Treasure Your Exceptions

Extreme and rare genetic disorders are key to our understanding of human biology – including other, more common diseases – yet this research area has largely been ignored. Could a multi-stakeholder approach help industry make up for lost time?

“Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten paths; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature by the careful investigation of cases of rarer forms of disease” (1).

Dr William Harvey is best known for his discovery of the circulation of blood in the 17th century. However, the quote above, written by Harvey in 1657 just six weeks before his death, illustrates his idea that to fully understand biology – and therefore many common conditions – we need to look at the rare and extreme forms of diseases.

Rare Lessons

Over 300 years later, modern medicine has still not completely adopted this principle, although there are a few notable exceptions. These include Sir Archibald Garrod – an Edwardian doctor whose research into four rare metabolic diseases (alkaptonuria, cystinuria, pentosuria and albinism) led him to conclude that they are inherited, and inspired the understanding that diseases could be genetic in origin.

In an address to the Medical Society of London entitled ‘The Lessons of Rare Maladies’ in 1928, Garrod paid tribute to William Harvey’s insight, commenting “that the study of nature’s experiments is of special value, and that many lessons which rare maladies can teach could hardly be learnt in other ways” (2).

Perhaps it is possible to say of rare diseases that their study is fundamental to the understanding of human biology and to coin a new term, ‘fundamental disease’, to describe this relationship. Fundamental diseases may be defined as those which manifest themselves as extreme and rare genetic disorders that offer a unique opportunity to better understand other diseases, including many common ones. Due to their rarity, fundamental diseases have been largely ignored – until now.

Fundamental Thinking

Professor Frederick Kaplan has pointed out just why it is that rare conditions are so informative of more common ones: “Nature does not use different genes, molecules and pathways for common conditions than it does for rare ones. Rather, it is often the rare disease that actually reveals which gene, molecule or pathways nature hijacks in its common infirmities” (3).

Common diseases generally have multifactorial causes, making them extremely difficult to unravel at the molecular level and confounding the development of highly selective treatments. However, a fundamental disease may be traced to a specific genetic cause, and the knowledge gained by studying them can be applied to other conditions. For example, the study of the rare genetic disease familial hypercholesterolaemia (FH) led to the discovery of the low-density lipoprotein (LDL) receptor and the role of LDL cholesterol in the development of cardiovascular disease (4).

LDL and Statins

Historically, there has been controversy about the exact role of LDL in the development of cardiovascular disease, and whether reducing cholesterol would provide any clinical benefit. The discovery of the LDL receptor’s role, from studies of patients with FH, resulted in an understanding of the regulatory mechanism by which the LDL receptor controls cholesterol synthesis by a negative feedback mechanism.
mechanism on HMG-CoA reductase – the rate-limiting enzyme involved in cholesterol production.

More importantly, it also elucidated how the LDL receptor itself is controlled and how drugs such as statins, which inhibit cholesterol synthesis by inhibiting HMG-CoA reductase, could selectively lower LDL in the blood. Statins are now used to treat millions of people with raised cholesterol.

Some of the features we consider to be core to the definition of a fundamental disease, contrasted with the features of common diseases, are set out in Table 1. By this definition, it will be seen that all fundamental diseases are rare, but it is not necessarily the case that all rare diseases are fundamental.

**Insulin Resistance**

Another good example of the possible importance of fundamental disease research is insulin resistance, when the body becomes less responsive to the glucose-lowering activity of insulin, and therefore unable to accurately control its blood glucose levels.

It is a very common problem, playing a central role in the development of type 2 diabetes, and is a central feature of the metabolic syndrome. It is frequently associated with obesity, but also occurs, in an unusually severe form, in patients with certain rare genetic forms of severe insulin resistance or lipodystrophy. These genetic defects can be grouped into those affecting insulin signalling and those affecting adipocyte developmental function.

The study of patients with these specific genetic defects is yielding insights into the mechanisms of more common forms of insulin resistance (5). The hope is that the study of these fundamental diseases may lead to new treatment options for type 2 diabetes, one of the fastest-growing diseases in the world.

In addition to the above conditions where there may be a direct relation between the fundamental disease and a common disease, the knowledge gained by studying the former can have much wider implications. For example, if an enzyme replacement therapy (ERT) is developed for a specific rare and fundamental disease, it may well be possible to use the same techniques to develop ERTs for several other diseases. Similarly, a gene therapy for one genetic disease will pave the way for the development of other gene therapies using the same technology.

### Promoting Research

One of the biggest problems with research into fundamental diseases is that, until recently, they have been largely ignored by the scientific community and the pharmaceutical industry. The most likely reason for this is that their importance has not been recognised. By referring to these diseases as rare, it has been an uphill struggle to muster support from the general public, to enthuse scientists and to engender interest from the commercial sector.

However, with the recent considerable growth in the effectiveness of patient groups and the building of communities of rare disease patients – assisted by the explosion in availability of social media – a new era is dawning in which patients themselves are taking a leading role in R&D. There are now several examples of patient group charities helping to set up research departments in academia, develop animal models and even take drugs into clinical development.

One such charity, Findacure, was founded with the aim of building a movement to promote the R&D of treatments and, potentially, cures for fundamental diseases, on behalf of patients and their carers. It aims to empower the patient sector to take control of their disease area and help patient groups meet the challenges of medical research and drug development. These groups rarely have the knowledge or expertise to initiate basic and/or clinical research for their disease, so the charity provides tools and advice on matters from how to raise funding and engage with industry, through to orchestrating a clinical development programme (6).

### Development Costs

However, one of the biggest issues for research into fundamental diseases is that, commercially, they are uninteresting. Most affect a small patient population and so present limited business opportunities for a pharma company that would need to invest a large amount of funding into R&D of new medicines.

There are a range of incentives to help improve the situation for rare diseases – for example, orphan drug legislation which provides financial benefits during the development process and several years of market exclusivity following approval.
of a medicine for a rare disease (orphan drug) to help recoup the development costs.

However, it seems that, in some cases, the more traditional models of drug development are not as appropriate for markets with very small patient populations. There are many examples of orphan drugs with extraordinarily high prices – for instance, the world’s current most expensive drug, Solaris, costs more than $400,000 per year for patients with paroxysmal nocturnal haemoglobinuria.

While orphan drugs clearly provide significant value for patients, the high prices of these medicines may be unsustainable in the long term if the number of orphan drugs continues to rise. With increasing pressure on prices, pharma companies may be discouraged from continuing to develop treatments for rare diseases.

Towards a New Model

Ideally, there should be a new model for developing drugs for rare diseases – one that does not require a single party to make a huge investment and take the substantial risk all by itself, but which combines the talents of several stakeholders united by a social enterprise. The advent of the European Framework Programme for funding healthcare research has helped to facilitate such multi-stakeholder consortia.

Because drug development is very expensive, even when run on a shoestring, it has been difficult to create such consortia prior to the availability of these relatively large grants. For example, the FP7 grant programme funded a consortium comprised of three hospitals, two universities, a research institute, three small- to medium-sized businesses, two patient organisations and a pharma company, to join together in the development of a treatment for a rare metabolic disease: alkaptonuria (7).

Partnerships with patient groups can improve the overall quality of the trial, by allowing patients to take an active role in the planning and running of the research. Patient groups may also be well-placed to use their existing networks to increase patient recruitment once drugs are taken to clinical stages.

In addition, partnerships with academia could reduce the costs of initial drug discovery. GlaxoSmithKline, for example, already runs a programme called Discovery Partnerships with Academia, which seeks to bring academic research into a drug development programme. The development arm of Findacure aims to use this model of a multi-stakeholder social enterprise to drive the development of promising new treatments for fundamental diseases where there is no commercial interest.

Wider Knowledge

Research into fundamental diseases increases our overall knowledge of common conditions and human biology; however, they are rarely investigated, and are usually ignored. The examples here demonstrate that the importance of fundamental diseases goes beyond the few people affected by one rare condition.

The title of this article, ‘Treasure Your Exceptions’, comes from the Cambridge geneticist, William Bateson, and summarises this idea perfectly: that exceptions are usually the key to understanding the common (8). With this aim in mind, fundamental diseases should become a viable option for future research and drug development programmes.

References
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