Comment

A model worth considering?

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I'd like to introduce you to Scott Johnson, who thinks he has a better way of translating basic research discoveries into therapies for human diseases. Like many of the other people who have made a difference in the battle to cure diseases that pharmaceutical companies and governments have largely ignored - for example, the actor Michael J Fox in the case of Parkinson's disease and the financier Michael Milken in the case of prostate cancer - Mr Johnson has a very personal reason for wanting to see a particular disease cured. In 1976, when he was 20 years old, Scott Johnson was diagnosed with multiple sclerosis. He's 50 now, and he knows that, without a cure, his life expectancy is predicted to be about 7 years less than the average for a healthy adult. But that isn't the main reason that Scott Johnson is a man in a hurry. He's in a hurry because he thinks he's figured it out, and when you think you've figured it out, you're naturally anxious to see if you're right.

Based on his track record, it might be unwise to bet against him. Multiple sclerosis didn't prevent him from a successful business career with the Boston Consulting Group and several Silicon Valley startups. That wouldn't make him the first businessman who thought he could apply the principles of corporate management to a new area (government is a favorite one), not by any means. But Mr Johnson doesn't want to run a state, or even a city. He wants to change the way cures for diseases are found.

In 2003 he left business to start the Myelin Repair Foundation. The origins and progression of multiple sclerosis, which is thought to be an autoimmune disease, are mysterious and unpredictable, but the hallmark of the disease is the destruction of the myelin sheath that surrounds the axons of nerve fibers of the central nervous system. The resulting scar tissue (sclerosis) gives the disease its name. When Scott Johnson heard about myelin, he decided that the fastest route to a cure for multiple sclerosis was not to focus on the causes of the disease but rather to find a way to repair the damaged myelin. Hence the name of his foundation, and its goal. Having decided that, the question then became how best to get there. Johnson looked at existing models for what is now often called translational research and decided that none of them was very efficient. "In traditional medical research, numerous individual scientists work in relative isolation, often in competition, focused on their specific field of expertise. With little or no collaboration, discoveries are transferred by publication, resulting in sequential investigations and greatly expanding the length of time necessary for validation and translation to further drug development and clinical trials," he says. He came up with a different model.

The Myelin Repair Foundation set about finding a way to accelerate the basic science necessary to achieve its goal of licensing at least one myelin repair drug target by 2009 that would lead to treatments for multiple sclerosis. To accomplish this, the Foundation developed what it calls the Accelerated Research Collaboration™ (ARC; the name is trademarked, actually) model, a business-science hybrid model for medical research that was designed to break down what Johnson saw as the barriers inherent in the traditional medical research model. He thought that, if he was right, this new model might be able to drive new discoveries toward clinical trials in record time.

Instead of the traditional single-investigator-driven model typical in virtually all academic research, the ARC model combines the efforts of multiple investigators into a collaborative, outcome-focused effort. Johnson tried to identify a set of top-flight basic research laboratories, some of which were not initially working directly on multiple sclerosis, and convinced them to get interested in both the disease and his approach to tackling it. Selection was based on their complementary knowledge and expertise, and their past contributions to understanding the key biological processes and interactions that control myelination. These were people who would quite likely have been competitors in the traditional research model. Five labs were chosen, scattered all over the US and Canada. To enable communication among

them, the Foundation set up a web-enabled infrastructure designed to facilitate daily interaction and data exchanges; discoveries are therefore shared immediately, without the delays associated with the publication of scientific papers. A requirement of being part of the ARC scientific team is the commitment to design experiments that are part of a larger research plan focused on identifying therapeutic targets that will lead to patient treatments. The model provides a framework for establishing membership and technology transfer agreements with each participating university. Patents are filed on all discoveries that may contribute to potential treatments.

The Foundation believes the ARC model can be applied to any medical research problem once relevant basic scientific discoveries have been made. It states that more than 40 different disease research organizations have made contact with the Myelin Repair Foundation to learn about the ARC model and its potential application to each organization's research; these include the American Cancer Society, The Down Syndrome Research and Treatment Foundation, the Juvenile Diabetes Research Foundation and the Harvard Stem Cell Institute.

It's important to get past the marketing language and the PowerPoint slides showing in iconic form the revolutionary new approach to doing science. Versions of what the Myelin Repair Foundation is trying to do have existed for decades, differing in details but not in aims or overall philosophy. What is significant about the Foundation and its ARC model is that it has attracted so much attention. What does that tell us about the state of scientific research in the genomics era?

I think what it tells us is that the scientific community has sold the public on enormous increases in support for basic biomedical research by promising that such research would lead to cures for diseases, and that the public is growing impatient with the pace of that translation. Nowhere is this more evident than in the various genomics programs: the Human Genome Sequencing Project, the Structural Genomics Initiative, the Haplotype Mapping Initiative - all these and more have been funded because their proponents promised that the results generated by these massive, expensive programs would lead to a new era in medical treatments. As, of course, they will, but it's reasonable to ask whether the mechanisms for getting there are optimal. The excitement in some quarters over the Myelin Repair Foundation model suggests to me that government funding agencies have not managed to find, or at least to implement, mechanisms that encourage collaborations and that reward innovation and risk-taking. More than ten years after the human genome sequencing project began, it still takes, on average, more than 12 years and almost a billion dollars to make a drug. The Myelin Repair Foundation aims to license at least one myelin repair drug target to a major pharmaceutical company by 2009, five years after its inception. Given that much target validation is done outside of the pharmaceutical industry, it's hard to know how much of an acceleration that represents. The likelihood is that it will still take close to 12 more years before a drug reaches the market.

But consider the case of Gleevec, Novartis's Bcr-Abl tyrosine kinase inhibitor for chronic myelogenous leukemia. The Philadelphia chromosomal rearrangement producing the activated kinase was observed in leukemia patients in 1960. The kinase itself was first identified as a possible cause of the disease in 1985. It was shown to be a cause of leukemia in mice in 1990. Gleevec was approved by the US Food and Drug Administration in 2001. Depending on whether you consider the story to have begun in 1960 or in 1985, it either took 17 years or 32 years to proceed from first glimpse of the target to the clinic. Seventeen years would be just about what the Myelin Repair Foundation can expect if its model works, maybe a bit faster if they're lucky. That wouldn't represent much of an acceleration at all. But going from 32 to 17 years would be a pretty big deal.

Genomics was supposed to produce a revolution in human health. It will, of course, but I think it's legitimate to question whether our mechanisms for translating the results of such research into real therapies aren't also ripe for a revolution. The RoadMap Program of the National Institutes of Health (NIH) has run into a lot of criticism; it is seen as an attempt by the NIH Director, Dr Elias Zerhouni, to drive biomedical research away from basic science towards translational research. As far as I can tell, that isn't what it's about at all. For one thing, it only consumes a very small portion of the total NIH budget. For another, it was conceived as a blueprint for how everything should be done; it was designed to be a laboratory in which different research models and different funding mechanisms could be tried out. I don't think that's a bad idea at all, and I think the criticism of it is based partly on its unfortunate name ('Laboratory' would be so much better than 'RoadMap') and partly on the fear that somehow it's taking money out of our own research pockets. Given the number of wasteful initiatives in other NIH Institutes and Centers, this is hardly a fair criticism. It's also totally inconsistent. I've heard many investigators claim, with much justification, that government scientific funding agencies are far too conservative. To go blithely from that charge to a charge that the RoadMap is too radical strikes me as bordering on silly.

Considering that our scientific enterprise is peopled largely by trained experimentalists, it's surprising that there is so much resistance to trying out new things. Fear that the experiment may fail would never be an acceptable reason for not doing it on the part of one's own graduate students or postdocs. The ARC model that Scott Johnson is so excited about may or may not represent a better way of doing certain things, but at least he's trying the experiment.