COMMENT

Accelerate medical breakthroughs by ending disease earmarks

Identifying connections among genetic diseases can accelerate the development of new therapies. If this potential is to be realized, argues Sharon F. Terry, research funding must no longer be focused on individual diseases.

One of the most valuable rewards of the genomics revolution is the way it has shed light on the inter-relationships among diseases. Before the sequencing of the genome, and the ensuing era of genome-wide association studies and medical resequencing, there were few tools with which to discern the most valuable biochemical targets for diagnostic tests and effective treatments. As a recent *Wall Street Journal* article states: "Traditionally, [pharmaceutical] companies would bombard an illness with a variety of chemicals until they hit on a combination that worked, usually focusing on common diseases that promised lucrative returns. Often, they didn't know what really caused the disease or why a particular drug worked."[1] This 'hit or miss' approach requires 15 years on average to develop a treatment for even common diseases. The vast majority of rare and neglected diseases still have no treatments[2].

A fundamental change is taking place, however. Our growing understanding of the human genome is helping scientists to unravel the complex and intersecting biological pathways involved in health and disease. Within those pathways are thousands of possible targets for new medicines. So many, that at first the task of sorting through them seemed overwhelming. But as our understanding has grown, scientists have begun to realize that the genetic and biochemical relationships among diseases can be exploited to accelerate breakthroughs. Different diseases can share symptoms, biological pathways and even genetic causes. By analysing similar biological pathways across two or more diseases, it's possible to eliminate less important targets and home in on the most powerful molecular triggers of disease.

Two pharmaceutical companies (Regeneron and Novartis) have recently done just that by developing drugs for a very rare genetic condition known as cryopyrin-associated periodic syndrome (CAPS)[3,4]. These companies are interested in CAPS because it is caused by a genetic mutation that makes patients overproduce the molecule interleukin-1. That molecule is also implicated in a wide range of common diseases, such as diabetes, juvenile rheumatoid arthritis, gout and certain lung conditions. These diseases can manifest in a range of ways, and there are probably multiple genetic and environmental factors influencing them. It's very hard to pinpoint the ultimate causative factors in most common diseases.

Why bother studying CAPS? Why not go straight to these common diseases and work at unravelling them? Because CAPS' cause is simple — a known genetic mutation — and that mutation's effects are very obvious. When patients with CAPS are given a drug that is supposed to block interleukin-1 overproduction, it's easy to determine whether the drug works because most patients' symptoms very quickly start improving. Thanks to this innovative research, there is finally a treatment for CAPS. The pharmaceutical companies, meanwhile, can take the same drugs that relieve CAPS and test them against other, much more common diseases in which they think interleukin-1 has a role. That's exactly what Regeneron and Novartis are doing.

This is not just about selling rare diseases as gateways to understanding common diseases. Cross-disease research can move in any direction. For example, the drug losartan (Cozaar; Merck) was developed for hypertension — one of the most common diseases in the developed world — but it has been shown to be effective in treating the rare genetic condition Marfan syndrome[5]. Some of the health problems patients with Marfan syndrome experience are related to altered signalling in a molecule known as transforming growth factor-β, which losartan targets.

The flow of knowledge can also travel from one common disease to another. One of the world's best-selling cancer drugs, rituximab (Rituxan/MabThera; Genentech, Biogen Idec, Roche), targets the molecule CD20 on B cells in the immune system. B cells are also implicated in arthritis, and rituximab is now approved to treat both CD20-positive non-Hodgkin's lymphoma and rheumatoid arthritis. Both diseases hinge upon the way CD20 B cells act. Connections among diseases are becoming more and more important. For example, inflammation is starting to be widely recognized as a key cause of many conditions, from cancer to cardiovascular disease[6,7].

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Together, these findings about common pathways in different diseases are building a powerful new knowledge base for medical research. Deepening our understanding of these crosslinks among diseases will decrease the randomness of drug discovery and make it easier to match already-approved drugs to diseases that are not yet treatable. We are entering a new 'systems' era in medical research, and our policies must reflect that. The explosion in knowledge about genetics and biology has handed us a fantastic opportunity to throw out our ineffective old methods of 'one-off' disease research, which puts conditions in competition with one another for resources. Finally, we have a new tool kit that gives us a great opportunity to hit 'home runs' against multiple diseases at once.

However, collaboration is not the norm, and disease earmarking may be one of the key factors that discourage scientists from working together or from trying out new ideas. Cancer survivor and journalist Clifton Leaf interviewed dozens of cancer experts and came to the conclusion that the 'war on cancer' has fostered "a dysfunctional 'cancer culture' — a groupthink that pushes tens of thousands of physicians and scientists toward the goal of finding the tiniest improvements in treatment rather than genuine breakthroughs; that fosters isolated (and redundant) problem solving instead of cooperation; and rewards academic achievement and publication over all else."[8] What Leaf describes so well is the fundamental conundrum in research as it is practiced at present: scientists advance by promoting their own theories, not by working collaboratively.

The advocacy community has a major role in reinforcing these research silos. Many disease advocacy organizations are keenly focused on their own goals and have allied closely with the researchers working on their problems. But crying out "me first" when it comes to funding won't help us to capitalize on our remarkable new research tools and knowledge. In this new age, in which we are finally gathering abundant information about genes and biological pathways, it doesn't make sense to use the same tactics we used when that information was scarce. Whether big or small, advocacy groups measure their effectiveness by how well they can get earmarks. In many cases, these groups are taking money away from research that ultimately might benefit many diseases, which could include their own target disease.

If we are ready for the bold idea that politics should not determine disease research funding, then we can come up with a more intelligent and systematic way to fund disease research. There remain thousands of diseases that we need to cure, and no one is more important than another in the realm of science. It's time to abandon the old 'disease by disease' approach that pits patients and their advocates against each other, slowing scientific progress for all patients and their families.

So, should medical scientists decide what gets funded? Few scientists are given the proper incentives either to innovate or to collaborate. We need to rethink the funding paradigm so that scientific opportunity — the translation of basic science into treatments — and health are what matters most. It's a big challenge, but surely we can find ways to improve this system. Directors of federal health-related agencies and their advisors must make the hard choices that will allow high risks for potentially high returns, increase the motivation to collaborate and lead to easier data sharing. Such a culture shift in the scientific community is necessary to complement the shift we are calling for in the advocacy and political communities. I am aware that this culture change will be risky and that it requires organizations to lead boldly while others retreat to the safe harbour of earmarks. It requires brave leadership from forward-thinking visionaries who understand that the measure of success is not an earmark but real-time progress against disease.

Imagine what could happen if all of us worked together with a single goal of finding new treatments in the most efficient way. Of course, the budget and appropriation process must include some prioritization and differentiation, but we can eliminate disease earmarking without disrupting the entire funding process. Let us step into the future as real collaborators building an infrastructure and a process that accelerates medical research overall, faster than what any organization or agency can do alone. Let's consider the health of our children, our families and our communities as our first priority and our organizations and agencies as the tools to get there.

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