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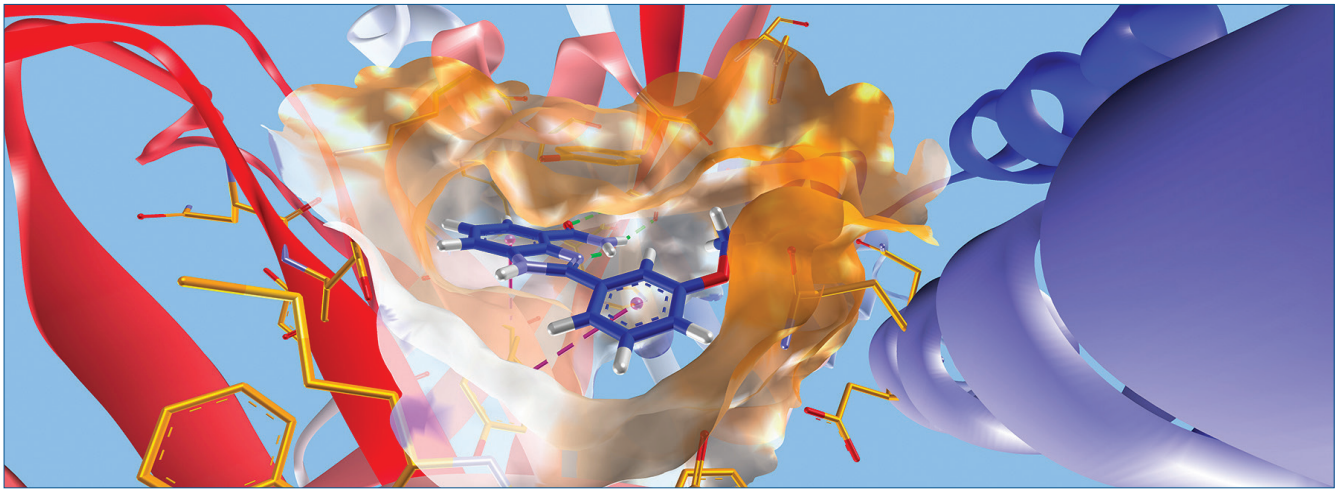
MYSTERIUM INIQUITATIS. NOT THE END OF A DISCIPLINE BUT A FIELD OF NEW OPPORTUNITIES (WITH SOME CAUTION)

Some years ago, a catholic Italian writer, Sergio Quinzio, wrote a visionary romance,* Mysterium Iniquitatis*, where the last Pope promulged, ex cathedra, the dogma of the end of the Catholic Church. For some strange reason, this came to my mind when the executive committees of European (including Italy) medicinal chemistry societies started discussing whether chemical biology should be included in the scope of medicinal chemistry.
Is this an 'apostasy' or is it perhaps the birth of new opportunities? Here my reflections.

Medicinal chemistry is the art of ideating, designing and synthesizing new molecular entities whose overall properties make them suitable to exhort a positive therapeutically role in a living system (be it a human, an animal or a plant organism) without producing harness. The tools used by this art are creativity, understanding of underlying biological processes, ability to visualize the three-dimensional shape of a molecules in its biological context, ability to forecast the effect of even minor chemical modifications on the fate of the molecule within a living system. This all, implanted into a robust organic synthesis background, essential to translate ideas into new molecules. While this definition (which is paraphrased from the official IUPAC definition) is rather robust, its operational application within the drug discovery pipeline, which is the ecosystem where medicinal chemistry finds its '*raison d'etre*', has changed considerably during years, and as a matter of fact the one's self-recognition of her - or himself as a medicinal chemist has changed accordingly. A 'medicinal chemist' has used to be a good synthetic chemist interested in biology, a 'drug designer', an ADME-oriented scientists, to a 'chemical pharmacologist', with expertise in the systems (patho)biology. The impact of these changes in the recognition of the discipline's positioning in the scientific arena is complex and will be commented below. But a few things are certainly well assessed and can be directly stated. The first one is that medicinal chemistry is

an applicative science, where the accomplishment of its ultimate goal (a therapeutic substance active in humans or animals) strongly depends on the existence of an industrial background motivated to support this extraordinarily expansive and complex process. It must be noted that the modern era of drug discovery has always been 'evidence-driven', and steered by disciplines which in that moment were able to provide the strongest evidence for a given hypothesis. For many years, drug discovery has been chemistry-based, and the extraordinary success of the 'pharmacocentric' dopaminergic hypothesis of schizophrenia, or the impact well beyond medicine of benzodiazepines or SSRIs, are just few but remarkable examples. From the Nineties on, the scenario has changed, and drug discovery has evolved towards a genuine biology-based process. Obviously, small molecules are still needed to fill in the pills given to patients, but in the general perception (more in the perception than in reality, to say the truth) this is not an issue, since '*molecules can be done, in one way or another*'. Chemistry has become a commodity for the pharma industry, as its value is eventually estimated by the price and lower prices must be found in remote markets, and even if the art of medicinal chemistry is still present in the process, as the value of the molecule is obviously not in the price but in the overall properties which make it a true product of science and creativity, medicinal chemists have been progressively marginalized from the decisional processes in industry. This is my personal understanding of the cultural background upon which the president of the EFMC has opened, a year ago or so, the question whether chemical biology should be included into the scope of the European Federation of Medicinal Chemistry. As a matter of fact, the proposal has eventually been approved and the acronym EFMC should now read as European Federation for Medicinal Chemistry and Chemical Biology (disclaimer: despite my strong doubts, I voted for the change). Now, the question arises why a scientific society should change the name. The question cannot be only semantic but should reflect either a change in the discipline's perception or a practical motivation in terms of visibility, opportunities, and promotion of the society's members. Let's start from the latter point. Perhaps some of the readers may remember that years ago the American Chemical Society opened a poll to change the name of the Division of Medicinal Chemistry (MEDI) into Division of Drug Discovery. I proudly voted against this proposal which was in fact rejected. It is, however, interesting to recall the motivations that pushed the ACS to open the poll. The strongest one was the scarce appeal that the initiatives of the MEDI had in terms of congress attendees and as general engagement on its activities. This is, and I apologize for the simplification, more or less the same driver of the present discussion. No doubts that in general and political context the term 'chemistry' is loosing appeal, and this is reflected in the public calls, for example those under the H2020 framework, where the explicit reference to 'medicinal chemistry' is seldom present. The idea is that the incorporation of the 'sexier' term 'biology' in the scope and aim, should facilitate the involvement of larger communities into common programs and should also reassign to medicinal chemists (MCs)/chemical biologists (CBs) more decisional power. Provided that some (if not most) of the operational tools are shared between MCs and CBs (see below), I judged it an acceptable idea. After all, the community will be still composed of people interested in using and creating chemistry to interfer with biology. Said this, it should be a point of reflection asking why medicinal chemistry has progressively lost appeal. I think part of the responsibility is up to us,



and we are still on time to remedy the situation. We have often advocated to our role of 'inventors of molecules', and we have often filled our lectures, our papers of concepts that should more appropriately refer to medicine, pharmacology or other biomedical disciplines. Often, we have given the idea that '*molecules can be done, in one way or another*' and that the important part of our projects are the clinical needs, the proof of concept, the animal models, and so on. This is drug discovery, not medicinal chemistry. Our job would have been to valorize, within the drug discovery process, the fundamental role of medicinal chemistry, and the difficulty which is behind the art of preserving the activity of molecules while making them non-toxic, bioavailable, penetrant, metabolically stable, and so on. On the contrary, often and often we have given it as granted, thus jeopardizing the expertise which (should) make us proud of being medicinal chemists. To be provocative enough, if I were a decision maker, why bothering behind medicinal chemists, if the hot spots in the project are clinical need, proof of concepts and so on? Now let's move to the more scientific part of the problem. Is chemical biology really part of medicinal chemistry? The following papers in this issue of *La Chimica e l'Industria* might help the readers to make their mind up to the problem, but one should consider that while chemical biology is the study of cellular process through the use of chemical probes, and thus it is inherently a biology-focused approach, it is quite evident that chemical probes must be designed and synthesized in order to make them appropriate for that particular aim. And designing and synthesizing molecules with the aim of optimizing their interaction with the biological counterpart is certainly part of the tools of trade of medicinal chemistry. Furthermore, once identified to be a key modulator for a given pathway, that molecule can certainly became the starting point towards becoming a potential modifier for a disease state. Thus, chemical biology can certainly be a fertile field where medicinal chemists can seed their art, with two words of caution. The first one is that I strongly encourage our community to keep on this broadening of scope of the discipline, but having always in mind that the focus of our activity is chemistry, is creating and optimizing molecules. I would not come to the situation where our congresses and journals are populated by beautiful communications on basic cellular biology discoveries keeping the molecules and their inventors in an ancillary and undeserved role. The second one, kept on silence so far, is the impact that this broadening may have in teaching 'medicinal chemistry'. In Italy, and in many other countries, medicinal chemistry is a core discipline of the Schools, Faculties and Departments of Pharmacy, and pharmacists must be trained on the importance of the structure activity relationships and on how (physico)chemistry influence the fate of a drug in the body. Again, this must not be jeopardized by a spurious and uncontrolled broadening of competences, and care must be given in preserving the expertise and the background which shape the identity of medicinal chemistry.