La chimie médicinale confrontée aux nouveaux paradigmes de la recherche thérapeutique

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The pharmaceutical research after the wreck of the One Gene Paradigm.

Pharmaceutical Research met nearly a dead end since some years. More and more clinical development programs had to be abandoned in the late phases 2b and even 3. New pharmacologically highly active and selective molecules were continuously pushed in development; however these molecules revealed to be therapeutically inefficient.

This lack of success have been widely attributed to economical, societal and organisational causes by many management expert consultants; the parades that have been developed have been the adoption of an attrition model for development projects — the more projects you launch, the more you have a chance to get one blockbuster — followed as a consequence by mega mergers politics. Very few scientists were heard who pointed that the true reason of the lack of productivity was actually hardly scientific! The *"one disease, one gene, one target, one molecule, one blockbuster"* is now recognized not to be the unique model of a real pathology and the Ehrlich dream of the Magic Bullet vanishes in a dull grew dawn. Other evidences came from single-gene knockout in different models where only few deleted genes revealed effect on phenotype. The application of population genetics methods to the comparison of healthy versus sick populations, also called Genome Wide Association Studies (GWAS) appears now to be the key of the construction of biological networks; genetic SNIP variations conjugated to environment factors may affect significantly the level of expression of the genes; then the cell regulation is perturbed either directly, or indirectly through the modification of the level of the metabolites, or through with the concurrent interference of environmental factors. Hence the new drugs will have to interfere with several biological targets at the same time, eventually with a lower affinity for each target.

Hence, it is absolutely necessary for the Pharmaceutical Research to the abandon the One Gene Paradigm, and for the Pharmaceutical Development to abandon the attrition model — the Fantastic Funnel — so that the enormous bulk of money hopelessly spoiled in hopeless late phase studies could be pushed upstream to a vigorous research based on the building of much better models of pathologies.

From there one may anticipate the emergence of two tracks for new drugs:

– the poly-pharmacy associating several old molecular active entities, eventually repositioned from their initial pathological application and generally at much lower doses
– the multi-targets new small molecules optimizing one molecule for a weaker affinity for a set of selected targets.

In this perspective, the room for highly selective and affine biologics seems very narrow, and medicinal chemists may expect glorious perspectives.

***Un itinéraire atypique**. Universitaire et industriel accompli (30 ans de recherche universitaire suivis de 20 ans en responsabilités dans l'industrie pharmaceutique), récemment retraité de la société Sanofi-Aventis où il occupait dernièrement la position de Directeur Scientifique Affaires Industrielles, Bertrand CASTRO a été auparavant Professeur à l'ENSCM et Directeur du CCIPE (devenu depuis l'IGF) à Montpellier.*