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The Curious Incident of the Translational Dog That Didn't Bark

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Abstract

There is a general assumption that it is now time for more translational research and less basic research. Science policy leaders have sent mixed signals, and the community has responded by submitting more grant applications focused on translational or applied research. Nothing could be more treacherous, because in order to develop innovative therapeutics we must more fully understand the complexities of biology, a goal requiring more, not less, basic science.

Keywords

Basic Science; NIH; Science Policy; Funding; Precision Medicine

A paradigm shift

Sherlock Holmes, the unflappable sleuth of Baker Street, once solved a case by pointing out "the curious incident of the dog in the night-time." "But, sir," the flustered Scotland Yard sergeant remonstrated, "the dog did nothing in the night-time." "That was the curious incident," Holmes replied[1]. Not too long ago, the National Institutes of Neurological Diseases and Stroke (NINDS), a component of the National Institutes of Health (NIH), had need for a statistical Holmes.

The NINDS had released a report showing that between 1997 and 2012, NINDS expenditures on applied research increased from 13 to 29 percent while the proportion of basic research declined from 87 to 71 percent [2]. That was the curious incident. The leadership of NINDS was astounded because it is an NIH Institute highly committed to basic science and yet the translational share of the NINDS research portfolio had increased while the basic science portfolio fell.

Understandingly puzzled by these findings, the NINDS leadership explored the causes of the decrease in basic science funding. They found that the main determinant of the shift was the decreased number of grant applications in basic science. Most likely this was because scientists believed that they would have a better chance to be funded if their proposals were angled toward the translational or applied side. NINDS hadn't solicited grantees to shift

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from basic to translational in their grant applications but without hearing a single “woof” in the night, researchers had reframed their work, at least for NINDS.

Impact of basic research on translational success

The NINDS case shows the pernicious influence of the current assumption among scientists and among all too many science policy leaders that we need to focus more on translational science in order to reach cures more quickly. We are deeply troubled by these findings. If we consider the history of biology, we can identify four turning points which changed its course: (i) The great cell biologists of the 19th century, including Rudolph Virchow, the German physician widely known as the father of pathology, and the French physiologist Claude Bernard established the pivotal idea that individual cells function autonomously, while being part of the whole organism; (ii) The publication by Charles Darwin in 1859 of the *Origin of Species* changed biology from a descriptive to an analytical science, probing the physics of living things and the engine of evolution; (iii) The discovery of the molecular structure of DNA by Watson and Crick in 1953 and the rapid decoding of the DNA replication mechanism opened the field of molecular biology by giving scientists a powerful toolbox to study, modify, and fix the building blocks of life; and (iv) the series of key advances in imaging, biochemical analysis, and the modeling of complex processes in simpler organisms. Credit for this fourth milestone properly includes many, but four are first among the many: Antonie van Leeuwenhoek, E.B. Wilson, Keith Porter, and George Palade.

Collectively, the efforts of these leaders led to our growing understanding of the cell, with its various organelles and subcomponents, and the beyond-complex mechanisms that govern its functioning. More importantly, none of these discoveries and none of these scientists who made them had the treatment of a specific disease as the goal of research. Their discoveries nevertheless not only changed our fundamental knowledge of how cells work but they ultimately affected our understanding of physiology and in turn the practice of medicine.

It is hard to overstate the progress that biomedical research has achieved since the middle of the last century. We are firmly convinced that all sensible observers will agree that it was driven by fundamental discoveries by a few, and by the integrative work from thousands of other basic researchers who filled in the body of knowledge. Given these tremendous advances, there are those who argue that scientists know enough basic biology and should focus on immediate translation. The opposite is true. The more we discover about cells, the more we realize how little we understand and how much we have to learn. Our limited knowledge from the early 21st century has already had major impacts on long intractable diseases.

The case of the interface of basic and translational research in the field of inflammation response is particularly illuminating because of the transformative progress that has occurred in the past couple of decades. Advances have been possible because of the decades-long understanding of anti-tumor necrosis factor (TNF), which came from basic research in biochemistry and cellular biology of infection, tumor regression and septic shock. Key discoveries by Bruce Beutler, Anthony Cerami and Jan Vilček in the basic role of cytokines in immunity and inflammation directly led to the development of treatments for a number of

significant diseases. Both Beutler and Vilček were also involved in the translation of their basic research into the development of clinical drug target candidates, and the approval in 1998 of blockbuster drugs such as Remicade (Infliximab) for Crohn's Disease and Enbrel (Etanercept) for rheumatoid arthritis, which represent one of the leading causes of disability in the US and is among some of the most common chronic disease problems [3,4]. Both of these drugs, through different mechanistic approaches, act by reducing the levels of TNF in autoimmune disease and their development certainly would not have been possible without the large body of work carried out by investigator-initiated research in the field of cellular response to inflammation. Indeed, the crucial role of NIH basic funding in the innovations that led to Enbrel are noted on the patent by Beutler and Peppel, which states that, "This invention was made with government support under grant no. P01-DK42582-01 awarded by the National Institutes of Health. The government may have certain rights in the invention" [5].

Many other basic science discoveries have generated health achievements. For example, Acute Lymphoblastic Leukemia (ALL) is the most common form of cancer in children. Thirty-five years ago, 95% of patients affected by this cruel disease would die; today, the mortality rate is reduced by 85%, and each year 6,000 kids are cured. It is the elucidation of several oncogenic pathways and the identification of candidate genes, together with genomic profiling that has made these stunning advances possible [6]. For HIV/AIDS, it was basic understanding of retrovirus biology coupled with translational efforts that led to the development of anti-retroviral therapies that made possible the conversion from a death sentence to a manageable, chronic disease. The understanding of the serine protease tissue plasminogen activator (t-PA) in blood clotting, and the ability to produce its recombinant form, also led to new treatments for ischemic stroke, once a leading killer in the developed world, which are saving 20,000 people a year in the US [7].

Every disease is ultimately a disease of the cell, and we could not have achieved any of these astounding successes cited if we had not studied the biology of the cell. Without understanding its extraordinary complexity, we simply navigate blindfolded, and this ultimately impacts how long it takes to develop cures. Indeed, today's bottleneck in drug discovery is not implementing a screen of millions of compounds but rather it is designing assays to understand the underlying biology, which is the key to accelerating cures.

Getting back to the basics

Basic science is the quintessential shared public good. Basic research cannot be addressed without government support because, by its very nature, basic research is too unfocused, too hard to predict or steer, and too slow to satisfy stockholders. Furthermore, the private sector will not pour large amounts in research that might or might not have immediate practical value. Ironically, without these basic findings, the private sector is unable to efficiently develop therapeutics.

Building a lighthouse is a good metaphor for understanding the concept of public good. A ship owner has no incentive to spend money on building his lighthouse. If he builds one, other ships will equally benefit from its use, so there is no competitive advantage for him.

However, if the government builds the lighthouse, it will protect all ships equally. A single ship using the benefit of the lighthouse does not exclude others from using it as well. A light house represents a public good, keeping navigation safe, effective and efficient.

Basic research is our beacon. None of us, even the great philanthropists of the age, could long sustain the vast enterprise of schools, laboratories, and technology centers, which push basic research forward. But if individuals cannot carry that alone, we can shape basic research by providing the right incentives. For example, to encourage basic scientists to submit basic research proposals not couched under a different light, the NINDS is leading a multi- Institute funding opportunity which takes into consideration the results of its own analysis, mentioned above. This program announcement focuses exclusively on encouraging non-disease related basic research[8], and sets aside $7.2 million/year to fund ~20 applications. This is a good sign of the NIH explicitly sending the message to encourage basic science applications to Institutes that can often erroneously be perceived as only translational or clinical.

Furthermore, we can emphasize question-driven research and fund scientists who ask good questions. We could look beyond the cosmetics of highly-detailed projects with pre-defined aims and rigorously plotted time tables. The Director of the National Institute of General Medical Sciences (NIGMS), Jon Lorsch, published a provocative blog challenging the concept of hypothesis-driven research, and instead touting what is often overlooked, the importance of question-driven science (http://loop.nigms.nih.gov/2014/03/hypothesis-overdrive/) (Text box 1). As basic scientists, we can both recall how often an elegant, pre-conceived hypothesis on paper left us boxed in, pounding away at experimental dead ends and losing sight of the larger questions we'd set out to answer. Hypothesis-based experimentation sounds great in a textbook or on a grant application, but it is all too frequently deceptive. The risk of the hypothesis-driven approach is that testing is built on the weight of current evidence to support the classic statement "my hypothesis is." Such efforts also send the wrong signal to other scientists who feel they must oversell the value of a discovery that hasn't been made.

It goes without saying that a basic science and question-driven scientific approach alone will not take us all the way through drug development. If we want to capitalize on cell biological advances for further development, we need a more nimble development system. We know that the vast majority of failures in drug development occur at the Phase II efficacy test. Pharmaceutical companies report up to 80% failure rates at this point in the pipeline So, if we need to fail often, let's try to fail fast, possibly cheaply as well, and move on to the next test.

In this direction, our vision for a renewed focus on question-driven cell biology complements an experimental approach championed by the National Institutes of Mental Health (NIMH) which developed the so-called FAST procedure to fund Phase II clinical trials [9]. While challenges clearly exist, this approach is focused on experimental medicine projects with target engagement and a focus on the mechanisms of disease providing short term funding to prove or disprove Phase II efficacy. NIMH's FAST approach could change

clinical trials from the model of an endowed long-term experiment to, pop-up field trials that could quickly move a project on to the next phase, or move it out.

The precision medicine initiative recently launched by President Obama, which builds on a landmark study of the National Academies [10] is in perfect synch with this approach—that of melding basic science together with the practice of medicine [11].

All of this leads back to our starting point: only by unraveling the deeply intricate cell biological process can we actually accelerate the speed of discovery and its translation into therapy for disease. The easier task – and one the pharmaceutical companies should provide – is constant prospecting for useful applications for development and delivery. The discovery engine is easily described: it is based on curiosity-driven, publically-funded academic research, supported by robust, question-driven funding management. The resultant "non-hypothesis, non-translationally" driven basic science "product" is knowledge, which will frequently appear in unexpected places. This model is based on basic science and basic curiosity: when the dogs don't bark in the night, there has to be a reason.

Text box 1

Hypothesis versus question-based research

Basic Research[2]-- aimed at understanding the structure and function of cells, molecules, networks, or biological systems (e.g. the nervous system). Can involve studies performed *in vitro* or *in vivo*, in cells, in various organisms, in animals, in plants, or in humans.

- **Basic/Basic:** focused on understanding the normal system.
- **Basic/Disease-Focused:** focused on understanding disease mechanisms.

Applied Research[2]—aimed at developing or testing diagnostics, therapeutic agents, or preventive interventions. Can involve studies performed *in vitro*, in animals, or in humans.

- **Applied/Translational:** up to, but not including, first in human studies
- **Applied/Clinical:** first in human studies through phase III clinical trials.

Question-driven research (http://loop.nigms.nih.gov/2014/03/hypothesis-overdrive/**)--** the focus is ahead of hypotheses; addressing problems as questions becomes the goal and allows for the inclusion of multiple models and hypotheses rather than testing of a particular idea. The focus is on answering questions such as how does this system work? What does this protein do? Why does this mutation produce this phenotype?

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