

Mixing the Old with the New: Drug Repurposing for Immune Deficiency in the Era of Precision Medicine and Pediatric Genomics



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The decreasing cost of next-generation sequencing technologies has made it feasible for clinicians to obtain a molecular diagnosis in patients suspected of suffering with a rare disease. In pediatrics especially, this genomics approach has shed new light on the genetic and molecular basis of a large number of rare diseases.¹ The use of these pediatric genomic technologies offers a pathway to personalized precision medicine, wherein therapies can be individually tailored to the patient's genes, lifestyle, and environment.

Although rare diseases are infrequent by definition (less than 1 in 1500 in the United States, or less than 1 in 2000 in Europe), collectively they are a common occurrence.² Once the disease is diagnosed, the challenge for precision medicine lies in the development or identification of an appropriate therapy. This has not been an easy task. Of the more than 7000 rare diseases based on European Organization for Rare Diseases statistics (<http://www.eurordis.org/about-rare-diseases>), only approximately 600 treatment options are available.

Disorders of the immune system are prominent in the catalog of inherited rare diseases. Primary immune deficiencies, for example, often result from mutations of genes required for lymphocyte development and activation.³ The application of pediatric genomics has led to the identification of many new immune deficiency disorders. Activated phosphoinositide 3-kinase- δ (PI3K δ) syndrome, or APDS, is one such disorder.

Autosomal dominant APDS is caused by a gain-of-function mutation in either regulatory subunit 1 (p85 α) or the delta catalytic subunit (p110 δ) of PI3K δ .³ PI3K δ is highly expressed in lymphocytes and myeloid cells. It is activated by the B-cell receptor and the T-cell receptor, as well as by costimulatory, cytokine, and growth hormone receptors. Because of the broad range of signal transduction pathways affected, gain-of-function mutations result in a combined immune deficiency phenotype. Patients display evidence of both B-cell and T-cell dysfunction. They present with the classic antibody deficiency phenotype of recurrent sinopulmonary infections with encapsulated bacteria and poor responses to challenge with bacterial polysaccharides. IgG deficiency can be

either subset selective or generalized, whereas IgM serum levels may be elevated. Although infections with opportunistic organisms are uncommon, patients with APDS also suffer from the classic T-cell deficiency phenotype of severe, recurrent, or persistent infections with herpes family viruses (eg, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and varicella zoster virus). CD8 T-cell numbers may be enhanced, presumably due to an accumulation of senescent CD8⁺CD57⁺ T cells. Benign lymphoproliferation (lymphadenopathy, hepatosplenomegaly, and focal nodular lymphoid hyperplasia) is common, and there is a higher risk of lymphoma. Immune cytopenias (thrombocytopenia, hemolytic anemia, and neutropenia) as well as autoimmune disorders (juvenile arthritis, glomerulonephritis, thyroiditis, and sclerosing cholangitis) are also seen.

With the genetic lesion defined, clinical trials of p110 δ inhibitors are well underway.⁴ However, the development of a new drug is inherently slow, costly, and risky.⁵ Moreover, it can be difficult to recruit participants aged 12 or younger for clinical trials.⁴ Rather than identifying, testing, and obtaining approval for a new drug whose side effects are unknown, an alternative approach is to bring medications with known safety profiles to new patient populations.⁶ This process of off-label use is termed drug repositioning or repurposing.

A recent bibliometric review of drug repurposing found that of the approximately 35,000 drugs or drug candidates identified by scanning >25 million papers in PubMed, more than 60% had been tried in more than one disease, including 189 drugs that had been tried in >300 diseases.⁷ Drug repurposing approaches (Table 1) include phenotype association, pathway/network association, genomic/epigenetic association, gene variant-specific transcriptional association, and high-throughput brute force.^{2,6,8} A sixth approach category is serendipity, wherein the chance use of a drug for one condition is observed to ameliorate or reverse a second. Notable examples of drug repurposing include the use of aspirin to prevent cardiovascular events⁹ and colorectal cancer,¹⁰ sildenafil (Viagra) to treat pulmonary hypertension,¹¹ thalidomide to treat multiple myeloma,¹² and minoxidil to treat male pattern baldness.¹³

In this issue, Valencic et al¹⁴ report the use of the pathway-network association approach for the treatment of an 11-year-old girl with APDS, who was heterozygous for the mutation 56 c.1425+1G>A in PIK3R1. In the best traditions of drug repurposing, they report that a search of the literature showed that theophylline, a common drug used for the treatment of pulmonary obstruction, inhibits the action of PI3K δ at concentrations in the therapeutic range for the medication for asthma and apneas.¹⁵ Treatment with theophylline in this patient resulted in amelioration of her symptoms, a striking reduction in the frequency of sinopulmonary infections, and substantial improvement in scholastic performance.

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No funding was received for this work.

Conflicts of interest: The author declares that he has no relevant conflicts of interest. Received for publication April 4, 2018; accepted for publication April 4, 2018.

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J Allergy Clin Immunol Pract 2018;6:2168-9.
2213-2198

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<https://doi.org/10.1016/j.jaip.2018.04.002>

TABLE I. Approaches to drug repositioning

Indications for the consideration of off-label use in a rare disease of a medication approved for a common disease ^{2,6,8}
Phenome association
• The drug is used to treat a shared disease phenotype
Pathway/network association
• The drug is used to influence a shared biochemical or signal transduction pathway
Genomic/epigenetic association
• The drug is used to influence the same transcriptional pathways
Gene variant-specific transcriptional association
• A transcriptional associated with the genetic variant is matched to a drug that induces an opposing transcriptional program
Brute force
• Automated high-throughput screening • Automated reasoning algorithms • “Big data” responsive web design analyses of large patient datasets
Serendipity
• Chance use of a drug for a common condition is observed by a health care professional to ameliorate or reverse a second condition • Reports from patients, social media, or patient advocacy groups

Although the value of a systematic approach to drug repurposing by pharmaceutical firms, academic institutions, or governmental agencies is undeniable, this report by Valencic serves as a clarion call for further consideration of drug repurposing not only in the treatment of rare primary immunodeficiency disorders but also in atopic asthma and allergy.⁸ Medical history teaches us that on occasion a new treatment approach beneficial to tens or even millions can be only a case report away.

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