

The discovery value of “Big Science”

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The increasing complexity of biomedical research is leading to the exploration of new models for large-scale collaborative research. This Big Science approach, however, has created anxieties and potential tensions between investigator-driven research, and research guided by a more organized, collaborative effort. Another potential tension exists between research conducted purely in search of new knowledge and research aimed at finding solutions. We argue that big biomedicine—the work of coordinated multidisciplinary groups that use the latest technologies to solve complex problems—can be an important way to harness the creativity of individual investigators, stimulate innovation, and supply the infrastructure, experimental systems, and resources needed to solve the urgent health problems confronted by our global society. We discuss this using the example of the Global HIV Vaccine Enterprise.

Big Science and biomedical research

Big Science may be a controversial issue among biomedical scientists today, but the idea is not new. 40 years ago, nuclear physicist Alvin Weinberg coined the term Big Science to describe the large-scale approaches that were needed to develop modern nuclear technologies (1). Weinberg foresaw a similar need in biomedical science, but cautioned that the success of such large-scale approaches would depend on their acceptance by biomedical scientists and the government agencies that support them. Weinberg was correct in predicting the current resistance to Big Science, and he was not shy in condemning that resistance. “Biomedical science is not done, or, more important, is not supported by the public simply because it gives intense satisfaction to the dedicated and successful biomedical researcher.” Weinberg stated, “It is supported on a really large scale because out of it have come means of eliminating man’s infirmities.” Albert Sabin subscribed to a similar philosophy, calling for a “concentrated attack on the more complex disease problems” and the need to develop the

necessary mechanisms to facilitate and coordinate collaborative research (2).

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Neither Weinberg nor Sabin saw any contradiction between the Big Science approach to biomedicine and the more traditional ways of doing science. Weinberg emphasized that nothing he had said to promote a collaborative approach to science implied that he considered individual research obsolete. In calling for more biomedical science, he “pleaded both for more Big Science and for more Little Science.” Sabin also expressed his strong support for Little Science. “The importance of an individual scientist’s search for knowledge for its own sake as the very foundations of scientific endeavor must continue to be supported and expanded if science is to provide the means for the solutions of the many problems of importance to human welfare.”

We fully agree with them. We strongly believe that the ability of science to address and solve some of the major global health problems will require both the creativity of individual investigators and the infrastructure, systems, and resources needed to efficiently

harness scientific knowledge to develop practical solutions. These two approaches to biomedical science are not in contradiction, but are complementary and mutually stimulating.

The evolution of the biomedical research enterprise

With the increasing complexity of science and the extraordinary difficulty of some of the problems we are tackling, scientific research is evolving into a highly elaborate enterprise with multiple partners that must work in a well-coordinated fashion. Physicist Albert-Laszlo Barabási recently described how most great thinkers of the past published alone, yet built on each other’s work in an informal communications network of scholars that historian Derek De Solla Price called “the invisible college.” (3, 4) In the 20th century, science became an increasingly collaborative enterprise, but usually of small groups (e.g., Watson and Crick). The invisible college of the preceding century later began to take formal shape and became more organized, with invisible links being replaced by coauthorships of publications. More recent developments are leading to large collaborations, such as the Human Genome Project (HGP), the popular prototype of big biology.

When the HGP was proposed and launched some 20 years ago, it was received with mixed feelings and many objections, caused especially by the fear that it would monopolize funds that would otherwise support investigator-initiated research. The HGP was also perceived of as a project of limited scientific value that was not driven by any specific hypothesis (5, 6). Other objections were more technical, including the argument that the technologies necessary to sequence the human genome were not available (7). However, when the working draft of the human genome was published in 2001,

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it was considered the crown jewel of 20th century biology, heralding the coming of age of Big Science in biomedicine (5).

It can be argued that the eventual success of the HGP depended mostly on the development of technologies for DNA sequencing rather than on the solution of fundamental scientific questions. From that perspective, the HGP could be considered more of an engineering project than a purely scientific one, and thus it might not serve as a model for more scientifically challenging areas of research. However, the many problems encountered in sequencing the human genome were not trivial, and the solutions were grounded in the best science. Many lessons were also learned from the HGP that are relevant to other large-scale biomedical projects (8).

An earlier experiment on large-scale science was the “War on Cancer,” officially launched by President Nixon in 1971 as the National Cancer Act. It aimed to support research and the application of the results of research, to reduce the incidence, morbidity, and mortality from cancer (“insofar as possible”). A major difference between the War on Cancer and the HGP was the need to solve many fundamental scientific questions in cell and cancer biology before that knowledge could be used practically in prevention and treatment. Two of the arguments that were raised against the War on Cancer were that money couldn’t buy ideas, and that research was a process that was best left unfocused. Nevertheless, the program developed a research agenda that was broad enough to attract brilliant people who generated many new ideas but, at the same time, maintained the necessary focus on the applications of the results of research (9, 10). Cancer may not be conquered yet, but the overall incidence, mortality, and morbidity from cancer have decreased. Although it is difficult to attribute these gains directly to the War on Cancer, surely this program had a major impact on the outcome. In addition to the expected advances in cancer, the science derived from this program paid many other dividends. One such dividend

was the further development of the field of retrovirology, which allowed for the rapid identification, isolation, and study of HIV, the retrovirus that causes AIDS.

Other biomedical fields are now stepping into big biology, and new initiatives are striving to integrate Little with Big Science (11). One of these initiatives is the Global HIV Vaccine Enterprise (the Enterprise).

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The Global HIV Vaccine Enterprise

Soon after HIV was identified as the cause of AIDS in 1983–1984, there was an expectation that an effective vaccine would be easily developed and rapidly deployed. The intense research effort conducted during the last 20 years has produced important information on the virus and the disease, but a safe and effective vaccine remains elusive. To confront this challenge, in 2003 a group of leaders in the field of HIV vaccines proposed the creation of the Global HIV Vaccine Enterprise (12). They recognized that current attempts to develop such a vaccine were insufficient in scale and/or focus, and that a renewed HIV vaccine research effort was required.

The Enterprise proposes to complement individual investigator-driven research with a Big Science model to address this problem, taking full advantage of new scientific opportunities, creating new strategies for collaborative partnerships, and organizing a more coordinated global effort. To achieve its goal, the Enterprise proposes to (a) prioritize key scientific questions and rapidly direct resources to try to answer the most critical questions; (b) support product development, manufacturing, and testing of novel candidate vaccines; and (c) implement common standards and processes to maximize learning through the sharing of data and materials.

The Enterprise model represents a new way of thinking about problems, with the formulation of a shared scientific strategic plan. It represents a new way of solving problems, using common tools, optimized resources, and iterative learning. Most importantly, it represents a new way for scientists to behave as a global community of problem-solvers, sharing materials and information while recognizing the need to find the correct balance between collaboration and competition, both of which are important driving forces of scientific discovery and innovation.

The Enterprise is being developed not as a new organization, but as an alliance of independent organizations that are committed to accelerating the development of a preventive HIV vaccine by implementing a shared scientific strategic plan, mobilizing additional resources, and collaborating more intensely among HIV vaccine researchers worldwide. The Enterprise Scientific Strategic Plan makes broad suggestions in different areas in the HIV vaccine R&D continuum, providing a road map that funding and research agencies can use to plan or align at least some of their activities in a coordinated fashion (13).

The first two initiatives launched in support of the Enterprise plan are the Center for HIV Vaccine Immunology (CHAVI), and the Collaboration for AIDS Vaccine Discovery (CAVD). CHAVI is a virtual center supported by the National Institute of Allergy and Infectious Diseases (NIAID), which is composed of a large consortium of universities and academic medical centers working on new vaccine strategies to overcome key immunological roadblocks in HIV vaccine design (14).

The CAVD is being developed as a highly collaborative network of sixteen research consortia supported by the Bill & Melinda Gates Foundation (15). Eleven of the consortia are working on different approaches to developing HIV vaccines, guided by the creativity of individual investigators. These vaccine discovery teams are supported by five central service facilities, which conduct immunological evaluations and data and statistical analysis for the whole

network, allowing for real-time comparison of the results. The CAVD grants are not intended to focus on basic discovery research. Instead, they target a perceived strategic gap in the HIV vaccine research and development continuum, which is the translational or maturation phase. This phase is aimed at harnessing the vast amount of knowledge derived from basic research to produce the proof-of-concept experiments required to proceed with confidence to the product development phase. To ensure that the whole effort is bigger than the sum of its parts, the sixteen CAVD consortia and centers are bound together by a communication and alliance management strategy, and by legal agreements to share materials and data among the different CAVD laboratories and, with time, with the rest of the Enterprise partners and the scientific community at large.

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In addition to CHAVI and the CAVD, other projects and initiatives are currently being aligned with the Enterprise Scientific Strategic Plan and philosophy, and will be launched in the near future. The ultimate success of the Enterprise will be judged on its real contribution to accelerating the development of an HIV vaccine. In this regard, it is important to recognize that the major challenges we confront in the development of an HIV vaccine are scientific, and scientific problems need scientific solutions (16). Therefore, a successful Enterprise will need to bring together the Big Science of the proposed large collaborative networks and the Little Science approaches needed to explore a range of highly innovative ideas.

Tensions between Big Science and Little Science

This Big Science approach to organizing HIV vaccine research has understandably created anxieties among some members of the scientific community that are reminiscent of those raised

when the HGP and the War on Cancer were first launched (17, 18).

One conflict is between what some people call "individual thinking," where science is based entirely on the creativity of individual investigators working more or less in isolation, and "group thinking," where scientific exploration is guided by the collective wisdom of experts. We would like to argue that there is no real tension between these two approaches, and that the individual creativity of investigators can be augmented by a more targeted and collaborative plan and vice versa (19). The key to success is to be able to constantly explore new concepts and ideas, to make calculated risks, to make decisions based on evidence not on advocacy, and to enhance the individual research effort with mechanisms that allow us to harness new knowledge to produce new solutions.

Although the creativity of individual investigators is often touted, it is also important to recognize that such creativity can, in practice, be limited by the "current scientific paradigm," a concept proposed by physicist Thomas Kuhn in 1962 (20). He argued that the academic community is extremely homogeneous and conservative, which creates an environment that may not be entirely conducive to innovation. Promoting truly innovative ideas can be very risky. If these ideas are funded (which is not often the case), they have a high possibility of failure. Thus, paradoxically, the same scientific community that places a high value on creativity and innovation has established peer-review mechanisms that maintain scientific progress within the boundaries of the current paradigm. According to Kuhn, real scientific progress occurs when a new paradigm emerges that is more satisfactory than the current paradigm and drives the work of the scientific community.

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Another identified tension is one that could exist between investigator-

driven basic research and targeted research. The first is driven by the search for basic knowledge, and the latter by the search for solutions. Again, we would like to argue that there is no real tension here. Both driving forces of science are equally important and, indeed, they often synergize, as was convincingly argued by the late political scientist Donald Stokes in his book "Pasteur's Quadrant" (21). The basic science effort needs to be protected at any cost, he argued, not only because of its intrinsic value but also because it is the engine that drives any future application.

Certainly another major source of tension is the competition for financial resources between the larger, more expensive collaborations, and the individually led efforts (22). With a balanced funding approach such tensions can be mitigated.

Future directions

Four decades after Weinberg and Sabin challenged the biomedical community to take the bold step of thinking big, large-scale biomedicine is still struggling to develop. Now is the time to understand the benefits of the concept and embrace it.

However, even as the biomedical community moves in this direction it must recognize that innovation is the key to the success of both Little and Big Science (23, 24). Some of the Enterprise partners are already discussing a new project to support novel high-risk/high-reward ideas in HIV vaccine research, such as complementing the CAVD with an innovation component. Such programs are vital to maintaining an exciting scientific environment and attracting the new generations of scientists who are most likely to find the solutions to some of the intractable problems we are confronting in biomedicine today (25). To bring young scientists to the field, regardless of whether it is framed as Big or Little Science, we may need to address the so-called "Matthew effect," proposed by sociologist Robert K. Merton, to describe the advantages that well-established scientists have in gaining recognition, visibility, and research resources (26).

When the ultimate result of a Big Science project, such as the Enterprise,

is a product such as a vaccine or a medicine, a critical requirement for success is partnership with industry. Pharmaceutical and biotech companies bring skill sets that are highly complementary to those found in academia such as automation technology, project management, medicinal and process chemistry, and manufacturing science. They also bring innovative biomedical scientists who can contribute to the effort.

When society is faced with diseases with consequences as dire as those associated with AIDS, we cannot afford to work selfishly in silos and for personal gain. There are too many people waiting anxiously for the solutions that we must deliver.

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