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EDITORIAL

Major issues in translational medicine

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The goal of modern medical research is to apply fundamental scientific findings and discoveries to develop treatments that help or cure diseases. This has become a core principle, often known as the "basic science model." However, this model is considered imperfect, as many effective treatments were developed before the underlying biological and molecular principles were understood. Recent scientific advances have not always led to real clinical improvements. To address this, the field of translational science has emerged to focus on accelerating the process of moving basic science discoveries into substantial health improvements for patients. This path, however, is not progressing as smoothly as one might expect, and the main problems are briefly discussed in this editorial.

Major problems in translational medicine include scientific challenges, such as the poor predictive power of results obtained with animal models in relation to humans, insufficient funding and other resource limitations, and regulatory hurdles that slow down or block the translation process. Other obstacles include real difficulties in interdisciplinary collaboration, a lack of standardized infrastructure, insufficient training, and the need for better communication between researchers, clinicians, and the public. These issues collectively contribute to the "translational gap," also known as the "Valley of Death," which is the gap between basic research and its potential clinical applications.[1,2] More precisely, it refers to the gap between potentially promising basic scientific discoveries obtained in laboratory practice and their successful application in the form of new treatments, therapies for patients, and eventual market availability. This gap is an important barrier in drug and therapy development, with high failure rates and numerous obstacles in translating models to humans.

The poor predictive power of animal models stems from significant biological differences between species.[3,4] This leads to a high failure rate for drugs in human trials. In both toxicology and efficacy, results from animal studies often fail to translate directly to human pathologies. Many safe compounds prove harmful in humans and *vice versa*. Factors contributing to this include poorly designed studies and the lack of key methodological safeguards, such as randomization or blinded outcome assessments.

Studies have shown that animal models are highly inconsistent at predicting eventual human toxicity. Their success rate may be very low for some toxic responses. Many drugs judged safe in animals are later found to be toxic in humans, and some safe human drugs may be eliminated because they appear dangerous in animals. These kinds of incompatibilities are often difficult to predict. Therefore, even when a drug is highly effective in an animal model, this does not guarantee that it will work in the same way in human trials. For example, many cancer vaccines effective

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in animal models have failed in large-scale human trials.[5] The high failure rate of drugs in human trials is a strong indicator of the poor predictive value of animal models. It is estimated that over 90% of drugs that seem safe and effective in animal models fail to be confirmed in human clinical trials.

The principal human contribution to these problems is poor study design. Many animal studies lack crucial elements found in clinical trials, such as randomization, blinding, and proper statistical analysis. This can lead to an overestimation of results obtained in fundamental animal studies. Other human-born shortcomings in translational research include inadequate funding and supply of resources, a lack of trained staff, complex and lengthy regulatory processes, and bureaucratic delays. Further issues involve cultural differences between basic scientists and clinicians, fragmented infrastructure, poor communication, and the inherent high risk and cost of moving discoveries from the lab to clinical practice.[6] The fundamental scientific challenge of the incomplete understanding of biological mechanisms also significantly impedes progress. Finally, the growing problems of scientific fraud, paper mill publications, and overinterpretation of results are increasingly hampering the efficiency of translational medicine at an increasing pace.

Two principal alternatives may help address the shortcomings outlined above: (i) Human-based research and (ii) novel, innovative approaches. A shift toward human-based research, such as personalized medicine and *in vitro* models, is gaining momentum. Human-based research is a broad category, including two main fields: Human subjects research, which studies living individuals through interventions or interactions, and human-relevant biotechnologies using human cells, tissues, or data to model human biology and predict human responses. While human subjects research is governed by regulations to protect participants, human-based biotechnologies use advanced technologies, such as organoids and computational models to develop more predictive, human-relevant research methods. Currently, there is an urgent need to develop and implement novel approaches to drug toxicity and efficacy studies that provide more reliable predictions for human responses.

Alternative methods in translational medicine include advanced technologies, such as omics (genomics, proteomics, metabolomics) for personalized medicine, novel pre-clinical models, such as three-dimensional organoids and "clinical trials in a dish (CTiD)" for faster drug screening, and different clinical trial designs, such as adaptive and pragmatic trials.[7] CTiD is a pre-clinical drug development method that tests the safety and efficacy of a given therapy on a representative sample of human cells or tissues in a laboratory setting before moving to human clinical trials. This approach, which uses technologies, such as induced pluripotent stem cells and organs-on-a-chip, aims to predict population-level responses to a drug, identify potential responders and non-responders, and reduce the high cost and failure rate of traditional clinical trials. In addition, "reverse translation," which moves findings from patient data back to the laboratory, and drug repurposing are used to accelerate the development of treatments, as clearly demonstrated during the COVID-19 pandemic.

Understanding the nature of challenges associated with translating animal model research into human clinical practice should be common among professionals in translational medicine. The brief description of the key issues included in this editorial can help beginners navigate these challenges and avoid potential errors.

Conflict of interest

Jacek Z. Kubiak is the Editor-in-Chief of this journal. The author declares that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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