Loss-of-function genetic diseases and the concept of pharmaceutical targets

In their article, Brinkman and coauthors[1] suggest that rare genetic disorders can be a mining field for the discovery of novel drug targets, and thereby for novel drugs. They underline the fact that the current number of pharmacologically active molecules is small compared with the number of human genes, and that existing drugs target an even more limited list of proteins. Central to their argument is the point that, for many common diseases, it is possible to find at least one Mendelian monogenic disease that resembles the common disease. They build on this to suggest that a more thorough characterization of the monogenic human phenome could uncover more targets, and hence be a way to reverse the decrease in the number of drugs that are under development, a trend that is partially due to a paucity of validated targets.

Given the space limitations, it is impossible to enter into the heated debate on how many potential targets there are in the human genome[2,3] or whether the future of drugs will be made of target-selective or non-selective molecules[4,5]. Instead, I wish to consider some elements regarding the question of how far the strategy proposed by Brinkman *et al.* can be implemented, and to put it into a broader context.

Brinkman *et al.* use several convincing examples to make their point that the knowledge obtained from monogenic disorders is beneficial to drug discovery for related common diseases. The main question that arises is whether these are truly examples of a general trend, or instead, exceptional cases?

From a rare-disease perspective, the problem with most of the 5,000 or so Mendelian diseases, is that their physiopathology is poorly understood — and when they are well understood it is usually because they affect receptors or pathways that have long been studied for their implication in common diseases. This is, for instance, the case for channelopathies, which benefit from an extensive pharmacopea that targets ion channels, and of metabolic diseases, for which essential enzymatic pathways were established several decades ago. Taking the argument further, it can be noted that, in the struggle against genetic diseases, a crucial issue resides in the fact that there is no identified target for most of them.

Another major problem with genetic diseases is that most of them have no treatment. Although many of the arguments developed by Brinkman and others for mining them as a source of clues to treat common diseases make sense scientifically[1,6,7], any global extrapolation of the putative outcome of such a strategy must be tempered by this basic consideration.

A criticism that could be made of Brinkman *et al.*'s demonstration is that it gives little weight to a key difference between common and Mendelian diseases. In their quest for targets, drug discoverers tend to adopt a molecular biologist's way of thinking that makes a single gene product the cornerstone of every disease. This trend is unquestionably the result of a justified need to have a Cartesian approach in drug discovery and a mechanistic explanation of drug action. However, the downside of it is that this quest for the target has imprinted the reductionist view that most common diseases might be modelled around modulations of a single gene product. It is worth recalling here that this intellectual frame is now being challenged[4]. From a clinical perspective, many high-prevalence diseases (hypertension, cardiac insufficiency, diabetes, obesity and many mental disorders) are progressive organ dysfunction. It is difficult to imagine that they can be conceptually reduced to a single gene modulation without a significant loss of information. Yet this crucial aspect is often overlooked in drug discovery. Identifying the mode of action of a new drug is a necessity; however, assuming that a single target can reconstitute the physiopathology of a common disease is probably incorrect for most of them. Because organs need genes to function, it is of no surprise to the geneticist that some gene impairments have clinical consequences that resemble those of common diseases that affect the same organs. It is a slightly different assumption to say that the gene involved in the genetic disease can be a target or even a marker for the common disease it resembles. Still, this confusion exists. Therefore, the argument that monogenic diseases might be considered as models for common diseases is

built on oversimplified premises and should not be generalized beyond a few specific examples.

What can be learned from genetic diseases? To take an example from Brinkman *et al.*, it is reassuring for the drug developer to know that the target of the prostate anti-hyperplasic drug 5-alpha-reductase 2 (Proscar) is a protein that, when inactivated, leads to a reduced prostate size[1]. But have we learned much from this, given that prostate is a hormone-dependent organ and that 5-alpha-reductase is the enzyme that converts testosterone to its active form, a fact that has been known for several decades?

The real value of monogenic disease with respect to common diseases lies elsewhere — in the non-hypothesis-driven assignment of genes to a cellular function. Genes that, when mutated, lead to similar phenotypes to common diseases are often involved in the same cellular function. Geneticists working with model organisms, notably invertebrate ones, have been using this rule for almost a century as a primary key to infer the function of genes. The identification over the past 20 years of more than 1,500 human genes responsible for Mendelian diseases has simply opened the eyes of the drug developers to something that is daily bread for model organism geneticists. In terms of sheer biological discovery, monogenic disorders are the spontaneous human equivalent of mutations induced in *Drosophila melanogaster*, *Caenorhabditis elegans*, mice and other model organisms for the sake of understanding gene function. The information gained from such studies constitutes the foundations on which biomedical knowledge is built. Unfortunately, its translation into treatments remains a daunting and complicated task.

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