A Review on Advancement and Development in Drug Design

Emeka Henry, Obinwa[1]; Mariam Taiwo, Oloye-Akorede[1*]; Bessie Edikan, Tommy[1]; Chinaza Blessing, Obinwa[2]; Izzah Opeyemi, Quadri[3]

[1]Department of Chemistry, University of Medical Sciences, Ondo-City, P.M.B. 536, Ondo-State, Nigeria.

[2]College of Nursing, Philippines College of Health Sciences, Manila, Philippines.

[3]Department of Chemistry, University of Ilorin, Kwara State, Nigeria.

***Corresponding Author**

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ABSTRACT

Drug discovery is a complex, multi-disciplinary process to identify new therapeutic candidates for treating diseases. It begins with target identification and validation, pinpointing and confirming biological targets involved in disease. This is followed by hit identification, where compounds that interact with the target are found using high-throughput screening, computational methods, or fragment-based techniques. Lead optimization enhances these compounds' efficacy, selectivity, and pharmacokinetic properties. Preclinical testing assesses optimized leads' safety and biological activity in laboratory and animal studies. Successful candidates progress to clinical trials, conducted in phases to evaluate safety, efficacy, and side effects in humans. Upon successful clinical trials, drugs undergo regulatory review to ensure they are safe and effective for public use. Post-marketing surveillance monitors long-term safety and efficacy. Advances in genomics, proteomics, and bioinformatics have significantly improved drug discovery, highlighting its collaborative and interdisciplinary nature, crucial for developing new and effective therapies. This article explores recent advancements in drug discovery, highlighting innovative technologies such as artificial intelligence (AI), CRISPR gene editing, mRNA technology, targeted protein degradation, and organs-on-chips. Through specific case studies, the practical applications and successes of these advancements, providing insights into their impact on the drug development process.

Keywords: Review, mRNA technology, drug discovery, genomics, pharmacokinetics, bioinformatics, proteomics and clinical trials.

INTRODUCTION

The field of drug discovery has undergone significant transformation in recent years, driven by technological advancements and innovative approaches. Drug discovery is known as the process of finding chemical entities that can become therapeutic agents [1]. Drug design and discovery is a critical field within pharmaceutical sciences dedicated to the development of new therapeutic agents. This intricate process involves identifying and validating biological targets associated with diseases, discovering chemical compounds that can modulate these targets, and optimizing these compounds to create effective and safe medications [23]. The journey from initial target identification to a marketable drug involves multiple stages, including preclinical testing, clinical trials, and regulatory approval. Traditional methods, while effective, are often time-consuming and costly. Advances in technology, such as computational biology, genomics, and high-throughput screening, have revolutionized this field, making it more efficient and precise [8]. Drug design and discovery is a collaborative effort that integrates expertise from biology, chemistry, pharmacology, and medicine, aiming to address unmet medical needs and improve patient outcomes. Recent breakthroughs in Artificial Intelligence (AI), have significantly reduced the time and cost of identifying new drug candidates. For example, Insilico Medicine's AI identified a drug candidate for IPF in just 46 days. **CRISPR Gene Editing** based therapies for sickle cell disease and beta thalassemia have shown promising results in clinical trials, potentially offering cures for these

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genetic disorders [14]. **mRNA Technology**, the success of mRNA vaccines for COVID-19 has paved the way for mRNA-based therapies for other diseases, including cancer and genetic disorders. **Targeted Protein Degradation**: PROTACs developed by Arvinas have shown potential in selectively degrading disease-causing proteins, with ARV-110 in clinical trials for prostate cancer, and **Organs-on-Chips** technology provides a more accurate model for drug testing, reducing reliance on animal models and improving predictive accuracy. All these have revolutionized the landscape, offering faster, more efficient, and precise solutions [34]. Drug design entails the development of compounds that are structurally compatible with the molecular targets they interact with. This implies that a synthetic approach must already be in place or developed based on the inherent physicochemical properties of the compounds involved [6]. This article delves into these advancements, providing real-world examples and case studies to illustrate their impact.

Drug development process

The process of drug discovery involves identifying potential drug targets, designing and synthesizing molecules that interact with those targets, and testing their safety and efficacy in preclinical and clinical trials as well as reviewing by regulatory agencies. Drug development, from the initial discovery of a promising target to the final medication, is an expensive, lengthy, and incremental process [20].

1. Discovery and development
2. Preclinical research
3. Clinical research
4. Post-market review/ safety monitoring

Drug discovery and development

Target Identification

Target identification is a critical step in the drug design process. It involves identifying the molecular structures or biological pathways that are involved in a disease. These targets are typically proteins, genes, or RNA molecules that play a crucial role in the pathology of the disease. They include:

Target-based pharmacology: It involves identifying the drugs that are effective in treating a particular backward and then working backward to identify the molecular targets that they interact with [3].

Computational/bioinformatics: This involves using computational methods to analyze large datasets of genetic and biological information to identify potential drug targets [20].

Genetics: The identification of genes that are associated with a disease can provide clues to potential drug targets [15]. This can involve sequencing the genomes of affected individuals or studying genetic mutations that are linked to the disease.

High-throughput screening [28]: This involves testing large numbers of molecules or compounds to identify those that have a specific effect on the disease target.

Knowledge-based approaches: These rely on existing knowledge of the disease and its underlying mechanisms to identify potential drug targets.

Target Validation

Target validation is a crucial step in the drug development and discovery process. It involves confirming that a biological target—typically a protein, gene, or RNA molecule—is directly involved in a disease process and that modulating this target can have therapeutic benefits. Effective target validation ensures that drug discovery efforts are focused on the most promising targets, reducing the risk of failure in later stages. Moreover, some diseases are restricted to higher primates, whereas most mechanistic animal studies are carried out in rodents. Hence, not all indication-specific challenges can be addressed at this early stage of drug discovery [10].

Steps in Target Validation

Genetic Validation

1. **Gene Knockout/Knockdown Studies**: Using technologies like CRISPR/Cas9 or RNA interference (RNAi) to delete or reduce the expression of the target gene in cell lines or animal models. Observing the resulting phenotype helps determine the role of the gene in the disease [18].
2. **Overexpression Studies**: Increasing the expression of the target gene to assess its effects on disease progression.

Biochemical Validation

1. **Protein Function Studies**: Examine the biochemical activities of the target protein, such as enzyme activity, binding properties, and interaction with other molecules, to understand its role in the disease [30].
2. **Ligand Binding Assays**: Assessing the binding of potential drug molecules to the target protein to confirm that modulating this interaction can have therapeutic effects [12].

Cell-Based Validation

1. **Cellular Phenotype Assays**: Observing changes in cell behavior (e.g., proliferation, apoptosis, migration) upon modulation of the target using small molecules, antibodies, or genetic tools [14].
2. **Pathway Analysis**: Studying the impact of target modulation on cellular signaling pathways involved in the disease [4].

Animal Model Validation

1. **Disease Models**: Using animal models that replicate human disease conditions to study the effects of target modulation. Successful outcomes in these models provide strong evidence for target relevance [11].
2. **Pharmacological Studies**: Administering compounds that modulate the target in animal models to observe therapeutic effects and potential side effects.

Clinical Validation

1. **Biomarker Studies**: Identifying and validating biomarkers that correlate with target modulation and disease outcomes in clinical samples [24].
2. **Translational Research**: Integrating data from preclinical studies with clinical observations to confirm the target's role in human disease [16].

Lead Compound Identification

Researchers screen thousands of compounds to find potential drugs (lead compounds) that can interact with the target. This can be done through high-throughput screening, computational drug design, and other techniques. A lead is a synthetically or stable, feasible, and drug-like molecule active in both primary and secondary assays with acceptable specificity, affinity, and selectivity for the target receptor. This mostly requires the definition of the structure-activity relationship as well as the determination of synthetic feasibility and preliminary evidence of in vivo efficacy and target engagement [26].

Optimization of Lead

The Leads being identified are subjected to optimization work. The step is believed to be essential in contributing to the drug discovery process. In this stage, leads are modified to provide “best” analogs displaying improved potency, efficacy, pharmacokinetic and pharmacodynamics properties. The changes are accomplished by chemical changes chosen by structure-activity analysis. If a target structure is known, the structure-based design could also be employed in introducing the changes. As this process involves simultaneous optimization of multiple parameters, it is quite time-consuming and a costly step. In the entire drug discovery process lead optimization step is thought to be a rate-limiting step [19].

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Preclinical research

Preclinical studies are in vivo and in vitro studies that usually occur in animals. These studies are conducted initially in animals without the disease of interest to test toxicology, then later in animal models of the disease that allow for assessment of disease-modifying effects. The purpose of this research is to obtain approval from FDA and other regulatory agencies for an IND that will in turn allow for subsequent research in human subjects.

In Vitro Studies: In Vitro means ‘‘in the glass’’ as these studies are conducted in test tubes or cell cultures to determine the biological activity and toxicity of lead compounds. The studies are conducted using components of an organism that have been isolated from their usual biological surroundings, such as microorganisms, cells, or biological molecules [13]. These studies are used to assess the biological activity of drug candidates, understand the mechanism of action, evaluate cytotoxicity and potential side effects as well as screen for the most promising compounds before advancing to in vivo studies.

In Vivo Studies: Animal studies are conducted to evaluate the pharmacokinetics (how the drug is absorbed, distributed, metabolized, and excreted) and pharmacodynamics (the effects of the drug on the body) of the compounds. Toxicity studies are also performed to identify potential side effects. Successful preclinical development integrates data from both in vitro and in vivo studies to create a comprehensive understanding of a drug candidate. In vitro studies are often used for initial screening and mechanistic studies, while in vivo studies provide critical information on the drug's overall biological effects. The combination of these approaches helps to build a robust body of evidence supporting the safety and efficacy of a drug candidate before advancing to clinical trials [1].

Failure to follow FDA guidelines for conducting preclinical evaluations may result in an IND application being rejected, and lead to repeating the test, potentially leading to significant delays in drug development. These FDA guidelines include meticulous quality control, oversight, and comprehensive reporting of results. It is also worth noting that these preclinical studies may suggest a potential role for the compound in animal diseases and thus a veterinary medicine application for the compound. This offers important benefits, including the potential to gather additional safety data and faster access to the veterinary market as compared to human applications, which can lead to revenue from sales in the Veterinary medicine market that may support further development in humans [17].

Clinical Research

Clinical research is a critical phase in the drug discovery and development process, which involves the study of drug candidates in human subjects to evaluate their safety and overall therapeutic value. Through carefully designed and ethically conducted clinical trials, researchers can ensure that new drugs are both effective and safe for public use, ultimately contributing to advancements in medical treatment and patient care. According to WHO, a clinical research trial is a research study that assigns humans to one or more health-related interventions to assess the effects on health outcomes. Clinical research trials have been performed when satisfactory information regarding the quality of non-clinical safety is available which has been approved by the governed authority of the drug or device. Initially, the trials have been known to depend upon the product quality in conjunction with the various stages involved in the development of the product. Initially, the investigators select the volunteers or patients in small quantities and conduct the clinical trials. Once, positive data have been collected regarding safety and efficacy, the patient number is increased [22].

It is divided into several stages, known as clinical trials which are:

Phase 0

Phase 0 trials represent a pivotal innovation in the field of clinical research, introduced by the U.S. Food and Drug Administration (FDA) in its 2006 Guidance on Exploratory Investigational New Drug (IND) Studies. These trials are designed to expedite the development pipeline of promising pharmaceuticals by determining, at an early stage, whether a drug or agent behaves in human subjects as expected based on preclinical studies.

A key aspect of Phase 0 trials is the administration of single sub-therapeutic doses of the study drug to a small cohort of subjects. This unique approach allows researchers to collect preliminary data on the pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug interacts with the body) of the agent. Through these trials, developers can make more informed decisions about whether to proceed with more extensive and costly phases of clinical testing. [21].

Phase 1 Clinical Studies

Phase 1 clinical trials represent the initial foray of a new drug into human subjects, marking a crucial step in the drug development process. These studies predominantly focus on assessing the short-term toxicity of the drug. The primary objective is to determine the drug's safety profile and to identify the maximum tolerated dose (MTD). This helps ensure that subsequent trials can be conducted with minimal risk to participants. Short-term toxicity is evaluated through a series of carefully monitored dose escalations, where small groups of participants receive increasing doses of the drug. Physicians meticulously observe the outcomes to detect adverse effects, gauging the body's immediate response to the medication. This phase is critical not only for establishing safety but also for providing insight into the drug's pharmacokinetics and pharmacodynamics. [9].

The main aim of a phase I trial investigating cytotoxic agents is to establish the maximum tolerated dose and describe the dose-limiting toxicities by recommending a safe dosage range for phase II trials. The total probability of response is up to 6%. Moreover, the responses (mainly partial responses) are observed within the range from 80 to 120% of the recommended dose in later trials. This low response rate is far from patient expectancy: over 85% of patients participating in phase I studies expect at least a stabilization of their disease. Most cytotoxic phase I protocols require a very minimal life expectancy estimated at 3 months, which is a minimum period of observation for the evaluation of side effects. This 3-month period is necessary to differentiate the morbidity caused by the advanced disease from that caused by the new cytotoxic agent. However, there are no clear or reliable guidelines for life expectancy among this population [27].

Phase II

Once the initial safety of the drug has been established, the drug will undergo a phase II trial. The main purpose of a phase II trial is to investigate the drug's short-term safety and therapeutic effectiveness in patients with the disease or condition that the drug is intended to treat. The patients are given the different drug dosages found to be safe in the phase I trial, allowing the drug’s efficacy and adverse effects to be compared between different dosages. This phase is critical for identifying the optimal dose that balances effectiveness and safety. When the efficacy and safety of the drug have been demonstrated in patients with the disease or condition, the drug will proceed to a phase III trial. Phase III trials involve a larger group of patients and aim to confirm the drug's efficacy, monitor side effects, and collect information that will allow the drug to be used safely. Success in phase III is crucial for the drug to be considered for approval by regulatory authorities [25].

Phase III

Phase III clinical trials serve as the gold standard for evaluating the efficacy and safety of an experimental therapy in comparison to standard treatment. The first critical step in planning such a trial is defining the statistical hypothesis, generally positing that the new therapy will offer superior efficacy without introducing significant risks. Once the hypothesis is established, a pre-determined number of patients from the target population are selected and randomized to receive either the experimental therapy or the standard treatment. This randomization aims to eliminate bias and ensure that any observed differences can be attributed to the therapies being tested. Patients are managed and monitored following a detailed protocol, which outlines the endpoints of interest. The primary endpoint is particularly crucial, as it is designed to capture a measurable clinical benefit of the experimental therapy over the standard one. An independent data monitoring committee oversees the trial's progress. This committee has the authority to recommend stopping the trial early if interim results indicate significant findings, whether they suggest clear benefit, harm, or futility. The outcomes of the trial can reveal whether the experimental therapy offers advantages over the standard treatment, either broadly across all patients or within specific subgroups. This robust methodology is crucial for ensuring that new therapies brought to market are both effective and safe for the population they intend to serve [7].

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Phase IV

Pharmacovigilance is a vital component of drug safety and efficacy, particularly in Europe. It involves the continuous monitoring and evaluation of pharmaceuticals after they have been approved for public use. This process is mandatory for all pharmaceutical companies that have introduced products to the market. These companies are obliged to compile and submit periodic safety update reports (PSURs) on their new drugs post-approval. These post-marketing or safety surveillance trials, also known as phase IV clinical trials, play an essential role in identifying any adverse effects that may not have been apparent during the earlier phases of clinical testing. Phase IV trials provide a broader data pool because the drug is now being used by a larger, more diverse population over a more extended period. This phase of testing is crucial, as it ensures that any harmful effects, which might be rare or develop only after long-term use, are identified and addressed.

The significance of pharmacovigilance is underscored by notable cases where post-marketing surveillance led to the withdrawal of drugs from the market due to safety concerns. For example, the anti-inflammatory drug rofecoxib (marketed as Vioxx) and the cholesterol-lowering agent cerivastatin (known as Lipobay in Europe and Baycol in the United States) were withdrawn after being associated with severe, sometimes fatal, adverse effects. These examples highlight the importance of ongoing pharmacovigilance in protecting public health. By continually monitoring the safety of marketed drugs, regulatory authorities and pharmaceutical companies can take swift action to mitigate risks, ensuring that the benefits of a drug outweigh its potential harms. This continuous assessment not only safeguards patients but also maintains trust in pharmaceutical products and healthcare systems [29].

Phase V

Translational research has emerged as a critical term in the literature to encapsulate the application of community-based research toward evaluating new clinical treatments within extensive public health practices. This approach aims to bridge the gap between laboratory discoveries and real-world implementation, ensuring that scientific advancements translate into tangible health benefits for the general population. Traditionally, Phase V trials, often termed "field research," have been instrumental in this context. These trials are meticulously designed to test the generalizability and effectiveness of newly developed mechanisms or treatments across large, diverse populations [2]. This phase is pivotal as it moves beyond the controlled conditions of earlier clinical trials to assess the real-world impact, ensuring that new treatments are not only efficacious in theory but also practical and beneficial in everyday public health settings. By focusing on large sample sizes and diverse demographics, translational research and Phase V trials together ensure that medical innovations are accessible, effective, and equitable for all segments of the population [2].

Post-Marketing Surveillance

After a drug is approved and marketed, it continues to be monitored for long-term safety and effectiveness. This phase involves pharmacovigilance activities, additional clinical trials, and studies to explore new therapeutic uses or formulations.

Challenges in Drug Development

The drug development process is indeed complex and fraught with numerous challenges [11, 12].

1. **Length and Cost**: Developing a new drug can take between 8-12 years and cost over £1 billion. This includes extensive research, clinical trials, and regulatory approvals.

2. **Complexity and Uncertainty**: The process is highly complex and uncertain. Only a small fraction of compounds that enter pre-clinical trials make it to human testing, and even fewer get approved.

3. **Unknown Pathophysiology**: For many diseases, especially neurological disorders, the underlying biological mechanisms are not fully understood, making it difficult to identify suitable drug targets.

4. **Limitations of Animal Models**: Animal models often do not accurately replicate human diseases,

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leading to potential failures in later stages of development.

5. **Heterogeneity of Patient Populations**: The genetic and biological diversity among patients means that a one-size-fits-all approach is often ineffective.

6. **Regulatory and Financial Pressures**: Navigating regulatory requirements and managing financial risks are significant challenges. Regulatory bodies have stringent requirements that must be met, which can be time-consuming and costly.

7. Diagnosing and monitoring new drugs' effectiveness.

8. **Business and Management Skills**: Effective drug development requires scientific expertise and strong business and management skills to navigate the industrial and regulatory landscape.

Solutions to the Challenges

The challenges in drug development require a multifaceted approach they are: [11, 12]

1. **Advanced Technologies:** Utilizing AI and machine learning can help in predicting drug behavior, optimizing clinical trial designs, and identifying potential drug candidates more efficiently.

2. **Better Understanding of Diseases:** Investing in fundamental research to understand the pathophysiology of diseases can lead to the identification of more effective drug targets.

3. **Improved Animal Models:** Developing more accurate animal models that better mimic human diseases can improve the predictive power of pre-clinical studies.

4. **Personalized Medicine**: Tailoring treatments to individual genetic profiles can increase the efficacy of drugs and reduce adverse effects.

5. **Biomarker Development:** Identifying and validating biomarkers can enhance the diagnosis and monitoring of diseases, as well as the assessment of drug efficacy.

6. **Regulatory Innovations:** Streamlining regulatory processes and adopting adaptive trial designs can reduce the time and cost of bringing new drugs to market.

7. **Collaborative Efforts:** Encouraging collaboration between academia, industry, and regulatory bodies can facilitate the sharing of knowledge and resources.

8. **Financial Incentives**: Providing financial incentives, such as grants and tax credits, can support research and development, especially for rare diseases and conditions with high unmet needs.

9. **Enhanced Data Sharing:** Promoting open data initiatives can help researchers access valuable information, accelerating the discovery and development of new drugs.

10. **Training and Education:** Investing in the training of scientists and professionals in both scientific and business aspects of drug development can improve the overall efficiency and success rates.

These solutions, when implemented effectively, can significantly mitigate the challenges faced in the drug development process.

Innovations in Drug Development

1. **Biologics**: Therapeutic proteins, antibodies, and vaccines are an expanding area in drug development, offering new treatment options for various diseases.

2. **Personalized Medicine**: Tailoring treatments based on individual genetic profiles to increase efficacy

and reduce adverse effects.

3. **Artificial Intelligence and Machine Learning**: These technologies are being used to predict drug interactions, identify potential compounds, and optimize clinical trial designs.

4. **CRISPR and Gene Editing**: Advanced gene-editing techniques are opening new avenues for treating genetic disorders.

Novel Concepts and Specific Advancements [14, 15, 33, 34]

1. **Quantum Computing in Drug Discovery**: Quantum computing leverages the principles of quantum mechanics to perform complex calculations at unprecedented speeds. Companies like IBM and Google are exploring quantum computing to simulate molecular interactions and predict drug efficacy more accurately. This technology can potentially revolutionize the drug discovery process by solving problems currently intractable with classical computers.

2. **AI-Driven Multi-Omics Integration**: Multi-omics involves the integration of various omics data (genomics, proteomics, metabolomics, etc.) to provide a comprehensive understanding of biological systems. AI algorithms are being developed to integrate and analyze multi-omics data, leading to the identification of novel drug targets and biomarkers. This approach enhances personalized medicine by tailoring treatments based on an individual's unique biological profile.

3. **Synthetic Biology and Bioengineering**: Synthetic biology involves designing and constructing new biological parts, devices, and systems. Researchers are using synthetic biology to engineer microorganisms that can produce complex drugs, such as antibiotics and anticancer agents, more efficiently and sustainably. This approach can reduce production costs and improve drug accessibility.

4. **De Novo Drug Design Using AI**: De novo drug design involves creating new drug molecules from scratch using computational methods. AI-driven platforms, such as those developed by companies like Exscientia and Benevolent AI, are capable of designing novel drug candidates with desired properties. These platforms use deep learning to predict the biological activity and optimize the chemical structure of new compounds.

5. **Organoid Technology**: Organoids are miniaturized and simplified versions of organs produced in vitro from stem cells. Organoid technology is being used to create patient-specific models for drug testing, allowing for more accurate predictions of drug responses and reducing the need for animal testing. This technology is particularly useful in cancer research, where organoids can mimic the tumor microenvironment.

6. **Nanomedicine**: Nanomedicine involves the use of nanotechnology for the diagnosis, treatment, and prevention of diseases. Recent developments in nanomedicine include the creation of nanoparticles that can deliver drugs directly to cancer cells, minimizing side effects and improving therapeutic outcomes. Nanoparticles can also be engineered to cross biological barriers, such as the blood-brain barrier, to treat neurological disorders.

CONCLUSION

The field of drug development and design has seen remarkable advancements, driven by technological innovations and a deeper understanding of biological systems. Despite the inherent challenges, such as high costs, lengthy timelines, and complex regulatory landscapes, the industry continues to evolve, offering new hope for effective treatments. It is a complex and multifaceted process that involves identifying potential drug targets, designing and synthesizing molecules that interact with those targets, and testing their safety and efficacy in preclinical and clinical trials. Through carefully designed and ethically conducted clinical trials, researchers can ensure that new drugs are both effective and safe for public use, ultimately contributing to advancements in medical treatment and patient care. The advancements in drug discovery technologies have

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significantly accelerated the development process, improved the precision of treatments, and opened new therapeutic avenues. AI, CRISPR, mRNA technology, targeted protein degradation, and organs-on-chips represent the forefront of innovation, offering hope for more effective and personalized treatments. Continued research and development in these areas are essential to further enhance drug discovery and address unmet medical needs.

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