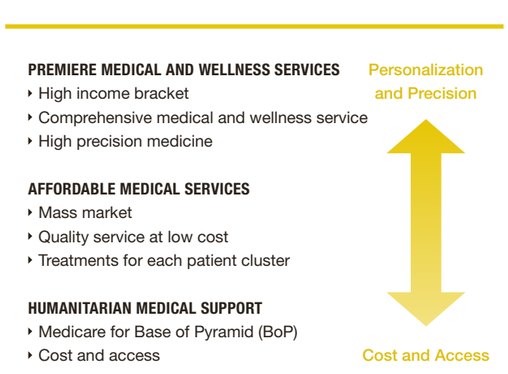
THE GRAND CHALLENGE OF SYSTEMS BIOMEDICINE

Written by Hiroaki Kitano

Innovation in biomedical science research and its application presents a global challenge. On one hand, there is an emerging emphasis on innovation in personalized and precision medicine. On the other, there are still significant issues in relation to access to—and the cost of—medicines for the base of pyramid (BoP) segment. I would argue that one of the key areas of focus for urgent innovation that needs to be addressed is a dramatic improvement in the efficiency and effectiveness of the delivery of novel medicines, coupled with an appropriate positioning of such medicines to deliver the ambitions of personalized, preventive medicine (Figure 1). While personalization of medical practices offers tremendous benefits to patients, often represented by genome-based stratification of patients for clinical decision-making, it impacts the pharmaceutical industry negatively because of the consequent and inevitable market fragmentation. Drugs that used to be developed to treat a broad range of patients are now being used to target those who can be identified to have an increased chance of responding and/or are at a reduced risk of side effects. The challenge this presents for pharmaceutical companies is how to achieve this dramatic improvement in the current practice of drug discovery and development, while at the same time leveraging the clinical benefits of personalized medicine, and still be financially viable, despite necessarily focusing on the treatment of much smaller patient populations. The search for drugs to treat rare diseases is on a similar track, and here the costs must be dramatically reduced for pharmaceutical companies to be able to invest in projects covering a broad range of rare diseases.

National fiscal and health economic priorities demand the development of approaches that deliver precise patient segmentation for optimal and cost effective treatment as well as those aimed at preventive and pre-emptive personalized therapies. It is imperative to recognize that the increasing medical cost associated with the prevalence of chronic, debilitating diseases in an increasingly aging society will continue to impose major pressures to fiscal sustainability in many developed countries. Unless we manage to mitigate such fiscal pressure on the public medical purse, it will likely result in catastrophic economic consequences. How to provide quality medical service while mitigating these fiscal pressures is one of the biggest challenges faced by countries with a rapidly aging population, and thus should represent one of the highest priorities for attention.

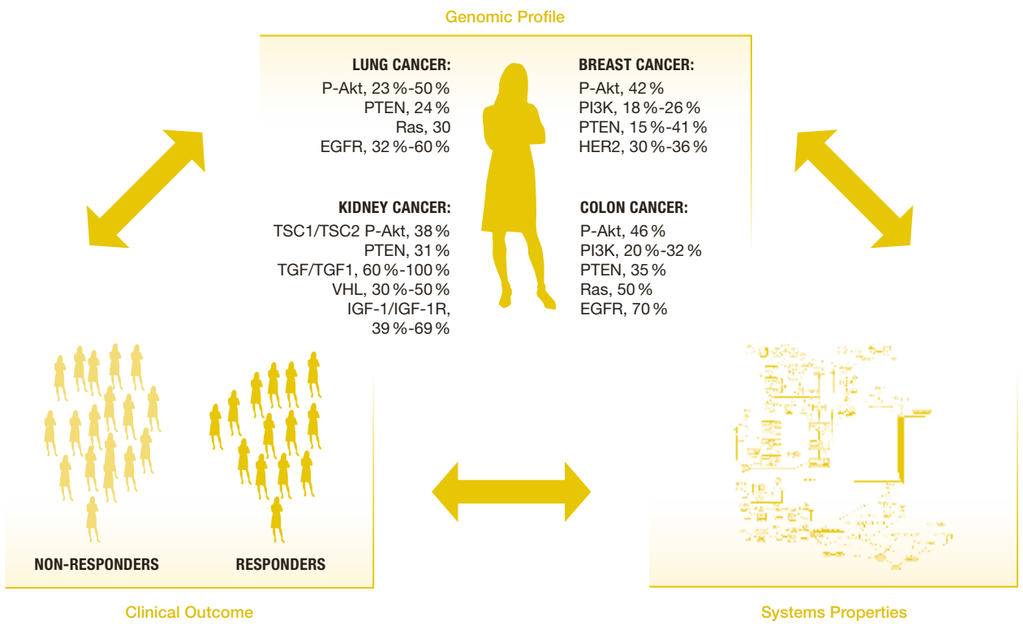
Improvements in drug discovery are also demanded for the treatment of diseases prevalent in developing countries because they cannot afford to pay for expensive drugs. Thus, tackling the joint imperatives of improving the delivery of innovative medicines and the effective stratification of patients are the common threads underpinning an approach to solving one element of the global health care agenda.



▸ ***Figure 1:*** *Segments of medical need*

A Systems Approach Is the Solution

A systems approach that addresses the dynamic properties of the functional interaction networks in biological systems is one of the key elements in offering a possible solution to the global health care agenda. It can be applied ubiquitously to all segments of medical need. Patient stratification using mere statistical analysis over genome or clinical data hits its limits when it has to handle rare incidents or multiple



affecting factors, such as multiple genetic alterations in a specific segment of patients. Conventional Genome Wide Association Studies (GWAS) and similar approaches require impractical sizes of cohorts, even if it could identify any meaningful signatures. Our group is currently developing a method termed Genome Network Association Study (GNAS) that uses biological network structure to link genomic variations with clinical outcome/disease susceptibility, thereby enabling the detection of multiple and highly relevant biomarkers (Figure 2). While the validity of such a method has still to be shown, the development of a technique to identify valid biomarkers for multifactorial diseases needs to be developed that incorporates insight from a system-level understanding of the targeted biological systems.

▸ ***Figure 2:*** *Conceptual diagram for Genome Network Association Study*

Stagnation in the delivery of effective novel medicines is widely recognized to be an issue in the industry and outside of it. Numerous reports suggest that a shift is required toward more mechanism and a systems-based approach to improving drug R&D productivity. The need for a systems approach is further warranted because the chronic diseases that prevail in the elderly population, where there is significant unmet need, are mostly polygenic, multifactorial in nature. That is, multiple genes along with epigenetic and environmental factors are involved in the development of the disease and are thus likely to require multiple targeting of the proteins involved. This requires a sophisticated

approach to identifying and designing drug candidates that interfere with these targets, or the use of multiple compounds with high selectivity to each of the target molecules involved. There is evidence of some early successes in using a systems approach to drug discovery.

Now the next step must be to build on such pioneering successes to transform the entire biomedical industry, not just pharmaceutical companies, through the evolution of systems biomedicine and thereby lead to significant improvements in targeting unmet medical needs.

Moonshot

The Apollo Program during the 1960s was one of the most successful grand challenge projects that resulted in the accomplishment of the manned missions to the moon. The US committed to the goal of "landing a man on the moon and returning him safely to earth." The mission was largely an engineering project, but one that also enabled the development of many areas of new science through the demands for innovation and improvements. However, the actual goal of the Apollo project was much more than a manned mission to the moon. NASA officially stated that "Project Apollo's goals went beyond landing Americans on the moon and returning them safely to earth: to establish the technology to meet other national interests in space; To achieve preeminence in space for the United States; To carry out a program of scientific exploration of the moon; To develop man's capability to work in the lunar environment." (NASA website: http://www.nasa.gov/mission_pages/apollo/missions/#.Uo_hm2ROpD8)

The pressures and needs we face in health care demand a big science approach in the biomedical analogous to those used more commonly in astrophysics and similar hard sciences. So, what are possible equivalents of the Apollo Program in the biomedical area? One option is to develop a comprehensive computational model of the human, developed from a molecular base. While there is a wide variety of biological models of specific biological processes, these are fragmented, and do not automatically or easily become integrated into a consolidated model of human biology, physiology and pathology. Our ability to develop a large-scale integrated model of a biological system, particularly that of homo-sapiens, would be a major accomplishment, and the technologies developed during this challenge would have a knock-on impact beyond biomedical sciences themselves. A series of meetings has already been held where such challenges were considered with the aim of fostering emergent innovations. Some projects are already working toward this, most notably in Europe. They include the Virtual Physiological Human (http://www.vph-institute.org), the Virtual Liver Network (http://www.virtual-liver.de/wordpress/en/) and the Japanese HD-Physiology Project (http://hd-physiology.jp/).

Turning "Unknown Unknowns" into "Known Unknowns"

One argument against such an initiative would be "the science is not there yet." Proponents of such a claim caution that such models cannot be sufficiently accurate because there are many biological mechanisms yet to be understood, thus it is too early to be elevated to a formal initiative. While I agree there are many unknowns, the grand challenge of integrated modeling is to uncover what are "unknown unknowns" from "known knowns" and "known unknowns." In developing computational models, one needs to describe very explicitly and organize precisely what we know about the system, and during this process one often discovers that there are many things we believed we knew but we actually do not. Thus, the practice of modeling has a significant role in turning "unknown unknowns" into "known unknowns," helping researchers to focus explicitly on emerging unknowns.

Virtual Big Science

One may argue whether such an integrated model can be cost effective, or if it is worth pursuing instead of approaches creating "fit-for-purpose" models for each disease or biological process of interest. This is a valid point; however, just like the Apollo project, setting such a major goal itself has an impact in focusing the mindset and fostering widespread collaboration. There are numerous diseases that require systemic analysis where integrated systemic models are essential. Creating numbers of fragmented models would not enable us to create consistently integrated models unless there is a globally agreed agenda and a tangible project to consolidate such models.

We must recognize the reality that most biology and medical sciences are small science in terms of the scale and mode of collaboration. Researchers have their own questions and agendas to pursue and collaborate within their network. At the same time, there are projects that involve a large number of institutions and researchers. The human genome project is a remarkable example of a big science project in biology. Other projects such as FANTOM also involve large groups of researchers aiming at a common goal.

Should the integrated modeling initiative be launched as a big science program akin to the human genome project? Certainly, we do need a central core group that is dedicated to designing and executing a whole program and to developing an integrated model. At the same time, it is not practical to centralize all research that is required for development of the model. Thus, the project requires mechanisms to involve and integrate a broader range of researchers perusing their own questions in a way that accelerates their research through participation in the grand challenge project. This hybrid mechanism of project operation needs to be well designed and managed, the necessary infrastructure needs to be developed to make project execution a reality, and a sophisticated scheme implementing proper social engineering would be required.

Standards and Platforms

Development of standards and platforms for the grand challenge is central to and one of the most critical components necessary for success. Looking back at the Apollo Program, it was the Saturn-V launch vehicle that served as the platform throughout the project. Different missions were accomplished by changing modules to be launched by the standard Saturn-V launch vehicle. This enabled the project to separate scientific exploration and engineering execution. Fortunately, there is increased recognition in the biomedical community for standards and platforms, partly required due to the practical issues of handling large data sets generated from high-throughput data. Numerous data and model representation standards such as SBML, SBGN, BioPAX, MIAMI, MIRIAM, CellML, and FieldML have been defined and accepted in the community. An initiative such as The Garuda Alliance represents a new move toward development of a standard platform that enables a high level of interoperability.

Summary: "All Systems Go"

A *Nature* article reporting on such an initiative, headlined "All Systems Go," stated that we are now ready to initiate a well planned major initiative to accomplish the stated goals. The foundations required to initiate such challenges are available and more are emerging rapidly. We now have stronger confidence than a decade ago in the feasibility of the project. In addition to the practical goals stated, the initiation of such a project will impact all segments of basic biology and biomedical communities by providing a drive toward addressing a common agenda that requires a higher level not just of collaboration, but integration. This will trigger a fundamental transformation in the mindset of the researchers and institutions involved. To paraphrase John F. Kennedy, who died 50 years ago, we shall embark on this grand challenge and these goals "not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills."

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