# Lost in translation

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In 1969, one of the more memorable incidents in the public advocacy of science took place. The American physicist Robert Wilson was asked to testify before Congress in support of the construction of the Fermi National Accelerator Laboratory (Fermilab). Wilson was a first-rate amateur architect who saw accelerators as works of art. He lovingly designed Fermilab with his own hands and, in order to add to the aesthetic appeal of the place, turned the surrounding acres into a wilderness housing bison and geese. His efforts paid off; Fermilab would become the largest accelerator in the United States and CERN's primary competitor.

In 1969, Wilson was asked to justify the expenditure for the multi-million-dollar laboratory in front of Congress. The Cold War was raging, most research and especially physics research was being viewed in the context of national security, and Wilson was specifically asked what contribution the new laboratory would make to national defence. He replied in words that should be etched on the foundation stone of every centre of basic research. The research, he said, had no direct bearing on national defence. Instead,

> 'It has only to do with the respect with which we regard one another, the dignity of men, our love of culture. It has to do with: Are we good painters, good sculptors, great poets? I mean all the things we really venerate in our country and are patriotic about. It has nothing to do directly with defending our country except to make it worth defending.'[1]

In saying these words, Wilson was appealing to the heart of what makes any country great. It is not the expensive cars, the shiny malls, the great financial houses and the cornucopia of industrial food that truly contribute to a country's progress. At one point or another in history, Athens, Florence, Takshashila, Baghdad, Oxford, Gottingen, Copenhagen and Philadelphia were primarily known not for their wealth and the splendour of their monuments, but for the unmatched wealth of ideas about science, art, economics, democracy, freedom and human dignity that their citizens generated. These ideas are now the bedrock of much of modern civilization. Many of these ideas were solutions to practical problems, but most only sought to explore and push the boundaries of human creativity, curiosity, passion and tolerance. The creators and dreamers of these ideas were less concerned about their practical application and more concerned about their ability to answer questions about human origins and nature, our place in the cosmos and our relationship to other human beings.

Why am I retelling the story of Robert Wilson? Because I believe it strikes at the heart of what these days is fashionably called 'translational research'. Just like physics research was being viewed through the lens of national defence in the 60s, basic biomedical studies run the risk of being viewed through the lens of translational research in the 2010s. The approach is clearly not popular among leading researchers. In 2009, Nobel laureate Martin Chalfie gave a talk at the meeting of Nobel laureates in Lindau, Germany titled 'Adventures in Non-Translational Research' (http://www.lindau-nobel.org/MediaContainer.AxCMS?LaureateID=10342&type=lectures). Chalfie is not alone; as just another example, a few months ago I attended a lecture by Thomas Steitz, another Nobel laureate. Steitz who won the Nobel Prize for his exploration of the structure and function of the ribosome proudly announced at the beginning of the talk that 'the only kind of translation I have worked on is that done by the ribosome'.

So what is translational research? Many definitions seem to abound and Wikipedia seems to be as good a guide as any (http://en.wikipedia.org/wiki/Translational_research): 'Translational research is a way of thinking about and conducting scientific research to make the results of research applicable to the population under study and is practiced in the natural and biological, behavioural, and social sciences.' The goal of translational research, especially in medicine, seems to transform basic biomedical research discoveries from 'bench to bedside'.

In the last few years this kind of thinking has swamped the public discourse on science. New centres are being founded and funded whose mandate is to translate basic research into products directly benefiting humanity. The National Institutes of Health (NIH), USA, the largest biomedical research agency in the world, has embraced a new National Center for Advancing Translational Research. The Director of NIH, Francis Collins, has not tired of pointing out the exciting advances in discovering new drugs which would be made possible by harnessing data from the human genome project[2]. Not surprisingly, the press has eagerly jumped on the bandwagon, with reports pitching translational research and personalized medicine regularly appearing in the country's leading papers (http://www.nytimes.com/2011/01/23/health/policy/23drug.html?pagewanted=all). Echoing leading scientists, the press seems to be telling us that we should all look forward to supporting translational research in its various guises.

All this makes the idea of translational research sound promising. And yet there must be a good reason why distinguished Nobel Prize winners like Chalfie and Steitz bristle at the constant mention of translational research. The reason is actually not too hard to discern. The problem is not with applied research per se. Nobody can doubt that applied research, especially done by the pharmaceutical and biotechnology industries has saved innumerable lives in the last 100 years. As Pasteur said, 'there is science and the applications of science', and he saw them lying on a continuum. No, there is nothing wrong with trying to turn basic ideas into practical products.

What is wrong is that translational research is being seen as a panacea that will address the flagging rate of new biomedical advances. The thinking seems to declare that if only more people were given more money and deliberately focused on direct application, we would suddenly see a windfall of new therapies against disease. This thinking suffers from two major problems.

The first is that history is not really on the side of translational research. Most inventions and practical applications of science and technology which we take for granted have come not from people sitting in a room trying to invent new things, but as fortuitous offshoots of curiosity-driven research – the kind that Chalfie and Steitz have dedicated their lives to. Nuclear magnetic resonance for instance was discovered by physicists who were tinkering with atoms in magnetic fields, not ones who were trying to find a useful method for determining the structures of organic and biological molecules. The discovery of most drugs built upon basic discoveries about human physiology and anatomy made by physicians and researchers who were simply trying to find more about how the body works. The new class of drugs inhibiting protein kinases for instance ultimately owes its development to the discovery of phosphorylation, a fundamental discovery by biochemists Edmond Fischer and Edwin Krebs that was a result of purely basic scientific thinking about how chemical signals are communicated by cells.

If the history of science teaches us anything, it is that curiosity-driven basic research has paid the highest dividends in terms of practical inventions and advances. Tinkering, somewhat aimless but enthusiastic exploration of biological and physical systems and following one's nose have been the ingredients for some of the key inventions that have transformed our lives. Radar, computers, drugs, detergents, plastics and microwave ovens were all made possible not because someone sat down and tried to discover them, but because they arose as fortuitous consequences of elemental, pure research. The hype of translational research not only deflects attention from curiosity-driven basic research, but also creates the illusion that asking people to discover new things is the best way to generate new ideas. In fact, trying to discover new things by forcing people to discover them will only siphon-off funds from those who have the actual capability of discovering these things. Thus in the case of the translational research centre at NIH, there are already complaints from biomedical scientists about the new institute diverting funds from the basic-science arm of NIH, the National Institute of General Medical Sciences (http://news.sciencemag.org/scienceinsider/2011/01/collinss-plan-to-reshuffle-nih-d.html).

The second important problem with translational research is that it puts the cart before the horse. First come the ideas, then come the applications. There is nothing fundamentally wrong with trying to build a focused institution to discover a drug, say, for schizophrenia. But doing this when most of the basic neuropharmacology, biochemistry and genetics of schizophrenia is unknown is a great diversion of focus and funds. Efforts based on incomplete knowledge would only result in a squandering of manpower, and intellectual and financial resources. Such misapplication of resources seems to be the major problem for instance with another new centre for drug discovery that the NIH plans to establish (http://news.sciencemag.org/scienceinsider/2011/01/collinss-plan-to-reshuffle-nih-d.html). The institution seeks to channel the newfound data on the human genome to discover new drugs for personalized medicine. This is a laudable goal, but the problem is that we still have miles to go before we truly understand all the implications of this data. It is only recently that we have started to become aware of the 'post-genomic' universe of epigenetics and signal transduction. We have barely started to scratch the surface of the myriad ways in which genomic sequences are massaged and manipulated to produce the complex set of physiological events involved in disease and health[3].

And all this does not even consider the actual workings of proteins and small molecules in mediating key biological events, something which is underlined by genetics but which constitutes a whole new level of emergent complexity. In the absence of all this basic knowledge which is just emerging, how pertinent is it to launch a concerted effort to discover new drugs based on a vastly incomplete framework? It would be like trying to construct a skyscraper without fully understanding the properties of bricks and cement.

Chalfie, Steitz and others like them are also right to criticize the frenzy that translational research generates in the popular press. We live in an age when buzzwords are eagerly generated and lapped up by the media. These buzzwords usually run roughshod over subtleties and ambiguities which the press seldom has a taste for indulging. Needless to say, committing national resources and public attention to translational research when most of the basics are still to be understood is an endeavour fraught with great risk and uncertainty. It would be far wiser to bolster basic research that can bring us to the brink of real application. There are places where such research is conducted. They are called universities.

Ultimately, the importance of basic research goes back to what Robert Wilson said to Congress. It has to do with the same reasons that we created the Mona Lisa, painted the Sistine Chapel, built Chartres Cathedral, wrote The Love Song of J. Alfred Prufrock and composed the Goldberg Variations. Da Vinci, Michelangelo, T. S. Eliot and Bach were all trying to find the essence of man's soul and his relationship with the universe and with his fellow men. So were Einstein, Newton, Faraday and Darwin. They were not trying to invent a better mousetrap, but the world did beat a path to their door. Similarly, once our basic understanding of biological systems is firmly in place, translation will willingly follow.

1. Hilts, P. J., *Scientific Temperaments: Three Lives in Contemporary Science*; Holiday House, 1984.
2. *Nature Rev. Drug Discov.*, 2001, **10**, 471.
3. Gilham, N., *Genes, Chromosomes and Disease: From Simple Traits, to Complex Traits, to Personalized Medicine*; FT Press, 2011.

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