PERSPECTIVE

The Future of Translational Medicine: Accelerating Open Convergence

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> Open [adjective] Allowing access, passage, or a view through an empty space; not closed or blocked up.
> Converge. [verb] Come from different directions and meet at (a place).
> [oxforddictionaries.com]

Open convergence takes the transparency and accessibility principles of the open science movement and marries with the integrative, multidisciplinary concepts of convergence. The future of translational medicine will likely involve an acceleration toward open convergence, which embraces data that exist outside the confines of traditional bench and bedside research. Open convergence accelerates recent trends in translational medicine, including reverse translation, precision therapeutics, clinical trial transparency, value-based health care, and patient-centered research.

CONVERGENCE, OPEN SCIENCE, AND OPEN CONVERGENCE

Convergence in science has gained increasing attention and is both powerful and compelling, with great potential for driving breakthrough innovation.[1] In general, convergence integrates a variety of perspectives, disciplines, and stakeholders as a crucible for innovation. The concept is straight-forward and is well illustrated, for example, by the progress and the promise of self-driving cars, which emerge from the convergence of accelerating machine learning, increased computing power, and the rise of ride-sharing. One might argue that all those ingredients are necessary to manifest a self-driving car innovation, but they needed to converge with the right set of circumstances. After all, the concept of ride-sharing was not invented by traditional taxi cab drivers. In a similar way, convergence in science brings together knowledge, methods, and expertise across different types of data and approaches, disciplines, and stakeholders. Convergence facilitates new frameworks, which, in turn, drive scientific discovery and innovation. Clinical pharmacologists and translational scientists are pioneers at convergence, long before it was labeled as such. The prototypical example of convergence in clinical pharmacology is linking pharmacokinetics and pharmacodynamics with mathematical modeling, which has brought together different kinds of data and thinkers for many years and revealed new insights for drug development and biomedical research. The same is true for translational medicine, connecting bench-to-bedside and vice versa. However, the palette is bigger today and will increase explosively in the future. For translational medicine, convergence includes collaboration and integration of big data, real-world data, artificial intelligence, machine learning, quantitative data sciences along with more traditional experimental medicine, clinical trials, and clinical pharmacology.

Open science emphasizes transparency and accessibility as the dictionary definition of the word "open" would suggest. It is a scientific movement that drives transparent and accessible knowledge, shared and developed through collaboration. Specifically, open science seeks to make many aspects of scientific research, including publications, data, physical samples, reagents, models, code, and other materials, open and accessible to scientists as well as the society at large.[2] Again, clinical pharmacologists and translational scientists have been pioneers here as well from open model code through green and gold open access publications. Related to open science is the democratization of health and science. We need to treat data and knowledge democratically because it helps to accelerate research.

The concept of open convergence in translational medicine (or really any area of science) is to take the idea of scientific convergence and apply the transparency and accessibility principles of open science. Open convergence is originally an information technology term related to converged and hyper-converged infrastructures existing in one configuration, a usage distinct from the

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idea here of open convergence in science. For translational medicine, the open convergence framework helps fulfil a vision that includes precision medicine through patient-centered research. Open convergence is not a brand new concept, but rather is intended to unify the components of current trends with an underlying conceptual framework, which will become increasingly relevant in the future. The remainder of this commentary details how open convergence drives areas of translational medicine, including reverse translation, exceptional responders, and the role of consortia.

REVERSE TRANSLATION

The principles of open convergence are critical for effective reverse translation. Translational medicine has been defined as part of the strategic plan in service of the American Society for Clinical Pharmacology and Therapeutics.[3] In this definition, the essential component of translational medicine is "to improve human health via a 'bench-to-bedside' approach." Furthermore, "It may include application of research findings from genes, proteins, cells, tissues, organs, and animals, to clinical research in patient populations, all aimed at optimizing and predicting outcomes in specific patients." Translational medicine can also be divided into forward and reverse translation, as shown in **Figure 1**.[4] Forward translation is the application or translation of laboratory research to clinical experiments or patients. Forward translation drives the traditional activities of drug discovery and development. The idea behind reverse translation acknowledges that a one-way application of bench-to-bedside research is limiting. Reverse translation is the application or translation of clinical, patient-centered data to laboratory research. Thus, translational research starts with and returns to the patient, aligned with a focus on patient-centricity.

Open Targets (opentargets.org) is an example of an effort using the principles of open convergence to further translational medicine and, in particular, target validation.[5] The organization is a public–private partnership across a variety of different stakeholders that integrates publicly available human genetics and genomics databases for drug target identification and validation.

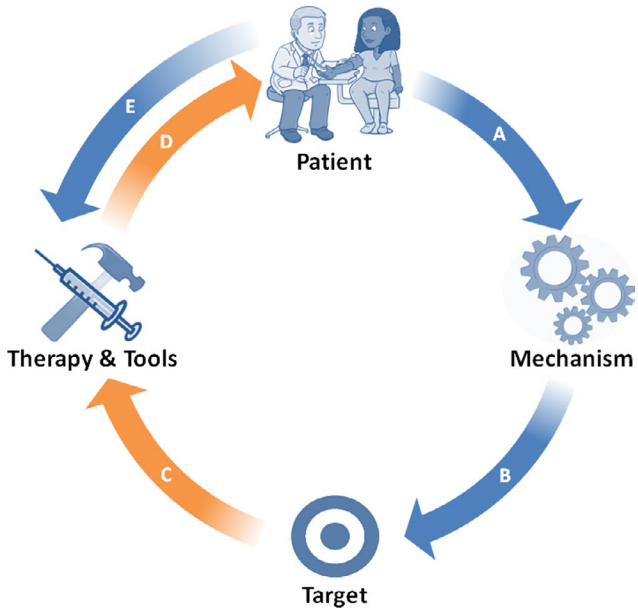

Figure 1 Patient-centered forward and reverse translation. Adapted with permission from ref. 4. Steps of forward (orange) and reverse (blue) translation. Reverse translation starts with deep characterization of the patient informing the disease mechanism (A), which, in turn, drives deeper understand and better selection of targets (B). Forward translation advances identification of a therapeutic target to discovery and optimization of new potential therapies and corresponding tools, including biomarkers (C), to testing in patients (D). Reverse translation also includes learnings from patients that are directly reflected back to drug discovery and development tools or to refinements of a therapeutic (E).

The publicly facing platform integrates—or converges—available information relevant to targets and diseases and allows facile visualization of evidence. The organization has a second component, which is more focused on private efforts, to conduct high throughput experiments generating additional target-centered data in human systems to test relevant hypotheses and improve the strength of causal links between targets and diseases in select therapeutic areas, including oncology, immunology, and neuroscience (**Figure 2**). In order to drive those projects, Open Targets uses the partner technologies,

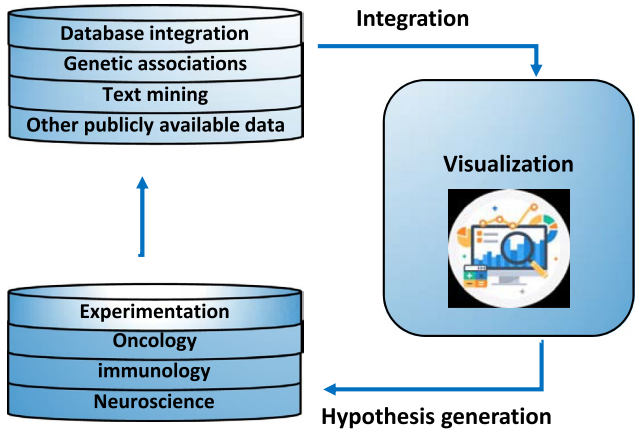

Figure 2 Reverse translation with the Open Targets workflow. The publicly facing platform integrates available information relevant to targets and diseases, including genetic associations, text mining, and other publicly available data, allowing facile visualization of evidence. The organization has a second component, which is more focused on private efforts, to conduct high throughput experiments generating additional target-centered data in human systems to test relevant hypotheses and improve the strength of causal links between targets and diseases in select therapeutic areas, including oncology, immunology, and neuroscience.

including gene editing, induced pluripotent stem cells, single-cell genomics, organoid and tissue culture, large-scale genomics and epigenomics, genomewide association studies, next-generation sequencing, and bioinformatics. Reverse translation has been well illustrated by the discovery of variants in proprotein convertase subtilisin/kexin type 9 (PCSK9) that were associated with low cholesterol in humans. Subsequently, this discovery played a critical role in understanding the mechanism of PCSK9 in the control and metabolism of low-density lipoprotein cholesterol, its role in cardiovascular disease, and the identification and validation of PCSK9 as a drug target.[6] Discovery, development, and approval of monoclonal antibody inhibitors of PCSK9 occurred over the course of only 12 years, but with public–private partnerships like Open Targets using the principles of open convergence, this type of research can be further accelerated.

EXCEPTIONAL RESPONDERS

The flip side of disease-causing variants may be exceptional responders. Patients are exceptional responders if they exhibit dramatically positive response to existing therapy. These patients were once dismissed as miraculous exceptions rather than exceptional responders. In work published in 2012, one patient with bladder cancer, who experienced a greater than 2-year complete response after treatment with the mTOR inhibitor everolimus, was found to have loss of function mutations in *TSC1* and *NF2*, genes in the mTOR molecular pathway.[7] Further sequencing revealed additional *TSC1* gene mutations in other patients, some again correlated with everolimus response. This example serves as a proof of principle that exceptional responders can identify molecular variants correlating with exceptional response and of therapeutic interest. In 2015, the National Cancer Institute (NCI) launched the Exceptional Responders Initiative, a large-scale effort toward determining the molecular etiology of exceptional responders. Cancer tissue samples, molecular analysis, and detailed clinical information from exceptional responders will drive a detailed analysis. The design, planning, conduct, and analysis of the study are driven by the principles of open convergence, with wide-reaching, curated access planned for the resulting database.

THE ROLE OF CONSORTIA

One highly visible trend in translational medicine and the biomedical enterprise in general is the rise of consortia. Precompetitive collaboration in the form of consortia or otherwise has grown in number and value in the biomedical community. The principles of open convergence are similar to those of precompetitive collaboration. Consortia are ideal proving grounds for the concept of open convergence, combining integrative, multistakeholder approaches with transparency and accessibility. One piece of evidence for an increased role of consortia comes from scientific literature references. A PubMed search comparing 1999 with 2018 citations (20 years) shows a 28-fold increase in references to "consortium" (1999: 20 citations; 2018: 565 citations) vs. 3-fold rise over the same period in references to "university" (1999: 26,772 citations; 2018: 83,484 citations). Of course, this is an imperfect comparison for many reasons, but serves to illustrate the rapid growth of the consortia approach.

One framework for categorizing consortia efforts is with four broad goals that encompass steps along the research and development value chain: (i) developing standards and infrastructure, (ii) data generation and aggregation, (iii) knowledge creation, and (iv) product development.[8] Open convergence is particularly helpful for consortia with goals for data generation and aggregation as well as knowledge creation. Open Targets is, in fact, an example of a data generation and aggregation effort. An excellent example of knowledge creation is the Biomarkers Consortium (BC), which is a public–private biomedical research partnership under the Foundation for the National Institutes of Health (FNIH) as a neutral convener. Over its 12-year history, the BC has converged multiple diverse stakeholders and had many patient-centered accomplishments, developing and qualifying biomarkers that have facilitated different areas of drug development. For example, the BC facilitated the development and qualification of new clinical outcome assessments and patient-reported outcomes for the treatment of skin infections and bacterial pneumonia, resulting in approval of six new antibacterial therapeutics to date, an area previously plagued by a paucity of treatment end points.[9] As a multistakeholder convener, the FNIH BC and the US Food and Drug Administration (FDA) drove a workshop to define and evaluate a general framework for assessing the evidentiary criteria needed for biomarker qualification, which has since gained substantial regulatory acceptance.[10] These examples demonstrate the impact of open convergence and precompetitive collaboration as manifest at the FNIH BC.

CONCLUSION

Open convergence is crucial in the current era and future of translational medicine, driving precision medicine, multiple drug treatment modalities, clinical trial transparency, and ultimately value-based, patient-centered biomedical research and practice of medicine. Data and diversity of disciplines outstrip the ability of individual scientists, demanding the collaboration at scale with the integrative, multidisciplinary concepts of convergence as well as the transparency and accessibility of open science. The future of translational medicine will likely involve an acceleration toward open convergence, demanding a commitment to the principles of convergence and open science. Clearly, open convergence requires enhanced collaboration across the many stakeholders whose disciplines need to be integrated, including academics, patient advocacy groups, regulators, and the biopharmaceutical industry. Open convergence holds much promise for the realization of a new era of therapeutics, precision medicine, and value-based, patient-centered biomedical innovation.

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CONFLICT OF INTEREST

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