JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 14, No. 6, June 2018 "Happy Trials to You"

"Pharmaceutical Medicine and Translational Clinical Research"

Divya Vohora and Gursharan Singh, editors, 2018, 497 pages, Academic Press, $125

Review by Norman M. Goldfarb

"Pharmaceutical Medicine and Translational Clinical Research" covers the pharmaceutical development and commercialization process from "Identification of Unmet Medical Need" to "Types of Pharmacoeconomic Analysis." In many areas, the book goes beyond high-level discussion into technical detail, as illustrated by the section on target validation:

> Subsequent to identification, a potential drug target needs to undergo the process of validation, wherein its function in a disease state is ascertained. There are multiple approaches towards validation, and some of them will be discussed here.
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> Use of antisense technology is a popular route, wherein short oligonucleotides (single stranded nucleic acids), complimentary to a specific region of a messenger RNA of interest, are designed. The interaction of the oligonucleotides with the target mRNA results in disruption of translation and subsequently impedes the synthesis of the protein. To exemplify, knockdown of tetrodotoxin-resistant sodium channel $Na_v1.8$ by antisense oligonucleotides, obliterated intrathecal N-Methyl-D-Aspartate-induced mechanical hypernociception in rats, thereby highlighting the importance of these ion-channels in pain pathophysiology.
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> An alternative approach is RNA interference (RNAi) technology, wherein silencing of the target gene in a cell or an organism is triggered by introduction of a double stranded RNA (dsRNA) specific to the gene. The long dsRNAs are cleaved by the RNase, Dicer, into small interfering RNAs (siRNAs), which are double stranded fragments of 21-25 nucleotides with some unpaired base pairs at each end. Subsequently, the siRNAs are unwound into two single strands, referred to as a guide and a passenger strand, respectively. The guide strand is incorporated into the RNA interference specificity complex (RISC), and it locates the mRNA possessing the complimentary sequence, resulting in cleavage of the target mRNA and shutting down of the translation machinery. This approach of using long dsRNAs is marred by variability in response, overall decrease in mRNA levels, and expensive design. Alternatively, these issues can be overcome by design and, subsequently, direct introduction of 21-25 nucleotide long siRNAs into the cellular machinery. The potential utility of the above modality in target validation is exemplified by an experiment…wherein mice injected with siRNA against the chemokine CCR2 and subjected to ischemia-reperfusion, demonstrated lower infarct size and marked decrease in cardiac inflammatory monocytes as compared to control siRNA administered mice, thus demonstrating the role of CCR2 in inflammatory cell trafficking in cardiac tissue.
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> Employing genetically modified animals for target validation is an appealing methodology, as it permits the scrutiny of the phenotypic consequences of gene manipulation. Development of knock-outs, knock-ins, conditional knock-outs, and transgenic animals are instances of genetically modified animals. An animal lacking a particular gene from the embryonic stage is one approach to studying the in vivo functions of diverse genes. For example, contraction to carbamylcholine was virtually abolished in the urinary bladder from muscarinic M_3-receptor knock-out mice, suggesting that contraction was predominantly due to M_3 receptor activation. In gene

knock-in animals, the desired gene is inserted into a specific locus in the target genome and can hence be said to be a gain of function mutation. To exemplify, knock-in mice with deficits in the AMPA receptor GluR1 Serine 831 and Serine 845 phosphorylation had a higher threshold and longer latencies to pentyle-netetrazole-induced seizures in postnatal day 9 as compared to wild type mice, thereby supporting the validation of this potential therapeutic target for neonatal seizures.

In a conditional knock-out approach, the gene of interest is deactivated in the target tissue at a specific time point, thereby limiting the risk of embryonic lethality and developmental abnormalities, which are often experienced with conventional knock-out models. The utility of this approach in target validation can be exemplified by a study…wherein they show that mice in which GPR88 receptors located on adenosine $A_{2A}R$ neurons were conditionally knocked-out demonstrated decreased anxiety-like behaviors in light/dark and elevated plus maze tests.

Transgenic animals are also an attractive validation tool wherein a foreign gene is intentionally inserted in their genome. For example, transgenic LXR α mice demonstrated improved myocardial glucose tolerance and reduced cardiac hypertrophy in a mouse model of obesity-induced type 2 diabetes, thus supporting use of therapies targeting LXR α for cardiovascular diseases.

A limitation of the genetic approach to target validation is that genes generate various isoforrns of the protein, which may have slightly different functions, and variations in proteins can also be a consequence of post-translational modifications. Hence, an improved and emerging approach to target validation is the proteomics approach, which aims at the modulation of the activity of the target protein itself.

The book includes 33 chapters by 25 contributors (mostly based in India) in eight sections:

- Overview of Pharmaceutical Medicine
- Drug Discovery and Development
- Pharmaceutical Law and Ethics
- Pharmaceutical Industry and Intellectual Property Rights
- Generics, Supergenerics, Biologics, Biosimilars and Biobetters
- Medical Services
- Pharmacovigilance
- Drug Utilization and Pharmacoeconomics

Reviewer

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