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Translating Translation

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Abstract

The term ‘translation’ has emerged as a dominant concept in biomedical science over the last decade, but confusion around what the term means, and how it differs from translational research and translational science, is common. This article aims to help address this issue by clarifying the distinctions.

As director of the leading US public agency focused on translational science, the National Center for Advancing Translational Sciences (NCATS), I speak frequently to diverse audiences about translation and its relatives, translational research and translational science. Despite the widespread use of these terms, I have found widespread variation in their intended meaning, and frequent confusion among scientists, physicians, patients and policy makers about what translation is, how it differs from translational research and translational science, and how each relates to areas of biomedical research with which they may be more familiar. With the hope of advancing scientific and public discourse on translation and its potential and challenges, I offer here some definitions and distinctions.

Linguistically, the word ‘translation’ is derived from the Latin trans and latus, meaning ‘to carry across’. Unlike terms that describe other areas of biomedicine (for example, ‘cancer’, ‘diabetes’ and ‘musculoskeletal’), ‘translation’ has not only widely used non-medical meanings, such as the process of rendering one language into another, but also unrelated scientific connotations, such as the synthesis of proteins from information contained in mRNA. In my role as NCATS director, I have been asked by well-meaning inquisitors whether NCATS studies linguistics, or whether there really is an entire NIH centre devoted to understanding how proteins are made from mRNA. Such misunderstandings represent a serious impediment to the public and scientific conception of what the field of biomedical translation entails.

Given the goal of NCATS, clarity and consensus on these terms are crucial at the agency. NCATS’ definition of translation is broad and inclusive: translation is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioural changes. This definition is intentionally holistic with regard to directionality, stage of intervention development and modality.

Several words or phrases in this definition are worth expanding on further. ‘Process’ reflects that unlike linguistic translation, biomedical translation is not a one-step event, but multistep and recursive. ‘Observations’ reflects that translation starts with the first-time perception of

phenomena, which must be demonstrated to be reproducible and robust. ‘Laboratory, clinic and community’ reflects that (contrary to frequent parlance), translation need not start with a basic science observation and move towards the clinic and eventually public health; in fact, until relatively recently, most successful translation began with a clinical or public health observation that led to basic discoveries. Thus translation is bidirectional. Finally, with regard to ‘interventions’, translation is modality-agnostic; the translational process is conceptually similar whether its intended result is a small-molecule drug, a biologic (such as an antibody, oligonucleotide or aptamer), a device, a medical or surgical procedure, or a behavioural change (such as diet, exercise or smoking cessation). Thus ‘translation’ refers to an overarching conceptual and practical multistep process.

By contrast, ‘translational research’ is defined by NCATS as the endeavour to traverse a particular step of the translation process for a particular target or disease. The word ‘research’ in this term is worth emphasizing. An unfortunately widespread misconception about translation is that it is a straightforward, even routine endeavour, with minimal scientific challenge and with success being the usual outcome. The term ‘drug development pipeline’, and its connotation of a linear process from discovery to application, is an example of, and a perpetuator of, this misconception[1]. The reality is quite different. As translational research projects seek to move from reductionist, simple systems (such as genes, proteins and cells) in laboratory settings to more complex systems (ultimately genetically and environmentally diverse humans), and from controlled or regulated settings to medical applications in real-world environments, the complexity as well as the research and operational challenges increase exponentially. Using these definitions of translation and translational research, it is clear that in addition to NCATS, virtually every institute and centre at the NIH has some aspect of translation in its mission and performs and supports translational research, as does every biotechnology and pharmaceutical company, as well as many non-profit organizations.

So what is the ‘translational science’ that is NCATS’ mission? NCATS defines it as the field of investigation which seeks to understand the scientific and operational principles underlying each step of the translational process. Translational science is thus quite distinct in purpose and operation from translational research. Whereas translational research focuses on the specific case of a target or disease, translational science is focused on the general case that applies to any target or disease. Its focus areas are the common causes of in efficiency and failure in translational research projects (for example, incorrect predictions of the toxicity or efficacy of new drugs, lack of data interoperability and ineffective clinical trial recruitment). As these causes are the same across targets, diseases and therapeutic areas, advances in translational science will increase the efficiency and effectiveness of translational research in all therapeutic areas. Like any other science, translational science seeks to elucidate general operative principles in order to transform translation from an empirical, phenomenological process into a predictive science.

Defined in this way, translational science is clearly a nascent field. For historical and cultural reasons, translation has traditionally been practiced as an empirical craft, not studied as a science. The limits of empiricism in translation are evident in its persistently high failure rate and cost, which have continued to increase despite enormous efforts using the empirical

paradigm[2]. A thought experiment and a counterfactual are useful here. The thought experiment is to imagine what drug development would be like if the general principles of small molecule–target interactions were known, such that activity of any compound on any target could be predicted effectively a priori. Failures due to unanticipated toxicity and lack of efficacy would decrease by orders of magnitude. The counterfactual can be seen in the advance of molecular genetics over the past 50 years, which has been made possible by the continuous and ultimately successful pursuit of general theoretical and operational principles, and has transformed the field from an observational exercise into an efficient and effective field of science and medicine.

Like any other science, translational science will advance via research — that is, translational science research — that seeks to develop an understanding, technology, theoretical principle or paradigm that will make the development of any therapeutic intervention more efficient and effective. The aggregate study of the results of individual translational research projects is one approach to elucidate translational science principles; conversely, individual translational research projects test the veracity of translational science principles and lead to their progressive advancement.

Three final points may help further clarify the linguistic tangle around translation. First, I am often asked whether clinical research and translational research are the same. From the definitions above, it follows that they are not; much translational research is preclinical (from target validation to filing of an investigational new drug (IND) application or equivalent), and much clinical research is not translational, but is rather focused on advancing fundamental understanding of human physiology and pathophysiology.

Second, I have found that contrasting the intentions of fundamental and translational science can be helpful in furthering understanding of translation. The intent of much research, including all basic research in the biomedical field as the term is usually defined (see Related links), is to understand the normal structure and function of living organisms (including humans), and the characteristics and causes of abnormal structure or function (that is, disease). By contrast, the intent of translational research is to ameliorate, via physical or behavioural intervention, the abnormal structure or function of an organism that is causing, or may lead to, disease. Put simply, basic and translational research in the biomedical field seek to ‘understand’ and ‘fix’, respectively.

Third, basic and translational research are complementary, interdependent and mutually informative. Basic research provides pathophysiological understanding and mechanistic targets to translate, and translational research provides health benefits from that research, as well as insights from human interventions that lead to new opportunities and needs in basic research.

Thirty-five years ago, Lewis Thomas dubbed clinical medicine the “youngest science”, as it was just then evolving from its empirical ‘shamanesque’ past into a data-driven predictive future[3]. Translational science is the new youngest science, with boundless promise to transform science and medicine.

Notes

1. Wagner JA, et al. A dynamic map for learning, communicating, navigating and improving therapeutic development. Nat Rev Drug Discov. 2018; 17:150.
2. Scannell JW, et al. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov. 2012; 11:191–200. [PubMed: 22378269]
3. Thomas, L. The Youngest Science: Notes of a Medicine-Watcher. New York: Penguin; 1985.