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Editorial

A critical evaluation of the process of drug discovery and evaluation: is the current approach the best possible one?

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The molecular revolution was supposed to accelerate the process leading to the rational design of the drug. The sequencing of the human genome few years ago raised widespread hope in the treatment of disease created by increased investment in biomedical research. But this goal failed to be achieved. Instead, 2000 outlined the beginning of a fall in new drug submission to regulatory agencies worldwide.

At a time when basic biomedical knowledge is dramatically increasing, the gap between bench discovery and bedside application appears to be expanding. This means that fewer new products can be approved and made available to patients. There is concern that hoped-for advances in medicine and new treatments for diseases may never materialize. What's wrong then?

According to Thomas Kuhn (The structure of scientific revolutions, 1962)*, "*when a prevailing paradigm fails to make productive predictions then the difficulty may lie with the paradigms on which the research is based"*. This means that our current approach may need to be revisited.*

For the past 100 years Western biomedical science has stood on two philosophical pillars: the anatomical paradigm of medicine (organ-specific problems are the result of tissue specific protein and gene defect), and Mendelian paradigm of genetics (specific for nuclear DNA genes). A new paradigm at least for the common age-related diseases must be generated that encompasses the strengths of Mendelian and anatomical paradigm with the energetic paradigm and the mtDNA qualitative paradigm (DC Wallace, Genetics *2008).*

Another paradigm that has dominated drug discovery but that may need to be reconsidered is the concept of designing drugs able to act on individual drug targets. Based on the assumption that designing very selective ligands will lead to safer and more effective drugs, most modelling efforts and even animal or clinical trials are typically designed to address a single disease target. In spite of the (theoretically) high risk/benefit profile of target-based drugs, however, toxicity is still a leading cause of attrition at all stages of the drug development process, and efficacy is not as expected, as shown by the frustratingly poor discovery of new disease-ameliorating molecules. According to these considerations, the network pharmacology may represent the next paradigm in drug discovery (AL Hopkins, Nature Chem Biol *2008).*

Our "regulatory" mission to favor the delivery of safe and efficacious new treatments to the patients who need them is thus increasingly difficult to be accomplished.

Furthermore, the above uncertain and unsatisfactory scenario means that, as regulators, we have to assume very difficult decisions in the absence of ideal information. For instance, considering that our financial resources in health care are limited, we have to cope with uncertainty on deciding on drug pricing and reimbursement.

For regulatory bodies, significant challenges in this new scenario include the development and validation of new possible regulatory approaches. Our ambition, in this context, is to parallel the science walk and to promote the scientific debate in the field of drug discovery and evaluation.

Of course, to ensure a timely uptake of innovation in this area, scientists from academia and industry will have to share with regulators advances in this direction. Finally, to fully accomplish our mission, attention has to be paid to the patients' point of view and expectations.