REVIEWING SEVERAL STRATEGIES TO INCREASE THE SUCCESS OF DRUG RESEARCH AND DEVELOPMENT INITIATIVES

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Abstract

New therapeutic drugs have become more expensive and time-consuming during the last 30 years. Despite pharmaceutical companies spending in research facilities and scientific tools, efforts to increase compound flow along the drug development pipeline have mainly failed.

Non-systematic literature research identified pharmaceutical R&D success methods. The review discusses genomes and proteomics, medication repurposing and repositioning, collaborative research, underdeveloped therapeutic domains, outsourcing strategy, pharmaceutical modeling, and artificial intelligence. This method yielded the following medications. Genomics and proteomics have found numerous therapeutic targets and improved target identification and validation, reducing efficacy-related drug attrition. Phenotypic and target-based screening systems may allow serendipitous and rational drug discovery. Sharing resources and ideas decreases early drug development overhead expenses. Innovative drug targets in neglected therapeutic areas are encouraged by drug regulators.

Contract research organizations let pharma businesses focus on their strengths while outsourcing. Current and novel pharmacological modeling and artificial intelligence software and technologies allow in silico computation for more efficient computer-aided drug creation. These strategies may enhance pharmaceutical research and innovation if utilized wisely.

Keywords: *Target-based screening, Artificial intelligence, Proteomics, Phenotypic, Repositioning, Repurposing*

Introduction

Diseases always battled humans. Historical plague control items. Biology and organic chemistry enhanced drug discovery. The former helped scientists comprehend pathophysiology and accurately identify metabolic derangements driving disease phenotypes. Organic chemistry synthesized and semi-synthesized novel medicinal molecules for present and future medical needs [2]. British bacteriologist Alexander Fleming accidentally discovered penicillins in 1928. Penicillin began medication development. Drugs boosted life and longevity [3].

Drug development fell in the 1980s [4]. Less than one in 10,000 potential therapeutic molecules that begin drug development reach the clinic [5]. We may have exhausted the low-hanging fruit, making innovative drugs harder to sell. Increased efficacy, potency, toxicity, ease of administration, and cost [6]. Combinatorial chemistry and high-tech platforms to identify lead compounds may yield very lipophilic (greasy) molecules with poor water solubility and pharmacokinetics [7]. Discovering and developing new medicinal compounds now costs US$2.6 billion per molecule due to these factors. Mergers and acquisitions have limited the number of pharmaceutical companies willing to take financial risks [8].

Certain diseases continue to plague governments and civilizations, but most can be treated. Unmet medical demands are significant for neoplastic diseases, diabetes, Alzheimer's disease, immunological disorders, HIV-AIDS,

neglected tropical diseases (NTDs), and rare diseases [9]. These illnesses need new treatment ingredients.

Identifying a disease or disease area with an unmet medical need is the first step in drug development. Elucidating the illness's molecular foundations and establishing animal disease models and test platforms are pre-discovery steps. Following that, therapeutic objectives are chosen. In the hit-to-lead discovery phase, the drug development team begins with initial hit compounds and alters them to boost potency, reduce adverse effects, and improve physicochemical features. Following pre-clinical studies and drug development, a candidate medication becomes a clinically effective medical product with demonstrated effectiveness, safety, dose, and tolerability [11].

Strategies for improved success in the drug discovery and development process Key approaches

Pharmaceutical R&D programs have used several strategic methods to speed up medication discovery and development. They include genomics and proteomics, phenotypic and target-based screening methods, repurposing and repositioning pharmacological substances, collaborative research, underserved therapeutic areas, outsourcing, pharmaceutical modeling, and artificial intelligence.

Exploitation of genomics and proteomics

Genetic or molecular abnormalities predominate [12, 13]. Single gene mutations cause sickle cell, cystic fibrosis, muscular dystrophy, and Huntington illnesses [14]. Gene mutations and lifestyle variables promote diabetes and cardiovascular disease [12]. Drug discovery identifies genes as disease, disease-modifying, and druggable [15]. Disease-causing gene mutations [16]. Functional proteins from disease-modifying genes cause and progress illness. Druggable genes generate proteins with drug-recognition domains [17].

Target-based pharmaceutical development requires meticulous target identification and confirmation to show disease phenotypic requirement. Effectiveness concerns cause 52% of clinical trial drug failures, preventing downstream attrition. Figure 2 shows attrition causes [18, 19]. Genomic analysis may be utilized to repurpose existing drugs [23]. Genomics finds druggable targets.

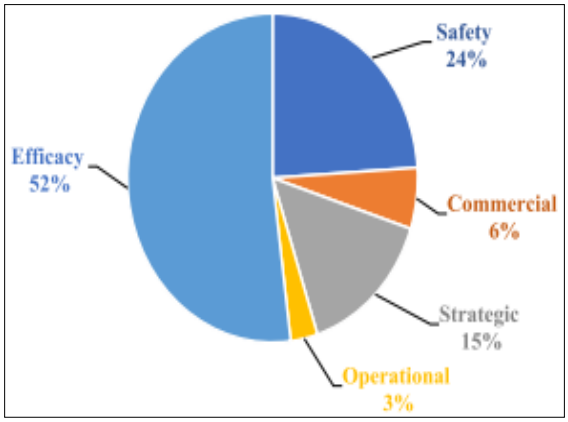

Fig. 2 Causes of attrition in drug discovery and development

genes [17, 24]. Genomic target validation has extended using antisense technology, siRNA that replicates natural RNA interference (RNAi), and transgenic animal models [25].

Genomics extends beyond target selection and validation. Pharma R&D developments imply genetics may be used to recruit clinical trial participants, favoring those most likely to benefit from the intervention. This ensures that the drug's effect will be evident if it treats the target ailment and absent if not. Hence, therapy explains the outcome. Genomics predicts molecule-specific toxicity [22].

Academics and practitioners are using pharmaco-genomics to improve medication discovery and development [22].

The 2002 human genome description provided a wealth of potential medicinal targets. DNA, RNA, GPCRs, enzymes, and ion channels target. [27]. Extensive genomic research is predicted to assist drug development [28].

Popular drug research uses proteomics [29]. Proteomics discovers, classifies, and measures cellular proteins to understand disease development and chemotherapeutic manipulation [25]. Drug development for antineoplastics, neurological, cardiovascular, and rare illnesses using proteomics [30]. Gel electrophoresis, MS, and yeast hybrid systems are used in proteomics [31]. New drug targets and genes may be found using these strategies.

Complementary phenotypic and target-based screening platforms

Efficacy investigations include phenotypic (whole-cell) and target-based (biochemical) screening. Phenotypic screenings first reveal substances that may offer the needed pharmacological effect without understanding the molecular mechanism of action. Phenotypic endpoints drive them empirically. Phenotypic drug screening delivers more information and demonstrates therapeutic relevance earlier in drug development. The strategy is more physiologically relevant in biological systems that mimic the genuine physiological environment because it acknowledges that pharmacological effects are induced by numerous sources [33, 34]. It facilitates serendipitous drug discovery [32, 35]. Yet, target-based screening is hypothesis-driven, rigorous, and rational. It entails discovering and isolating a biological target that controls a desired pharmacological activity. It employs HTS-friendly molecular and biological methods [36].

Molecular biology and genomics replaced phenotypic screening with target-based screening [37]. First-in-class compound discovery has declined due to target-based drug discovery [34]. Phenotypic drug discovery has generated more first-in-class drugs than target-based screening, according to US-FDA data [38]. 78 of 113 first-in-class drugs registered between 1999 and 2013 were found using target-based screening [39]. When using whole animals, phenotypic tests can't screen and are hard to use to represent diseases like Alzheimer's [40]. Several studies have demonstrated that animal models cannot predict human therapy outcomes [41].

For 30 years, molecular screening has focused on target-based drug discovery [33, 42]. HTS can screen a large chemical library because to improvements in protein cloning. Due to its great screening capacity, target-based platform has become the standard drug discovery method as businesses strive to bring novel compounds to market [36]. Target-based medication development begins with disease pathophysiology and biochemical pathway discovery.

Target-based drug discovery shows how drugs work. Phenotypic drug discovery yields first-in-class molecules, whereas target-based drug discovery yields best follower drugs [38]. The rational, methodical approach produces more selective, potent molecules with better pharmacokinetic and toxicological properties. Target-based drug discovery is quicker, simpler, and can disclose the mechanism of action. Computational

modeling, molecular biology, combinatorial chemistry, proteomics, and genomics are also possibilities.

Since pharmacological effects result from complex interactions in intact physiological systems, phenotypic drug discovery better predicts human disease therapy than target-based methods. Thus, pharmaceuticals must be rationally developed to improve toxicological profiles and give well-defined mechanisms of action of the pharmacologically active substances to improve pharmacokinetics and pharmacodynamics. Hence, using both methods together will increase drug discovery efficiency, with the phenotypic technique providing first-in-class molecules with proven efficacy early on. Target-based medication development will employ active molecule-target chemical interactions to improve follower molecules.

Repurposing and repositioning of existing drug molecules

Medications developed for one reason may help other therapies. Drug repurposing may test these molecules for new diseases without structural changes [46]. Drug repositioning changes the chemical structure to boost a desired side effect and decrease the main effect [47]. Both strategies may resurrect abandoned molecules and expand therapeutic usage of current drugs. Table 2 highlights drug repurposing and repositioning achievements. Due to dose-limiting gastrointestinal adverse effects, 1980s anticancer drug miltefosine was discontinued. Effectively refocused as antileishmanial [49]. Its latest anti-infective use is granulomatous amoebic encephalitis [50].

Sildenafil is another excellent drug repurposing. After treating patent ductus arteriosus-related pulmonary arterial hypertension, sildenafil and other phosphodiesterase type 5 inhibitors became popular for treating erectile dysfunction [51, 52]. Systematic structural changes raised hypoglycemia and lowered antibacterial activity in the R&D of antidiabetic sulfonylureas from sulfonamide antibiotics [53]. Using pharmacokinetics, toxicological, and other data, drug repurposing and repositioning saves time and money [8, 46]. Protozoan and helminthic medication repurposing is feasible [54]. Repurposing/repositioning may save many experimental drugs [54]. Experimental screening and in silico approaches repurpose or reposition drugs [47].

Table 1 Advantages and disadvantages of phenotypic and target-based drug discovery approaches

Advantages	Disadvantages
Phenotypic drug discovery	
Allows establishment of the therapeutic relevance early in the drug discovery process	Difficulties in modeling some diseases
Does not require knowledge of the mechanism of action	Policy changes considering animal rights activism
Enhances the chances of serendipitous discoveries	Does not allow utilization of high technology platforms; low screening capacity
High chances of discovering first in c class molecules	Complicated analysis due to confounding factors
The process closely simulates the normal physiological environment	Rational drug design is not applicable with this model
Target-based drug discovery	
Allows elucidation of the mechanism of action	Observed responses may not be physiologically relevant in the natural environment
Very high chances of developing best in class molecules	Requires knowledge of the underlying mechanism of action a priori
Allows screening of vast chemical libraries; high screening capacity	Chances of serendipitous drug discovery are minimized
Allows utilization of high technology platforms	

Collaborative research

Pharmaceutical corporations naturally fight to offer new blockbuster medications. Early market participants profit. Pioneers may develop brand awareness and physician and patient loyalty before competition [55]. Early entrants may enhance items and set pricing. Pharma companies regularly create chemicals with similar medicinal goals. Due to substantial

pharmaceutical R&D funding, recurrent research wastes resources that may be utilized for other diseases with unmet medical needs. Collaborations have helped pharma R&D. Pharma-academia collaboration, precompetitive research, and PPP models [56].

Precompetitive research by pharmaceutical, biotechnology, and academic drug development organizations helps find and innovate drugs.

Table 2 Examples of successfully repurposed drugs

Drug	Original indication	Repurposed indication
Zidovudine	Anticancer	Antiretroviral
Miltefosine	Anticancer	Leishmaniasis
Sildenafil	Pulmonary arterial hypertension	Erectile dysfunction
Thalidomide	Sedative	Erythema nodosum and multiple myeloma
Sirolimus	Immunosuppressant	Lymphoproliferative syndrome
Bupropion	Antidepressant	Smoking cessation aid
Rituximab	Anticancer	Rheumatoid arthritis
Raloxifene	Osteoporosis	Breast cancer
Gabapentin	Antiseizure	Post herpetic neuralgia
Eflornithine	Cancer	Hirsutism
Minoxidil	Antihypertensive	Alopecia
Pramipexole	Parkinson's disease	Restless leg syndrome

Precompetitive research confirms a treatment strategy before drug discovery and development. Target discovery, validation, chemical library sharing, biomarker and assay creation, and precompetitive cooperation minimize research costs by sharing resources and information, enhance efficiency by concentrating on core competences, and stimulate scientific innovation [57]. Video-conferenced virtual universities monitor precompetitive collaborative development. Precompetitive collaborations Biomarkers Consortium, Innovative Medicine Initiative, and TranSMART [59]. TransMART holds government, academic, and patient advocacy group clinical trial and basic research data [60, 61]. In 2011, the US-FDA established drug registration criteria to highlight the advantages of pre-competitive collaboration [62].

Under-served therapeutic fields

A company must plan drug research before commencing. Therapeutic molecule market entry economics are crucial. To keep the discovery industry viable and support new drugs, each drug development candidate must have an acceptable return on investment. Hence, most pharmaceutical R&D is concentrated on high-return therapeutic areas including cancer, immunotherapy, endocrinology, neurology, and cardiology [41]. NTDs and rare diseases, which have minimal financial rewards, are overlooked, hence new discoveries are rare [70]. Rare genetic diseases have few patients and minimal economic potential. Vector-borne NTDs harm billions in resource-poor countries. Pharma businesses may lose money because these folks have little purchasing power [71].

NTDs and uncommon diseases may provide novel drug targets for more profitable diseases. Orphan drugs may safeguard firms against blockbuster patent expirations [73]. Drug companies may explore [74].

Outsourcing strategies

Outsourcing involves contracting out services formerly conducted in-house or to gain additional skills. Outsourcing drug development may improve efficiency. Target identification, validation, disease model construction, lead discovery and optimization, pre-formulation research, and individual or full clinical trials might be outsourced [76]. CROs may help pharmaceutical companies focus on their strengths.

Outsourcing to specialists speeds up development and saves money. CROs outperform pharmaceutical companies in clinical trials [77]. Outsourcing medication

research and development cuts costs, boosts efficiency, and optimizes resource allocation [78]. Competent partners and careful project implementation maximize benefits [79]. Controls are needed to ensure contracted businesses follow the ethical guideline during studies [8].

Pharma AI modeling In silico models estimate drug molecule pharmacokinetics and pharmacodynamics [80]. Virtual screening, which replicates drug-receptor binding processes, has considerably increased drug discovery efficiency. CADD concentrates in vitro validation screens. Second, the CADD may assist the medicinal chemistry team increase receptor affinity or DMPK properties including absorption, distribution, metabolism, excretion, and toxicity (ADMET). Lastly, the CADD facilitates rational drug design by "growing" initial molecules one functional group at a time on the target site (de novo drug design) or by assembling fragments into distinct compounds (fragment-based drug design) [81]. CADD employs ligand- and target-based virtual screening to exclude compounds with poor physicochemical and toxicological characteristics and select those with the desired activity.

Next, quantitative-structure activity relationship (QSAR) models relate structural and physicochemical properties of a homologous sequence to biological activity. A mathematical model predicts test substance properties by reducing known compounds' chemical structures to molecular descriptors. The model picks active molecular descriptors [82]. Target-based virtual screening employs computer models to analyze compound docking against the target's three-dimensional structure (X-ray crystal structure or homology model) [83–85]. Each test chemical is placed on the binding site and graded for binding affinity. In vitro production and evaluation of top-scoring compounds [86]. These models may aid drug development with targeted screening. To avoid expensive late-stage failures, problematic substances are detected early in therapeutic development. Combining ligand-based and target-based virtual screening increases results [32, 87].

Modeling and simulation are used in clinical drug development [88]. Modeling relies on empirical patient data polynomials. To improve efficiency, quality, and cost, bio-simulation may drive clinical trial design, planning, execution, and evaluation. In clinical trials and in specific populations like children, geriatrics, pregnant women, and others with restricted physiological circumstances that impact drug disposal, pharmacodynamic and pharmacokinetic models predict optimal dosage levels. Clinical studies are quicker and cheaper using modeling [89, 90].

AI is used more in drug development. Reliable prediction models need large chemical and biological information. AI can analyze billions of potential molecules for hit detection, prioritize offered alternatives, and validate biological targets, according to scientists. In late drug development, it may help lead optimization and clinical trial design. Hence, strategic AI adoption may considerably accelerate R&D efforts to generate creative, effective, and safe drugs to meet unmet clinical needs [92]. To cure complex disorders, generative deep learning networks may propose wholly novel substances with the right physical and biological properties. They can also optimize compounds. To identify lead

molecules with excellent physicochemical, biological, and pharmacokinetic features, AI uses machine learning to multi-objectively optimize lead molecules [93].

Conclusion

Rising drug development costs have not improved medicine delivery. Instead, fewer drugs are being developed. Overreliance on high-tech platforms, demanding drug registration and approval requirements for innovative drugs, and the depletion of obvious and easy-to-reach therapeutic targets necessitating study of increasingly sophisticated biological systems are the primary drivers of productivity loss.

Genomes and proteomics can now discover and verify pharmaceutical targets. Target identification and validation will reduce over 50% of drug failures owing to poor effectiveness. Phenotypic and target-based drug development may find first-in-class compounds and safer, more effective, more potent best-in-class following molecules. Encouraging research into rare and neglected diseases would safeguard corporations with patent-cliffed blockbuster products. Computer improvements will assist choose successful customized displays. Pharmaceutical modeling and AI will improve medication discovery and development. Well-implemented outsourcing allows enterprises to focus on their core competencies while delegating other development processes to CRO professionals, speeding discovery and lowering overhead.

Abbreviations

ADMET: Absorption, distribution, metabolism, elimination, and toxicity; Intelligence; Acquired immunodeficiency syndrome (AIDS); Computer-aided drug design; ' Drug metabolism and pharmacokinetics; Deoxyribonucleic acid; G protein-coupled receptors (GCPRs): US-FDA; GlaxoSmithKline; HTS: High throughput screening; Mass spectrometry; Public-private partnerships; QSAR: Quantitative- structure activity relationship; R&D: RNAi: RNA interference; RNA interference; siRNA. TDR: Tropical Disease Research and Training Program; WHO: WHO

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