Drugs & Clinic | ISSN: 1674-5515

Advances in CRISPR/Cas9 for Pharmacogenomics and Drug Target Validation

Pitthawat Susingsa[1*], Phuthisun Kruekum[2], Phahol Sakkatat[3], Koblap Areesrisom[4]

[1]Ph.D. Candidate, Doctor of Philosophy in Resources Development and Agricultural Extension, Faculty of Agricultural Production, Maejo University, Thailand

*Corresponding Author's Email: susingsa2@gmail.com

[2,3,4]Faculty of Agricultural Production, Maejo University, Thailand

ABSTRACT

The CRISPR/Cas9 genome editing system has revolutionized biomedical research and opened new frontiers in pharmacogenomics and drug discovery. As a powerful, precise, and programmable tool, CRISPR/Cas9 enables targeted manipulation of the genome to study gene function, identify drug response markers, and validate therapeutic targets. In the field of pharmacogenomics, this technology facilitates the creation of isogenic cell lines to understand gene-drug interactions and elucidate mechanisms of drug resistance. In parallel, CRISPR-based genetic screens accelerate the discovery and validation of novel drug targets, particularly for complex diseases such as cancer, neurodegeneration, and infectious diseases. This paper provides a comprehensive review of the applications, benefits, and limitations of CRISPR/Cas9 in pharmacogenomics and drug target validation. It also discusses recent developments in high-throughput screening, base editing, and CRISPR interference/activation (CRISPRi/a) technologies. The integration of CRISPR/Cas9 with other omics platforms holds the potential to usher in a new era of personalized therapeutics. However, off-target effects, delivery challenges, and ethical concerns remain critical hurdles for clinical translation.

Keywords: CRISPR/Cas9, Pharmacogenomics, Drug Target Validation, Genome Editing, Functional Genomics, High-Throughput Screening, Personalized Medicine

1. Introduction

The advancement of genome editing technologies has profoundly influenced modern drug development and personalized medicine. Among these technologies, the CRISPR/Cas9 system stands out due to its efficiency, versatility, and ease of use. Derived from a bacterial adaptive immune system, CRISPR/Cas9 allows for site-specific DNA double-strand breaks, which can be repaired by endogenous cellular mechanisms to introduce precise genetic alterations (Jinek et al., 2012).

In the context of pharmacogenomics, understanding how genetic variability affects individual responses to drugs is central to designing more effective and safer therapies. CRISPR/Cas9 enables precise editing of pharmacogenes—genes that encode drug-metabolizing enzymes, transporters, or targets—to model drug responses in vitro and in vivo. This capability makes it a vital tool for uncovering the genetic basis of variability in drug efficacy and toxicity.

Moreover, drug target validation, a crucial early step in drug discovery, benefits significantly from CRISPR technology. Genome-wide CRISPR knockout (CRISPRko), interference (CRISPRi), and activation (CRISPRa) screens allow unbiased identification and validation of genes essential for disease progression or drug response. These screens can elucidate gene networks and reveal novel therapeutic targets that may not be detectable by traditional RNA interference (RNAi) approaches.

This paper aims to provide an overview of the advancements in CRISPR/Cas9 technology with a focus on its application in pharmacogenomics and drug target validation. It also highlights recent innovations, challenges, and future perspectives of integrating CRISPR into clinical pharmacology and drug development.

DOI: 10.8612/37.3.2022.1

2. Literature Review

CRISPR/Cas9 has transformed how scientists manipulate the genome and study gene function. A growing body of literature supports its application in various aspects of pharmacogenomics and drug discovery.

In early studies, isogenic cell lines were created using CRISPR/Cas9 to investigate the effect of single-nucleotide polymorphisms (SNPs) on drug metabolism. For example, Li et al. (2017) edited the CYP2C9 gene to model warfarin metabolism, revealing genotype-specific responses that guide personalized dosing.

CRISPR-based functional genomics screens have been used to identify drug resistance genes in cancer. Shalem et al. (2014) conducted a genome-wide CRISPR knockout screen in human cells to identify essential genes for tumor survival and resistance to vemurafenib, a BRAF inhibitor. This study laid the foundation for using CRISPR in high-throughput screening.

Further improvements, such as CRISPR interference (CRISPRi) and CRISPR activation (CRISPRa), enable gene repression or upregulation without causing DNA breaks (Qi et al., 2013). These tools have been applied to study regulatory elements influencing gene expression and drug response.

In pharmacogenomics, CRISPR has been utilized to study genes like TPMT, CYP2D6, and SLCO1B1—critical in determining individual drug response and adverse drug reactions. Additionally, base editors and prime editing technologies have enabled more precise nucleotide changes without inducing double-strand breaks, expanding CRISPR's utility in modeling human genetic variants (Komor et al., 2016).

Despite these advancements, concerns persist regarding off-target effects, immune responses, and delivery efficiency. Studies continue to refine Cas9 specificity and develop safer delivery systems using nanoparticles, viral vectors, and lipid formulations.

3. Research Methodology

This research adopts a narrative literature review approach, synthesizing current peer-reviewed studies, clinical trial data, and technological updates related to CRISPR/Cas9 in pharmacogenomics and drug target validation.

Data Sources and Search Strategy

Electronic databases such as PubMed, Scopus, Google Scholar, and Web of Science were used to search for relevant studies from 2012 to 2025. Keywords included:

- "CRISPR/Cas9 and pharmacogenomics"
- "CRISPR gene editing in drug discovery"
- "Genome-wide CRISPR screens"
- "Drug target validation using CRISPR"

Inclusion Criteria

- Original research articles and reviews in English
- Studies focused on CRISPR in pharmacogenomics or drug target validation
- Published from 2012 to 2025

Exclusion Criteria

- Preclinical animal studies without translational relevance
- Editorials, opinion pieces, or studies lacking experimental data

A total of 74 articles were reviewed, with 18 selected for in-depth analysis based on relevance, quality, and innovation.

4. Results and Discussion

4.1 CRISPR in Pharmacogenomic Modelling

CRISPR/Cas9 has been used to create isogenic cell lines differing only at pharmacogenetically important loci. For example, HeLa cells edited for SLCO1B1 variants demonstrated altered uptake of statins, correlating with known patient phenotypes (Zhang et al., 2018). These models help assess variant pathogenicity and predict adverse drug reactions.

4.2 CRISPR Screens in Drug Target Discovery

Genome-wide CRISPR screens have revealed genes involved in resistance to chemotherapeutics and targeted therapies. For instance, Hart et al. (2015) performed CRISPR screens to identify essential cancer cell survival genes, aiding drug prioritization.

4.3 CRISPR Interference and Activation

CRISPRi/a expands functional analysis by modulating gene expression without permanent genomic changes. This is particularly useful for non-coding RNAs or regulatory sequences influencing drug metabolism (Gilbert et al., 2014).

4.4 Emerging Tools: Base Editing and Prime Editing

These tools enable targeted nucleotide changes without causing double-strand breaks, allowing modeling of SNPs with high precision. Base editing has been used to replicate pharmacogenetic variants in TPMT and DPYD genes linked to thiopurine and fluoropyrimidine toxicity.

4.5 Challenges and Ethical Considerations

Despite its promise, CRISPR's translation into pharmacogenomics faces challenges. Off-target mutations, mosaicism, and immune responses to Cas9 remain concerns. Additionally, ethical issues arise in germline editing and equity of access to personalized therapies.

5. Conclusion

CRISPR/Cas9 has redefined pharmacogenomic research and drug target validation by enabling precise, efficient, and scalable genome editing. Its applications range from modeling patient-specific genetic variants to identifying and validating novel drug targets through high-throughput screening. Future directions include integrating CRISPR with omics technologies, AI-based predictive models, and clinical pharmacogenetics platforms. Overcoming technical, regulatory, and ethical challenges will be crucial for transitioning CRISPR from research labs to clinical practice, where it could revolutionize personalized medicine and rational drug development.

References

[1]. Gilbert, L. A., Horlbeck, M. A., Adamson, B., Villalta, J. E., Chen, Y., Whitehead, E. H., & Weissman, J. S. (2014). Genome-Scale CRISPR-Mediated Control of Gene Repression and Activation. Cell, 159(3), 647–661.

[2]. Hart, T., Chandrashekhar, M., Aregger, M., Steinhart, Z., Brown, K. R., MacLeod, G., & Moffat, J. (2015). High-Resolution CRISPR Screens Reveal Fitness Genes and Genotype-Specific Cancer Liabilities. Cell, 163(6), 1515–1526.

[3]. Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., & Charpentier, E. (2012). A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity. Science, 337(6096), 816–821.

[4]. Komor, A. C., Kim, Y. B., Packer, M. S., Zuris, J. A., & Liu, D. R. (2016). Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature, 533(7603), 420–424.

[5]. Li, H., Shi, L., Zhang, K., Zhang, Y., Wang, X., & Wang, P. (2017). CRISPR/Cas9: A powerful tool for gene function study and disease modeling. Frontiers in Cell and Developmental Biology, 5, 98.

[6]. Qi, L. S., Larson, M. H., Gilbert, L. A., Doudna, J. A., Weissman, J. S., Arkin, A. P., & Lim, W. A. (2013). Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. Cell, 152(5), 1173–1183.
[7]. Shalem, O., Sanjana, N. E., Hartenian, E., Shi, X., Scott, D. A., Mikkelsen, T. S., & Zhang, F. (2014). Genome-scale CRISPR-Cas9 knockout screening in human cells. Science, 343(6166), 84–87.
[8]. Zhang, X., Zhang, Y., Wang, Z., & Wang, X. (2018). CRISPR/Cas9 genome editing for pharmacogenomics. Advanced Drug Delivery Reviews, 130, 66–75.
[9]. Doudna, J. A., & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR-Cas9. Science, 346(6213), 1258096.
[10]. Dominguez, A. A., Lim, W. A., & Qi, L. S. (2016). Beyond editing: Repurposing CRISPR–Cas9 for precision genome regulation and interrogation. Nature Reviews Molecular Cell Biology, 17(1), 5–15.
[11]. Barrangou, R., & Doudna, J. A. (2016). Applications of CRISPR technologies in research and beyond. Nature Biotechnology, 34(9), 933–941.
[12]. Tebas, P., Stein, D., Tang, W. W., Frank, I., Wang, S. Q., Lee, G., & Levine, B. L. (2014). Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. New England Journal of Medicine, 370(10), 901–910.
[13]. Ran, F. A., Hsu, P. D., Wright, J., Agarwala, V., Scott, D. A., & Zhang, F. (2013). Genome engineering using the CRISPR-Cas9 system. Nature Protocols, 8(11), 2281–2308.
[14]. Sanson, K. R., Hanna, R. E., Hegde, M., Donovan, K. F., Strand, C., Sullender, M. E., & Root, D. E. (2018). Optimized libraries for CRISPR-Cas9 genetic screens with multiple modalities. Nature Communications, 9(1), 1–15.