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How to rekindle drug discovery process through integrative therapeutic targeting?

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1. Introduction

The rate of clinical failures of drug candidates during Phase I is greater than 90%, based on 9985 clinical and regulatory phase transitions recorded and analyzed from 7455 development programs, across 1103 companies in the Biomedtracker database from 2006 to 2015 [1]. This dismal success rate is less than a chance encounter, and the statistic becomes far worse if you take into account the drug targets culled from the human genome sequencing efforts. The consequences of clinical candidate failures are many, notwithstanding the astronomical developmental costs incurred, precipitous decline in share value, and workforce attrition. The root cause has most often been linked to the Phase II Valley of Death, but almost 30% of the clinical failures have clearly been due to lack of efficacy. One of the main reasons for limited therapeutic efficacy of drug leads is partial understanding of the disease pathophysiology, overall deficiency in developing therapeutics targeting overlapping dysregulated pathways, and choosing therapeutically irrelevant drug targets. Linking a particular disease with cellular biology, deciphering the pathways involved, associating the genes participating in these pathways, pin-pointing the critical genes involved, and eventually leading to the identification of a druggable therapeutic target require a multipronged, highly integrated, and concerted efforts by biology and medicinal chemistry. Developing drugs has never been easy; with most of the low hanging fruits already plucked, a paradigm shift involving a truly holistic, yet disruptive, approach is paramount in transforming the high stakes, cataclysmic game of chance from precipice to a

Declaration of interest

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predictable and successful outcome in rekindling drug discovery process through integrative therapeutic targeting.

2. Disruptive, yet integrated, approaches

2.1. Intellectual property − tesla model

Disruption − the force that both fuels and rises out of innovation − is key in reaching the next frontier in pharmaceutical innovation. A case in point is intellectual property rights through issued patents dampen innovation. The original rationale for granting patents was to encourage inventors to share their inventions, not just to reward inventors with monopoly profits. A certain amount of intellectual property law is plainly necessary to achieve this. Most patents are now as much about defending monopoly and deterring rivals as about sharing ideas. This discourages innovation! However hard and bitter it may be, the pharmaceutical industry needs to consider adapting the example set by Elon Musk, CEO and Chief Architect of Tesla Motors, of *implementing and practicing an 'open source' philosophy to Tesla's large patent portfolio and that Tesla wouldn't pursue any legal action against anyone using them in good faith.* It is high time for the pharmaceutical industry to embrace, metaphorically speaking, a community-driven 'WikiPharma,' a Wikipedia-or 'Waze-type shared knowledge,' openly accessible innovation model to harvest data and create a crowd-sourced path toward a safer and faster road to the discovery and development of life-saving medicines. One potential way would be to utilize a self-curated Wikipedia-like contribution which has some data entry standards employed to make the data easily searchable with respect to field, technology used and results portrayed. Pharmaceutical industry ought to give serious consideration for such a game-changing concept [2–4].

2.2. Plethora of innovative approaches

Open innovation platforms and academic research in early discovery have unraveled numerous drug targets in cancer, metabolic, neurological, and infectious diseases [4]. Academic programs also contributed to inclusion of unconventional chemical scaffolds and design new routes of chemical synthesis and development of *in silico* and simulation tools. Polypharmacology-based screening for drug repositioning and combination therapies for identification of efficacious and safe drug candidates utilizes both traditional high-throughput screening (HTS) and/or *in silico* screening tools to identify chemical scaffolds that can modulate several targets in the same family or unrelated new targets [5]. The novel therapeutic agents include not only small molecules and biologics, but also include treating disorders using nucleic acid-based silencing approaches. RNAi-based approaches have also provided a clever way to address more undruggable targets via exon skipping drugs or viral mediated therapies [6]. Pharmcoproteomics is an innovative proteomics approach to evaluate the effect of drug candidates on cellular targets in the context of the target subcellular translocation-and cellular localization-dependent functions. Proteomics data are being used to uncover specific and off-targets that can modulate drug efficacy and specificity and cause adverse drug interactions. There is also a revived interest in the use of proteolysis-targeting chimeras (PROTACs) as tools to inhibit protein function of undruggable targets like transcription factors, scaffolding proteins, or overexpressed, mutated fusion proteins by recruiting E3 ubiquitin ligases and targeting them for degradation via ubiquitin-proteasome

pathway [7,8]. Drug discovery platforms also aim to incorporate use of biomarkers in evaluating target biology and drug efficacy. Exosomes have emerged as critical biomarker-based tools that reflect with hi-fidelity, various stages of disease development and progression. Since the exosomes released from different cell types contain source cell-specific proteins, bioactive lipids, miRNAs, and other nucleic acids, the use of exosomes as biomedical tools in diagnostics is becoming increasingly significant [9]. The early discovery programs are also increasingly integrating ADMET parameters during analog design for structure-activity relationship studies. Novel safety and ADME/Toxicology testing platforms are contributing toward more reliable outcomes that can reduce cost and attrition rates in preclinical discovery programs.

Technological advancements integrated into the current drug discovery-scape have the potential for improving outcomes in lead optimization and clinical trials. At times, the boundaries between the two approaches are blurred, but there are some key technologies influencing both experimental ‘wet bench’ approaches and the ‘in silico’ data integration and analysis approaches.

2.2.1. Gene editing technologies − CRISPR

CRISPR has revolutionized the way we do discovery biology. This exquisite technology comes from a bacterial defense mechanism used to destroy invading DNA. The small DNA repeats in the bacterial genome produce short RNAs which recognize and bind to the invading DNA while bringing the DNA cleavage enzyme Cas9 to its location to cut the DNA, so it becomes ineffective while ensuring a copy of short piece of the invading DNA is reproduced and inserted into the bacterial genome to ensure ‘memory’ of this invading species. Due to its ease of use, precision, and efficiency, CRISPR is now widely used for gene knockouts, point mutations, transcriptional regulation, and chromosome translocations in almost all cell types, including cancer cell lines, induced pluripotent stem cells (iPSc), and stem cells [10]. The germline or somatic editing with CRISPR/Cas9 has resulted in generating more human disease-relevant models in mice, rats, dogs, and nonhuman primates, within very short periods of time and at low costs. The technology also enables introduction of genetic heterogeneity observed in complex diseases that accumulate multiple mutations during progression. Experimental evidence for the use of CRISPR-Cas tools are seen in reports on correction of mutations for muscular dystrophy in mouse, sickle cell anemia in blood, and MYBPC3 in human embryos. CRISPR-based *in-vivo* and *ex-vivo* therapeutic agents that are approaching clinical studies are being reported from companies like Editas Medicine (editasmedicine.com), Intellia Therapeutics (intelliatx.com), and CRISPR Therapeutics (cripsrtx.com). While holding great promise, CRISPR/Cas9 process also introduces off-target insertions and deletions of genes. Since antibodies against Staphylococcus-and Streptococcus-Cas9 were detected in human serum, the role of host immune system in modulating Cas9-based gene therapy is another critical factor that will need to be considered while evaluating the success of CRISPR/Cas-based gene-editing therapies. Further improvements in CRISPR technology include designing more accurate specificity algorithms for gRNA design, more specificity eSpCas9 nuclease variants and Cas9 alternatives (Cpf1, Cas13, etc.), all of which may help in reducing off-target effect frequency.

While CRIPR technology holds great promise, the potential risks associated with gene editing, for example, possible increase in cancer risk, extensive DNA damage at places far away from the intentional edit, etc., are just coming to light, however.

2.2.2. Phenotypic screening

Phenotypic screens are enjoying a renaissance due to the relatively higher success of phenotypic screens compared with targeted discovery in the identification of first-in-class drugs. Earlier phenotypic screens were performed on two-dimensional cultures of cancer cell lines grown in multi-well plates. Recent years have seen a shift toward the use of more clinically relevant, three-dimensional culture systems using either single cell types grown into spheroids shaped by plate well geometry to more complex co-cultures of several cell types representing physiological interactions between different cell types. Higher order screening systems use iPSc derived from patients or differentiated into disease-relevant cell types, primary stem cells or primary cells isolated from tumors/surgical samples. Organoid culture models of normal tissues and tumors mimic physiological human spatiotemporal cell-cell interactions and with their extracellular matrix. The models though not perfect, do exhibit some degree of functional maturity and offer a system to evaluate drug screening, target specificity, and compound profiling that may allow more direct translation of compound behavior in clinical trials [11,12]. The emphasis on relevant screening models that will allow more direct translation of preclinical data into clinical trial settings is seen in the National Cancer Institute's (NCI) goal to replace its NCI-60 cancer cell line panel with the cells derived from patient-derived xenografts (PDX) obtained by growing explants from patients into mice. Since phenotypic screens generally identify compounds with no direct link to mechanism of action or specific target, the value of small molecules increases once their mechanism of action or their target(s) are identified. In addition to compound-affinity chromatography and photo-crosslinking/western analysis/mass spec of labeled compound, CETSA/mass spectrometry has emerged as a powerful tool to identify all cellular targets to which the compound binds. Overall changes in cell environment on compound binding are routinely performed via small interfering RNA (siRNA) knockdown, expression profiles at gene, RNA or protein level, protein interaction networks and signaling pathway modulation. One of the ways to expedite drug discovery while keeping the cost low, is finding new indications for FDA approved drugs or for clinical collections with good safety profiles that did not clear clinical trials. Mining available literature, patents, and databases on molecular targets in disease, compounds, drug efficacy, and safety as well as screening cell lines from patients or cell panels representative of disease models are all utilized in identifying activity of drugs in novel indications. The repositioning screens can be carried out in cells in 2D or 3D systems. Since several molecular changes may form basis for observed pathologies, a combination of drugs that act synergistically may show improved efficacy over single treatments.

2.2.3. Precision medicine and pan-omics

Precision medicine is a complex, multifaceted 'novel' approach to the prevention, diagnosis and treatment of disease, predicated on the analysis of individual patient data. It is being practiced in clinics for the treatment of several types of cancer and rare diseases based on identifying drugs targeting mutations uncovered from genomic and exon sequencing of

patient DNA. Reports on the use of integrated omics datasets in clinical setting are lacking, but basic research has used various omics approaches to stratify and categorize specific cancers or autism spectrum disorders based on their molecular signatures. Inactivation of VHL-mediated proteolysis and hotspot mutations was identified as a common molecular event in >100 clear-cell renal cell carcinoma patients via whole-genome, whole-exome and RNA sequencing, and analysis of methylation patterns. The pan-omics integration still faces challenges such as lack of clinical and statistical guidelines for data analysis and interpretation across disparate omics datasets speed of analysis, access to cloud computing, source validation, and quality control in the datasets [13]. The use of machine learning tools in extracting associations across omics datasets, reading large volumes of research/clinical data within minutes, finding biomarkers, phenotypic records, and gene signatures, searching medical records for patient selection for clinical trials design, will greatly benefit preclinical and clinical research. Recent success of the T-cell-based Immuno-oncology personalized therapies for treatment of certain types of cancers offer great promise in recruiting engineered, patient-derived T cells and NK cells to fight cancer and other diseases.

2.3. In silico approaches − genetic modalities

Genetics is often the route chosen for target identification and validation, a result of Genome-Wide Association Studies (GWAS) linking certain genetic variants or mutations to a disease condition or having a direct biomarker in the gene causing the disease. While we utilize the results of genome wide sequencing data and incorporate gene expression data within the rationale for pursuing drug discovery efforts of specific pathways and proteins, the use of genetics to aid in finding a cure is often left behind. Compensatory mutations that can rescue the original mutation is an area that can add another possible avenue to consider when searching for a disease-modifying drug. Can a drug against a protein in another pathway solve/prevent the condition caused by the original mutation? Cancer cells have a mutation which in part is responsible for their phenotype. When this mutation is combined with another mutation (which also by itself has no effect on the cell) the cell is doomed − hence being *synthetic lethal.* Finding compounds that cause this effect is a potential source of new drugs and a new mechanism of action for treating cancers. If two mutations can work together to provide lethality, could the reverse not also be true − synthetic health? This approach would seek non-related mutations which cure the phenotypic disease or at least slow it down. This strategy could also be used in drug−drug combination types of approaches and creation of chimeric compounds [2].

2.4. Big data integration and artificial intelligence (AI)

We are in the age of big data, metadata, annotations, accompanying graphics, text mining, etc. Big data is transforming the future of R&D and drug development through AI. We stand to finally make good use of an overwhelming wealth of diverse and disparate measurements and observations, which may now be mined with sophisticated new algorithms that have been necessitated by the many emerging demands of our exceptionally information-intensive world. Interpretation and mining of big data generated from global systemic approaches in basic and clinical research, and from biomedical records is currently being facilitated by smart algorithm analysis of established and evolving integrating platforms [13]. Deep learning algorithms help in establishing correlations and associations by mining diverse and

disparate datasets. Large searchable databases [5] have been established for almost all areas impacting human health, including sequences from DNA, RNA, mutations (genomics, transcriptomics), regulatory elements (ENCODE), epigenome (epigenomics), pharmacogenomics, metabolomics, changes in gene expression of cell lines challenged with pharmacologic or genetic perturbations [14] (Library of Integrated Network-based Cellular Signatures or LINCS). Several databases have inbuilt algorithms for integrated specialized datasets as seen with the Connectivity Map [15] CMap) and the current Next Generation Connectivity Map (L1000) that integrates information from genes, drugs, and diseases through common gene-expression signatures or NIH supported BD2K-LINCS Data Coordination and Integration Center (DCIC) [16] that processes and integrates Big LINCS datasets.

AI encompasses deep learning algorithms that are designed to extract information from disparate large annotated datasets (images, genomics, and other-omics datasets) using more sophisticated neural networks. The AI searches datasets for model building, and extracts features and patterns to define rules of analysis and train the algorithms. AI is emerging as a critical tool that has potential to accelerate all aspects of drug discovery, diagnostics, and clinical programs. Deep-learning tools can serve as starting points for a new target discovery program or for drug repositioning or bring new drug combinations to improve current standard of care for the treatment of simple and complex diseases alike. Machine learning has the potential to catalog millions of single-step organic chemistry reactions to speed up multistep chemical synthesis design. The algorithms also learn the rules of synthesis and intelligently predict synthetic routes to molecules not included in the training set. There are at least 76 startups that use AI for various aspects of early-and late-stage drug discovery [17].

A major trend in de-risking early biotech projects is leveraging preclinical and clinical big data, providing a critical due diligence process through the addition of a real-time objective data criterion. By the meaningful use of big data, one gains a far greater insight on the identification of trends, and a better perspective on the odds of spotting preclinical and clinical development pitfalls much early on … fail early and fail faster.

3. Scientific unity in global diversity of therapeutics

The traditional and modern therapeutics are also often culture-driven and also culture-specific. The immense global diversity of the systems of healthcare − Eastern and Western − is often daunting to most of the scientists. However, people, in general, are more pragmatic and there is a world movement toward healthcare by lifestyle changes, naturals, nutritionals, and nutraceuticals [18]. This trend is also aggravated by the impact of adverse reactions to modern drugs, antibiotic resistance, high cost of drugs/healthcare, and unsatisfactory results in relief of many chronic diseases. Notwithstanding the dramatic and often miraculous advances in modern medicine, this disillusionment needs to be understood and addressed. Firstly, trans-cultural sensitivity is needed to appreciate other world views on health, and secondly, we have to evolve some semblance of scientific unity in global diversity of health systems. Though the ontology and epistemology of these systems are quite diverse, scientific

explanations of their healing mechanisms can be very enabling. These are needed in terms of the phytoactives and the targets of therapeutics response. According to W.T. Jones, CalTech:

> *the great sin against the human spirit is closure against the diversity and variety of experience − a narrow dogmatism that insists on the absolute and exclusive validity of some particular language and the particular version of reality … And the central virtue, therefore, is openness to experience, caritas for the differences and diversities …*

Drug discoverers have to be catalysts in facilitating the underlying reasons how the natural drugs and processes work.

3.1. Observational therapeutics

It is often not realized that 75−80% of the population in some Asian and African countries use natural or herbal products for primary medication [19], and that 50−60% of modern drugs can be traced back to their roots into phytochemical scaffolds from natural drugs of Ayurveda, Traditional Chinese Medicine (TCM), and other traditional systems of medicine [20]. Experiential evidence, gained over centuries, hence affords great promise toward moving forward as well.

In recent years, the novel bedside hits and leads in therapeutics have emerged as opportunities for drug discovery through repurposing and reverse pharmacology (RP) approaches. Clinician pharmacologists in modern medicine, Vaidya scientists in Ayurveda and practitioners of TCM can be major stakeholders and collaborators in drug discovery, by sharing their bedside novel hints, hits and leads of therapeutic interventions. These natural remedies work at multiple targets and at different levels of biological organization. Natural drugs have again emerged on the global stage, after the 2015 Nobel Prize awarded to William Campbell, Satoshi Omura, and Youyou Tu for their discovery of avermectins and artemisinin, respectively. In the words of Ben Shen, we are witnessing a new golden age of natural product drug discovery, in that natural products possess enormous structural and chemical diversity that cannot be matched by any synthetic libraries of small molecules and continue to inspire novel discoveries in chemistry, biology, and medicine [21].

RP is the science of integrating well-documented clinical/experiential hits into leads by transdisciplinary exploratory studies, and further developing these into drug candidates by experimental and clinical research. The three domains of RP − experiential, exploratory, and experimental − are innovative in their choice of protocols and models [22]. The *experiential* stage involves open studies in patients (n = 30−50) with a standardized traditional medicine formulation which has already shown activity in Ayurvedic pharmacoepidemiology/ observational therapeutics. The *exploratory* stage involves *in vitro* and *in vivo* models of drug targets to confirm the therapeutic activity and tolerability, based on the findings of the earlier stage. The *experimental* stage involves clinical trials with larger sample size (n = 200−300), with multiple sites and expert 3−4 investigators. Such an approach is cost-effective for drug discovery from Ayurveda and other systems of traditional medicine. When phyto-molecules are identified for their specific drug-targeting activity, these can also serve as novel scaffolds for new chemical entities which can have multiple targets [23].

Likewise, the business case for the development of certain drug leads which have undergone a significant amount of pre-clinical and often clinical assessment may no longer be appealing to pharma; but academia, foundations and nonprofits may still find value and *reposition or repurpose* these fallen angels through their in-house programs starved of promising candidates [2].

Finally, the discovery of the anti-hypertensive plant − *Rauwolfia serpentina* − can well illustrate how an initiative in Ayurveda led to a global revolution in pharmacology and new drug discovery [24,25]. It was in the year 1931 that Sen and Bose discovered the anti-hypertensive activity of the plant in humans and dogs. The world had to wait up to early 50s before the alkaloid reserpine of the plant became available. Meanwhile, Indians were already availing of the standardized extracts of the plant for their hypertension. The pioneers had also observed the side effects of the plant namely, depression, Parkinsonism and gynecomastia in patients. Eventually, many drugs were developed for these conditions because of the understanding provided by the action of reserpine on the depletion of amines. Many clinical studies and experience with Ayurvedic drugs still await an organized RP approach for new drug discovery.

4. Expert opinion

Modern drug discovery approaches take too long, cost too much, and with too many clinical failures. There are many reasons for this unsustainable business model, but most importantly, the approaches are not comprehensively holistic. RP, deep rooted in traditional medicine, laid the foundation for the emergence and evolution of modern drug discovery approaches as a highly formal and regimented science. Advances in genomics, assay and combinatorial chemistry technologies, informatics and robotics led to increased screening operations significantly compared with traditional discovery methods. Many diseases are complex, heterogeneous, and multifactorial, have several phenotypes, variable risk factors, and responses that are influenced by genetic variations, age, gender, and environmental factors like diet, microbiome, and lifestyle choices. Since target-based drug discovery, a solely bottom-up rather than top-down approach, limits effective translation, a target-agnostic approach may be necessary to identify disease-relevant microRNAs and biomarkers, leading eventually to pin-point the most therapeutically relevant drug target, and avert later stage clinical failures. What makes a drug target a therapeutically relevant one with potential clinical success depends on a number of criteria that are disease-and company-specific. Apart from intellectual property, competition, and commercial success, the drug target must meet or exceed stringent selection and validation crit,eria so that the clinical stage attrition is minimized.

A disruptive, yet holistic, approach encompassing many of the technologies we have outlined and elucidated here is extremely imperative for the discovery of drugs that are first-in-class, representing new drug-target mechanisms of action. Further, translational medicine experience − observational therapeutics − is critical for a therapeutic target hit to leap from being an *in vitro* active compound to become a candidate with clinical potential. We propose innovative network science that holistically addresses the selection and validation criteria toward the identification of a therapeutically relevant drug target.

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