin 19; Blue = Nucleus. Scale bar = 50um [Adapted from: Cerchiari et al. PNAS 2015].

For testing purposes, the cells can contain added bar code markers. This will allow identifying cells that are part of the new organ rather than from the original one. This identification will help test whether the artificial organ is working correctly.

This project creates the new organ's vasculature and bile ducts, but the artificial organ will not have nerves. Thus the artificial organ will not have nerve-mediated feedback control. For liver replacement, however, the lack of regulation by nerves may not be significant. This is because blood flows into the liver primarily from veins, which are at a low and nearly constant pressure independent of most body activities. Thus an artificial liver may perform reasonably well without feedback control.

Alternatively, in a second-generation version, myelin sheaths containing living Schwann cells can be installed into the organ during fabrication, as part of the extracellular matrix. Nerves matched to empty myelin sheaths maintained by Schwann cells can grow through the sheaths, following them like water flowing through a conduit, thus re-innervating peripheral structures such as limbs. The same process should enable re-innervation of vascular and other key areas of the artificial liver.

This observation on the artificial organ having only some of the functions of the natural organ is an instance of a more general property of artificial organs: a lifesaving treatment does not require that the artificial organ perfectly replace all functions of the original organ. This trade-off is particularly relevant for organ transplants, where waiting for a donor organ can only provide for a few patients.

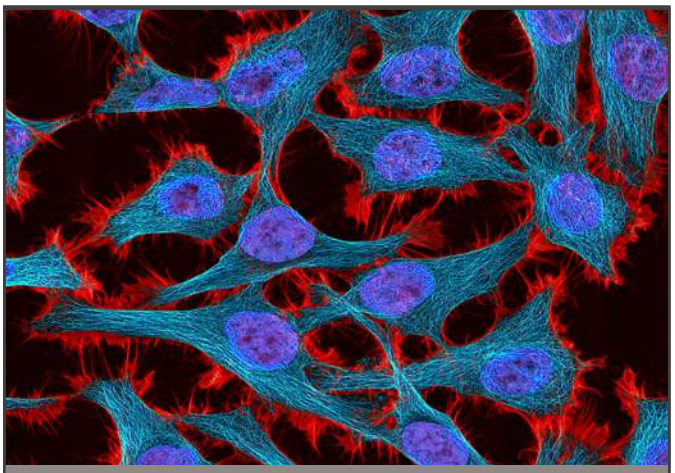
The estimated cost for the project is $40 million over 3 years. The three-year time horizon is based on parallel processing on all of the different sub-problems that require engineering solutions.

An extension of this approach to organ replacement is an organ bank of artificial organs. This involves growing artificial livers as described above and then cryopreserving them for later use, when patients require them. In addition to the challenges of growing the organ, this extension requires overcoming chilling injury of liver cells, so that banked organs perform as well as newly grown ones. This organ bank will reduce the time patients must wait for their transplant, which is particularly important in the context of acute liver poisoning, in which the liver must be ready to go within hours or a few days at most of the poisoning event, which can only be achieved by being able to stockpile the organs.

On the other hand, an artificial organ from such an organ bank will not have been grown from the patient's own cells, so will require managing immune response to the new organ, similar to that required when using donor organs. Fortunately,

however, for recipients who can schedule their transplants a few months in advance, new techniques promise to enable donor-specific tolerance induction while the designated organ remains in the freezer, enabling the recipient to receive an organ of any tissue type without the need for life-long immunosuppression and without ever rejecting the organ.

The techniques developed in this project could extend to more complex vascular organs, such as the heart or the kidney, based on the experience derived from the liver.



Multiphoton fluorescence image of HeLa cells stained with the actin binding toxin phalloidin (red), microtubules (cyan) and cell nuclei (blue). Nikon RTS2000MP custom laser scanning microscope.Image from Tom Deerinck, National Institutes of Health.

Cancer Treatment Based on Telomeres

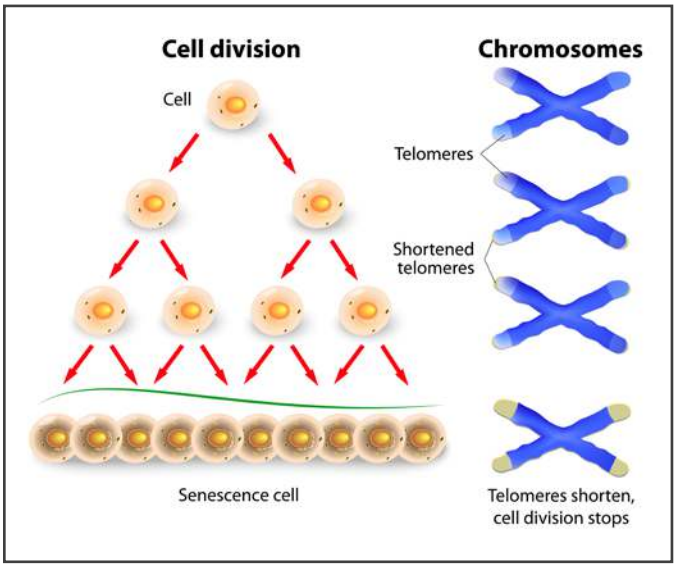
A major challenge for chemotherapy cancer treatment is the harm done to healthy cells by insufficient precision of targeting the drug to cancer cells, and the resistance of some cancer cells to the drug. One approach to dealing with this problem is to focus on the ends of chromosomes, i.e., the telomeres. In most healthy cells, telomeres shorten with each cell division, which prevents cells from dividing indefinitely. To avoid this limitation, cancer cells need to maintain their telomeres as they divide.

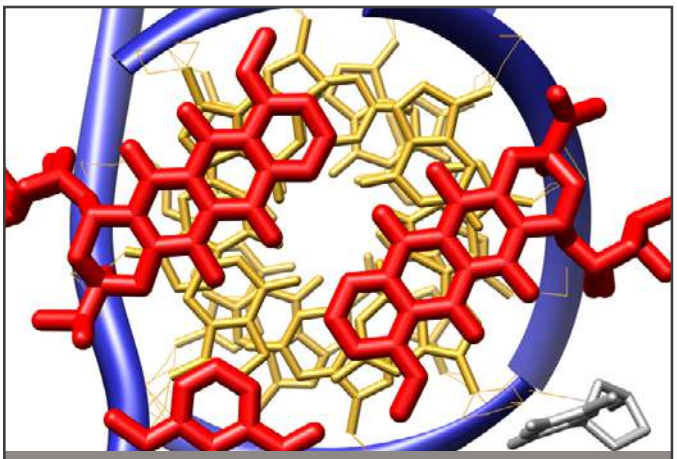
This observation suggests that an effective drug target would be to inhibit proteins involved in lengthening telomeres. Unfortunately, cells have two mechanisms to increase telomere length, and it has proved difficult to develop drugs that reliably block both methods, do not harm healthy cells and avoid cancer cells developing resistance.

As an alternative to inhibiting proteins involved in telomere repair, this project aims to stabilize the folded structure of telomeres, preventing their elongation, and hence preventing cellular repair mechanisms from accessing the telomeres to increase their length. This requires designing molecules that selectively and strongly bind to folded telomeres, and that can be delivered into the cell nucleus. The therapy must also avoid modifying telomeres in healthy cells, either because the molecules only act when inside cancer cells or they can be selectively targeted to cancer cells.

Currently, some compounds are known stabilize the folded structure of telomeres. These compounds can be manufactured with 90% yield and appear safe for use in cells. This approach is an example of targeting large-scale DNA structure rather than its primary structure (i.e., sequence of bases) [Luedtke 2009].

Starting with variations of these compounds, the project will perform in vitro tests of how well the compounds bind to folded telomeres based on existing techniques [Monchaud and Teulade-Fichou 2008].





Small molecules interacting with DNA quadruplexes (DNA structures investigated as new genomic switches that may have great therapeutic applications). Image from D. Monchaud & M.-P. Teulade-Fichou, Org. Biomol. Chem. 2008, 6, 627

Circular DNA nanomachine operating in whole human blood (the fluorescent dye indicates the mechanical state of the machine). Image reproduced by permission of Elton Graugnard from Nanoscale, 7, 10382 (2015), DOI: 10.1039/C5NR02283E

DNA Robots to Treat Type-1 Diabetes

Ideally, medical treatments would occur only at the specific cells and times requiring treatment. Drug delivery aims to achieve this using drugs targeted to particular cell receptors. Improved precision for devices allows improving targeted drug delivery with logic operations based on sensed chemical environment. This can combine multiple signals to determine target cells.

As a current example of this capability, DNA robots can determine whether to release a chemical inside a cell based on a few logic operations on sensed RNA in the cell. Minimal robots consist of a few strands of RNA, chemically modified to be stable inside cells. They can be delivered into specific cells, e.g., via nanoparticles [Bath and Turberfield 2007; Pinheiro et al. 2011]. More complex devices can consist of DNA origami with thousands of base-pairs assembled from hundreds of individual strands [Douglas et al. 2012, Katsnelson 2012].

The actions of DNA robots can be combined, with the output of one being the input of another. In this way, the final chemical output to change behavior in the cell can be the result of multiple logic operations. This process can include signal amplification, where one output signal releases many others in the next stage of logic operation.

Chemical modifications of DNA robots affect binding kinetics — hence the time required for the device to detect its input and release its output. Thus DNA robots not only perform abstract logic operations but can also respond, with a delay, based on the duration of the signals. Extending this behavior to multiple robots allows responding to a series of chemical events within the cell that occur with specific time delays and in a given sequence.

DNA robots are cheap to manufacture. For example, $20 buys a trillion DNA robots at current prices. Thus enough robots to tag all ~10 trillion cells in the body with 1-100 DNA robots would cost about $200-$20,000. Moreover, design software for DNA robots is available (e.g., at www.nupack.org and cadnano.org).

This project investigates extending the simplest DNA robots to act based on information from multiple interacting cells. This capability relies on detecting inter-cell communication. Specifically, surface-bound DNA robots produce a chemical signal when robots on the surfaces of different cells come in contact.

An application of this capability is to identify the subset of immune cells that attack beta cells in type-1 diabetes. Surface antigens are known for beta cells and immune cells, allowing targeting of

DNA robots to the surfaces of each of those cell types.

An immune cell remains next to a target cell for several minutes if interacting, while the contact time is much shorter if the immune cell is not activated. For this application, chemical modifications for DNA robot operation must have a similar time scale to trigger the sensor. This timing avoids false positives from an immune cell that briefly touches a beta cell but does not interact with it.

In more detail, the proposed procedure is as follows. First, tag immune cells and beta cells with DNA robots. Then wait for the immune cells to circulate. Immune cells that target beta cells bring DNA robots close together on their surfaces for long enough to trigger the reaction, resulting in releasing the signal into those immune cells.

In one version of this application, the signal released by the DNA robots on the immune cell is a fluorescent marker. Since only those immune cells that target beta cells will have this signal, subsequent fluorescent-activated cell sorting will isolate those immune cells. Examination of those cells will identify specific markers on immune cells that target beta cells. This information enables selective removal of just those immune cells from the patient, e.g., through drugs that target cells with those markers. This procedure will remove the attacking immune cells without affecting the rest of the patient's immune system.

Another version of this application uses a signal that disables or kills the immune cell. Since the signal is only released into immune cells that attack beta cells, only such cells will be affected.

The first version of this procedure provides information on the target immune cells without harming them. This allows the attending physician to evaluate the information before acting on it. This separation of an information-gathering stage from treatment allows checking the accuracy of the targeting procedure before proceeding to the treatment stage of the procedure. The second version of the procedure, by contrast, combines the identification and elimination of target cells without further human intervention. This combination requires target identification with a high degree of reliability.

This research project requires people experienced with methods to attach DNA robots to the surface of cells with specific markers. The DNA will require chemical modification so the robots remain on the cell surface long enough for the inter-cell interactions to take place. Since these robots will be applied to many immune cells, the procedure for attaching the robots and the duration of their stay on the surface must not harm the immune cells. Moreover, after sufficient time for immune cells to circulate and find beta cells, the body must harmlessly degrade and remove the DNA robots.

Once suitable DNA robots are available, the project must verify that cell-to-cell communication takes place, and this results in the exchange information between DNA robots on interacting cells. Subsequently, this technology can label immune cells that attack beta cells.

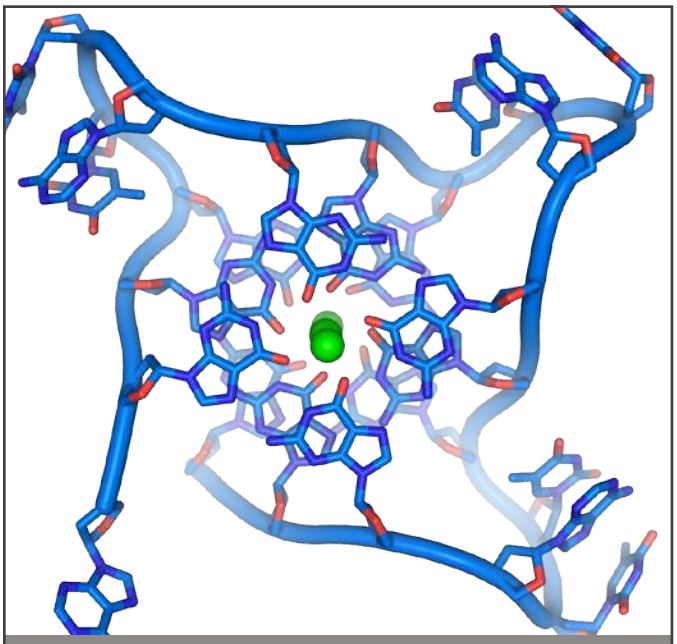
In vivo testing will collaborate with diabetes research groups, who already have animal models and test procedures for evaluating safety and efficacy of new treatments.

This project has an estimated cost of $0.5 million/yr over several years, with a team consisting of a few post docs.

This procedure generalizes to other autoimmune diseases, making it a powerful approach to applying a small amount of computation to greatly increase the precision of diagnostic or therapeutic medicine.

Evolutionary Material Design Applied to Binding Heavy Metals

The increasing capabilities for synthesizing complex molecular structures highlights the difficult design challenge of identifying useful structures to make. This project addresses the design challenge by applying evolutionary methods to combinatorial variations of compounds. This involves creating many variants within a class of molecules, testing them for efficacy, selecting those with the best performance and repeating the process with variants of the selected population of molecules.



Crystal structure of parallel quadruplexes from human telomeric DNA. The DNA strand (blue) circles the bases that stack together in the center around three co-ordinated metal ions (green). Image from Thomas Splettstoesser.

One approach is to mix DNA, dendrimers and nanoparticles; assemble them randomly; select the best ones; and replicate them with some variation. For example, this evolutionary process could automate the process of finding ligands that bind specific molecules with high selectivity.

This project will focus on peptoid chains, with molecular weight of about 5 kilodaltons, consisting of precise sequences of blocks made of amino acids. Attaching these compounds to gold nanoparticles will create a combinatorial library of molecule shapes, with up to 1015 variations. These molecules will then be tested for how well they bind to target molecules of interest, e.g., virus particles. As an example application of this use of evolutionary design, the project will search for compounds that bind heavy metals.

The project will proceed in three phases. The first phase uses the evolutionary method to explore many combinations of known peptoids that bind metals. Selection pressure will be applied by environmental stress, such as how they react to fluid shear or how cells respond to the particles. For instance, when using fluid shear, those compounds that bind strongly will resist disruption by the fluid flow.

The second phase is a systematic study of effective compounds found through the evolutionary exploration. This study will identify binding mechanisms and suggest

variations of the successful compounds that could improve binding. These variations will be created and tested.

The final phase will develop applications for the resulting molecules. These could include bio-mining, environmental remediation and treating heavy-metal poisoning. The molecules could also be a platform for highly specific metal sensors for use in other applications.

The project will require $3 million/year for 5 years, and an interdisciplinary team of about 12 post doc positions with skills in chemistry, data analysis and applications for heavy-metal binding.

pH Sensors

The increasing precision of fabrication technology allows large-scale manufacture of cheap sensors with better accuracy, smaller size and greater stability than current sensors. This is leading to a wider range of feasible medical diagnostics, including sensors that patients can use for extended periods of time. Such sensors can capture variation over days or weeks, thereby providing better indication of patient health and response to treatment than is possible with occasional sensing limited to when a patient sees a medical professional.

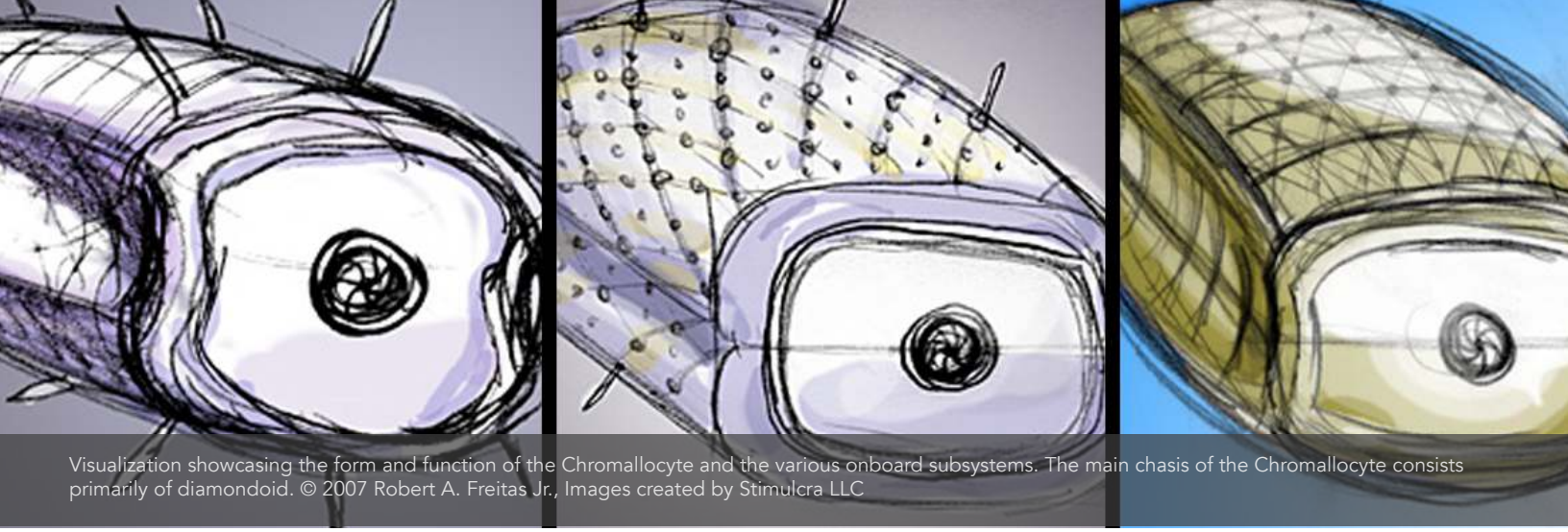
As an example of the benefits of such sensors, this project will develop a cheap, real-time oral pH sensor. It will consist of a patch to stick on a tooth for a few days. After use, the patient will remove and dispose of the patch.

An important design issue for sensors is whether and how they obtain power. One possibility is an unpowered sensor that, for example, reports pH by changing color. A cell phone camera detects the color change and provides the sensor reading. Alternatively, a sensor could obtain power intermittently via an RF antenna in the patch. In this case, the sensor gets power when read by a nearby device, such as a cell phone. For greater sophistication, the sensor could have onboard power, such as a small battery, to allow collecting and storing information over a period of time for eventual download to a cell phone.

This would allow providing more sensor readings than just when the user decides to interrogate the sensor with a cell phone.

This project will design, fabricate and test the sensor. In particular, the team will evaluate the sensor's measurement stability and develop a calibration procedure to produce accurate readings.

The project team will collaborate with other companies to create health apps using the information provided by the sensor. This will involve finding correlations between repeated pH measurements and medical diagnoses. Since these applications may require considerable time and funding to obtain FDA approval, the company will also identify entertainment applications for people interested in tracking daily changes to their oral environment, e.g., based on their dietary choices. Such applications could reach market soon after the sensor is available. These will also provide feedback on the user interface and data on normal variation in pH, which could later improve the interpretation of sensor readings for medical diagnosis.



Visualization showcasing the form and function of the Chromallocyte and the various onboard subsystems. The main chasis of the Chromallocyte consists primarily of diamondoid. © 2007 Robert A. Freitas Jr., Images created by Stimulcra LLC

NEXT STEPS

The development of atomically precise tools is a significant opportunity to improve medical treatments of a wide variety of diseases and their fundamental causes. The research projects presented at the workshop illustrate near-term potential directions for investigating this opportunity. In aggregate, these projects require a few tens of millions of dollars per year over 5 to 10 years, to advance development of atomically precise tools and evaluate their potential medical application.

A useful follow-up on these projects would be quantitative estimates of the performance of their required tools, to compare with current advances. For instance, exactly what must sensors measure, and how accurately and rapidly must they deliver their measurements. These would be relatively small, low-cost studies that could reduce risk by testing whether the ideas are feasible with precise tools becoming available over the next few years.

The workshop's focus was on the technical feasibility of atomically precise tools and their application to medicine. However, the workshop also briefly discussed the practical issue of funding exploratory, high-risk and high-reward medical projects.

For instance, developing and applying atomically precise tools to fundamental causes of disease requires sustained funding for interdisciplinary teams to develop strong collaborations and create and apply the new tools. In particular, at the early stages of development, funding will be mainly for creating new tools and basic biological knowledge to apply them effectively. Only later will these developments become viable clinical approaches to fundamental causes of disease. Thus the initial stages of the projects may not appeal to funders with focus on near-term treatment of specific diseases.

Other practical issues are the regulatory environment for bringing new treatments to market and the IP process blocking innovation by making it expensive for a single group to identify, negotiate and pay for the wide variety of patents that could be involved in creating and using high-precision tools. Although beyond the scope of this workshop, the next steps should include addressing these practical concerns.

Projects discussed at the workshop are not the only possibilities for exploiting atomically precise devices. Thus, small interdisciplinary groups could explore possibilities for additional projects. Especially useful would be projects likely to address fundamental causes of disease, which could help treat multiple diseases.

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