Drug repurposing and beyond: the fundamental role of pharmacology

Dear Sir,

On 13th-14th June, 2014, the University of Calabria (Rende, Cosenza, Italy) provided the venue for "DRUG REPURPOSING AND BEYOND: THE FUNDAMENTAL ROLE OF PHARMACOLOGY", the first Italian meeting devoted to this hot topic.

It is widely recognized that the time lag between filing a basic patent on a new molecular entity and the commercialization of that entity as a drug is extremely long and costly, taking more than 11-12 years, and generating an average cost estimated to be in excess of US$1 billion (Sternitzke, 2010). It is calculated that only 10% of experimentally effective drugs are finally approved and less than 20% of marketed drugs make enough money to cover the costs related to their research and development (R&D) (Khanna, 2012). Moreover, adverse effects incompatible with further marketing of the product may appear even long after its clinical approval. This scenario has led the regulatory agencies (FDA, EMA) to impose increasingly stringent and rigorous approval guidelines, thus further hindering the clinical translation of new drugs (Tralau-Stewart et al., 2009). Nowadays, approximately 20 new molecular entities enter the clinical setting each year, at a cost that is a hundred times higher than that of new drugs entering the clinical arena in the 1970s (G. Hirsch, MIT Newdigs Programme, 2010).

Most failures in the drug development pipeline are due to inadequate efficacy or to a lack of safety emerging in phase III clinical trials or after drug approval (Miller, 2010). In the period 2011-2012 failures in earlier phases (e.g., phase II) were found to be significantly increased, while those in phase III were reduced, nevertheless standing at around 52% (Arrowsmith and Miller, 2013). The reason for this lies, at least in part, in the fact that the FDA, the EMA and sponsors (mainly pharmaceutical companies) are demanding to see significant improvements in efficacy with respect to placebo or to already available therapies (Trist, 2011). Moreover, the clinical validation of the target is becoming a difficult task, since animal models designed on the basis of a single target are not able to guarantee clinical proof of concept or, when adequate animal models do not exist, target validation has to be done in humans (Trist, 2011).

Given the limits imposed by biostatistics, a reliable clinical study cannot be performed in a small number of individuals; furthermore, the activity (phase II), efficacy and safety (phase III) of the new molecular entity need to be validated in a large cohort of patients, through multicenter studies that make it possible to take into account individual variability and cultural differences (in both the experimenter and the patients) between distinct geographical areas (Prof. E. Donato Di Paola, UNICZ, Catanzaro). According to protocols for clinical trials, all the figures involved in the study (the sponsor, the principal investigator, etc.) have to be identified and approval is required from an independent ethics committee that defines the inclusion and exclusion criteria for recruiting the individuals who will be involved in the study, the monitoring procedures and all the issues related to informed consent, insurance and publication of the data. The recently approved Regulation (EU) No. 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use is aimed at standardizing the procedures among the member states, in order to make clinical studies more flexible and more efficient, avoiding administrative delays yet without compromising patient safety or public health. All the EU member states should align with the Regulation and divergences of approach between different countries should be kept to a minimum. As highlighted in the Regulation, a rapid yet in-depth assessment is crucial for clinical trials regarding severely debilitating and/or life-threatening medical conditions, as well as pathological conditions for which therapeutic options are limited or non-existent, as in the case of rare diseases. It is thus important to foster clinical trials for the development of orphan medicinal products (Prof. E. Donato Di Paola).

Despite these efforts, the current R&D process remains very slow and costly, because of the aforementioned safety reasons and, in particular, the limited clinical efficacy of novel therapies. The availability of information regarding the safety of various drugs used for several years in the clinical setting in a large number of patients, together with patent expirations, is opening the way for their potential exploitation in the treatment of medical conditions different from those included in the previous approval by the regulatory agency. A similar scenario can be envisaged for drugs whose development has reached advanced preclinical or clinical trial phases (phases II and III), but which have not reached the market because of reasons unrelated to safety concerns (Chong and Sullivan, 2007; Petsko, 2010). In this latter case, the availability of already known compounds and of data on their effects, provided by the pharmaceutical companies, would be crucial in implementing the rescue of drugs that have never

reached the clinical setting and could allow pharmaceutical companies to recover the costs spent on their R&D (Tobinick, 2009; Mullard, 2011).

This was the rationale of the monothematic meeting "Drug repurposing and beyond: the fundamental role of pharmacology", the first meeting on this topic in Italy, held at the University of Calabria (Cosenza, Italy) on 13th and 14th June 2014 and sponsored by the Italian Society of Pharmacology. This novel R&D approach first appeared in the United States a few years ago, with a series of agreements between pharmaceutical companies, the NIH and universities. More recently, it has also been seen in Europe with the EU-funded NewMeds project, which is based on a partnership between university and industrial researchers (AstraZeneca, Janssen, Eli Lilly, Lundbeck and Pfizer), for the development of second-generation antipsychotics.

During the meeting, several presentations highlighted the neuroprotective efficacy of drugs already employed for other indications in animal models of brain ischemia. This is of interest since the availability of promising drugs that may be developed for the treatment of ischemic stroke could be crucial in improving the therapeutic options for a medical condition which presents unmet needs. The macrolide antibiotic azithromycin reduces brain damage and neurological deficit induced by middle cerebral artery occlusion in rodents via modulation of the immune system, and a multicenter clinical study aimed at assessing the effectiveness of this drug in stroke patients has already received approval from the ethics committee of the coordinating center (D. Amantea, UNICAL, Cosenza). Another example of drug repurposing that offers promise for the treatment of ischemic stroke is C1-inhibitor (C1-INH), an endogenous complement inhibitor, commonly used in deficiency of C1-INH (hereditary or acquired angioedema). The recombinant inhibitor binds with high affinity to mannose-binding lectin, thus reducing cerebral damage in transient and permanent focal cerebral ischemia, and it shows a wide time window (> 6h) (F. Orsini, Istituto Mario Negri, Milan). A wide time window is also associated with the neuroprotection exerted by treatment with a combination of the epigenetic drugs etinostat (MS-275, histone deacetylase inhibitor) and resveratrol (sirtuin-1 inhibitor). The efficacy of these two drugs is related to their ability to modulate RelA acetylation, and to the ability of this, in turn, to block the induction of pro-apoptotic pathways (A. Lanzillotta, UNIBS, Brescia). Other drugs, with a well-known tolerability profile in humans, also constitute promising tools for the treatment of different brain injuries on account of their documented neuroprotective efficacy in preclinical models. These include Levo-pramipexole derivatives (D. Buonvicino, UNIFI, Florence), antithrombin (O. Cuomo, UNINA, Naples), memantine or topiramate in combination with hypothermia (E. Gerace, UNIFI, Florence), and RXR agonists (M. Certo, UNICAL, Cosenza).

Drug repurposing is a highly dynamic process that follows the evolution of translational sciences, which are continuously expanding as a result of the development of new technologies and intense research activity geared at improving understanding of the pathogenetic mechanisms underlying most diseases. In fact, the development of new experimental technologies has led to a better understanding of the "classical" targets in the pathophysiology of diseases. Thus, the role of pharmacology is crucial for target rediscovery, offering novel stimuli for the application of drug repurposing strategies. This is consistent with the contents of the keynote lecture "Aryl hydrocarbon receptor: a novel drug-repurposing target to control inflammatory responses" given by Prof. F. Fallarino (UNIPG, Perugia). This lecture highlighted the role of L-kynurenine, a byproduct of tryptophan catabolism produced through indoleamine 2,3-dioxygenase 1 (IDO1), in the development of tolerance of the immune system. The data shown demonstrate the involvement of the aryl hydrocarbon receptor (to date mainly considered in relation to its toxicological properties) in the induction of a tolerance state that protects mice from infections caused by Gram-positive or Gram-negative microorganisms (Bessede et al., 2014).

The role of IDO1 in tryptophan metabolism in plasmacytoid dendritic cells (pDCs) also underlies the repositioning of proteasome inhibitors in autoimmune diabetes. Regulation of proteosomal degradation in pDCs could represent an innovative strategy for enhancing IDO1-mediated immunoregulation in type 1 diabetes (C. Orabona, UNIPG, Perugia).

Further examples of target re-evaluation include the transduction mechanisms associated with the GPER receptor as novel therapeutic targets for cancer treatment (M.F. Santolla, P. Avena, UNICAL, Cosenza). Dissection of the whole machinery of autophagy is offering huge scope for drug repurposing and target rediscovery for the treatment of glaucoma and pain (R. Russo, UNICAL, Cosenza and L. Berliocchi, UNICZ, Catanzaro, respectively).

Dr Paola Bezzi of the Department of Fundamental Neurosciences of the University of Lausanne demonstrated, through the use of advanced imaging techniques, the crucial role of astrocytes in the modulation of neuronal transmission (Bezzi and Volterra, 2014). The vesicular release of gliotransmitters allows astrocytes to integrate and process synaptic information, by controlling and modulating synaptic transmission and plasticity (Santello et al., 2013). The original data presented by Dr Paola Bezzi and by two young post-docs from her research group (F. Petrelli and L. Pucci, Lausanne) demonstrate that the modulation of the mechanisms involved in the release of neurotransmitters from astrocytes may offer new perspectives for the treatment of psychiatric disorders, such as attention deficit and hyperactivity disorder, schizophrenia and obsessive-compulsive disorders, clinical settings in which drug repurposing is already offering several therapeutic opportunities. Thus, the complex molecular apparatus involved in the fine regulation of neuroglia interaction offers extraordinary possibilities for the discovery and validation of novel targets.

Drawing on the numerous successful examples and on the abundant preclinical evidence potentially transferrable to the clinical setting, and with the aim of reducing development time and costs, both researchers and clinicians

nowadays consider repurposing a useful strategy for regenerating drugs, leading to the discovery of novel functions and to better efficacy. Thus, although research is currently oriented from bed to benchside, the fundamental role of basic research, taking place primarily in the academia, is strongly recognized. In addition to classical approaches, bioinformatics, data mining and the use of novel screening platforms are aiding in the selection of drug candidates to be validated in preclinical and clinical settings. Pharmaceutical companies are well integrated in this context, promoting the improvement and the application of novel technologies aimed at either drug-derived repositioning or disease-derived repositioning.

In summary, the many initiatives being organized to promote drug rescuing or repurposing are offering pharmaceutical companies and the academic world useful and profitable opportunities to (re-)discover novel and innovative therapeutic applications and to promote treatment opportunities in critical areas such as cancer, nervous system disorders and rare diseases.

*Diana Amantea PhD, Michelangelo Certo PhD, Giacinto Bagetta MD**

Department of Pharmacy, Health Science and Nutrition, Section of Preclinical and Translational Pharmacology, University of Calabria, Rende (CS) Italy
** Correspondence to: g_bagetta@virgilio.it*

Acknowledgments

The collaboration offered by the Administration of the Department of Pharmacy, Health Science and Nutrition, the residential center (Socrates Residence) at the University of Calabria and Cascina Global Service srl, is gratefully acknowledged. Special thanks go to the Italian Society of Pharmacology for sustaining the entire cost of this first Italian meeting on drug repurposing.

References

Arrowsmith J, Miller P (2013). Trial watch: phase II and phase III attrition rates 2011-2012. Nat Rev Drug Discov 12:569.
Bessede A, Gargaro M, Pallotta MT, et al (2014). Aryl hydrocarbon receptor control of a disease tolerance defence pathway. Nature 511:184-190.
Bezzi P, Volterra A (2014). Imaging exocytosis and recycling of synaptic-like microvesicles in astrocytes. Cold Spring Harb Protoc 2014 (5).
Chong CR, Sullivan DJ Jr (2007). New uses for old drugs. Nature 448:645-646.
Khanna I (2012). Drug discovery in pharmaceutical industry: productivity challenges and trends. Drug Discov Today 17:1088-1102.
Miller G (2010). Is pharma running out of brainy ideas? Science 329:502-504.
Mullard A (2011). Could pharma open its drug freezers? Nat Rev Drug Discov 10:399-400.
Petsko GA (2010). When failure should be the option. BMC Biol 8:61.
Santello M, Calì C, Bezzi P (2012). Gliotransmission and the tripartite synapse. Adv Exp Med Biol 970:307-331.
Sternitzke C (2010). Knowledge sources, patent protection, and commercialization of pharmaceutical innovations. Research Policy 39:810-821.
Tobinick EL (2009). The value of drug repositioning in the current pharmaceutical market. Drug News Perspect 22:119-125.
Tralau-Stewart CJ, Wyatt CA, Kleyn DE, et al (2009). Drug discovery: new models for industry-academic partnerships. Drug Discov Today 14:95-101.
Trist DG (2011). Scientific process, pharmacology and drug discovery. Curr Opin Pharmacol 11:528-533.