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Bioinnovation Enterprise: An Engine Driving Breakthrough Therapies

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Biological advances have radically expanded our insights into the underpinnings of health and disease. New knowledge has formed the substrate for translation - expedited in turn by the biotechnology and pharmaceutical industry into novel therapeutic solutions impacting the management of patients and populations. Indeed, this Bioinnovation Enterprise has become the dominant growth sector in drug development and the engine driving the translation of breakthrough therapies worldwide. This annual *Therapeutic Innovations* issue highlights recent exceptional advances by the Bioinnovation Enterprise in translating molecular insights in pathobiology into transformative therapies.

Changes call for innovation, and innovation leads to progress

Li Keqiang

The revolution in biological discovery and previously unanticipated strides in technology are transforming patient management and healthcare delivery.¹ This transformation reflects the logarithmic growth in molecular innovation driven by public investment in creating platforms for healthcare solutions that benefit populations, now and for future generations.² This scientific evolution propels the development of precision solutions, exploiting insights in pathophysiology at the molecular level that provides mechanism-based targets for advanced therapies, amplifies the ability to affect cures, and eliminates adverse events.³ Indeed, the growing toolbox of next-generation platforms has produced unprecedented opportunities to personalize pharmacological and technological therapies that can be positioned across the spectrum of diseases, populations, and geographies to reach the global community.⁴ In turn, the emerging framework established by molecularly targeted diagnostic and therapeutic paradigms transforms the traditional one-size-fits-all approach to patient management into individualized healthcare solutions.⁵

The profound impact of this scientific revolution on global health can best be appreciated by considering the overwhelming success of the output of therapeutic innovation in the biotechnology and biopharmaceutical sector recently highlighted in this journal.⁶ Indeed, in the last 30 years, this “Bioinnovation Enterprise” has emerged as one of the largest growth sectors in drug development, with >200 therapies emerging for >250 indications from >4,000 biotechnology companies worldwide with a combined value of \$185 billion. In 2012, biotechnology product sales worldwide were an estimated \$163 billion, which constituted ~19% of the total prescription product sales. Of 119 overall products categorized as blockbusters (sales over \$1 billion per year), 47 (39%) were biotechnology products. The prominence of this sector in therapeutic innovation is reflected by the fact that the overwhelming majority of new molecular entities approved by the FDA over the last 3 years,

and those predicted to transform the care of patients in their respective disease classes, are products of the evolving Bioinnovation Enterprise.^{7,8}

Case in point, the impact of this innovation is highlighted by emerging paradigms for the management of asthma.⁹ This disease currently afflicts 300 million people globally, a number which is expected to rise to 400 million by 2020. While most patients are satisfactorily controlled on established treatments, 5% remain poorly controlled. In that context, innovative treatments have the potential to provide options for these unfortunate patients. Moreover, the economic and healthcare benefits of treating poorly controlled asthma are substantial and in Europe the total cost of asthma is ~€17.7 billion. Mitchell, El-Gammal, and O'Byrne⁹ highlight how this field has been transformed by mechanistic insights gained in molecular mechanisms underlying epithelial inflammation. Allergens bind to surface receptors on bronchial epithelial cells releasing a number of cytokines which initiate inflammatory cascades. They mobilize and activate inflammatory T cells, eosinophils, and basophils which secrete other cytokines, promoting IgE synthesis from B-cells and increasing airway hyper-responsiveness, mucus hypersecretion and airway remodeling that are canonical features of allergic asthma. The identification of these cytokines, their receptors, and their roles in the inflammatory cascade have yielded targets for humanized monoclonal antibodies that interrupt select pathways essential to the pathobiology of allergic asthma. There are more than 20 therapeutic monoclonal antibodies either approved or in various stages of clinical development that target molecular components of the inflammatory cascade. Progression of these agents through their developmental programs will transform the management of refractory allergic asthma globally.

Beyond airways, insights in cytokine cascades mediating inflammation has provided remarkable opportunities in the management of inflammatory bowel disease (IBD), including Crohn's disease (transmural inflammation) and ulcerative colitis (mucosal inflammation).¹⁰ This continuum of diseases afflicts about 10,000 new patients each year, with a prevalence of about 500,000 patients in the U.S. The most impactful advance in the management of IBD over the past 20 years has been the development of monoclonal antibodies directed to tumor necrosis factor

alpha (TNF- α). Unfortunately, although anti-TNF agents are effective, only ~50% of patients achieve clinical remission, long term corticosteroid-free remission rates are only 20-30%, and there is a significant loss of response reflecting the formation of neutralizing antibodies. Moreover, while anti-TNF agents reduce inflammation, they do not block the underlying pathogenic triggers and treatment cessation is associated with disease within one year in more than 50% of patients. These considerations highlight the unmet clinical need for novel agents to manage IBD. While approaches in clinical development include monoclonal antibodies to inflammatory cytokines, Vanhoe, Nys, and Vermiere¹⁰ review other novel approaches that leverage recent mechanistic insights into molecular mechanisms underlying mucosal inflammation. Indeed, IBD is characterized by the influx of immune cells into inflamed sites in the mucosa mediated by adhesion molecules suggesting the potential therapeutic value of strategies targeting anti-leukocyte migration. Vedolizumab, a monoclonal antibody targeting $\alpha 4\beta 7$ ligand which is responsible for the trafficking of lymphocytes to the inflamed gut, was recently approved by US and European regulatory agencies and is a major advance for the management of patients with IBD.^{8, 10} Similarly, transforming growth factor (TGF)- β is a cytokine mediating counter-regulatory mechanisms modulating inflammation. In turn, the anti-inflammatory effects of TGF- β are blunted by over-expression of SMAD7 in IBD. Mongersen is an antisense oligonucleotide developed to suppress the expression of SMAD7 and reveal the anti-inflammatory effects of TGF- β . Indeed, a recent phase II trial of Mongersen led to a clinical response that was sustained for over three months, indicating enduring therapeutic effects. As further molecular insights are gained into the pathophysiological mechanisms of IBD, next-generation therapies will be directed to modulating the mucosal barrier, microbiota, and endoplasmic reticulum stress.¹⁰

Worldwide, atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of death, and in the U.S. accounts for ~\$ 315 billion health care expenditure each year. One key conceptual advancement in efforts to optimally manage ASCVD was the role of atherosclerotic plaques in the pathophysiology of ischemic vascular disease and the relationship between circulating levels of cholesterol and plaque formation. Indeed, inhibiting plaque formation by

controlling serum cholesterol levels is one of the essential therapeutic strategies to prevent ASCVD and cardiovascular mortality. In that context, the field was transformed by the molecular discovery 40 years ago that statins could inhibit HMGCoA reductase, the rate-limiting enzyme in the de novo synthesis of cholesterol. This was a breakthrough in the management of hypercholesterolemia syndromes, and statins are first line therapy to reduce serum cholesterol levels and the incidence of ASCVD and cardiovascular mortality. However, many patients experience muscle symptoms and other adverse events that limit compliance. Further, ~70% do not attain LDL-C treatment targets even when adherent to statin therapy. Moreover, recent practice guidelines recommend statin therapy that expands the populations requiring adequate control of serum cholesterol, doubling the number of patients to about 13 million, and the associated cost of treatment. These considerations underscore the need for improved therapies to control serum cholesterol and ASCVD. This field recently has been transformed again, and Shantha and Robinson¹¹ describe the 2003 discovery of PCSK-9 as a novel enzyme expressed in liver, intestine, kidney and the nervous system. It resides in a complex with LDL receptors enhancing endosomal and lysosomal degradation of those receptors. Gain of function mutations of PCSK-9 reduce LDL receptors on the cell surface, resulting in familial hypercholesterolemia associated with increased ASCVD. Conversely, patients with loss of function mutations in PCSK-9 have elevated amounts of LDL receptors at the cell surface, with reduced circulating levels of cholesterol and reduced risk for ASCVD. Based on these novel mechanistic insights, monoclonal antibodies that inhibit PCSK-9 were developed as a treatment to raise cell surface LDL receptors and lower circulating cholesterol levels and ASCVD risk. Indeed, alirocumab and evolocumab reduce serum cholesterol in statin-naïve and statin-resistant patients. Moreover, meta-analyses suggest that these agents significantly reduce ASCVD and overall mortality, without significant treatment-related adverse events. Alirocumab and evolocumab were approved in the summer of 2015 for patients on maximal statin therapy with familial hypercholesterolemia or cardiovascular disease who might benefit from additional cholesterol lowering.

Beyond the formation of cholesterol plaques, the other key component contributing to the pathophysiology of ASCVD is platelet activation and the formation of thrombi which occlude affected vessels. Molecular dissection of platelet signaling has revealed key points of intervention to reduce platelet activation and thrombus formation. Contact with a plaque induces receptor-mediated platelet adherence and deposition. Subsequent release of ADP and thromboxane cause the rapid activation and local recruitment of additional platelets. In turn, the activated platelet plasma membrane serves as a critical receptor and cofactor for initiating coagulation with the ultimate generation of thrombin enabling formation of an insoluble, cross-linked fibrin clot. While normal hemostasis ensues when the platelet-fibrin thrombus seals wound, thrombus formation in the context of an atherosclerotic plaque produces pathologic vessel occlusion. First generation approaches to blocking thrombus formation leveraged the discovery that thromboxane, a key mediator of platelet activation, was synthesized from arachidonic acid through a cascade in which cyclooxygenase was a rate limiting enzyme. Thus, aspirin, an irreversible inhibitor of cyclooxygenase, is one mainstay of therapy to prevent platelet activation and clot formation. The field was propelled by the discovery of the role of P2Y purinergic receptors in mediating ADP-dependent platelet activation, and agents that block these receptors have transformed therapeutic paradigms that prevent thrombus formation. However, while these paradigms provide clinically significant improvements in the anti-thrombotic management of patients with ASCVD, absolute reduction in thrombotic events remains relatively low and is associated with a substantial risk of major bleeding. In their review, Bray and Holinstat¹² describe next-generation molecular insights which are providing advanced tools to manage thrombotic disease. Thus, thrombin activation is the final key step in the coagulation pathway and a significant regulatory step in platelet activation. Platelets express unique G-protein coupled protease-activated receptors (PARs) which are activated when thrombin binds to and cleaves the amino-terminus, initiating a cascade of intracellular calcium signaling mediating platelet activation. Recognition of the importance of PARs in platelet activation and thrombus formation was rapidly translated in a biopharmaceutical

program to develop orally-available receptor antagonists. In the summer of 2014, the first PAR antagonist, vorapaxar, was approved by the FDA to prevent recurrent cardiovascular events in patients with a history of ASCVD.

These examples underscore the evolving significance of the Bioinnovation Enterprise in translating molecular discoveries in the laboratory into novel healthcare paradigms that transform disease therapy and prevention in patients and populations. This significance is further highlighted by George, Vaid and Summer¹³ who review the recent approval of nintedanib and pirfenidone for the treatment of idiopathic pulmonary fibrosis. Following decades of unfruitful exploration, these inhibitors of inflammation, fibroblast function and collagen deposition are the first approved treatments for this devastating disease and considered to be highly impactful.⁸ On the horizon, emerging platform technologies are moving from the laboratory bench to the bedside to transform our most basic concepts of patient management. In that context, Subbotina et al.¹⁴ review the promise of morpholino oligonucleotides for gene editing to correct what was previously considered to be irreversible disease-causing mutations. Further, advances in biology are complemented by innovations in bioengineering, and Iezzi¹⁵ reviews transformative progress at the interface of brain and machine in the form of retinal implants to restore vision. Additionally, acceleration of translation reflecting the revolution in biology, in turn, drives the evolution of companion structures required to maximize the impact of these transformative discoveries. Berry¹⁶ provides a cogent review of innovations in clinical trial designs that optimizes drug efficacy with molecular and pathophysiological disease subtype. Moreover, Fujita¹⁷ describes innovations in regulatory sciences in Japan to overcome the unique challenges of deploying regenerative cell therapies to patients and populations.

The Bioinnovation Enterprise is poised to transform the rapid pace of knowledge generation in pathobiology into therapeutic innovations for global populations. The impact of this transformation on the drug development and healthcare delivery landscapes will undoubtedly escalate over the coming years, driven by the dual engines of exponential

knowledge growth and commoditized technologies with de-risking pipeline development and de-escalating costs. One cautionary note in this otherwise optimistic paradigm is indeed the cost of this remarkable innovation to individuals and society. For diseases involving millions of patients and transformative therapies priced at \$10,000 to \$100,000 a year, the unsustainability of the model is revealed by simple arithmetic. Biopharmaceutical executives, investors, third party payors and governmental agencies must collaborate to define the appropriate balance between individual patient health, society's best interests, and a fair return on investment that will propel the next generation solutions.

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