What's in a number?

Ten years ago, the first estimates of the existing number of drug targets were made. This month's issue features an article and poster that together summarize current drug targets and associated characteristics, providing a basis to better understand the potential for future therapeutic exploitation.

The human genome project was anticipated to clarify two key questions for drug discovery: first, the extent to which particular human genes were responsible for diseases; and second, the number and nature of molecular targets relevant to research for therapies for these diseases.

Although neither of these questions could be answered in the mid-1990s, it seemed desirable to at least estimate the number and biochemical functions of drug targets that could then be identified as providing the basis of contemporary drug therapy. In an attempt to do so, Stefan Ryser and I analysed the most recent (ninth) edition of Goodman and Gilman's classic textbook, *The Pharmacological Basis of Therapeutics*, then available and tried to reduce the mechanisms of action for all medicines covered by the text to one or several targets that could be identified in molecular terms.

Viewed from today, we took a rather generous approach. Regulatory approval was not the *sine qua non* for inclusion, and the description of mechanisms of action did not always allow for the unambiguous identification of a single molecular target. In some cases, the extrapolation from a complex cellular structure to an enzyme or to a receptor might have been somewhat arbitrary. Nevertheless, the resulting figure of 483 molecular drug targets (human genome-derived as well as viral or microbial targets) was widely accepted as an important piece of information. If anything, it surprised many because it was so small. Compared with 100,000 genes, then a popular estimate for the total number of human genes, a few hundred genes seemed to represent a tiny fraction. But even in the context of only 30,000 genes, which according to recent knowledge represent the informational content of the human genome, 483 targets seemed like a very small number.

Subsequent studies, which are all cited in the paper by Overington and colleagues on page 993 of this issue, resulted in even lower estimates, mainly because the methods applied were more restrictive than our approach. In spite of the differences between various groups, however, they all — with one exception — arrive at numbers of drug targets not larger than a few hundred. Overington *et al.* now propose 324 distinct molecular targets, of which 266 are human genome-derived, while the remaining 58 are of microbial or viral origin. They have approached their subject with clear definitions and the best data available today, and for this reason their article could well become the standard reference for further studies in this field.

We can be reasonably sure that present-day drug therapy is indeed based on a very small number of molecular drug targets. We also take note (again) of the limited repertoire of biochemical mechanisms that seem to be associated with 'druggable' proteins. However, we cannot yet be certain whether the small number of drug targets reflects an evolutionary principle, such as an innate 'protection' of living structures against external chemicals, especially small molecules, or whether we are still at the beginning of a scientific endeavour that will eventually enable us to address a much greater number of molecular drug targets than we can reach today.

With this in mind, it is interesting to reflect on how the targets that Overington and colleagues have listed became known over time. The authors note that the addition of novel proteins to the exclusive club of already known targets is a rare event: of the 361 new molecular entities approved by the FDA between 1989 and 2000, only 6% targeted a previously undrugged protein domain. Nevertheless, the case of the protein kinases has shown that new families of drug targets can still be found.

If, however, the number of druggable proteins remains relatively small, a greater variety of pharmacological and therapeutic effects can only be generated by addressing not one but several targets simultaneously. The ideal of 'one compound–one target' would then have to be replaced by a different paradigm, in which a defined agent addresses several molecular targets in a predictable and reproducible way: 'polypharmacology'.

What is already true for the treatment of cancer might well become the dominating paradigm for the treatment of many other complex diseases: they might be more effectively controlled through multiple points of regulation than through a singular point of attack. At some point, therefore, it might be more important to ask for the *pattern* of targets that can be reached with a single agent than to search for the best possible *single* target underlying a pathophysiological mechanism.

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