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Editorial

The Rescue and Repurposing of Pharmaceuticals: Augmenting the Drug Development Paradigm

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Drug development is a highly complex, difficult, comprehensive process that involves multiple strategies and pathways with the ultimate goal to efficiently determine the optimal and safe use of a drug for the treatment of disease, relief of

see related article on page 36

suffering, and/or enhancing quality of life. The standard paradigm is fraught with numerous and frequent complex challenges that may cause the innovator to cease further development at any phase of the preclinical or clinical development path. The cost of drug development in intellectual resources, corporate capacity, competitive focus and dollars, is enormous. It is estimated that only 10% to 15% of potential drugs complete preclinical assessments, surviving the so-called "valley of death," and enter the clinical development process where only ~ 5% of these compounds make it to US Food and Drug Administration (FDA) approval. The time from compound–target selection to FDA approval can be as long as 12 to 15 years and including failures, the cost can exceed 1.5 to 2 billion US dollars. No institution, corporation, or integrated collaborative, regardless of size, scientific depth, and marketing prowess can sustain such costs in time and dollars and continue to develop new chemical compounds targeting new, refined targets that substantially improve health and cure disease. Numerous strategies have been proposed and implemented to improve the time and financial efficiency of the drug development process, including systems–based approaches capitalizing on high throughput computational approaches, modeling, and integrated networks incorporating chemical, pharmacologic, and genomic profiles, with varying degrees of refinement.[1,2] The ability to rescue a drug that was once studied for a specific use and found safe but ineffective and archived by its innovator and then rediscovered and repurposed for a different use or, repurpose (repositioning) an already marketed drug for a use it was never intended for is a creative way of streamlining the drug development process for improved efficiency and success.

In this issue of the *Journal*, Rumore[3] briefly reviews repurposing strategy as it impacts pediatric practice and nicely catalogs and summarizes a host of drugs repurposed for pediatric patients (see Table 2). The drugs included in this Table are agents with contemporary clinical uses outside of their current FDA-approved labeling. Thus, appropriately omitted from this Table are the classic repurposed drugs in pediatrics that would include: N-acetylcysteine, originally approved for use as a mucolytic but now the drug of choice for the treatment of acetaminophen intoxication; propranolol, originally approved for use in patients with cardiovascular disease and now a primary treatment for hemangioma; and azidothymidine (AZT), a drug originally developed to treat cancer but shelved and later rescued for the treatment of HIV infection and prevention of vertical transmission. I only mention these agents as a reminder of how repurposing medications can have such a profound, positive impact on the care of infants and children worldwide. In addition, the author provides opinion in Table 2 regarding the strength of the published evidence supporting the novel, repurposed indication(s) that underscores our professional responsibility to continue to adhere to the time-held importance of thoughtful, critical clinical observation and

publication of novel therapeutic and serendipitous findings (e.g., propranolol).

In pediatric therapeutics, off-label use is sadly more often the norm rather than the exception. Off-label use can refer to the prescribing of a drug for its approved indication but in an age group not included in the FDA-approved labeling, the "therapeutic orphan" syndrome, or the use of a drug/device for an entirely different clinical indication. Although the practice of repurposing/repositioning is encompassed within the term off-label, I would encourage we continue to use these terms independently to focus the agenda and the weight of the evidence on these specific limitations we encounter on a daily basis in our clinical practices. Furthermore, encompassed within the term repurposing/repositioning is the action of rescue of an achieved, "buried, deep sixed, put on the shelf" compound. The actual number of these compounds and the depth and breadth of their linked data are unknown, but creative efforts and funding mechanisms have been established and are continuingly refined to uncover and make publicly available such data and funding for the research.[4–7] The wealth of possibilities from these efforts are truly incalculable.

Collaboration is the key to effective, efficient, contemporary drug development. Partnerships with multiple stakeholders including private/public industry, individuals, investors, academia, governments, and others are all necessary for redefining the drug development paradigm and capitalizing on all avenues for successful development. The US National Institutes of Health (NIH) continues to be a leader in this charge—one highly successful and visible program of collaboration is the Pediatric Trials Network whose defined studies have and will continue to lead in providing the data needed to support age-appropriate dose and safety labeling for off patent medications. In addition, the NIH recognized the immense value from creating and mining such databases of archived and repurposed compounds and the need for their leadership in establishing innovative and creative mechanisms for functional, cooperative partnerships.[4] In 2011,[4] the NIH director described the Institutes direct support in augmenting the available data on drugs and investigational compounds through the NIH Chemical Genomics Center for Pharmaceutical collection and the establishment of a new Center, the National Center for Advancing Translational Sciences (NCATS). These initiatives and others (reviewed in references 1, 2) have markedly expanded open access assessment of large numbers of compounds for rescue and/or repurposing. The NCATS has served as an engine in providing the leadership for processes to move beyond traditional obstacles to foster multilevel collaborations among previously unaligned groups, all focused on increasing the time/cost efficiency of drug development for the benefit of our patients.[8] Most recently in October 21, 2015, the NCATS posted a new funding opportunity announcement (FOA) for preclinical research based on repurposing tools (R21) to support "rigorous, pre-clinical studies that establish the rationale for a clinical trial, where the hypothesis originates from use of a published or publicly available method for identifying new indications for existing drugs or biologics (therapeutics)." The paradigm shift is here and if you are not contributing now, you need to be.

As Rumore[3] clearly outlines, these multilayered partnerships are absolutely necessary to capture the full potential of rescue and repurposing of pharmacotherapeutics for infants and children. Our leadership is necessary for success, and I encourage all pediatric practitioners to embrace, support, and contribute when possible, to the efforts of NCATS in actively leading the way. Rumore[3] suggests a call for an application process similar to the orphan drug act or the provision of orphan drug designation for pediatric supplemental new drug applications (SNDAs) as a means to stimulate investment and discovery activity. This is one approach to stimulate hypothesis generation, proof of concept clinical study, and appropriate positioning of previously overlooked compounds with exceptional therapeutic potential—as noted there are others. Complimenting these various efforts is the development of the Children's Pharmacy Collaborative.[9] Blatt et al[9] began this voluntary initiative by establishing a database that includes only those drugs for which there is pediatric experience. This team has been working hard at establishing collaborations and continuing to enhance the quantity of pediatric-potential drugs and data quality of database entries, as well as performing preliminary screens of potential links of cell-lines to compounds. The goal is to make this database available in the future. Individuals interested in learning more about this innova-

tive program can contact the lead investigator, Julie Blatt, MD, at jblat@med.unc.edu (personal communication, Dr Julie Blatt, February 5, 2016).

Rumore et al[3] notes the sad reality that the labeling contained in package inserts usually lags behind clinical practice, especially when it relates to the care of infants and children. This fact merely underscores the need for our continued vigilance in collating and interpreting all available evidence to support the safe and effective use of drugs for the treatment of ill pediatric patients, on or off-label. The rescue and repurposing paradigm is just another strategy to better define safe and optimal use of new and/or novel therapies and compliment a better understanding of the molecular basis of human diseases.

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