Battling Rare Diseases in a Blockbuster World

The advice about finding "safety in numbers" was not originally directed at patient groups, yet it applies just the same. Those who are diagnosed with a disease will have the most treatment options and the best prognosis if their condition is a common one. Americans with rare diseases—those with fewer than 200,000 patients—face far more difficulties than those whose conditions are well characterized.

As Henry J. Fuchs, M.D., senior vice president and chief medical officer for BioMarin Pharmaceutical Inc. in Novato, said, "The population is small. But the development costs are about the same as for a blockbuster drug." (Blockbuster drugs are those with annual sales exceeding $1 billion.)

Financing aside, the biggest obstacle to finding cures for rare diseases is a function of their scarcity. Because so few people are affected, it is hard to determine what causes these conditions in the first place. It is difficult to gather enough patients to ensure statistical validity in clinical trials. And with a limited group of potential trial candidates, the trial designers are under tremendous pressure to get it right the first time.

As formidable as the challenges to treatments for rare diseases may appear, California innovators are stepping up to make therapies available.

Translational Research Catalysts

In his fifth year, Paul and Debra Miller's son was diagnosed with Duchenne muscular dystrophy (DMD), a rare degenerative disorder that typically leaves its patients wheelchair-bound by their 10th birthdays, paralyzed by 18 and dead by 20. Both of the Millers had strong business backgrounds and founded CureDuchenne, a Corona Del Mar non-profit that helps biotech companies fund promising research. The organization has helped three biotechnology companies move promising compounds into Phase II trials. CureDuchenne also donated $200,000 to the University of California, Los Angeles in November 2009 for a new Center for Duchenne Muscular Dystrophy at the university.

The Millers' son is now 12 years old and, through aggressive steroid and other treatments, is doing well.

Beth Anne Baber, Ph.D., is another parent making a difference. She is a cancer researcher, as is her husband. So when they were told that their then 15-month-old son, Conor, had stage 3, high-risk neuroblastoma, "We knew that the survival rate for him was probably less than 40 percent," Baber said. Before long, Baber was committed to accelerating the use of personalized medicine in pediatric cancer.

Through the Nicholas Conor Institute for Pediatric Cancer Research, Baber and her founding partner, Martin Latterich, Ph.D., are working to lower research and development (R&D) costs and to speed the availability of diagnostics and therapeutics specifically for pediatric cancer. The institute's strategy is to target emerging technologies and actively translate them to the clinic while reducing R&D costs for the industry partner. The San Diego-based institute has ongoing collaborations with AltheaDx in San Diego, CollabRx, Inc. of Palo Alto and Prognosys Biosciences, Inc. in La Jolla.

In 2009, Conor marked his three-year anniversary of ending chemotherapy and remains staged as "NED" for no evidence of disease. He continues to have MRIs every three months to ensure that any recurrence is detected as early as possible.

Virtual Communities

Nicole Boice, a marketing professional and founder of the Children's Rare Disease Network, was touched by rare diseases when her friend Kelly's son was born with what eventually was diagnosed as Joubert Syndrome. "I experienced first-hand Kelly's and [her husband] Darryl's feelings of helplessness, isolation, stress, frustration and anger." She also was surprised to find that while each rare disease has a small patient population, there are approximately 7,000 identified rare diseases that affect more than 30 million Americans. At least 150 organizations are devoted to better understanding and treating rare disorders.

Using her marketing, branding, communications and social networking skills, Boice established The Children's Rare Disease Network, an on online community for all patients and caregivers who are trying to become more educated and better manage rare diseases. Based in Dana Point, the network serves as a clearinghouse for information on legislation pertaining to rare diseases, resources for specific disease research and information, and a referral site to enable parents and other caregivers to access the resources they need from a single portal.

Policy Change Agents

Emil Kakkis, M.D., Ph.D., has more than 18 years of experience in developing novel treatments for rare genetic disorders. At Harbor-UCLA, Kakkis developed an enzyme replacement therapy for the rare disorder mucopolysaccharidosis I (MPS I). He joined BioMarin in 1998 to finish developing that drug, Aldurazyme® (laronidase), an achievement realized through a 50-50 joint venture with Genzyme Corp.

In 2009, Kakkis was moved to focus his energies on improving the approval process for rare disease therapies. He founded the Kakkis EveryLife Foundation and launched the CureTheProcessTM campaign. The campaign "strives to inspire science-driven public policy that will increase the predictability of the regulatory process for rare disease treatments." Kakkis is advocating three key changes in the regulatory process. The first is to establish a new review office within the Office of New Drugs at the FDA staffed with experts in genetic and biochemical diseases. The second is to create new standards for evaluating the benefit of drugs for rare diseases in clinical trials. Instead of measuring clinical outcomes, which are difficult if not impossible to demonstrate in small patient groups with complex conditions, Kakkis said, clinical trials for rare diseases could measure changes in scientifically qualified biomarkers. And, third, the CureTheProcess campaign calls for a creative effort to design new paradigms for clinical study designs and analyses that are better able to detect individual benefit in a broad array of patients.

In July 2009, Senator Sam Brownback (R-Kan.) and Senator Sherrod Brown (D-Ohio) sponsored an amendment to the 2010 FDA appropriation bill that shows progress in the CureTheProcess effort. The amendment directs the FDA to assemble a team to evaluate various aspects of the regulatory process for rare and neglected diseases. Kakkis anticipates that spotlighting weaknesses in the current system will open opportunities for improvements in the future.

Industry

Amgen, one of California's pioneering, largest and most successful biotechnology companies, has succeeded by "following the science where it leads," sometimes into rare diseases. In 2008, Amgen introduced a new drug for use in adult patients with chronic immune thrombocytopenic purpura (ITP). Patients with ITP have low platelet counts, live with the possibility of dangerous excessive bleeding from even a minor injury, and have few long-term treatment options. Amgen's drug, Nplate® (romiplostim), has been approved for treating the condition in the United States, Europe, Russia and Australia.

BioMarin was founded in 1997 specifically to discover and develop therapies for rare and neglected diseases and thus far has commercialized three such new drugs. The company's approximately 700 employees continue to be committed to that mission, and through both its internal discovery efforts and licensing agreements, BioMarin maintains a solid product pipeline.

Working exclusively in rare diseases is a business model that advances science along with patient care, BioMarin's Fuchs noted. "Developing drugs for a rare disease can be helpful in understanding more common diseases," he said. Fuchs was part of the team at Genentech, Inc. that developed Herceptin® (Trastuzumab) for the subset of breast cancer patients whose tumors are marked by the presence of the HER2 gene. "Through Herceptin, we learned a great deal about monoclonal antibodies in cancer," Fuchs said, noting this knowledge is being used in new product development across the biomedical industry.

Patients and caregivers who are dealing with specific rare diseases may lack the safety of huge numbers. Yet the people who care about them are compensating with commitment and passion. They are revealing the underlying biology of rare disorders. They are rewriting the rules for advancing discoveries to patients. And they are drawing together the unprecedented potentials of gene therapy, personalized medicine, cooperative financing and public health policy to ensure that even the smallest subset of patients can be assured of safe and effective treatments.