The steps from translatable to translational research

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The common justification for much research funding is that the outcomes will move from the laboratory to the clinic and patient care, or be converted into jobs and money. The term “translational research” is widely used in this context by medical research institutes and an increasing number of university departments to convey the message to politicians and taxpayers that research activities ultimately serve the public. The intense focus on translation is also a result of the NIH road map and former NIH Director Elias Zerhouni, who deliberated on how to achieve this goal [1,2].

However, in some cases, translational research is merely a label to attract financial support but in reality, it is not. A more analytical and stratified definition of “translation” would therefore provide greater transparency to a sector of research that heavily depends on public funding. It would also provide an instrument to understand better the nature of the research that is being undertaken in research institutes or university departments. Finally, anyone who is interested in an institute that claims to perform translational research would get an accurate picture of how that is being interpreted and carried out.

As a starting point, it is useful to distinguish between translational research proper and translatable research: research that potentially could lead to translation. Indeed, there is confusion that comes from a lack of precision or a failure to classify activities correctly. Some of this arises from the frequent mixing of the terms “translational medicine” and “translational research”. A more detailed classification would therefore help to describe where a given project is placed along the chain of events from “translatable research” to “translational research”. For example, the Translational

Research Working Group I at the NIH uses a single term, “basic science discovery”—which is also labelled at T0—for all activities prior to clinical research (http://www.cancer.gov/PublishedContent/Files/images/trwg/TRWG_Oct06RT_ExSum_11-21-06.pdf; <http://www.tuftsctsi.org/About-Us/What-is-Translational-Science.aspx?c=129047765594202220>). A different approach by the Institute of Medicine’s Clinical Research Roundtable defines bottlenecks on the path to the clinic as T1—which prevent research findings being tested in the clinic—and as T2—which prevent the adoption of proven interventions as standard practice [3].

The common classification of translational research after T0 distinguishes four phases [4]. T1 is when a new treatment is first tested in humans in phases 1 and 2 clinical trials. T2 is when the results from a statistically relevant number of patients from phases 2 and 3 demonstrate the efficacy of the new approach. T3 is the phase when the new treatment is being tested more generally including phase 3 clinical trials. T4 is translating the findings from T3 into population health.

Notwithstanding some of the ambiguities, this classification has helped to highlight the steps involved in translational medicine. The phase that is referred to as T0 has not benefitted from a similar definition, which has given rise to claims that research is translational when, in fact, it is translatable and often quite a distance away from translational medicine. To achieve some greater clarity, I propose a classification scheme that would help to define the steps in pre-clinical research from discovery to translation (Fig 1). Some obvious variations on the scheme could serve a similar purpose to classify research with the aim of commercialisation. Analogous to the four phases of

translational research, it distinguishes four phases of discovery D1 to D4.

D1 is pure basic research to gain knowledge. It is essential and the basis for the following stages, but does not itself focus on clinical use or any other application. This could, for example, include understanding fundamental aspects of cellular or molecular biology or developing algorithms to integrate complex data from different sources.

D2 is disease-related research or oriented/strategic research: the context is defined by a disease, and the work is designed to obtain new insight or a starting point for diagnosis, treatment or prevention. This could include, for example, genomewide association studies to search for disease-related genes, epidemiological studies to identify linkages between environmental factors and a disease, studies to establish a connection between imaging data and a disease or studies to correlate genomics or proteomics and a disease.

Stages from DISCOVERY to TRANSLATION

D1 Basic research that has no projected practical (clinical, practice or commercial) aspiration.

D2 Disease oriented research that will generate knowledge that has potential to be used in subsequent phases.
Something might be linked to the disease.

D3 The initial potential practical outcome is identified and work is ongoing to build on the observation.
The protein (gene) is the ‘cause’ of the disease.

D4 Research lead optimisation pre-translation
This compound can influence the target.

Figure 1. The four stages towards translation.

D3 is the phase when the initial outcome of D2 research—such as a target molecule or a metabolic pathway—has been identified and when its link to the disease is being investigated. This research would try to understand the mode of action or role in disease of a gene product identified in D2, investigate a cell type in the immune system that is a target for a pathogen or analyse imaging data of a specific locus in the brain that correlates with the onset of a disease.

D4 describes the phase when the target from D3 is manipulated in some way to confirm its disease association. This could be by identifying a small molecule that can alter the activity of the target in a model system, a diagnostic system based on a biomarker, or the stimulation or blocking of an immune response.

After successfully completing D4, the path to “real” translation or T1 is obvious and the product, treatment or diagnostic test can be moved into clinical research. Not all of these steps are obligatory though, depending on the purpose and the previous phase. For example, an epidemiology study from D2 could reveal a serious health risk caused by an environmental factor, and the result could be immediately integrated into public policy (T4). The discovery of a target in D2 could result in immediate T2 work if there is already a drug in use for a different indication that interferes with the new target.

To obtain a better understanding of an institution or research group that claims to

perform translational research, the first step would be to collect data about every project. Typically, research groups work on a number of projects that can be classified as somewhere between D1 and T4. For instance, a basic research institute or university department will have a predominance of discovery and development-related research (D) as illustrated in Fig 2. A research cluster in a clinical setting may have little D1 or D2 activity and an emphasis on the translation phases. A medical research institute might have a mixture of the discovery and clinical research with projects that are looking for disease relevant insights (D2–D4) and others that are fully in the translational T-spectrum. Each organisation could formulate a profile appropriate for its mission and background, and the categorisation proposed here would allow them to monitor progress towards that goal. By assessing the projects annually, it will also be possible to measure the progress of projects or the overall institution over time and to make decisions on investing in particular projects.

As with all such systems, there is of course the risk of manipulating the outcome. For example, the mis-defining projects could “hide” an activity that does not fit the organisation’s mission. Alternatively, the assessors could distort the results to make the institute appear to be more aligned with the wishes of the funders or management. Notwithstanding these caveats, a classification of pre-clinical research could be very instructive to see the range of profiles in a

Figure 2. Potential profiles of biomedical research institutes.

research ecosystem. It would also provide managers and directors with a handy tool to ensure that research projects are complementary, such that they achieve a maximum impact on health, well-being and other desired outcomes.

References

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