Current Progress in Drug Target Identification and Drug Delivery

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On behalf of the editors, I am excited to introduce the International Journal of Drug Discovery and Pharmacology (IJDDP)’s debut as “Current Progress in Drug Target Identification and Drug Delivery” with an emphasis on cardiovascular system. Our enthusiasm for this inaugural issue stemmed from the unprecedented opportunity today to develop novel medications for major diseases. The explosion of multiple omics technology, single cell sequencing-prompt system pharmacology, artificial intelligence (AI)-driven structure modelling, remarkable progress in gene therapy, and material innovation for drug delivery, have massed to offer a unique era for us to focus our mindpower on developing new therapeutic modalities. Drug Discovery exemplifies “big science,” because it requires an integrated and effective machinery executing from academia, industry, healthcare system as well as regulatory agencies to identify, to evaluate, to develop, to approve new drugs and therapies. In this context, we collate 10 authoritative reviews to appraise valuable and timely information in key aspects of the drug discovery and delivery pipeline.

Wang and Du et al. from Beijing Key Laboratory of Drug Targets Identification and Drug Screening denote two approaches in drug discovery, i.e., phenotype and target-based approaches, each holding different advantages for screening novel drug candidates when pursuing successful marketing authorization [1]. They also outline the progress of modern drug discovery. Although, the attrition rates of drug candidates continue to increase, the authors discuss recent successes and ongoing advances in phenotypic screening and target-based screening. The authors also explore how strategic and technological innovations that fuel drug discovery, such as lead compound screening and testing applied in three-dimensional (3D) organoids, AI-aided approaches using algorithms for predicting in vivo activity and toxicity etc.

Over the past three decades, drug discovery has shifted away from phenotypic drug discovery towards target-based approach equipped with advances of high throughput screening technologies. Target-based approach is based on a rational method, comprising drug target identification and screening of drug candidates. In this issue, we include 3 articles exemplifying drug target identification. Zhang and Woo et al. from Peking University offer a comprehensive review on the recent progress in G-protein coupled receptors (GPCRs) research focusing on cardiac β-AR signal transduction [2]. The authors delineate differential effects of β-AR signalling in the heart due to their spatial distribution and associated regulatory factors such as GRKs and β-arrestins as well as CaMKII. Since 1994 Nobel Prize was awarded to the ground-breaking work on G-proteins, it led to a great deal of studies on GPCRs, therefore GPCRs become the most exploited membrane proteins with approximately 30% of currently used drugs targeting this receptor superfamily. One of the classic examples of successful drug discovery is Propranolol, β-blocker (selectively antagonizing the β1-AR), by James Black. Ever since then, several generations of β1-AR blockers have been evolved with improved selectivity and board applications. Zhang and Woo et al. [2], further describe the translational study of β2-AR agonists into therapeutic explorations. Since there are at least 800 GPCRs, the authors prospect that GPCR signal complexes will undoubtedly give rise to new opportunities to target novel sites on individual receptors, regulators and effectors, therefore there is clearly plenty of potential for the development of new GPCR-targeted drugs for treating major disease conditions.

Echoing to physiological systems and therapeutic applications of GPCR signalling, Solaro et al. from University of Illinois at Chicago describe that Hippo-YAP pathway downstream of GPCR signaling in the altered mechanical state is instigated by variants of genes expressing mutant sarcomere proteins to trigger a progression to dilated cardiomyopathy (familial DCM) [3]. The authors explain the hierarchical sensing and modulation of the mechanical state of the adult heart in health and disease cascaded by Hippo-YAP pathway.
Furthermore, they update recent progress in the discovery of small molecules such as TRUL11 and XMU-MP-1 modifying the Hippo-YAP pathway intended for therapy in cancer that provides important information related to the pursuit of agents for use in cardiovascular disorders such as DCM.

Under overarching G-protein system, there are two classes of G proteins. The first function as heterotrimeric G protein complexes as described above, while the second function as monomeric small GTPases (small G-proteins), among of the latter cohort Rac1 and Cdc42 are well-depicted members of the Rho family of small GTPases. Group I p21-activated kinases (Paks) are members of the serine/threonine protein kinase family, are downstream effectors of Rac1 and Cdc42. Zhang et al. from University of Manchester provide greater understanding of the structure, activation, and function of group I Paks, mainly Pak1 and Pak2 (Pak1/2), centring on their protective roles against cardiovascular disease [4]. Albeit Pak1/2 are historically regarded as oncogenes, however, the signalling programs regulating cell proliferation may be closely related to the programs that control growth of postmitotic adult cardiomyocytes. Inspired by this notion, Pak1 was then identified as a novel antihypertrophic regulator in 2011. Subsequently, an expanding body of evidence concerning cardioprotective roles of Pak1 in alleviating ischemic injury and arrhythmia has been generated. Nonetheless, its role in inflammation during the development of atherosclerosis remains arguably. Alike to Pak1, Pak2 is activated by allosteric regulation through the action of Rac1 and Cdc42. The striking property of Pak2 is to facilitate ER stress response through the activation of IRE1/XBP1 branch of unfolded protein response (UPR). This beneficial effect was also observed in defending hypoxia-reoxygenation, as well as ischemia/reperfusion injury. In parallel, Pak2 as a signalling nexus connecting the renin-angiotensin-alderosterone system (RAAS) activation, oxidative stress and UPR through regulation of Nrf2 expression was uncovered. Collectively, these findings confirm that Pak2 confers cardioprotective effects in several disease conditions. Owing to the role of Pak1/2 in the cardiovascular system, Zhang et al. rationalise strategies activating Pak1 and Pak2 could be a promising avenue for drug development [4]. A case of repurposing Fingolimod (FTY720), an FDA-approved anti-multiple sclerosis drug, for cardiac applications of alleviating cardiac hypertrophy and ischemic injury was described. FTY720 bears a similar structure to sphingosine-1-phosphate (SIP), which is able to activate Pak1.

Despite the advances in understanding the pathophysiology of cardiomyocytes, the main obstacle to progress has been a lack of fundamental knowledge of non-cardiac cells, for instance, inflammatory cells, especially macrophages, neutrophils, and monocytes. Wang et al. from Duke-NUS Graduate Medical School tackle a generic yet important topic, beyond cardiovascular system, on targeting inflammation to control tissue fibrosis [5]. Inflammation is the first response mechanism following tissue injury. Aberrant inflammatory responses can disturb extracellular matrix (ECM) homeostasis leading to progressive disruption in tissue architecture to form fibrosis, which routes to organ dysfunction. Fibrosis is the common outcome of a wide range of diseases, e.g. heart failure, and represents the leading cause of morbidity and mortality globally. The authors provide the current understanding of the pathogenesis of fibrosis, with particular emphasis on pleiotropic effects of inflammatory growth factors, cytokines, and chemokines in this process, and particularly point out that the complex role of inflammation molecules and the heterogeneity of different fibrotic disease contexts warrant further investigation in the pursuit of novel therapeutic targets for a specific type of fibrotic disease. In doing so, single-cell multi-omics approaches offer a powerful exploration of cell states and types at the single-cell level, helping investigators to generate new insights into the disease mechanisms associated with fibrosis.

Hyperlipidaemia is a common public health problem characterized by the increased levels of cholesterol, triglycerides and/or lipoproteins, attributable to the onset of many diseases such as type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular disease. The first-line drugs for this condition are statins and monoclonal antibody drugs blocking proprotein convertase subtilisin/kexin type 9 (PCSK9), however drug intolerance and patient incompliance are apparent. With the advent of Inclisiran, the first approved small interfering RNA drug targeting PCSK9 mRNA to induce cholesterol degradation, drug development has been striding into an utterly new era of biomaterial therapeutics. Chen et al. from Tongji Medical College offer “from bench to bedside” perspectives on design principles of RNA-based therapeutics using mRNA, ASO, siRNA, microRNA [6]. They further summarise current clinical trials of RNA drugs in hyperlipidaemia and discuss a few of bottlenecks limiting RNA drug development including the efficiency of cellular uptake, endosome escape, off-target effects, quality control of modifications and delivery systems.
Current drug development using the target-based approach devotes extensive effort to identifying the molecular mechanism of action of putative candidates. The conventional process of drug development suffers approximately 90% attrition rate, meaning that 90% of drug candidates do not reach drug approval stage. It is estimated to take usually 12–14 years and approximately $1–2 billion to move a drug from preclinical stage to the stage of approval. Thus, drug repurposing, defined as the re-application of known drugs for new indications, is an attractive shortcut owing to moderate cost, and rapid safety scrutiny. The most well-known case of repurposing is sildenafil, which is repurposed for treating erectile malfunction from its original cardiovascular application. Wu et al. from Tongji Medical College provide clinical trial information to describe a possibility of repurposing antidiabetic agent of sodium glucose cotransporter 2 inhibitors (SGLT-2i) for treating hypertension [7]. The authors profile at least 7 SGLT-2i to explain their effects on controlling blood pressure are likely through multiple mechanisms annotated as reducing myocardial preload, lowering the level of serum uric acid whereas increasing β-hydroxybutyrate level, inhibiting sympathetic overactivation, relieving oxidative stress and the final attempt in maintaining a stable level of canonical RAAS components.

To propel drug development, new platforms mimicking physiological condition for testing lead compounds are vital. Liu and Keavney et al. from University of Manchester collate primary information detailing recent progress in human-origin organoid/spheroid systems and their applications in preclinical studies [8]. The authors describe in great detail concerning cell compositions, distributions, structures and functions of 3D organoids differentiated from human stem cells. Preclinical applications of organoids as “mini organs” resembling intestine, liver, pancreas, brain, and heart are described. Finally, the authors point out a fascinating direction to develop ‘body-on-a-chip’ system, integrating multi-organoids modelling liver, cardiac, lung, vascular, testis, colon, and brain on one platform, which is applicable to study drug effects, side effects and off-target toxicity across different tissue types.

Notwithstanding an appreciable number of active compounds has been developed as therapeutic agents, a recurrent issue for their use clinically resides on the poor control over the body distribution and the limited dose at the site of action, hence their efficacy. The recent surge of new materials and technologies enables investigators to develop novel biomartials and devices for a better control of drug delivery. Tirella et al. from University of Manchester and University of Trento based on their own research experience present an overview of the properties of natural injectable hydrogels and recent development for their use to control the local release of therapeutic agents [9]. Hydrogels are water-based polymeric 3D network with advantageous properties for the delivery of bioactive components, ranging from small therapeutic agents to mammalian cells. This new system can release single or multiple therapeutic agents at a constant and known rate and at a known site (control in time and space), with the ultimate scope to maintain a constant concentration of the therapeutic agent. Hydrogels are typically composed of synthetic or natural polymers, and their blends. The authors provide a succulent review of currently tested polymers with regard of their advantages, drawbacks, and formulation process, among which alginate is the particular focus of this review. There are currently more than 30 injectable hydrogel products approved by the FDA and/or EMA for the treatment of various diseases, and a greater number is currently investigated preclinically. The authors conclude the review with an optimistic remark that the capability of injectable hydrogels to deliver multiple therapeutic agents offers a new dimension to drug delivery. A rapid clinical translation of the next generation alginate-based injectable systems is anticipated.

The recent advance in the medical nanotechnology has demonstrated its great value not only for diagnostics but also for drug delivery. Nanoparticles (NPs) possess notable features in terms of increasing target specificity, improving drug release, hence reducing side effects. Moreover, the encapsulation or conjugation of NPs with peptides, antibodies or small molecules can further enhance compound solubility, reduce toxicity, and improve chemical stability in the circulation. Xiao et al. from Kanion Pharmaceutical Co present 3 novel NP-based drug delivery systems tested in myocardial infarction condition, such as enzyme-responsive NPs, magnetic antibody-linked NPs, and extracellular vehicles (EVs)-based NPs [10]. The authors finally analyse that the rationale of developing NPs delivery system is accredited to its better bioavailability and biocompatibility, whereas its pitfall is safety issue. Future direction in NPs drug delivery is anticipated in aid of stem cell therapy and exploitation in Chinese medicine related substance delivery.

In closing, the collection of review articles in this themed issue illustrates a holistic picture of recent
progress in drug discovery and delivery following a logical manner. They show the diverse and ingenious strategies for identifying therapeutic targets, repurposing drugs, and tooling novel materials. Importantly, they also highlight the still unmet challenges and pitfalls that could be addressed by combining disciplines and working interactively. The stage is now set for the translation of these progress into new therapeutics that will affect many diseases. The editors hope the information presented in this issue will be useful not only to pharmacologists but also to a general readership with an interest in learning drug discovery across academia, industry and medical practices. Finally, the editors thank the authors and reviewers for their overall enthusiasm and enormous efforts in enabling this inaugural issue to cover such a broad range of contemplations for this rapidly evolving field.

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References


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