

# **IAF and Draper Labs Envision a Small Future**

**Institute for Alternative Futures**

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## Introduction

The Institute for Alternative Futures (IAF) and the Draper Laboratory held a workshop on the 15<sup>th</sup> of November 2004 in Cambridge, Massachusetts on the Future of Biomedical R&D in 2029. They recognized that the future of biomedical R&D is actually small, very small. The session forecast that a new tool kit of very small technologies is feasible, including micro-systems for drug delivery, micro-sensors to monitor patients, and micro-trials for drug development. Advances in imaging, biomarkers, organoids, systems biology, and multi-disciplinary collaboration will also accelerate advances in biomedical technologies, drug development, and healthcare.

Draper Lab Principal Director Paul Blasche welcomed participants, and expressed his desire to see some innovative ideas developed during the workshop. IAF President Clem Bezold facilitated the workshop with help from Jonathan Peck and Craig Bettles. Draper research scientists in the areas of biomedical engineering, microelectromechanical systems (MEMs), bio-informatics and other technologies shared their insights on the future. Outside experts from Center for the Integration of Medicine and Innovative Technology (CIMIT), the Massachusetts Institute of Technology (MIT), Harvard University, and Massachusetts General Hospital also attended. A list of attendees is available below.

## Workshop Objectives

The workshop participants were provided with a range of initial “provocative forecasts” developed by IAF. At the workshop these were explored, critiqued and refined and additional forecasts were added. Key forecasts were evaluated for their likelihood. Critical steps necessary for the development of the forecast were also identified.

The discussions considered:

- The general environment for innovation in biomedical technologies.
- Business models for future innovations.
- Changes in the regulatory environment for biomedical technology.
- Possible funding sources for future R&D.

## Forecasts for 2029

There were six main groups of forecasts discussed during the workshop. The first two forecasts presented below were developed by Draper research scientists. The last four were developed by the IAF team for the 2029 project.

### **Organoids Developed for Drug R&D**

**The distinction between in-vivo (living) and non-living systems for the discovery of biological phenomena, understanding disease processes and discovery of new drug**

**compounds has vanished by 2029.** The systems will be very complex systems of living & non-living systems called organoids.

Parallel thrusts in the development of nanoscale devices and the generation of in vitro biological systems have merged. Tools for identifying subpopulations on the basis of genetics and environmental exposures are available and help in targeting for the discovery of new compounds.

Organoids – replicas of human organs or components of them- will be developed and used to test the toxicity and efficacy of compounds outside the body. These will significantly lower the time and costs associated with the development of new drugs, particularly by discovering the toxicity of compounds earlier in the process, leading to drugs being discarded earlier in the process, or developed only for relevant subpopulations. Most animal testing will be eliminated because organoids will allow a more complete picture of the compound's effects on humans. The overall effect will be to drive price and spur the advance of personalized medicine.

Insights from advancing revolutions in systems biology and bioinformatics enable the replication of biological systems in the laboratory. Drugs are tested on organoids with the results uploaded into in-silico models to create a better understanding of the drugs properties. These capabilities accelerate the understanding of the full life cycle of interactions and effects of new compounds.

**Personalized medicine will require tens of millions of human trials focused on the individual patient (trials with an “N of 1”).** This will require major revolutions in our current approach to drug development and approval. Better models and understanding of why individual subpopulations react differently to different compounds will require better regulatory and health care information systems to ensure that this vital information is used properly and that patient privacy is respected.

Ex vivo tissue models will be an important intermediate step to creating the full fledged organoids needed for successful “N of 1” trials. In ten years doctors will be able to perform very small out-patient biopsies to collect tissue for testing personalized medicines. The biopsies will allow tissue to be engineered with the patient's own DNA profile.

To a certain extent, biomedical engineering is experiencing a paradigm shift from the development of tissue replacements to an in-vitro model for drug discovery. One of the key technological problems is developing three dimension matrixes of cells for replication. One solution may be the development of better nano-devices for fields other than medicine that can then be readapted by biomedical engineers to allow the precise movement of individual cells.

**The development of organoids for the research and development of drugs outside of the body is likely to take between 10 and 15 years.** The first applications during that time period would involve cell death forecasts for compounds. This will allow

researchers to better understand the toxicity of compounds on a cellular level. In 10 to 15 years, researchers will be able to do comprehensive efficacy tests on compounds in organoids before clinical trials in humans.

In the next ten years there will be better methods for using stem cells to create differentiated tissue types. The advances could be in either embryonic or adult stem cells, but the ability to create differentiated tissue from adult stem cells will be a key breakthrough for creating organoids with the same genetic pattern as individual patients. The use of animal stem cells to create differentiated tissue will also be important for using fewer animals in research and development.

The ability to create readouts for individual genomes will also be required. The readout would be a chart of the patient's genetic information. The workshop participants estimated that a full individual genomic readout would be available in five years, but that the computational power and sophistication needed to create models to understand and effectively use these readouts could take between 15 and 25 years.

### **Implantable Drug Delivery**

Drug discovery and drug delivery are going to be strongly coupled in the future through implantable drug delivery devices. **By 2029 there will be a prototype engineered biological system, operating inside the body, which senses disease, and then synthesizes and delivers therapeutic compounds in-situ.**

There are currently implantable drug devices with no feedback loops that use advanced materials to slowly diffuse drugs into the patient's system. Drug eluting stents and controlled release polymers are good examples of current drug delivery devices. Currently, there are also MEMs systems with one feedback loop containing a flow sensor to monitor and adjust the flow of drugs into the body.

**Two loop systems with a sensor to monitor and adjust the concentration of drugs into the body could be viable within 5 to 10 years.** Patients and doctors could also adjust their medication through outside systems. Both one and two loop systems would still be open systems requiring monitoring by doctors to prevent adverse reactions and adjust dosages.

Three loop systems incorporate a sensor to monitor patient response to the therapy and adjust drug flow and concentration. These systems could either be completely closed loop where a doctor would not need to monitor the patient or hybrid systems where a doctor or patient would electronically "authorize" any changes in drug flow or concentration. These systems will be technologically feasible in 15 to 20 years.

The use of implantable drug delivery systems will be delayed without a more viable business model and changes in the regulatory structure. Under current regulations, each dosage level and delivery method must pass separate clinical trials even if the drug being delivered has already been approved. Clinical trials for implantable drug delivery systems are also extremely expensive since the subjects have to undergo surgery.

A viable business model also needs to be developed. Possible new areas to explore are adjustable insulin MEMs that allow diabetics to monitor their blood sugar levels and add more insulin before meals, cancer and other chronic disease drugs that will allow patients more mobility, anti-inflammatory drugs delivered directly to joints, generic drug combinations for chronic diseases and for expensive biologics where smaller targeted doses might be cheaper and more effective than larger less frequent doses.

There are two main technological stumbling blocks to these systems. The first involves the power supply. Improvements in battery technology will allow smaller MEMs with more functionality. **In 25 years there may be biological systems that recharge implantable devices using the body's own organic chemistry.**

The second stumbling block involves drug stability and volume. The drug must be stable, able to be preserved for a long period of time, and effective in small doses. Drugs that do not last long or require large doses are not ideal for a MEMs system. **By 2029 many drug companies will develop new drugs, combinations of generic and non-generic drugs, and drugs that might be safe in small continuous doses, but toxic at larger doses, specifically for implantable drug delivery systems.**

## **Imaging and Bio-markers**

**Twenty-five years from now imaging and biomarker advances (libraries in the 1,000s) will expand the notions of disease to pre-disease and develop new business models.** The concept of disease will shift so that prevention and early stage treatment becomes the new paradigm.

Three quarters of private insurance and two thirds of Medicare is spent on people with five or more chronic conditions. The expense of patients with multiple chronic diseases will continue to grow as the population ages. The most effective way to fight these chronic diseases is through prevention.

Using better imaging technologies, such as functional MRI, along with bio-markers will make prevention the best way to fight chronic disease. Biomedical researchers will compile extensive libraries of pre-disease states. Advances in imaging and biomarkers will help doctors diagnose pre-disease and help patients monitor their health.

Improvements in imaging and biomarkers will also help accelerate the forecasts above. Better bio-makers will make personalized medicine cheaper while advances in imaging will accelerate the development of computational models.

## **Miniaturized Research Infrastructure**

**By 2029, bio-chips and nano-labs will proliferate, allowing research to operate at various scales from molecular to global.** Interconnected sensors communicate through a network that links trillions of information sources and a large human population contributes data directly through bio-monitors in the form of implants and wearables.

The development of a miniaturized research infrastructure will improve health by making it easier for researchers to monitor the effects of the environment (pollution, stress, ect.) on health. It will also allow for distributed phase four trials where the side effects and safety of drugs can be more effectively monitored.

- There are two main business models in development for distributed monitoring of health. The first model focuses on very sick, high risk patients where appropriate, timely intervention can prevent costly hospital stays and even death. Insurance companies would provide most of the funding in this model, but since this kind of intervention is very expensive, it becomes very important to narrow down the patients most likely to benefit. Chronic diseases with a clear path of progression, such as heart disease, are the likely targets for this kind of intervention.
- The second is consumer focused. In this model, consumers would pay to monitor their own health and preserve their independence. Elderly patients wanting to preserve their mobility and independence would be the largest market for this kind of technology.

Some of the main barriers to this forecast are getting the cost of sensors and computation down to the levels to make widespread deployment economically viable. Decreasing the size and increasing the stylishness of designs for these devices will also be important for opening up the market.

## **Evolution of Systems Biology**

**Biology becomes the preeminent science of the 21<sup>st</sup> century.** Predictive models of biological processes are reliable for most molecular processes including many key cellular pathways and a number of key organ systems. By the 2020s there are predictive models for ecological, national, community and family health, but their reliability is not very high.

The workshop participants agreed this was one of the most difficult forecasts to achieve by 2029. Building models for complex biological systems will require large advances both the understanding of systems biology and in-silico biology. The challenges are particularly high for in-silico biology since biology has many non-linear systems that are difficult to replicate in-silico.

Well developed virtual organs, such as the virtual heart, will be common, but other virtual biological systems will be rare. It will be possible, but not likely, to have virtual models for cells and proteins in 25 years. Integration of these in-silico systems into a virtual patient able to advance biomedical R&D might be beyond the 25 year timeframe.

## **Merger of Disciplines**

**Education in 2029 integrates brain research into the traditional curriculum, typically offering a lifelong trajectory of cross disciplinary expeditions undertaken with teams of people who work in various modes (face-to-face, virtual teams, and in isolation) for different periods.**

The workshop participants agreed there is an ongoing trend for more multi-disciplinary work among the hard sciences, and that trend is likely to grow stronger over time. Many also agreed that more multi-disciplinary work between hard scientists and social scientists (as well as ethicists) is also a future trend and that the exposure of scientists to these studies during graduate school is likely to grow.

However, they disagreed that there would be any merger of disciplines between hard science and the humanities, especially religious studies. They felt that there were many things that science could learn about religion, especially meditation, but that there was little that science could learn from religion. They were extremely skeptical about the value of having religious figures as collaborator in multi-disciplinary research.

## **Workshop Participants**

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