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Managing Innovation to Maximize Value Along the Discovery-Translation-Application Continuum

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Abstract

Success in pharmaceutical development led to a record 51 drug approved in the past year, surpassing every previous year since 1950. Technology innovation enabled identification and exploitation of increasingly precise disease targets ensuring a next generation diagnostic and therapeutic products for patient management. The expanding biopharmaceutical portfolio stands however in contradistinction to the unsustainable costs that reflect remarkable challenges of clinical development programs. This annual *Therapeutic Innovations* issue juxtaposes advances in translating molecular breakthroughs into transformative therapies with essential considerations for lowering attrition and improving the cost-effectiveness of the drug development paradigm. Realizing the discovery-translation-application continuum mandates a congruent approval, adoption and access triad.

Without tradition, art is a flock of sheep without a shepherd. Without innovation, it is a corpse

Winston Churchill

Biological discovery and the associated advances in technology have revolutionized clinical management paradigms and the delivery of care to patients and populations.[1] This evolution reflects exponential development of technological and molecular innovation, driven by private and public funding.[2] In turn, the biopharmaceutical industry has translated these molecular innovations into novel diagnostic and therapeutic modalities that are transforming the care of patients and diseases that were only dreamed of a generation ago.[3] Indeed, 2015 was the most successful year in drug development in more than 60 years, with greater than 50 new drugs approved for marketing. This portfolio includes 45 agents approved by the Center for Drug Evaluation and Research (CDER) of the FDA. Twenty of these approvals were garnered by biological drugs, the largest number in a single year in history, reflecting

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the transformation that is occurring in the biological and technological domains. Similarly, twenty of these approved agents featured first-in-class mechanisms of action, highlighting the impact of the multimodal “omics” revolution and zoomed-in insights into fundamental biological principles fostering drug development. This revolution is positioned to continue, and even accelerate, reflected in emerging fields, including genome editing that is poised to transform the management of disease and the pursuit of wellness through direct manipulation of DNA.[4]

This progress notwithstanding, successes belie inefficiencies in drug development associated with unsustainable costs. For example, in the case of oncology drug development, there is an estimated success rate of 5% from phase I, and only a 33% likelihood of success from phase III clinical trial.[5–7] In turn, these inefficiencies, coupled with the intensity of resource requirements in modern biopharmaceutical programs, requires about $2.9 billion and 10 years for the development of a new agent.[7, 8] Moreover, these costs appear to be growing at an annual rate of 8.5% above general price inflation.[8] These metrics suggest that there is an emerging unmet need to improve the efficiency of the drug discovery-translation and ultimately application paradigm.[1] Indeed, improving the efficiencies of the drug development process could remarkably impact downstream pricing of pharmaceutics to the end consumer and/or society which will unburden exponentially escalating global healthcare costs.

Remarkable Successes Transforming Patient Management

Success is simple. Do what’s right, the right way, at the right time

Arnold H. Glasgow—Multiple Sclerosis (MS) is the most common disabling neurological disease of young adults. While it most often affects people between 20 to 40 years old, it also can affect children and seniors. Signs and symptoms reflect inflammatory demyelination in the central nervous system (CNS).[9] MS patients often have a relapsing remitting disease, with episodic neurological dysfunction associated with inflammation in brain or spinal cord. In contrast, some patients experience progressive disease, with accumulation of disability over time. Over the past 20 years, 14 immunomodulatory therapies have been approved in MS in order to reduce the frequency of inflammatory relapses and prevent CNS damage.[9] Orthmann-Murphy and Calabresi[9] review the application of monoclonal antibody technologies to the management of patients with MS, which have been the most effective at controlling disease activity in MS patients. In that context, ocrelizumab recently received breakthrough designation from the FDA for the treatment of MS. It is a recombinant humanized antibody targeting CD20-expressing B cells. This antibody was specifically designed as humanized to reduce formation of human anti-monoclonal antibody responses in patients that could attenuate efficacy and produce adverse events.[9] In phase III trials, ocrelizumab substantially reduced the relapse rate and the progression of disabilities in patients with relapsing remitting MS.[9] Moreover, ocrelizumab is the first agent for primary progressive multiple sclerosis to achieve primary outcomes in a phase III trial, reducing the progression of disability by 24%.[9] Indeed, this agent is the first to be positioned to treat both relapsing remitting and primary progressive MS, representing a major advancement in the field.

Similarly, multiple myeloma (MM) is a hematologic malignancy characterized by clonal plasma cells within the bone marrow producing lytic bone lesions, hypercalcemia, renal impairment, and anemia. MM is the 2nd most common hematologic malignancy, with more than 30,000 new cases in the U.S. annually. While patient outcomes have improved over the last 30 years reflecting evolving management paradigms, relapse leading to death remains the key unmet medical need in this disease. In that context, Laubach et al review six regimens for this disease which received approval from the FDA in 2015, including daratumumab and elotuzumab, the first monoclonal antibodies for this disease.[10] Daratumumab is a humanized IgG1K anti-CD38 monoclonal antibody with anti-tumor activity reflecting antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis.[10] In contrast, elotuzumab is a humanized IgG1K monoclonal antibody directed against signaling lymphocytic activation molecule family member 7 (SLAMF7), a cell surface glycoprotein expressed by normal and tumor plasma cells.[10] Elotuzumab inhibits myeloma cell binding to bone marrow stromal cells, induces antibody-dependent cell-mediated cytotoxicity, and induces myeloma cell cytotoxicity through activation of SLAM7-expressing NK cells.[10] Daratumumab produced robust improvement in 12-month overall survival in phase II trials, the basis for its approval.[10] Elotuzumab, in combination with dexamethasone and lenalidomide, improved progression-free survival in phase III studies, forming the foundation for the approval of this combination.[10] These approaches represent a breakthrough for patients with multiple myeloma for which there were no previous effective therapies to prevent relapsing disease.

Cystic fibrosis is an autosomal recessive genetic disease with an incidence of 1:3,500 in Caucasian populations. This disease reflects structural mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), a chloride channel responsible for the secretion of electrolytes and, ultimately, water which hydrates mucus in lung, liver, pancreas, and intestines. Abnormal mucus viscosity carries the risk of progressive multi-organ failure, including lung function and pancreatic insufficiency. Palliative therapies have been the mainstay of treatment for this genetic disease.[11] Schneider et al review the impact of ivacaftor, the first FDA-approved agent that improved CFTR function by promoting the “open state” of one specific mutant form of this channel to improve chloride transport.[12] While this represented a major breakthrough in cystic fibrosis therapy, the mutant channel that it targeted was only about 4% of cystic fibrosis patients. To overcome this limitation, Orkambi was developed which is a combination of ivacaftor and lumacaftor which improves the processing and translocation to the cell surface of another mutant form of the CFTR.[12] This smart bi-strategy combines a CFTR “corrector” which rescues a major mutant form of CFTR with a “potentiator” that increases the channel opening expanding the therapeutically eligible population to about 28% of CF patients.[12] Indeed, in the US, Orkambi expands the eligible patient population from only about 1,950 patients treated with ivacaftor to 15,000 patients with sensitive CFTR mutations. While these advances represent exciting translation of biological insights into novel therapeutic paradigms for a critical unmet medical need, there is a note of caution with this combination of agents. As patients are exposed to this combination chronically, and more experience develops with it, there appears to be an emerging pattern of pharmacokinetic and pharmacodynamic interactions between the component drugs which may substantially attenuate their therapeutic efficacy.

Drug Development Paradigms Driving Unsustainable Costs and Timelines

There is no innovation and creativity without failure. Period

Brene Brown—While the products of the new biology are driving therapeutic innovation, this revolution in drug development is coming with a steep price tag. Whereas a decade ago, the fully loaded cost of developing a successful drug was about $1B, it is now closer to $3B, requiring about 10 years to bring to completion.[6, 7] While this is a complex and multi-factorial issue, in part these unfavorable cost and time dimensions reflect failures of novel drug assets at advanced stages of drug development, for example in phases I-III, where the likelihood of success should be ideally greater.[6, 7] Venkatakrishnan and Ecsedy[6], Zineh et al[7], and Musante[13] offer solutions for at least one piece of the complex drug development puzzle.[6] Indeed, they suggest that improved success rates in therapeutic innovation will emerge from an integration of the disciplines of translational medicine and quantitative clinical pharmacology to guide the drug development process.[14, 15] Specifically, a focus on these disciplines can provide unique insights into key knowledge domains that are essential for ensuring success in drug development. For example, patient selection strategies to identify those most likely to respond to the novel agent can be informed by the application of “omics” enabled by advances in informatics[16, 17] to realize the promise of clinomics-driven precision medicine.[6, 15, 18, 19] Similarly, mechanism-based studies of drug-target engagement and molecular pathway modulation can establish Proof-of-Concept creating the clinical qualification of the linkage between biological effects and therapeutic efficacy.[6] Further, rational dose selection for clinical trials can be informed by quantitative pharmacology and dose-ranging study designs that optimize the balance of benefit and risk.[6, 14, 15] Moreover, clinical programs must evolve to incorporate enhanced design paradigms integrating Bayesian statistics to efficiently optimize selection of patient populations, doses, and schedules.[6, 14, 15, 20, 21] Incorporating the emerging fields of translational medicine and quantitative clinical pharmacology should contribute to optimizing the cost and time dimensions of drug development.[6, 15, 18–20]

Regenerative medicine, including diverse technologies to protect and restore organ health, represent the vanguard of emerging therapies, positioned to transform disease management, longitudinal wellness, and healthy aging.[22] Indeed, the global regenerative medicine market should reach $67.5B by 2020, and represent over 10% of all healthcare within a decade.[5] Further, there is a growing number of peer-reviewed scientific reports (8,000+ in Pubmed) in this field.[5] Additionally, there are about 200 clinical trials registered in clinicaltrials.gov focusing on “Regenerative Medicine Therapy” with more than half in phase II and beyond.[5] Moreover, there are 704 companies in the field of regenerative medicine with more than half in the US.[5] However, like other drug development paradigms referenced above, development of regenerative medicine therapies is being hampered by a number of systemic limitations, as described by Allickson,[5] Abou-El-Enein et al,[23] and Pasqualini et al.[24] Thus, partnerships are essential, with the emerging shifts in industry that focus on academia for innovation.[5, 23, 24] Early collaborations with regulatory agencies can help facilitate progress in development, given their intimate knowledge of regulatory strategies and pathways.[5, 25] Developing novel paradigms for manufacturing these unique cell-based therapies will be essential to enable the broadest distribution of these revolutionary modalities to the widest

segment of the global population.[5, 23] Moreover, evolving novel in vitro biomimetic platforms can provide comprehensive model systems to ensure quality control for optimal performance in therapeutic applications.[24]

Innovation in the evolution of therapeutics has expanded remarkably beyond the boundaries of our past conceptions of classical small molecule drugs, reflecting emerging revolution in biological insights. While success in innovation in the biopharmaceutical sector have been substantial, those accomplishments are hampered by historical drug development paradigms that may not be “fit for purpose” in this new area of biotherapies. Beyond the inability to sustain escalating cost and time dimensions of current drug development efforts, there is a growing concern that the associated economics passed on to consumers of these therapies, including governments, insurers, and patients, will place many of these modern therapies beyond the reach of most global citizens.[26]

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