Animal Models and Juvenile Batten Disease

As the battle to find a cure for juvenile Batten disease continues, many have joined the fight. However, not all are of the human variety. Animals are key contributors to medical research. Mouse models are involved in 75% of research, largely because they have similar reproductive and nervous systems and suffer many of the same diseases as humans. Their short lifespans and fast reproductive rates make it easy to conduct "long-term" studies, while their size makes them cost-effective. Mice, genetically-engineered to have juvenile Batten disease, are hard at work contributing to our understanding of the disease, helping researchers watch the disease progresses and identify potential drug targets. These models have been highly informative.[16] However, because juvenile Batten mouse models have a very mild form of disease, researchers cannot use them to validate drug targets for severe neurological symptoms.[10] In other words, the drug targets we are most interested in. For this, we need larger, more complex animal models that truly mimic human disease.[1,4] Without these, we cannot truly understand how this disease progresses in children, validate the drug targets found in mice, or determine safe and efficacious dosage schemes. Luckily, Drs. David Pearce of Sanford Children's Health Research Center and John Swart of Exemplar Genetics are taking the lead on developing the first juvenile Batten disease large animal model, a genetically-engineered porcine (pig) missing normal CLN3 protein just like children with juvenile Batten disease.[6,9,12]

Pigs have long been used to model human disease. Because their development, anatomy and neurobiology are more similar to humans than mice, pigs have further advanced understanding and medical treatment of cardiovascular, gastrointestinal, and kidney diseases.[4,13,17] Recently developed neurodegenerative disease pig models of Huntington's disease and Spinal Muscular Atrophy have been shown to display human-like pathology and symptoms, suggesting that a juvenile Batten pig might do the same for us. We are excited that the first litter of juvenile Batten pigs will be born in 2015.[6,12]

Unfortunately, creating this resource is only half the battle. While Drs. Pearce and Swart will be hard at work characterizing the pig and using it to understand basic mechanisms of juvenile Batten disease, use

of juvenile Batten pigs within the pharmaceutical Industry is strictly prohibited. In order for a genetically-engineered (GE) animal to enter the commercial sector and be used by pharmaceutical scientists to test new medicines, it must complete a lengthy and often unpredictable regulatory approval process called a New Animal Drug Application (NADA).[14]

This means that, before GE pigs are sold or shared, Exemplar Genetics must demonstrate that the juvenile Batten pig is safe and effective for its intended use and tested across at least two non-continuous generations. The problem is, at this time, we do not know whether juvenile Batten pigs will be an effective model for the study and treatment of human disease. Additionally, the safety of the animal is difficult to assess since these animals are being bred to study a devastating illness; and third, these animals will not become part of the food chain. In short, NADA regulatory requirements do not "fit" the intended purpose of the animals. Assuming NADA guidelines will be enough to satisfy the FDA and result in approval, it will take a minimum of three years to obtain this data.[5,14]

Unfortunately, NADA guideline fulfillment may not be enough to satisfy the FDA. Regulatory decisions are often subject to political pressures unrelated to the safety of the product. Case-in-point, the FDA has stalled for more than four years on deciding whether to approve a genetically engineered salmon.[3,11] In fact, only one NADA has been approved since it was enacted six years ago. The road to approval is littered with inexplicable delays, canceled programs, and failed companies who could not survive the FDA's regulatory approval waiting periods. In 2012, the New York Times reported that AquaBounty, the company that produced the genetically-engineered salmon, had to reduce its staff by more than half and had only enough funds to make it through the next fiscal year.[7] It is estimated that AquaBounty has spent over $70 million to meet the shifting demands of the FDA and still has not obtained approval to sell its product.[8,15]

Beyond Batten Disease Foundation (BBDF) is taking a close look at what these delays and roadblocks will mean for developing treatments for juvenile Batten disease. BBDF-funded researchers have identified six drugs that could change the course of the disease by providing affected children and their families with increased quality of life and more time together. If we cannot test these drugs on Exemplar's GE pigs prior to clinical trials in humans, then families will be left with the decision to expose their own children to the unknown effects of these drugs. Companies capable of creating other juvenile Batten GMOs will choose to develop products with clear and timely regulatory pathways. The National Institutes of Health and

foundations like BBDF will be forced to shy away from funding models we cannot use regardless of their potential positive impact on the treatment of disease.

Danielle Kerkovich, PhD, Principal Scientist of BBDF, recently spoke at a Briefing in Washington, DC, organized by BIO.[2] BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations in the US and abroad. Together with Dr. Swart of Exemplar Genetics and Dr. Edwards of BIO, Dr. Kerkovich discussed the need for rapid pharmaceutical access to large animal models. [2] Additional visits to the US House of Representatives and Rare Disease Congressional Caucus were used to stress the added importance of preclinical testing with complex animals in rare diseases where low patient numbers otherwise hamper the creation of clinical trials. Activities, such as these, are one more way BBDF is shaping and advancing juvenile Batten disease research.

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