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Perspective

Forwarding New Therapeutic Approaches to Address Rare Diseases Global Concern

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Foundational Perspective: A Brief Snapshot of Rare and Genetic Diseases

The Big Picture Through a Statistical Framework

According to the United States (US) Department of Health & Human Services (DHHS), and more precisely, the Genetic and Rare Diseases Information Center (GARD) of the National Institutes of Health (NIH), more than 7,000 rare diseases have been identified. The definition for rare disease can vary across different regions. In North America, rare diseases are defined as disorders that affect less than 200,000 people, which in present data reveals an estimation at between 25-30 million people living with a rare disease. In Europe, a disease is considered 'rare' when affecting fewer than 5 people in 10,000, which can be translated, according to European Commission's Directorate-General for Health and Food Safety, into approximately 246,000 people throughout the 28 member countries of the European Union. The majority of these diseases are life threatening. Approximately, 80% of rare diseases are caused due to genetic defects. There are more than 600 orphan drugs approved by the FDA since the passage of the Orphan Drug Act. However, only 8% of rare diseases have US FDA-approved drugs. There are near 560 candidates in clinical development for the treatment of rare diseases. However, only 5% of rare diseases have treatment, whereas the remaining 95% of rare diseases still do not have any treatment options. Approximately 50% of the people with rare diseases are children. Among the principal limitations of access to treatment, even in developed countries, are associated with the lack of orphan drug legislation in many regions, high development costs and product prices - especially when an orphan drug is not first approval for the rare disease -, and limited and scattered number of patients with rare diseases constraining clinical trial access [1].

A Claim for Urgent Solutions for Severely Underserved Life-Threatening Diseases

This statistical and analytical illustration inherently comprehends an urgent need for new therapeutic approaches to make possible the treatment of rare and genetic diseases in a broader spectrum. A recent article published by Frost & Sullivan [2] remarks that since rare diseases affect only a small portion of the worldwide population; drug discovery, development, and optimization face significant challenges. While only some companies are focusing on rare diseases, some large pharmaceutical companies are making outstanding advances in drug research and development (R&D). According to a recently published review article from the US NIH [3], government organizations, venture capitals, R&D companies, life scientists, and patient advocacy groups had all contributed to progress in rare diseases research. Nonetheless, results exhibited a highly atomized strategy, leading to large costs of research and duplicated efforts. The researchers emphasize in the definition of the rare disease problem, involving thousands of rare diseases types and categories, vast preponderance of them with no approved treatment, and decades-long diagnostic pilgrimages for many patients. Julkowska *et al.,* 2018, also claim the solution only can come from global cooperation and collaboration among the many stakeholders active in rare diseases research, hence helping to capitalize proofs of concepts, and maximize the output of rare diseases research efforts globally [3]. The authors remark the collaboration framework initiated by the International Rare Diseases Research Consortium (IRDiRC) in Europe together with the NIH in the US. Similarly, Dawkins *et al.*, 2017, highlight the need for collaborative funding mechanisms to enable the financing of large, transnational projects that exceed national research programs [4]. Whicher *et al.,* 2018, recently published an article aiming for raising awareness among key stakeholders - researchers, payers, patients, patient advocates, and clinicians -, regarding the use of methodological and analytic approaches to overcome rare diseases challenges by identifying algorithms for matching study design to rare disease attributes, as well as, by inferring the role of research communities and infrastructure developers contributing to the efficiency of research on the treatment and management of rare diseases [5].

The Road Ahead: Groundbreaking Therapies Resulting from Novel Technological Approaches

Technology Synergy, In-Depth Knowledge, Causing Genes Identification, and Target Mutations

Recent advancement in the development of novel platforms of smart targeting small molecules, gene therapy, stem cell therapy, gene modification, and gene rectification technologies pose new prospects for therapies and cures for rare and genetic diseases are illustrated by Van Cauwenberghe, 2018 [2]. More than 80% of rare diseases are genetic in origin, so that gene and cell therapies are being proposed to treat them. Moreover, human stem cell therapy is suggested as one of the most promising alternatives. Furthermore, genetically modified stem cells and autologous induced pluripotent stem cells, synergistically coalesced with zinc-finger proteins and transactivator-like effector nucleases, are targeted as the selection of choice for the ex vivo repair of specific mutated deoxyribonucleic acid (DNA) sequences. Similarly, patient specific induced pluripotent stem cells can be edited and shifted back into the patient, leading to a new approach to precision medicine. In addition, once homed, stem cells secrete a vast number of paracrine factors that could become new therapeutic tools in the treatment of rare and genetic diseases. As a key technology differentiator, rare diseases having gain-of-function mutation and late onset are more likely to have a treatment option. Agreeing an article published by Chen and Altman, 2017, three primary insights can be leveraged during drug discovery focused on rare ad genetic diseases [6]. Firstly, diseases with gain-of-function mutations and late onset are more likely to have drug options. Secondly, drugs are more often inhibitors than activators. Thirdly, some disease-causing proteins can be rescued by allosteric activators in diseases due to loss-of-function mutations. The authors deeply depict a list of top targetable genetic diseases due to loss-of-function mutations. Therefore, next-generation small molecules, gene therapy, stem cell therapy, and gene editing for DNA repair are promising approaches to the treatment of rare and genetic diseases. This article briefly depicts the current landscape and the new trends in the development of novel therapies for rare and genetic diseases, focused on highly interrelated and synergistic approaches.

Critical Points to Focus for Success

Focus on Technology Synergy

The impressive advances in life sciences research and development (R&D) befallen in the past two-three years are playing a leading role in the transformation of the healthcare industry. A myriad of new developments in the fields of gene and cell therapies, empowered with nanotechnology advances, omics technologies and novel smart molecules approaches, are extensively enlighten drug discovery and development landscape for the effective treatment of rare diseases.

Focus on In-Depth Knowledge

In parallel, a profound and growing scientific understanding of many rare diseases, especially at molecular and genomic levels, is taking place, hence allowing leveraging the implementation of such new technologies to develop groundbreaking therapies. However, the underlying causes of many rare diseases remain vague and imprecise. Therefore, overcoming the challenge of finding new treatments to address rare diseases constitutes a vital goal for scientists.

Focus on Genes Identification

Due to approximately 80% of rare diseases have been linked to genetic abnormalities, next-generation sequencing (NGS) technologies has dramatically accelerated the identification of the involved genes by providing a potent, cost- and time-effective alternative for genetic analysis in the early stages of the process. Whereas the identification of causing genes in rare diseases in the '80s involved more than a decade of research, high throughput technologies have allowed scientists linking hundreds of mutations associated with rare diseases in just a few years.

Focus on Target Mutations

Small molecules targeting single gain-of-function mutations, thus inhibiting single disease-driver proteins rather than multiple pathways, as well as, loss-of-function mutations, in which allosteric activation may increase the activity of a mutated enzyme toward physiologically normal ranges, exemplify the most successful candidates.

The Rule of Five: Technologies Converging to Rare Diseases Treatment

Small Molecule Technologies

Many genetic diseases result from errors that lead to anomalies in transcription, splicing, or translation. However, targeting the flawed protein products with drugs is often ineffective. Small molecules that bind ribonucleic acid (RNA) offer the prospect of undertaking inborn errors by normalizing splicing or by suppressing or promoting translation.

Most relevant platform technologies identified in the space are: Small Molecule Accurate Recognition Technology (SMART); RNA-targeting Small Molecules (rSMs); Small Molecule Nanoparticles (SMNPs); Next Generation DNA Encoded Libraries; and PROteolysis TArgeting Chimeras (PROTACs).

Cell Therapies

Cell therapies have drawn much interest for their therapeutic benefits in immune modulation and tissue remodeling. Cell reprogramming through patient-specific induced pluripotent stem cells is prone as a major prospect in the future treatment of rare and genetic diseases.

Grondbreaking cell therapy advancements that may lead to novel treatments for rare and genetic diseases comprise: Mesenchymal Stem Cells (SCs); Induced Pluripotent Stem Cells (iPSCs) Platforms; and Stem Cells Producing Therapeutic Peptides.

DNA-Based Therapies

DNA-based therapies enable to target the disease more accurately. Novel DNA-based tools are emerging with the promise to offer more effective solutions to severely underserved clinical conditions. Highlighted therapies include: DNA Vaccines; Plasmid DNA; and DNA Nanoparticles.

RNA-Based Therapies

MicroRNAs (miRNAs)-based therapy has recently emerged as a promising strategy in the treatments of rare diseases. RNA interference exhibits great ability for the development of new classes of molecular therapeutic drugs that interfere with disease-causing or -promoting genes, particularly those that encode so-called non-druggable targets, not responsive to conventional therapeutics.

This category exhibits a profound interest for novel therapeutics, embracing: RNA interference (RNAi); Messenger RNA (mRNA)/microRNA (miRNA); and Nucleotide RNA Analogues/Aptamers.

Gene Editing Technologies

Being engineered for site-specific modifications in the genome, gene editing is paving the way toward an effective functional analysis of genes, genomes and epigenomes. Such a deeper understanding of the molecular underpinnings of disease states holds the promise to drive novel therapeutic applications for currently unmet medical needs such as rare and genetic diseases. Gene editing can be utilized across the entire drug discovery chain and constitute a primordial way to address rare and genetic diseases unmet needs. Gene editing technologies can be utilized in the identification of novel targets for a whole host of therapeutic areas. These are typically down through genomic screens. In addition, these technologies can aid in the validation of already selected targets. Highly complex genomic studies can be conducting using these technologies to assess point mutations, overexpression and multiple other characteristics. They can also be considered as direct treatment options, especially if the disease that is being targeted can be reversed or altered by genetic manipulation on the DNA level.

As the star of new genetic technologies, gene editing involves a series of relevant and unique approaches: Clustered Regularly Interspaced Short Palindromic Repeats -associated protein-9 nuclease (CRISPR/Cas-9); Transcription Activator-like Effector Nucleases (TALENs); Zinc-finger Nucleases (ZFNs); and Meganucleases.

Clinical Translation: Technology Transfer and Innovation Ecosystem

Technology Adoption in the Development of New Therapeutics for Rare and Genetic Diseases

Cooperation between academia and industry is clearly illustrated by Mavilio, 2017, as an opportunity to de-risk innovative approaches and accelerate the efficient development of therapies for diseases with high unmet medical needs and low-profit expectations [7]. Matalonga *et al.,* 2017, remark the emergence of the therapeutic use of small molecules as a promising approach for treating heterogeneous disorders [8]. In their review, the authors focus on the use of therapeutically active small molecules to treat inborn errors of metabolism (IEM), paying special attention to the molecular mechanisms underlying therapeutic properties of small molecules, methodologies used to screen for these compounds, and their applicability in preclinical and clinical practice.

The advent of new technologies allowing combining small molecule platforms with RNA new discoveries is reshaping drug discovery. RNA carries the genetic instructions for proteins to the cell's protein-making machinery. This means that a whole new class of largely untapped drug targets capable of providing new avenues to treat diseases in unmet medical areas still using traditional protein-binding drugs is close. Many genetic diseases result from errors that lead to anomalies in transcription, splicing, or translation. However, targeting the flawed protein products with drugs is often ineffective. Small molecules that bind RNA offer the prospect of undertaking inborn errors by normalizing splicing or by suppressing or promoting translation.

Stem cells imply long-term self-replication even after extended periods of dormancy, unspecialized functionality, and ability to differentiate into various specialized cell types under appropriate conditions. Hence, new treatments in this space are likely to disrupt conventional small molecule therapies. Institutions involved in stem cell therapy research have established mechanisms for sharing information across agencies, from regular and formal meetings to more collaborative ad hoc activities such as co-funding research and co-sponsoring workshops focused on stem cell therapy approaches.

The urgent need for medical solutions for cancer and rare diseases is demanding a more diversified spectrum of possibilities in which DNA gene therapies play a leading role. Although technology is impressively advancing, translation of research into marketable products modifying human DNA and gene transfer for therapeutic use, altering the nuclear genome, is still demanding notable efforts [9]. However, the introduction of new technologies such as plasmid DNA and DNA nanoparticles are helping to overcoming challenges around how to incorporate DNA into a gene. Compared to viral and RNA-based vectors, plasmids are easier and cheaper to produce, ship, and store, and have a much longer shelf life. Jones *et al.,* 2017, has deeply analyzed DNA repeat-based mechanism aiming for providing new therapeutic targeting approaches with a major focus on multiple trinucleotide repeat disorders [10].

MicroRNAs (miRNAs)-based therapy has recently emerged as a promising strategy in the treatments of rare and genetic diseases. According to Adams *et al.,* 2017, the role of regulatory RNAs such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in the development of a disease state has been profoundly studied over the past decade [11]. Indeed, the advent of RNA-based platform technologies lead to innovative RNA modifications and delivery entities, including nanoparticles, in the development of future RNA-based therapeutics for rare and genetic diseases.

RNAi exhibits great ability for the development of new classes of molecular therapeutic drugs that interfere with disease-causing or -promoting genes, particularly those that encode so-called non-druggable targets, not responsive to conventional therapeutics.

CRISPR/Cas9 technique is being heralded for precision and accuracy in genetic editing across a plethora of applications. The possibility of treating rare genetic disorders and correcting genetic traits is at the precipice of becoming a reality. Utilization of gene editing techniques is currently expanding rapidly across in human therapeutics, and these disruptive innovations will continue to impact the market over the next decade. In an editorial article, Hart, 2017, and Yin, 2017, remark the technology synergy evidenced across all the aforementioned approaches [12,13]. Hence, for instance, formulations based on Cas9 mRNA and synthetic guide RNA, or preassembled Cas9 ribonucleoprotein demand the use of nanoparticles and new delivery technologies [14].

Final Remarks

Rare and genetic diseases may finally find real solutions due to small molecules binding RNA may deliver the possibility of correcting inborn errors by controlling splicing or by suppressing/promoting translation. According to the results from clinical trials, novel solutions for hitherto incurable diseases are expected once R&D activities around iPSCs start to produce results in clinical applications.

Collaboration between cancer immunotherapy developers and large pharmaceutical companies seems to be the optimal road to develop novel therapeutics using groundbreaking technologies to address rare and genetic diseases concern. These risk sharing business models has a symbiotic environment where commercialization and marketing strategies will be easily handled by the seasoned biotechnology companies, while the research and development phases will be managed by the emerging technology companies.

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