Designing a Plan for Drug Discovery in Rare Pediatric Neurodegenerative Disease

By Danielle Kerkovich, Ph.D., and Amy Drew, M.A.

Editor's Note: There are currently no cures for neurodegenerative diseases, including Batten disease, a rare and fatal disorder affecting young children. While researchers have made headway in preventing genetic disorders through preconception carrier screenings and have found potential drug targets, the gap between basic research and clinical treatment development remains. To overcome this gap, write authors Dr. Danielle Kerkovich and Amy Drew, researchers in academia and the pharmaceutical industry, supported by government agencies and nonprofit institutions, must come together to share expertise and promote translational research.

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When a person hears the phrase "neurodegenerative disorder," a few names might spring to mind: Alzheimer, Parkinson, Huntington. One name that probably doesn't come up is Batten. In fact, even though it was first described in 1826, long before Alzheimer's or Huntington's, many people have never heard of Batten disease, a fatal neurodegenerative disorder affecting young children. As parents learn, a child who has inherited two copies of a dysfunctional *CLN3* gene begins to show symptoms of the disease, also known as juvenile neuronal ceroid lipofuscinosis (JNCL), between ages five and eight. The earliest sign is vision loss, which progresses to speech problems, mobility issues, and seizures in the preteen years. These are overlapped by declining mental capacity, attention problems, and other mood disorders. Ultimately, most patients succumb to the disease by their early twenties.[1,2] Though JNCL may not be the best-known neurodegenerative disorder, the need for treatment is just as urgent for these patients and their families as it is for those who suffer from more common conditions like Alzheimer's and Parkinson's.

JNCL is the most common form of a group of genetic disorders called neuronal ceroid lipofuscinoses (or NCLs). The NCLs include at least nine disorders that are inherited recessively, one faulty copy from each parent. These NCLs are each caused by a different gene abnormality, and are differentiated from one another by age of onset. Although Batten disease refers specifically to the juvenile form of NCL, some physicians refer to all forms of NCL as Batten disease, since all forms share the common clinical features of visual deterioration, seizures, declining cognitive and motor abilities, and premature death. Despite its obscurity, NCL is the most common form of neurodegeneration in childhood, affecting 1.2 out of every 100,000 live births worldwide and even more in Scandinavian countries.

The hallmark of JNCL pathology is the accumulation of ceroid lipofuscin, pigmented granules that build up in a cell's cytoplasm. While cells normally digest the granules and break them down into substances that can be reused or disposed of, in NCLs the granules instead collect within skin, liver, kidney, muscle, and brain cells. Researchers originally believed that the toxic effects of this accumulated material were what led to the death of neurons, but it is now known that there is no direct relationship between the pattern of accumulation and cell death.[3]

Current therapies for JNCL are supportive: Visual aids, anti-epileptic medications, and assistive technologies for motor functioning can improve symptoms and quality of life in the short term. But these interventions do not improve outcomes or meaningfully alter the course of

the disease, and the need for a treatment that can slow or reverse the pathology of the disease is urgent.

Building Blocks of Drug Discovery

The first step of drug discovery is to identify and validate therapeutic targets, typically specific molecules that researchers can manipulate to ameliorate a disease process rather than just its symptoms. The genetic element of Batten disease is an advantage in the search for a drug to treat it. Unlike other neurodegenerative disorders, like Alzheimer's, where the vast majority of cases do not involve known gene mutations, the genetic basis of Batten disease is clear: the disease develops because patients do not make normal CLN3 protein. Though researchers have yet to elucidate the vital function of this protein, restoring that function could mean effectively treating Batten disease.

Given the CLN3 protein's starring role in Batten disease, understanding its function would give deeper insights into potential drug targets. Although Batten disease was first described more than 150 years ago, the mutated gene (*CLN3*) was not isolated until 1995. Sixteen years and more than 450 peer-reviewed publications later, the structure, biochemistry, and functional role of the protein that the *CLN3* gene produces remain poorly understood. What is known is that CLN3 is a transmembrane protein and it is found in the membranes of many compartments throughout the cell, from energy-supplying mitochondria to protein-digesting lysosomes.[4]

Aside from CLN3 protein function, the other big mystery of Batten disease surrounds which subcellular site(s) or dysfunctional processes ultimately cause cell death. While researchers have yet to identify the exact culprit, many potential suspects are druggable, meaning that drugs have been designed to target these sites and pathways in other diseases. Lysosomes and mitochondria both contain the CLN3 protein and are affected in Batten disease, so either could contain potential drug targets. Fortunately, both compartments are druggable: Lysosomes are targeted by the anti-malaria drug chloroquine, and researchers have developed several different pharmacological agents that affect mitochondria and mitochondrial membrane proteins (like CLN3).

Clearly, there is potential for disease-modifying treatment. Both the basic research and the clinical development sides of the drug-discovery process need to combine and optimize their

efforts in order to bring effective therapeutics to fruition in neurodegenerative diseases like Batten disease.

Crossing the Valley of Death

This is, of course, easier said than done. By now, scientists are acutely aware of the valley of death that exists between the preclinical period, when studies identify compounds that have therapeutic potential, and the clinical development stage, when these compounds are assessed for safety and efficacy in human patients. The National Institute of Neurological Disorders and Stroke (NINDS) invests $1.7 billion annually "to reduce the burden of neurological disease" through the funding of biomedical discoveries.[5] This investment has been mirrored on the industry side, where research and development expenditures have been rising steadily. However, from 2000 to 2010, only 12 new drugs were approved for all neurodegenerative diseases combined.[6] Some medications for multiple sclerosis and Lou Gehrig's disease have been shown to slow disease progression, but there are currently no medications that can cure a neurodegenerative disease.

Scientists and drug-discovery experts alike have offered compelling explanations for this gap. One is the explosion and subsequent specialization of the field of molecular biology over the last 40 years.[7] Highly specialized researchers with little clinical or pharmacological experience are now left to their own devices to identify and validate disease targets, which can lead to a problem: Bench scientists can spend years focusing on a promising target without having the expertise to recognize that the compound is actually pharmacologically unfavorable. For example, protein aggregation inhibitors have been widely investigated in academia for their potential to prevent the accumulation of proteins that occurs in many neurodegenerative disorders, including Batten disease. Despite this potential, protein chemists in the pharmaceutical sector have typically found aggregation inhibitors unattractive because of the way they work: These drugs must interact with the target across broad protein surfaces, requiring either a large molecule that cannot cross into the brain or a high dose that can have untenable side effects.

Often, obstacles relate to functional differences between academia, where discovery occurs, and applied science, which lies mostly in the realm of the commercial sector. In academia, career advancement is measured by the frequency and impact of grant funding and subsequent publications. There is little incentive for scientists to move past the basic discovery

stage and, until recently, few resources have been available for doing so.[7] To address this issue, the NIH has taken several steps to encourage translation, beginning with the Molecular Libraries Program established in 2004 to identify new chemical probes, which are a means of exploring new targets for drug therapies. For investigators who have identified and validated potential drug targets and are ready to take their research to the next level, universities offer consultative expertise through a national consortium of on-campus institutes called Clinical and Translational Science Awardees (CTSAs). The CTSA program, established in 2006, gives interested researchers a leg up in translating their discoveries by providing pilot funding for projects with translational potential, supplying support staff dedicated to establishing connections with potential collaborators and mentors, and developing core facilities that support translational tools such as biostatistics. A much larger initiative, the National Center for Advancing Translational Sciences (NCATS), is set to be launched in 2012. This new NIH center will support early-phase drug discovery for projects across various NIH institutes, helping discoveries that have therapeutic potential to reach the point of commercial appeal.

To address the difficulty many researchers face in navigating the regulatory maze of translational medicine, the NIH has formed the Cures Acceleration Network (CAN) to hasten the research and development of high-need cures and to help establish protocols that comply with Food and Drug Administration (FDA) standards and other regulatory requirements that often lie outside the researcher's scope of expertise. Finally, the Therapeutics for Rare and Neglected Diseases (TRND) program, established in 2009, is the first federally funded drug-discovery effort specifically addressing rare and neglected diseases. It provides drug-discovery technology and expertise to rare-disease investigators pursuing innovative hypotheses for drug targets.

As several researchers have outlined, there are numerous issues in the translational research process that are specific to nervous system, pediatric, and rare disorders.[8,9] Nervous system drug trials are expensive, and evidence of their clinical effect is often more ambiguous than that of drug trials involving other body systems. The difficulty of showing efficacy using qualitative measures (such as memory and attention) for some nervous system disorders, especially taking into account the variation between patients, can make trials even more expensive and difficult than those that assess more straightforward quantitative measures like blood pressure.

Because of the unique challenges of drug development in neurodegenerative disorders, researchers have discovered many compounds that initially showed great promise but ultimately failed in the clinical phase. Sometimes failure is related to the safety of the drug, but more often researchers find a compound to be safe but ineffective at modifying the disease of interest. Giving scientists access to libraries that contain some of these compounds may empower them to repurpose a drug for a different disease where it may be more effective. This repositioning can significantly decrease the time it takes to bring a drug to market, as most of the compounds have already undergone preliminary studies and can be brought very quickly into the clinical stage. The tactic appears to pay off: 40 percent of the 49 new medications that reached their first market in 2010 were repositioned.[10]

As research subjects, children exhibit age-specific differences in physiology, pathology, and pharmacodynamics; a difference in age of a year or two between two adults seems inconsequential, but two children with the same age gap could show major physiological differences. The result of this is a global lack of baseline information.[11] The scarcity of pharmacologists dedicated to pediatric disease is also a challenge: In 2000, the European Union estimates, 75 million children were treated by 45,000 pediatricians but only 12 pediatric pharmacologists. Perhaps this is one reason why 50 percent of the medications used in children's hospitals are not specifically licensed for children.[12]

Studies of rare diseases often have trouble recruiting enough patients, and thus it is difficult to accomplish rigorous, statistically valid clinical trials that could establish efficacy. Rare diseases like Batten are also inherently less attractive to pharmaceutical companies, since they are likely to be less profitable. However, patients with rare diseases are no less deserving of a cure for their illnesses. Further, Batten disease exhibits several pathological characteristics that are common to other neurodegenerative diseases, so a drug developed to treat Batten could potentially be a boon to drug-discovery efforts in these other disorders as well.

With these points in mind, the NIH and other government agencies have introduced several initiatives focused on advancing rare-disease research. President Ronald Reagan signed the Orphan (rare disease) Drug Act in 1983 to incentivize the pursuit of drugs for these illnesses. The act provides manufacturers of orphan products market exclusivity, a tax credit, and research grants for testing new therapies for rare diseases. Additionally, the Rare Diseases Act of 2002 established the Office of Rare Diseases Research (ORDR) to provide information on and support

for research into rare diseases. The TRND program, mentioned earlier, currently funds five pilot projects in rare diseases. And this past March, Pennsylvania Senator Robert Casey introduced the Creating Hope Act of 2011, which authorizes the FDA to award the financial incentive of a transferrable priority review voucher to a manufacturer of a newly approved rare-disease drug, effectively reducing the duration of the FDA review process from ten months to six.[13]

While investigators hail the increasing number of nonprofit and academic institutions devoted to developing potential new drugs, this expansion requires investigators to make a difficult choice as they must try to find the center that contains compounds that are most likely to be successful. The Beyond Batten Disease Foundation and others are working together to create sharing mechanisms so that researchers will not be limited to on-site libraries but will have access to shared expertise and compounds across institutions.

While it is clear that an increasing amount of energy and capital are being put into addressing specific obstacles at individual steps of the long translational process, gaps remain between the steps. In essence, these programs provide the support beams that are vital to building a sturdy bridge to span the valley of death; the bridge itself that will connect these beams to each other still needs to be constructed.

Brainstorming Solutions

Given the many challenges of finding effective treatments for neurodegenerative disorders like Batten disease, prevention is currently the best treatment. Preconception screening, together with genetic counseling for potential parents who carry genes of recessively inherited diseases, has resulted in remarkable declines in the incidence of Tay-Sachs disease, another inherited neurodegenerative disease that results in death following the first few years of life. Despite this success, carrier screening has not been widely adopted by the medical community as a means of preventing other recessively inherited childhood diseases. Given the lower cost of testing compared to caring for children with these conditions, screening tests available to the general population may be a way to reduce suffering while bypassing the challenges of drug discovery altogether. The Beyond Batten Disease Foundation and the National Center for Genome Resources have worked together to develop a preconception carrier screening test for 595 severe recessive childhood diseases.[14,15] While it is hoped that the test will reduce the incidence of the disease in the future, the quest to find a therapeutic treatment continues.

Foundations and patient advocacy groups are becoming increasingly aware that while government programs can assist researchers at any stage of the translational research process, the foundations themselves must take on the responsibility of facilitating movement along a clear, continuous pathway from bench to bedside. In 2009, FasterCures brought together more than 600 medical research executives, scientists, policymakers, and funders from 575 organizations to participate in the first of what has become an annual solutions-focused dialogue about some of the most pressing challenges of translating basic discovery into disease treatment. That same year marked the formation of the Kakkis EveryLife Foundation, which has adopted the mission of making the regulatory process smoother for rare-disease treatments.

One of the best methods for foundations to steward their disease-specific missions across the valley of death is to literally bring the two sides together. In February 2011, for example, the Beyond Batten Disease Foundation, NCL-Stiftung, and the Batten Disease Support and Research Association (BDSRA) cosponsored the Drug Discovery in JNCL Conference with the goal of creating an action plan between academic researchers trying to understand the disease and drug-development experts highly experienced in all phases of the drug-discovery process. In place of the traditional scientific-conference platform, at which participating members present their recent findings in order to garner the interest of potential collaborators, the conference was structured as a think tank-style dialogue. Participants engaged in discussions regarding therapeutic targets specific to Batten disease; these discussions were designed with the help of experts from federally funded translational programs such as TRND and NCATS as well as leaders from the nonprofit medical research sector who are recognized for their ability to combine their ideals with business smarts to achieve treatment success.

This conference was the culmination of a continued effort to identify and meet the translational needs of researchers so they can provide patients and families with the greatest chance for effective treatment. It followed a year-long analysis of the state of the science in Batten disease that explored what critical information about the disease remains unknown, what information needs to be understood before moving forward, and what funding models would be most conducive to accelerating the transition from basic findings to treatment. Prior to the conference, participants attended an interactive Webinar series led by Batten disease researchers to introduce drug-discovery experts in North America and Europe to emerging findings in Batten disease. In turn, Batten disease researchers attended the 5th Drug Discovery for

Neurodegeneration: An Intensive Course on Translating Research into Drugs. This annual didactic conference, sponsored by the Alzheimer's Drug Discovery Foundation, focuses on training scientists in the process of translating research findings into treatments for neurodegenerative diseases.

The conference was an opportunity to establish specific milestones for future drug-discovery efforts in Batten disease and to launch functional working relationships between scientists and industry experts. Other fields, especially small, insular groups researching rare diseases, could potentially benefit from designing and implementing similar strategic research plans that are generated and implemented collaboratively, inviting input from experts at all levels of translational research. Nonprofit foundations can provide the venue for generating these plans as well as the structural oversight to keep them running smoothly.

The Future

It is shaping up to be a big year for neurodegenerative drug discovery and Batten disease research. As relationships between academic researchers and drug-development experts that were formed at the drug-discovery conference continue to evolve, both sides hope this effort will translate into progress in developing a treatment for those affected by Batten disease. The preconception carrier screening test will be an enormous step toward protecting future generations from Batten disease and 594 other rare inherited childhood diseases.

On a larger scale, the success of these initiatives in developing disease-specific strategies, education, and resource management could also encourage researchers of related rare pediatric diseases to implement similar programs. These nontraditional and direct efforts to foster collaborative research environments spanning from academia to industry may guide future approaches to crossing the dreaded valley of death. With the institutional framework and necessary tools in place thanks to heavy lifting by the NIH, FDA, and other organizations, nonprofit foundations now have the opportunity to construct a clear, navigable pathway that will empower researchers to turn an ordinary molecule into vital medicine.

Danielle Kerkovich, Ph.D., has extensive experience working with federally funded research through the Department of Veterans Affairs as the acting assistant director for rehabilitation research and spinal cord injury/central nervous system disorders portfolio manager of the Veterans Administration 157-hospital system. At the start of current U.S. military conflicts through 2007, she identified current gaps in health care for soldiers returning from Iraq and Afghanistan, designed more than 50 scientific review panels, authored congressional briefing books, and proposed unique funding mechanisms between the VA, the Department of Defense, and others. In addition, she has worked as an advisor to medical research foundations in pediatric cancer, cerebral palsy, and burn injury. Dr. Kerkovich has been a peer reviewer for the National Institutes of Health, the National Science Foundation, the National Institute on Disability Rehabilitation Research, and the Defense Advanced Research Projects Agency. She was recently appointed principal scientist of Beyond Batten Disease Foundation to develop investment strategies to create a pipeline of foundation-funded and collaborative research activity with the potential to move from basic science, to proof of concept, to clinical candidates for Juvenile Neuronal Ceroid Lipofuscinosis. She received her Ph.D. and M.S. degrees in biomedical sciences from the Albert Einstein College of Medicine of Yeshiva University with a focus in developmental neuroscience.

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