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Deconvoluting key biological mechanisms forms the framework for therapeutic discovery. Strategies that enable effective translation of those insights along the development and regulatory path, ultimately, drive validated clinical application in patients and populations. Accordingly, parity in *What* versus *How* we transform novel mechanistic insights into therapeutic paradigms is essential in achieving success. Aligning molecular discovery with innovations in structures and processes along the Discovery-Development-Regulation-Utilization continuum maximizes the return on public and private investments for next generation solutions in managing health and disease.

The whole is greater than the sum of its parts.

Aristotle

When considering therapeutic innovation, we naturally focus on biological discovery and the associated advances in technology, which have revolutionized clinical management paradigms and the delivery of care to patients and populations.[1] This evolution reflects the exponential growth in bio-innovation propelled by public-private partnership investment in generating platforms for solutions to health and disease that benefit communities, now and in the future.[2] This scientific revolution drives the development of increasingly precise solutions, leveraging insights in molecular mechanisms within a systems context underlying pathophysiology which offer biologically-based targets for novel therapies, enhance the ability to find cures, and restrict adverse events.[3] Indeed, the increasing toolbox of cutting-edge platforms has produced unprecedented opportunities to individualize and indeed optimize drugs, devices, and their delivery, that can be best aligned across the spectrum of diseases, communities, and geographies to reach global populations in need.[1] The biotechnology and pharmaceutical industry, in turn, has translated these biological advances into new preventive, diagnostic, and treatment approaches that are evolving health and the care of patients and their diseases in ways that were only imagined a decade earlier.[2] The developing framework established by biologically targeted biomarker, device, and therapeutic paradigms alters the one-size-fits-all method to managing patients into individualized health solutions.[4] These developments are poised to advance, and that acceleration is reflected in emerging fields like regenerative medicine which is poised to drive the management of degenerative diseases and wellness through direct manipulation of innate regenerative reserves for tissue and organ renewal.[5]

In every chain of reasoning, the evidence of the last conclusion can be no greater than that of the weakest link of the chain, whatever may be the strength of the rest.

Thomas Reid

Clearly, this revolution in biology and molecular discovery is the engine of disruptive innovation that ultimately propels the development of novel paradigms to maintain health and treat disease. However, regardless of the strength of that engine of invention, clinical translation of basic innovation can only advance at the rate of the slowest component of the Discovery-Development-Regulation-Utilization (DDRU) continuum.[2] Translation and ultimately adoption into the clinic can only be accelerated if we begin to streamline clinical trial processes.[6] Greater rates of success in clinical development will be achieved by innovation in the development of biomarkers that can predict responses, outcomes, and adverse events that advantage novel clinical trial designs.[7, 8] Regulatory decisions about relative value of developing therapeutics will reflect new paradigms in assessing relative risk and benefit.[9-11] Increased access to expensive biological medicines, whose associated prices are unsustainable for healthcare systems with finite resources, will be achieved through novel regulatory pathways encouraging the availability of biosimilars.[12] Ultimately, innovation in the components of the processes that translate novel molecular discoveries into cutting-edge therapies are as important, if not more so, than the molecular targets being translated.[2]

These considerations are underscored by considering the emerging field of regenerative medicine, which is revolutionizing all aspects of therapeutic disease management, with a particular focus on degenerative diseases.[13] The paradigm suggests that we can improve the endogenous regenerative capacities of tissues that undergo disruption because of injury,

disease or chronic insult by stimulating tissue-specific regeneration, and/or amplifying endogenous repair propensity.[14] For example, articular cartilage damage ultimately progresses to end-stage osteoarthritis, affecting about a million people in the U.S.[15] In that context, autologous chondrocyte implantation (ACI) regimens have become standard-of-care in specialized orthopedic clinics focused on osteoarthritis.[15] Similarly, myocardial damage from ischemic heart disease has produced an explosion in chronic heart failure with its associated morbidities and mortality. This is another example in which regenerative approaches through the provision of stem cells instructed to repair the damaged myocardium and restore cardiac function is potentially revolutionizing the management of heart failure.[13, 14, 16-18] However, while these technological approaches are poised to transform the outcomes of debilitating and deadly conditions, their penetration to the management of patients and populations is hindered by regulatory structures and regulations which have not kept pace. Indeed, there is marked variation in marketing, clinical practice guidelines, local and central regulation, as well as reimbursement policies across national jurisdictions.[19] In that context, the majority of research and development activities in this field are still undertaken locally by academic developers and small and medium-sized enterprises.[19, 20] These consideration highlight the need for improved coordination across medical and regulatory communities.[19, 20] Moreover, there is a need to build platforms for knowledge sharing, collaboration and learning among academia, developers and regulatory authorities.[19] New models of pre-competitive collaboration should be utilized to increase research efficiencies while collaborations between regulatory agencies and interactions with developers need to be strengthened and harmonized.[19, 20] The importance of these issues can best be appreciated by considering that

the FDA has declared these opportunities for innovation a key priority to advance regenerative therapies into patients and populaitons.[21]

Similarly, biomarkers have transformed health care management paradigms across a broad spectrum of diseases.[3] These include biomarkers that forecast who will develop a disease, those that prognose whose disease will advance, and those that predict who will respond to therapy.[8] Nowhere is the impact of biomarkers more apparent than in the management of patients with cancer.[22, 23] In that context, biomarkers can segment the population of patients with a particular type of cancer into the precise mutations that underlie their specific disease, providing a mechanistic target that, in many cases, is sensitive to an emerging biologically-directed therapy.[24] These biomarker-driven approaches to molecularly segmenting tumors by mutational identity is revolutionizing the development of novel biological therapies and the associated transformation of clinical trials paradigms to accelerate their approval and availability to patients that need them.[24, 25] In turn, this acceleration of discovery and development is reciprocally driving biomarker innovation, to identify more sensitive and specific diagnostic paradigms for predicting therapeutic results and eliminating adverse events of novel therapeutics.[8, 26] Development of the paradigm for model-informed proarrhythmic risk assessment of drugs is an example of innovation in the design of biomarker paradigms that minimize the risk of adverse events.[27] In addition, the rapid evolution of targeted therapies in oncology, many of which are toxic, has entrained the regulatory sciences to match that innovation with novel paradigms that quantify the relative benefit and risk of new therapies, to enable only compounds with the most favorable therapeutic and safety profiles to be approved for patients.[11, 26, 28] Beyond the classical biomarkers encompassing cell and molecular analytes,

emerging technologies encompassing wearable biosensors with their ability to actuate real time reporting of basic pathophysiological metrics are poised to transform the field by monitoring the therapeutic and adverse effects of novel agents.[11, 26, 28] It is noteworthy that while the pace of biomarker development is accelerating, there remain gaps in commercial incentives that drive biomarker innovation.[29] Moreover the growing dependence of clinical drug development programs on biomarkers has created previously unanticipated challenges in ethical frameworks surrounding human clinical trials.[7]

Bench-to-bedside translation continues to drive innovation across the DDRU continuum. Case in point, deconvolution of the contribution of the IL-23/TH17 molecular pathways to inflammatory diseases has revealed pathophysiological processes common to a variety of autoimmune-mediated conditions.[30] Indeed, the recognition of IL-23 and IL-17 as key cytokines in promoting inflammation and tissue destruction has led to the development of several biologic agents.[30] In turn, these mechanistic insights have been translated into unprecedented therapeutic achievements for conditions including psoriasis, psoriatic arthritis, and rheumatoid arthritis.[30] However, it is noteworthy that these agents, in the class of biologics, generally have been burdened by high costs which are unsustainable for health care systems with limited resources.[2] In that context, innovations in the regulatory sciences established the biosimilars program of the European Medicines Agency (EMA) and, more recently, the FDA which provide pathways for the development of economic generic alternatives once the patent life of innovator products has elapsed.[12, 31] In turn, these programs maximize opportunities for access to those important agents by the broadest populations of the neediest patients.[31]

In the context of the burgeoning opioid crisis, neonatal abstinence syndrome has become a major problem for babies born to addicted mothers.[32] Buprenorphine has demonstrated an efficacy advantage over standard opioid replacement therapy for the neonatal abstinence syndrome in both controlled clinical trials and treatment settings.[32] Buprenorphine is safe in the neonatal abstinence syndrome, and sublingual dosing has been demonstrated to be feasible in the neonatal population.[33] Indeed the use of sublingual buprenorphine resulted in a reduction in the median duration of treatment, median length of stay, and requirement for adjunctive therapies compared to oral morphine.[33] It is noteworthy that the total number of treated patients in these cohorts is modest, although the consistency in effect size in different populations provides external validity to the findings.[32, 33] However, these types of studies, in which cohorts of patients available to individual investigators are modest, can be remarkably accelerated in the future by building public-private partnerships across heterologous platforms to share data, patients, and approaches through digital technologies.[34, 35]

Advances in the development of prevention, detection, and treatment of diseases have amplified beyond the limits of our past concepts of canonical small molecule therapeutics, reflecting emerging insights into molecular mechanisms and biological targets.[2-4] While success in discovery innovation has been dramatic, the translation of those laboratory-based inventions into effective therapies for individual patients and scalable for populations has been hindered by a lag in parallel improvements in supporting structures along the DDRU continuum.[2] Emerging process improvements along this continuum should maximize the impact of discovery innovations by facilitating their translation into novel therapeutic paradigms to maintain health, and prevent and cure disease.

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