Overcoming Challenges in Translational Research

THE POWER OF BRINGING PATIENTS AND INVESTIGATORS TOGETHER

Abstract

Translational research emerged as the missing link between basic science and advances in clinical practice meant to markedly improve individual and public health. Knowledge acquired from basic science doesn't automatically improve public health, and the lack of intentionality in fostering translation of scientific discoveries contributed to the "valley of death" in research – a gap characterized by the failure to connect the bench to the bedside. Other factors such as misconceptions, miscommunication, and research studies that lack clinical relevance also add to the problem. Despite all the scientific progress made to date, an estimated 95% of human diseases have no treatment, a number that highlights the urgency of the matter.

According to the National Center for Advancing Translational Science, "translation is the process of turning observation 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 behavioral changes." Stakeholders involved in the process of research translation need to work together to close the gap by increasing collaboration, improving communication, and taking advantage of improvements in the field of biomarkers to promote precision medicine. Overcoming the valley of death will require change, and Sanguine Biosciences is at the forefront of promoting an innovative approach that directly addresses the challenges in translational research. Our goal is to catalyze translation by bridging the gap between investigators and patients.

The Translational Science Spectrum

Translational research seeks to harness basic science knowledge in developing innovative interventions for improving the health of individuals and the public. The term emerged in 1993 when the National Cancer Institute promoted an initiative to pave the gap between basic science and clinical research. The National Institutes of Health (NIH) continued to encourage translational research among its institutes and, in 2011, established the National Center for Advancing Translational Sciences (NCATS), which now oversees and promotes research activity to develop new treatments more quickly. The NIH's emphasis on fostering translational research stems from the fact that only a fraction of the several thousands of human diseases has effective treatment.

The NCATS defines translational science as "the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process." The proposed translational spectrum includes five stages of research that form a path from basic science to the implementation of new interventions to improve individual and public health. This path is

not linear or unidirectional, but converges all research efforts around the health needs of the individual and the public **(Figure 1)**. Basic research is the first stage and focuses on acquiring in-depth knowledge about health and disease mechanisms. In the next stage, preclinical animal models enable the screening of drugs that effectively improve pathological conditions and have appropriate pharmacokinetic and safety profiles. Clinical research follows and includes safety and efficacy trials and proof-of-concept and proof-of-mechanism studies. This stage of the translational spectrum identifies new drugs to treat human conditions and contributes to advance the knowledge of human health and diseases. In the clinical implementation phase, clinical providers apply new interventions to the general population care. Finally, the last stage of translation assesses the actual benefits of new interventions to public health. The long-term goal is to improve disease prevention, diagnosis, and treatment.

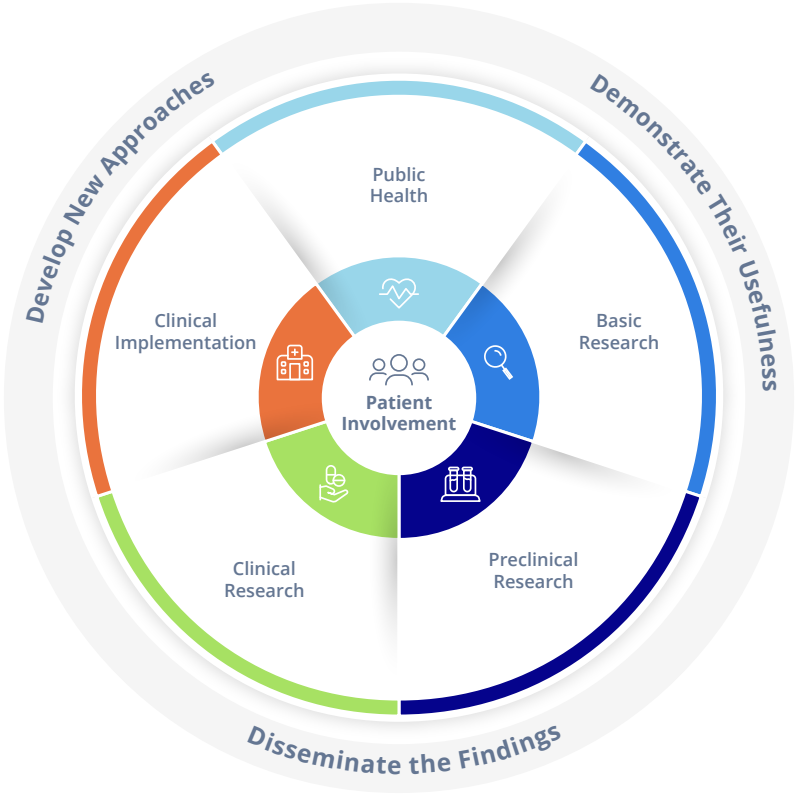

FIGURE 1. Translational Science Spectrum. **Graphic representation of the five stages of research activity required to translate knowledge from the laboratory to public health. The proposed model brings the various stages of translation closer and centered around the patient. Adapted from the NCATS translational spectrum available at https://ncats.nih.gov/translation/spectrum.**

Cutting Through the Valley of Death

Despite all efforts to increase translational research activity, the drug development process is costly and timely – over $2 billion and 10 to 15 years – and yet ineffective. Most of the time, the knowledge generated in the basic science stage fails to impact the discovery

of new interventions that improve overall health. A gap between basic science and clinical research exists, and the term "valley of death", coined by Seyhan in a recent review article, appropriately describes the urgency for change in the translational process.[1] The solution to bridging the valley of death is far from simple and straightforward; it requires an increased investment of resources and a collaborative approach between various stakeholders.

Basic and clinical researchers working in medical science have a common long-term goal – identify new interventions that effectively prevent, treat, and ameliorate symptoms of various diseases. Thus, the valley of death does not result from misaligned goals across the translational spectrum but likely from conflicting frameworks. Among all the barriers to effective translational research, misconceptions and miscommunication among stakeholders and clinically irrelevant studies require immediate attention.

Misconceptions

Translational research is a collaborative endeavor, and each part should agree on the purpose and values driving the process. Yet, the final milestone of translational research diverges in the view of different people. For some, translation ends when new drugs are properly developed and approved for human use. Others agree with the NTCAS proposition that translation is complete only when scientific discoveries have positively impacted disease prevention, diagnosis, and treatment.[2] The definitions and expectations around translational research are not a consensus across the medical and scientific community, which further widens the Valley of Death.

Another misconception among stakeholders is that translation happens naturally without intentional effort. Many believe that advancement in scientific knowledge automatically improves public health, and this notion renders the need for investment in translational research unnecessary. Data from past decades prove that this organic view of translation is inaccurate. Medical knowledge doubles every 18 years, whereas scientific and technological expertise takes only two years to increase in the same proportion.[1]

Miscommunication

The lack of appropriate understanding of the translational process, its importance, and purpose also contribute to miscommunication between the parts involved. Translational research aims to harness knowledge from basic science to clinical research to clinical implementation, but that does not mean that communication should follow this unidirectional model. The image that comes to mind when we think about the translational research process is a sequence of chevrons pointing in the same direction with the final goal of somehow improving individual and public health. This model completely lacks the complexity of information flow that needs to happen backward. When communication only occurs from left to right, the medical and scientific community misses the opportunity to use observations from clinical practice and population health to provide insight and shape hypothesis-driven studies to advance basic science.[2] The NCATS proposed a new complex framework that captures the complexity of the information flow and processes in translational research – the Drug Discovery, Development, and Deployment Maps (4DM)[3,4]. These maps deconstruct the chevron model and propose a dynamic information workflow integrating the various translational research stakeholders **(Figure 2)**.

FIGURE 2. Multidirectional model of communication to ensure adequate information flow between stakeholders in translational research. Adapted from the NCATS 4D Maps (Wagner et al., 2018a; Wagner et al., 2018b).

Clinical Relevance

Basic and translational science generates a large amount of data that, ultimately, might have little relevance to clinical practice. The NIH estimates that only 5% of drug candidates identified in preclinical animal models receive approval for human use. While a translation rate of 100% is unrealistic, understanding the factors that contribute to the lack of clinical relevance of preclinical studies might help optimize the process.

Preclinical studies often neglect rigorous methodological criteria, such as blinding, randomization, and pre-specified efficacy criteria, all necessary in human trials. This lack of rigor in design, conduct, analysis, and report contributes to the clinical irrelevance of preclinical research to the clinical practice. Drug candidates may seem promising when tested in animals but prove unsafe and/or ineffective when tested in humans.

Proof-of-concept and proof-of-mechanism studies also constitute an essential piece of the translation process. They often employ multiomics analyses using human biospecimen to characterize genetic, epigenetic, transcriptomic, proteomic, and metabolic changes associated with human diseases. Samples obtained from biobanks are convenient but may represent heterogeneous disease states and severities. Also, conditions for biosample collection, handling, and storage may be inconsistent in the same biobank. These factors introduce noise in the analysis and result in data misinterpretation. In the end, these experimental and analytic conditions will render research studies clinical irrelevant.

New Solutions to Old Challenges

The loss in translation is an old problem, and overcoming it demands innovative solutions. Awareness of the translation-related challenges is an essential first step, but bridging the valley of death requires improvement of the current approaches. An effective change also involves active and intentional collaboration between stakeholders in the industry, government, academia, and public.

> *"The definition of insanity is doing the same thing over and over again and expecting different results."*
>
> **– Albert Einstein**

Biomarker Profiling

The term biomarker collectively describes biological measures frequently used to assess health, disease, and response to a therapeutic intervention. While physiological and anthropometric characteristics, such as heart rate, glucose levels, weight, and body mass index, constitute biomarkers, the advancement of translational research relies on genetic, epigenetic, transcriptomic, proteomic, and metabolic biomarkers. Comprehensive biomarker analyses can help identify the molecular factors associated with disease onset, severity, progression, and prognosis.

Deep multiomics longitudinal profiling employs state-of-the-art technology to analyze biomarker data on specimens collected over various time points from the same patient. This innovative methodology contributes to better characterization of human conditions and the discovery of new disease-related biomarkers. Ultimately, investigators can use data to determine causality on the different disease subtypes and stages with more confidence.

Many studies have already been using samples from biobank to conduct deep profiling and characterize disease states. Biobanks offer researchers quick access to an extensive repository of samples from thousands and even millions of different people with specific health conditions. The convenience comes at the cost of one-time data point for each patient and the inability to conduct longitudinal prospective studies. This methodological approach misses two components of cohort studies necessary to advance translational research – longitudinal and prospective. Changing from retrospective to prospective is necessary to improve the translational process. In the long-term, a better understanding of diseases' pathophysiology will positively impact prevention, diagnosis, and treatment.

Precision Medicine

The implementation of precision medicine is a direct result of deep longitudinal multiomics profiling. A recently published review defined precision medicine as "the right medicine, for the right patient, at the right time." [5] The idea behind precision medicine is that patients with the same disease phenotype may respond differently to interventions because they present with a different biomarker profile.

Alterations in genetic, epigenetic, proteomic, and metabolic biomarkers contribute to heterogeneous profiles of various diseases. Patient stratification according to biomarker profile will enable the development of different interventions for patients with similar disease phenotypes but different molecular profiles. This approach may help identify effective treatments that otherwise would not show significant improvement in a study population that combines responders and non-responders. A better understanding of the diseases' pathophysiology and the causality relationship between biomarkers and symptoms will improve and expedite the discovery of new drugs. Biomarker-based precision medicine is a critical to advance translational research, but specimen from biobanks may not adequately contribute to advance this field. These samples often miss comprehensive annotation on demographic, medical, lab results, and patient-reported quality-of-life data, which are critical to associate diseases state with biomarker profile.

Patient Centrality

The value of patient centrality proposes that participants should be directly involved and engaged in research studies. Democratic rights ensure that people should have the right to participate in decisions that will eventually affect their lives. Patients and the general public are the ultimate beneficiaries of medical research, and as such, their roles in research need to shift from suppliers of samples and data to active collaborators. As van der Scheer et al. proposed, investigators should conduct "research with patients rather than to, about, or for the patient."[6]

Patients can bring to research studies a piece of information not available in the medical and scientific literature – experiential knowledge of living and coping with a specific disease. Patients are the only ones who know what causes problems for them, the sources of concerns, and their real needs. This qualitative data that only patients can provide has been one of the missing links in the advancement of basic, clinical, and translational research. The lack of professional and educational background in a particular field of research should no longer justify the exclusion of patients from the research process. As lay collaborators, their views on the topic are legitimate and can add value. Patient involvement is critical to advance translational research and should become a priority. Purchasing samples from biobanks does not give the investigators access to patients but only to their samples. As a result, studies lack critical information from the end beneficiary of the intervention that could meaningfully advance translation.

Communication and Collaboration

The advancement of translational research also requires the closure of the communication gap. Stakeholders involved in the process should intentionally implement a multi-directional communication as the 4D maps propose.[3,4] Bringing representants from academia, industry, government, regulatory bodies, financing organizations, and community together will ensure that all involved parts influence decision making and have direct access to new data and information. Organizational frameworks need to reflect the complexity of the translational process.

Sanguine's Innovative Approach

Sanguine Biosciences commits to improving translational research activity by bridging the gap between patients and investigators. A deep awareness of the valley-of-death-related challenges and a solid commitment to finding a solution moved us to develop a unique approach to catalyze translation. Our strategic business model thoroughly embraces the motivation to overcome these challenges

and the end goal of developing interventions to improve health. Sanguine pursue its mission directed by the values of patient-centricity, unity, and innovation. Patient-centricity ensures that patients have the opportunity to participate in medical research. Unity promotes effective collaboration with various stakeholders to meet the central goal of finding a cure for debilitating medical conditions. Innovation entails continuous improvement of methods and technology to better serve patients and researchers. Sanguine's operational model adds unique insights and timepoints, longitudinal collection, all-inclusive perspective, data-rich samples, and clinical relevance to the research our clients conduct **(Figure 3)**. Our metrics reflect Sanguine's superiority – over 600 studies completed, 99% patient recall rate, 93% study retention rate, and 9.6 patient satisfaction score.

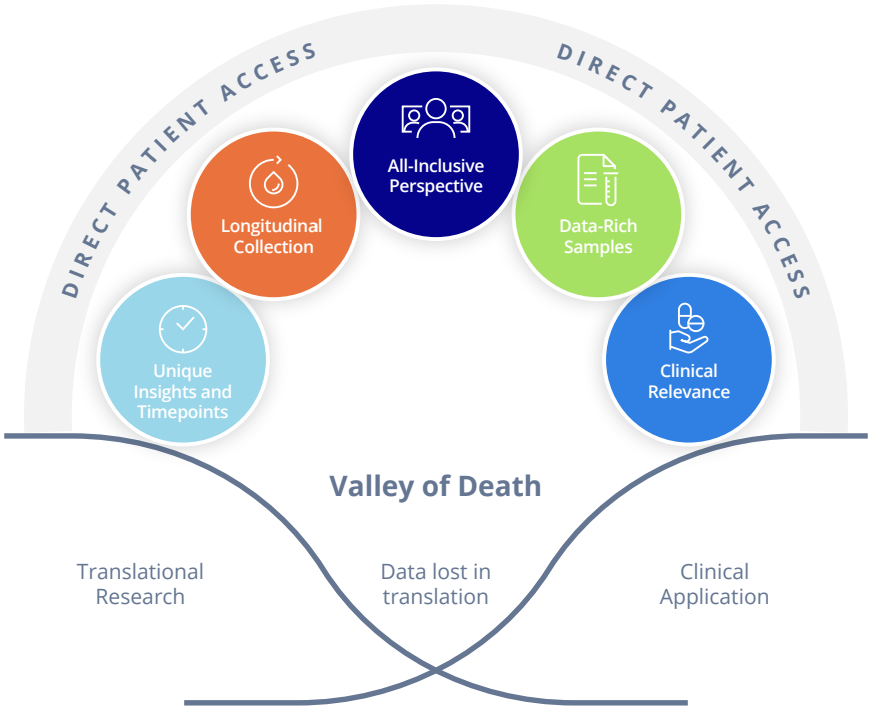

FIGURE 3. Sanguine's innovative approach to cut through the valley of death in translational research. Our mission is to bridge the gap between patients and investigators, and the approaches supporting our mission include unique insights and timepoints, longitudinal collection, all-inclusive perspective, data-rich samples, and clinical relevance. Adapted from Seyhan, A., 2019.

All-Inclusive Perspective

Patients are at the center of Sanguine's mission, and their role in each of the studies we support goes beyond composing a large sample size. The long-term goal of medical research is to advance disease prevention, diagnosis, and treatment, but the ultimate beneficiary of this process, the patient, is rarely involved. As a value, patient-centricity drives Sanguine's efforts to reduce the burden of participation in clinical research. We consider environmental and individual factors that contribute to disease severity and comorbidity, on a per-patient basis, as we design each study. At Sanguine, patients are collaborators who actively contribute to advance science and medicine for health conditions. We employ a "donation on-demand" approach that keeps participants informed, engaged, and empowered. Each research participant lies at the center of Sanguine's fully integrated service, which results in a mutually beneficial collaboration between investigators and patients.

Network-building events and active conversations on the topic of translation are critical steps to a more coherent definition of the translational research spectrum and its goals. Better communication among leaders in the field results in improved definitions of translation-related topics and increased awareness of challenges. The result is an enhanced strategy to overcome roadblocks and advance research. Sanguine's all-inclusive approach goes beyond and promotes information dissemination through various channels of communication.

Longitudinal Sample Collection

Longitudinal prospective sample collection is another distinguishing factor in our unique approach to catalyzing translational research. Prospective cohort studies offer many advantages over retrospective ones – more control in data collection, exposures, and outcome measures. Investigators who collaborate with Sanguine are not limited to a one-time biospecimen sampling; instead, our direct-to-patient access enables longitudinal data collection. In the end, our clients can implement a study methodology that supports a more accurate hypothesis testing.

Unique Insights and Timepoints

Sanguine performs sample collection by deploying a nationwide mobile workforce to patients' homes on the times and conditions specified by our clients. Our patient community of over 35,000 people is geographically spread across the U.S. in locations where we also have staff available to rapidly respond to client's requests for biospecimen collection. Sanguine allows access to patients during pre-specified timepoints and offers event-based sample collection during disease-associated occurrences such as flares, crises, and pain.

Data-Rich Samples

A relationship with Sanguine provides investigators with data beyond the biospecimen, which contributes to a comprehensive knowledge of the disease processes. In addition to access to the same patient at multiple time points, clients can request simultaneous collection of multiple biological samples (e.g., blood, urine, stool). Our clients have the flexibility to recontact medical record-verified participants and assess repeated data for trending. Sanguine also provides patient-reported outcomes data, such as quality of life surveys and questionnaires, that support the data acquired from biospecimen analysis. This holistic approach contributes to data-richness and empowers our clients to make significant contributions to advance translational research.

Clinical Relevance

Altogether, the above factors contribute to data collection that supports a clinically and physiologically relevant view of disease biology. Sanguine's approach contributes to precise knowledge about the mechanisms underlying health and disease. Investigators can better compare the molecular profiling between healthy individuals and those with dormant and active disease states. Increasing confidence in earlier stages of research through ethically sourced biospecimens and data collected in real-time is imperative for improving translational potential. Sanguine operates at the forefront of translational research to promote the development of new interventions that will improve disease prevention, diagnosis, and treatment in the individual and the public.

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