

## Preface

*The drug evaluation process is one of the most important challenges for regulatory agencies and public research institutions. As the Istituto Superiore di Sanità (ISS), which is the National Health Institute, our main mission in the field of drugs (and, in general, of medicinal products) is to guarantee the safety and the efficacy of drugs in order to protect public health. At the same time, however, we do have the precise duty to promote public health and to favor the translation of new treatments to the patients who need them.*

*In the last few years, however, the discovery of new disease-ameliorating molecules has been frustratingly poor. 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.*

*This suggests that the traditional process of drug development needs to be revisited. Adopting new, more integrated and more flexible approaches may improve the quality of the process and, thus, may lead to a more efficient patients' care. Of course, the new rules to be adopted have to be written in a rigorous, scientific-based way and a consensus has to be reached.*

*The ISS, together with the Agenzia Italiana del Farmaco (AIFA, the Italian Drug Agency), offers to promote the scientific debate concerning such an innovation.*

*The first three articles of this issue deal with the identification of possible new approaches to clinical trials.*

*The paper by John Orloff and Donald Stanski (Innovative approaches to clinical development and trial design) proposes an alternative strategy to the traditional drug development approach which separates clinical development into sequential, distinct phases. The proposed adaptive model increases flexibility and maximizes the use of accumulated knowledge in order to improve the effectiveness of clinical development.*

*The article from Alberto Grignolo describes the principles and the organization of the Clinical Trials Transformation Initiative (CTTI), a public-private partnership created in 2007 between the United States Food and Drug Administration (FDA) and Duke University for the purpose of identifying practices that will increase the quality and efficiency of clinical trials.*

*In his work New perspective and new challenges in clinical trial regulation in Italy, Carlo Tomino*

*provides a regulatory overview and proposes that, although well designed clinical trials remain the most reliable way to get unbiased information, there is probably the need to integrate CT data with other type of clinical research, in order to better manage the post-marketing uses.*

*The concept of evidence-based medicine (EBM) is the subject of another series of articles. The matter is effectively introduced by an article (Evidence-based medicine: what it can and cannot do), in which Goffredo Freddi and José Luis Román-Pumar critically discuss the limits and usefulness of such an approach.*

*In his paper Integrating clinical research into clinical decision making, Mark R. Tonelli considers that, although EBM has placed a general priority on knowledge gained from clinical research for clinical decision making, such a knowledge is not directly applicable to the care of individual patients. Clinicians should thus utilize other forms of medical knowledge, including pathophysiologic rationale and clinical experience, in order to arrive at the best medical decision for a particular patient.*

*The review by Dhavendra Kumar (The personalised medicine: a paradigm of evidence-based medicine) highlights the importance of translational genomic research as the key component in developing sound evidence-based diagnostic, therapeutic and prognostic clinical protocols for the practice of personalised clinical medicine.*

*The application of EBM to the field of HIV therapy is discussed in the paper by Carlo Federico Perno (The discovery and development of HIV therapy: the new challenges). The author considers that, although EBM remains a cornerstone of modern medicine, its structure needs to be adapted to the new challenges, made by an excess of information (not always fully reliable), by highly sophisticated statistical systems, and the limited number of independent controlled studies. The revision of the criteria of EBM, and their adaptation to the new tools available, may allow a better contribution to the definition of the best therapy for each single patient. Still in the field of HIV therapy, Lucia Palmisano and Stefano Vella report a brief history of antiretroviral therapy, telling us how unprecedented efforts in the fields of biology, pharmacology and clinical care have contributed to progressively turn HIV infection from an inevitably fatal condition into a chronic manageable disease.*

The issue of the treatment of neurodegenerative diseases as an unmet need is addressed by the article from Paolo Stanzione and Domenicantonio Tropepi. The authors point out that research for effective treatments is hampered by lack of knowledge on the pathologic processes underpinning these diseases and of reliable biomarkers. Clinical trials are difficult, and these difficulties produce frequent failures and waste of human and economic resources. In their paper, Maria Puopolo and Maurizio Pocchiari report possible weaknesses in the management of clinical studies in neurodegenerative diseases, ranging from poor preclinical studies, difficulties in the recruitment of patients, delay in the onset of treatment because of lack in early disease-specific biomarkers, and suboptimal design of Phase II clinical trials. Efforts are required from clinical researchers, statisticians, and regulatory people to the development of new strategies that should maintain rigorous scientific integrity together with a more ethical approach to human experimentations.

Alessandro Giuliani (The dawn of mesoscopic approach in drug development) proposes a mesoscopic paradigm (which prefers as candidate drugs those molecules weakly binding to a multitude of different receptors because they are more prone to be “network modifiers” inducing a systemic effect) as opposed to the reductionist paradigm (which accepts as candidate drugs those molecules that selectively bind to the receptor considered as crucial for the disease).

Another group of papers deals with the issue of translational research.

In their article Translating basic research in cancer patient care, Marcello Maugeri-Saccà and Ruggero De Maria point out that, in recent years, it has become evident that the interaction between basic researchers and physicians can provide a more concrete way to really improve patients' outcomes. Thus, the “translational research”, consisting in the integration of advancements in cancer molecular biology into clinical trials, by taking advantage of innovative technologies such as microarrays, genome sequencing and proteomic analysis, has led to the identification of predictive biomarkers, new targets for anticancer drug development and new generation technology-based prognostic tools. In this article are discussed the most relevant advances in cancer biology and treatment, resulting from “the bench to the bedside and back again” philosophy.

The paper by Filippo Belardelli et al. (Translational research on advanced therapies) outlines how fostering translation research of advanced therapies has become a major priority of both scientific community and national governments. Advanced therapy medicinal products (ATMP) development opens novel avenues for therapeutic approaches in numerous diseases, including cancer and neurodegenerative and cardiovascular diseases. However, there are important bottlenecks for their development due to the complexity of the regulatory framework, the high costs and the needs for GMP facilities and new end-points for clinical experimentation. Recently, a great importance has

been given to research infrastructures dedicated to foster translational medicine of advanced therapies. Some ongoing European initiatives in this field are presented and their potential importance is discussed.

In Italy, the Istituto Superiore di Sanità is the competent authority for the authorization of Phase I clinical trials. The authorization of a Phase I study represents the transition from the preclinical to the clinical phases, and it is thus a pivotal step in translational medicine. Transition from non-clinical to clinical testing requires special precautions to minimize risks, and this may be particularly true for advanced therapies. Indeed, the validity of conventional models to predict the safety and the efficacy of advanced therapies is generally poor. In the article The role of the Istituto Superiore di Sanità as the competent authority for Phase I trials in the translation of advanced therapies, Popoli et al. discuss the specific responsibility of the ISS in fostering the translation of safe and effective therapies for human diseases.

The issue of assessment of drugs for rare diseases is then the subject of another series of three papers.

Rare diseases are life-threatening or chronically debilitating conditions, affecting no more than five in 10 000 persons in the European Community, and are individually rare but collectively frequent. It is estimated that between 6000 to 8000 distinct rare diseases affect up to 6% of the total EU population.

In their paper Rare diseases and orphan drugs, Domenica Taruscio et al. identify the limited knowledge of natural history of rare diseases, the restricted market opportunities and the difficulties in setting up RCTs as the main obstacles to the development of innovative treatments for rare diseases.

Giuseppe Remuzzi and Arrigo Schieppati (Why a research for rare diseases?) consider that, although we have to take into account the urgent need of new treatments from the patients' perspectives, our duty is to guarantee the safety and efficacy of new drugs.

In his article Orphan drugs assessment in the centralised procedure Giuseppe Nisticò describes the EU incentives that have been adopted in order to encourage the development and commercialization of drugs devoted to rare diseases. The paper also points out some important open questions (e.g. whether the extent of incentives is sufficient to promote development or whether the rigidity of guidance requirements prevails over the unmet medical need for severe and lethal rare disorders).

The paper by Mariarita Cassese and Veronica Zuber deals with the issue of Clinical trials and gender medicine. The article underlines that, although for a long time clinical studies have been conducted almost entirely on men, it is now becoming evident that gender medicine is essential in research and clinical practice. This shouldn't be only a researchers commitment but also an undertaking of the International Medicine Agencies.

Sergio Dompé provides the industry point of view in his article How to cope with complexity and adapt new scenarios to patient care. The article considers that, while new therapies have reduced the mortality

rate in recent years and led to an improvement in the quality of life, many medical needs are still not fully satisfied. Cancer pathologies, AIDS, neurodegenerative diseases, psychiatric pathologies, diabetes, and rare diseases are only some of the challenges facing pharmaceutical research in its work to make new and increasingly effective therapies available. A substantial progress could also be achieved through innovative models able to carry out clinical trials that, while maintaining high standards of efficacy and safety in therapy, can identify genetic characteristics and processes before commencing trials on large number of patients.

Finally, the patients' point of view is represented in the Viewpoint Emerging complexity and possible new approaches from a patients' perspective, with the contribution of Rosaria Iardino and Antonella Celano. It is pointed out that any therapeutic intervention must be placed in a curing process that involves the patient as "person", with his/her wishes and needs. The cooperation of patients is proposed as an essential element to translate the new advances into adequate cures.

On their whole, these articles contribute in a complementary way to the scientific debate on the opportunity to reconsider our current approach to drug discovery and evaluation. If new rules will be identified, these will have to be strictly examined, verified and endorsed by scientists, regulators and industries. Of course, the final goal of any innovation in this field can only be to fill (or, at least, to reduce) the gap between bench discovery and bedside application in order to make the best cure available to each patient.

#### **Acknowledgements**

The support of Giovanni Caricati and Valeria Lorenzini is gratefully acknowledged.

This issue wouldn't have been realized without the precious editorial contribution of Federica Napolitani.

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