# Approaches for Rare and Neglected Diseases

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Rare diseases are devastating and often fatal to those who have them, but have nevertheless faced limited research interest due to a lack of commercial potential, a shortage of patients for clinical trials and other obstacles. New scientific tools and approaches offer the potential to overcome some of these hurdles.

For example, genomics is helping to unite patients in pursuit of diseases so rare that in some cases they are unnamed. Stem cells are being used to study and test potential treatments for rare genetic cardiovascular disorders at a single-patient level. And novel animal models are helping to make inroads against Batten disease, a rare, fatal neurodegenerative condition.

## Understanding Batten Disease

Only a single approved treatment is available to slow the progression of one form in a group of rare, fatal neurodegenerative disorders collectively known as Neuronal Ceroid Lipofuscinoses (NCLs), or Batten disease, which mostly affects children. NCLs are currently associated with mutations in 14 genes; NCL-associated proteins have been localized primarily to lysosomes.

Mouse and miniature pig models have been developed to better understand the molecular basis of various forms of Batten disease.[1,2,3] After detailed molecular, pathological and neurological characterization, these models are used as preclinical tools to test novel therapeutic approaches.[4,5]

In one case, a conversation between an investigator and a patient's parent about how the slow degeneration of Batten disease resembles autoimmune disease prompted the researcher to test mouse models for antibodies. This work led to the discovery of an autoimmune aspect of the disease, and to clinical trials with a related compound to slow the autoimmune process.[6]

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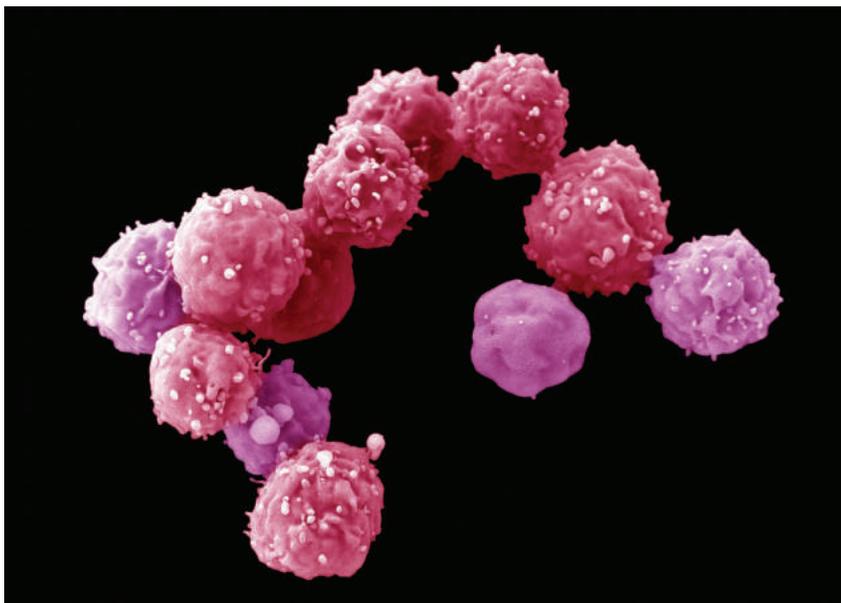
## Genomics Offers Opportunity

As the above anecdote illustrates, patient involvement can be a crucial element in rare disease research. The Rare Genomics Institute, a nonprofit institute, leverages cutting-edge biotechnology to help patients get an accurate diagnosis and advanced understanding of any rare disease.[7] So far, several hundred patients have benefitted from the institute's services.

Partnering with top medical institutions to get access to genomic sequencing and other services, this institute helps look for genetic changes that can explain an abnormality or syndrome in the patient, usually a child. The institute can connect the patient and provider with researchers who are working in this area or, in some cases, find researchers willing to investigate the patient's disease.

The institute also supports RareShare, an online social network for patients, families, healthcare professionals and others affected by rare disease. RareShare has more than 8,000 members in nearly 1,000 different rare disease communities.[8] These groups provide a sense of community for patients and allow them to share information that is not available online or through other more traditional sources.

## Stem Cell Approaches

Patients' cells have become a valuable research resource as well. Human induced pluripotent stem cells (hiPSC) can be differentiated into tissues that recapitulate patient-specific and disease-specific phenotypes, which can be used to design individualized treatment strategies. This technology provides a new methodology to model the pathophysiology of heart diseases to identify novel therapeutic targets[9,10] by deriving cells with patient-specific phenotypes.[11]

Cardiomyocytes, endothelial cells and vascular smooth muscle cells derived from hiPSCs enable accurate modelling of numerous cardiovascular diseases, including cardiomyopathies, arrhythmia syndromes, cardiometabolic disorders, vascular diseases and valvulopathies.[12,13] Recently, genome editing technologies have allowed researchers to establish a disease phenotype by introducing and repairing mutations in cardiac stem cells.[14]

These hiPSC-based platforms for drug discovery and cardiotoxicity testing are being incorporated into drug development pipelines and drug safety testing standards.[15]

As these approaches to rare disease advance our understanding, it is important to identify the right collaborators, such as drug companies, pathologists, regulators, animal model developers and patient advocacy groups and registries—to explore the disease mechanisms, perform preclinical studies and move to clinical trials.

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