Translational Cardiovascular Medicine (I)

Translational Cardiovascular Medicine: Now or Never

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Although it is a relatively recent discipline, "translational medicine" is definitely in fashion. Over the past 5 years, the term has been employed with increasing frequency in contexts as varied as the pharmaceutical industry, academic institutions, financial agencies or organizations providing health care services.

The concept underlying the idea of translational medicine is intuitive and persuasive, especially when utilized in applications for project funding. The breach that separates basic biomedical research (animal and in vitro) from clinical application grows on a daily basis and, despite an explosion of knowledge of the mechanisms of biological processes, this is not being translated into a corresponding increase in new treatments. In fact, in the pharmaceutical industry, the exponential growth in R&D in the development of new molecules is accompanied by a gradual decline in the number of drugs that finally reach the market.[1] In the academic field, it is no easier to explain why all the knowledge acquired in basic research (for example, the sequencing of the human genome or the development of knockout animal models) has had so little impact on medical practice. Neither animal experiments nor studies carried out in test tubes, or even phase I clinical trials, reflect the real situation of the patients in order to enable us to reliably predict the efficacy and safety of a new therapy.

In this context, the concept of translational medicine arises with an objective as simple to define as it is difficult to achieve: facilitate the transition of basic animal and in vitro research into applications that will result in health benefits.[2,3] Thus, the aim of translational medicine is to convert all the enormous effort devoted to preclinical basic research into social benefits (medical and economical). This is the objective that has led to the "Critical Path" initiative of the United States Food and Drug Administration and to the rechanneling of the funding of the National Institutes of Health (NIH), which has allocated more than 10 000 million dollars to translational medicine centers.[4-6]

The desire to improve the translation has rapidly revealed serious problems in the interface. In the first place, the performance of more and better clinical trials appears to be indispensable, but they require more funding, bureaucracy and dedication than basic research. Moreover, the recognition in bibliometric terms (number of articles and impact factor) is generally lesser than in basic research. This fact is now beginning to be acknowledged and the funding for clinical trials carried out in a predominantly academic (investigator driven) setting is gradually increasing.

In addition, in academic studies, need to examine in depth the basic and mechanistic aspects of biological processes and therapies has been recognized. It has also been acknowledged that phase I studies designed to test new devices and therapies should be made more flexible and, thus, priority is being given to this facet in the large public offers of funding (like the Seventh Framework Programme of the European Commission).[7]

As in other challenges in science, it is known that the keys to the success of translational medicine are based on the development of appropriate methods and systems that enable us to narrow the gap between bench and bedside (Table). In a broad sense, biomarkers acquire a key role in the prediction, on the basis of animal studies, of the efficacy and safety in humans, and it is considered that they could be the origin of 80% to 90% of the possibilities of successful translation. Some of these biomarkers do not exist in humans or may not be possible to obtain for ethical reasons. Thus, the need to develop a framework of reference for classification that helps to establish the predictive value of these tools has been pointed out. In this context, biochemical and genetic biomarkers, as well as those employed in imaging techniques,

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Tools of Translational Medicine

Development of new biomarkers (from sera, imaging)
Development of realistic animal models of human cardiovascular disease
Translational toxicology
Scoring systems for the predictive efficacy of the different biomarkers; calibration and validation in clinical trials
New models of clinical trials in humans the include novel mechanistic or purely descriptive approaches
Development of biostatistical methods to provide reliable multifactorial analyses in small populations
Human genetics

Modified from Wehling.[3]

acquire a special relevance, although it is true that the future predictive value of many of them is more intuitive than demonstrated.

In the cardiovascular setting, the need to narrow the gap between clinical and basic research became clear a few years ago with the first studies that tested new biological treatments in clinical practice. Over the past five years, the eruption of cell therapy has promoted an indispensable contact among clinicians, biologists, biochemists, etc. Regardless of the final outcome of cardiac regenerative therapy, there is no doubt that the paradigm of cardiovascular medicine is changing. A number of tools produced in basic research are already making inroads into modern cardiovascular medicine; these include pharmacogenetics, the exploitation of biomarkers, gene therapy and sophisticated imaging techniques to elucidate the mechanisms of disease.

An immediate consequence of the eruption of translational medicine into the clinical setting is the need to incorporate basic fundamentals into the present clinical training curriculum, both undergraduate and postgraduate. Moreover, the connection between clinical medicine and basic research continues to be extremely weak. In Spain, the undergraduate programs in the biomedical field must be renewed and adapted to the new demands, and there has yet to be a degree in bioengineering. A great effort must still be made to combine objectives and create multidisciplinary teams. That is the only way it will be possible to become competitive, generate attractive platforms for the sources of industrial funding and capitalize on economic returns of public financing, which is difficult to sustain over the long term. Initiatives of the Instituto de Salud Carlos III in Spain, such as setting up the Cardiovascular Research Center[8] or the Collaborative Research Networks (RETIC),[9-11] show a clear commitment in this respect.

In this issue of *Revista Española de Cardiología*, we initiate a series of chapters devoted exclusively to cardiovascular translational research. This entails the consolidation of a strategy to promote preclinical publication that has been potentiated in recent years.[12-18] Aimed basically at the clinical reader, this "Update in translational cardiovascular medicine" is designed for the purpose of providing the clinician with a closer look at the elemental concepts of applied basic research from a simple and comprehensible perspective. From *Revista Española de Cardiología*, we are making a modest attempt to establish a common language that enables clinicians to understand, although perhaps at a rudimentary level, the biological bases of diseases and the therapies that they apply in their profession. If we have helped in some way in this respect, we consider that the effort will have been worthwhile. As in previous initiatives,[19,20] the ultimate aim of the "Update" is merely to provide advance information concerning the tools that, over the medium term, will be employed in benefit of our patients. However, in this area, the potential benefits of continued training for professionals is also fundamental. We will attempt to contribute to preventing basic researchers and clinicians from wandering over the coming decade through cardiovascular medicine, isolated, disoriented and perplexed, while we witness a universe that has become alien and incomprehensible to us and in which, inevitably, we find ourselves "Lost in translation."

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