Summary – BioElectron Update
Guy Miller M.D., PhD & Matthew Klein M.D., MS, FASC

What is BioElectron and Where did Edison go?
Edison evolved from a discussion Dr. Miller had with several patients' families and a foundation head in San Diego approximately 10 years ago. One of the most important areas of medicine is biological energy, they said. If one could begin to understand how biological energy worked, then drugs could be developed for children with mitochondrial disease who desperately needed them and insights could be gained into some basic understandings of biology and begin to apply them. BioElectron, formerly called Edison, is getting larger and growing its mission of fixing kids, learning, and applying.

Ten years into that mission, BioElectron has helped many children and adults with inherited mitochondrial disease and has made some significant inroads in learning how mitochondrial disease works. Some of the basic underpinnings of biological energy and electron flow, known technically as redox in living systems, is now being applied more broadly, not only to medicine, but other areas outside of medicine, including the industrial biology.

Last January BioElectron's Board of Directors looked closely at truly representing the mission of the company. As BioElectron's technology is now being broadly applied, the board and advisors felt the name needed to reflect more accurately and publicly the full breadth of its mission. Given the focus on studying electrons and energy in biological systems, the name BioElectron was selected. All the people who worked at Edison, plus many more, are still with the company, spanning the disciplines of biology, chemistry, mathematics, physics, drug development, clinical science, molecular biology, and medicinal chemistry. BioElectron has a large multidisciplinary team that is tackling fixing kids, learning, and applying the mission of the company.

Although relatively quiet over the last year or two, BioElectron has been collecting data, talking to experts, and assembling a deep and skilled science and technical advisory board.

Dr. Klein discussed the challenges in developing drugs, not only for rare diseases, but the unique pathology and biochemistry associated with mitochondrial diseases, as well as the development status of EPI-743. Please refer to BioElectron's new website, http://www.bioelectron.com/, which includes a multitude of new therapeutic candidates in the pipeline for the development of a broad array of mitochondrial diseases and adult neurodegenerative diseases that have direct applications to mitochondrial disease (slide 2).

Dr. Klein also talked about the general regulatory process. The European Medicine Agency (EMA) has pioneered multiple ways of gaining drug approval in rare diseases. Colleagues are working closely with the Japanese equivalent in BioElectron's Leigh syndrome trial in Japan, called the PMDA.

BioElectron's next steps will be getting EPI-743 into a format with the appropriate regulatory structure so that it can assist as many patients as possible.

Challenges
When setting out to fix kids, learn, and apply, the challenges are many and significant, especially with drug development for mitochondrial disease (slide 3):

- **Heterogeneity** -- The first and probably most significant challenge is the extreme heterogeneity of mitochondrial disease, even within each individual subtype, such as Leigh syndrome or MELAS. There are differences in genetics and in the clinical aspects of disease. For example, two children with a diagnosis of Leighs or even children with a SURF1 mutation causing Leigh syndrome may look vastly different in terms of symptoms, rate of progression, and overall status of disease. These differences are due not only to traditional genetic inheritance issues but the particulars of mitochondrial inheritance, including the concept of heteroplasmy. BioElectron faced a large challenge in trying to study a drug in children when no two children had the same symptoms. When the goal is to study a drug and show that it is effective, it is difficult to do with a group of children who all have different aspects of the disease, are at different stages of their disease, and who are progressing at different rates.
- **Absence of a Validated Natural History**-- Before starting any drug program, it is vital to have a detailed natural history of the disease, outlining:
- symptoms
- timing of diagnosis
- rate of disease progression
- most bothersome symptoms to the patient/family
- potential reversibility for slowing of the symptoms

These are all very important because when designing a clinical trial, decisions must be made regarding:

- who to include (inclusion criteria)
- how long to study the drug's effect to show its impact on the disease
- the most important or common endpoints to target to show that the drug has made a difference in the way the patient's disease unfolds.

Without a comprehensive natural history, studies are more difficult. Keep in mind: Mitochondrial disease, where every disease subtype and every individual mutation within each of those subtypes, probably has its own natural history. The absence of natural history for a heterogenous set of diseases like mitochondrial disease is important.

- **Absence of Validated Clinical Trial Value Endpoints --** The FDA prefers proof that the drug is effective against a "validated endpoint," an endpoint that has been used in previous clinical studies to help get drugs approved for that disease. As no previous clinical trials have been done nor have drugs been approved for mitochondrial disease, no validated endpoints exist. For example, when trying to develop a drug for high blood pressure, a clear endpoint would be

that blood pressure goes down. In a disease like mitochondrial disease, that metric is not known yet.

- **Patient Logistics --** Mitochondrial diseases are highly morbid and patients with mitochondrial disease are very ill, may be hospitalized, and often require equipment such as wheelchairs or assistive breathing devices. When conducting clinical trials at three or four centers in the country, for example, it is just not possible for patients to get from Selma, AL to Akron, OH easily. For a child who has a wheelchair and breathing devices, and siblings at home, how does that child participate if he needs to be seen at a study site every month or every other month? When organizing clinical trials for Mito, therefore, a number of children or adults are automatically eliminated.
- **Absence of Clinical and Regulatory Precedent --** Not having previous clinical trials done in this area means there is not a set of endpoints that has been used and accepted by the FDA. Secondly, the FDA and other regulatory authorities don't know what Leigh syndrome, MELAS, or MERRF are as there has never been a drug approved for these diseases. A large educational component about these rare diseases is just not there. It has been difficult to get alignment and guidance on how best to move forward in developing a drug for a disease that is relatively unknown.
- **Disease Rarity and Disease Severity --** Most with experience with Mito understand that mitochondrial diseases are rare and very severe in terms of the impact on patients, which makes all the other challenges mentioned significantly greater. There are not thousands of patients enrolled in clinical trials with any one specific disease subtype, rendering large, randomized, controlled studies difficult. Also, the fact that the disease is so severe and rapidly progressive means that even if a patient meets all inclusion criteria, he or she may be so rapidly declining that getting to the study site, screened, enrolled, and put into a trial become impossible. In developing a drug for mitochondrial disease, BioElectron was aware of these challenges, but still decided to move forward and start treating children. EPI-743 studies cast a broad net across many different mitochondrial disease subtypes and some other diseases that are similar in terms of their biochemistry and pathology to mitochondrial disease, with the goal of demonstrating:
- the drug is safe and well tolerated, which, of course, is the most important thing;
- the drug has what is called predictable pharmacology, which means that when given in a certain dose a certain number of times a day, drug levels are reached that can have an effect;
- the drug has a clinical benefit measured against a whole number of different metrics.

Development Status

BioElectron now has conducted 18 clinical trials and treated over 400 patients, ranging in age from 22 days to 69 years old, living on six continents. After providing over 1 million clinical doses of EPI-743, the data clearly states that the drug is safe and well tolerated even in the most ill children, and has demonstrated predictable pharmacology with current dosing. Finally, as reported in several clinical studies, clear evidence of

clinical benefit has been recorded across a number of metrics (slide 4).

New Drug Application Process -- Leigh Syndrome
The overall regulatory status of new drug approval is lengthy (slide 5). Phase 2 of EPI-743 has been completed. Four components are needed for a new drug application, and EPI-743 has accumulated the necessary data to fulfill each of those portions:

- the non-clinical package is complete;
- the chemistry manufacturing and controls;
- the necessary regulatory guidance is in place;
- clinical – BioElectron has collected a body of evidence across trials that has demonstrated a beneficial effect of the drug as measured by a number of different important endpoints.

Next Steps include translating the signs of clinical benefit along with the large body of evidence demonstrating that the drug is safe and well tolerated into having EPI-743 available to patients who may benefit from this treatment (slide 6). BioElectron clearly articulated the challenges faced in the development of a drug for mitochondrial disease. BioElectron will work closely with the FDA, as well as regulatory authorities in Europe and Japan, to define the optimal path forward to get EPI-743 approved.

Questions
Q: Does the FDA need to change, fundamentally, how it evaluates drugs, given that as more is learned about the genotype and phenotype of mitochondrial disease, the variability and heterogeneity of this disease may not fit into past study models?

Dr. Miller: We have had great interactions with the FDA. I gently remind the mitochondrial community that in 2009, on the basis of the rarity of mitochondrial diseaseand truly, only a laboratory piece of data, the FDA issued an expanded access IND with amazing urgency to do two things:

1. Make EPI-743 available from a regulatory perspective as fast as possible, to help as many patients within 90 days of the end of life. The FDA took extraordinary attention to mitochondrial diseaseat a rate of action that was unparalleled: a turnaround time of one day. They assumed immense risk within the regulatory structure and guidance and surveillance because the drug had not gone through all four phases of clinical development. The risk/benefit was clearly seen by the FDA and our expert advisors. The FDA certainly has a keen appreciation of the urgency and severity of these diseases. These are not simply regulatory challenges but are challenges that clinicians face every day and are, of course, challenges that patients and families face. The FDA, PMD, and EMA are not quite as adversarial or obstructionist as people might make them out to be.

2. We want to make sure that any drug that would come to market in any of the regulatory structures would first and foremost do no harm. Those requirements are very clear and, of course, we support them. The BioElectron experience with the FDA has been positive. The FDA has expressed an immense sense of urgency in

the mitochondrial community to expedite treatments for children with rare mitochondrial disease. We feel a very positive sense of partnership with the FDA, and we both respect the missions and challenges of our organizations.

Q: Will you be seeking approval for EPI-743 for Leber's Hereditary Optic Neuropathy (LHON)?

Dr. Miller: One of the reasons we were drawn to LHON was the seemingly objective sense of vision. What we learned over the course of about 5-6 years is that, while vision certainly is objective, the subtleties of the differences of our loss of vision in LHON do not mirror other well-known diseases, such as macular degeneration. There really are no typical patients with LHON. So while we attempted to identify select patient populations that perhaps would mitigate some of these challenges, we learned rapidly that these challenges extend to virtually all diseases, whether they are mitochondrial optic neuropathies or systemic diseases. Notwithstanding, we are looking very closely at what is going on in gene therapy and fertility therapy with regards to genetic engineering of mitochondria, the so-called "three-parent babies." We are very interested in mitochondrial dysfunction of the retina and the eye, and we are looking very closely at how, when we are developing second-generation drugs, we can advance them.

Q: Define that optimal path forward. The bottom line is we all want to help that path, help construct that path as best we could from a patient advocacy standpoint. How can the patients and advocacy groups help you along that path?

Dr. Miller: Our wish is to see patients live long, productive lives, especially children. With regards to the regulatory path, our wish is that the individuals who are inside the Japanese FDA and the FDA today have taken note of the 10 or so challenges that Dr. Klein elaborated on, and have been able to make clear that the hypothesis-driven approach with a randomized controlled trial that works so efficiently for large homogenous diseases is just simply not applicable to rare, heterogenous diseases in the absence of agreed-upon endpoints. The natural history by virtue of the advances of medicine simultaneously changing while drugs are being developed, compounded by the extreme rarity of these diseases, requires a new way to make medicine available to these populations. We have been advocating this from the very beginning of the path of Edison. What we would love to see happen is a safe and vigilant path forward to approval based on the body of data that has been collected to date and a very clear way to demonstrate safety and tolerability. The good news is the FDA and the patient community and others are beginning to understand the path that we have been advocating is becoming common.

We are indebted to the patient community. Without the foundation of patients, Edison would have never been formed. We are passionate doctors and scientists from all different walks of medicine. While we appreciate the severity of the disease and want to make that impact, the passion of developing drugs and therapeutics is what we do. First and foremost, we need patient participation. It is very laborious and tedious to be involved in natural history studies to attempt to collect a systematic understanding of

these diseases. It's essential for the patient community to participate in these studies so we can further understand the truth of these diseases, and simply not the anecdotal reports. Patients offer a perspective of not only the clinical features of these conditions, but also the reported outcomes and, as new tools and technology become available, the detailed biochemistry and molecular basis of these diseases.

BioElectron will reach out to the mitochondrial community as we begin to build the regulatory dossier as the investigators do that in terms of their clinical trial assessment. But at the end of the day, the responsibility for gaining approval will be on our shoulders.

Q: What is the difference between a clinical trial and a natural history study?

Dr. Miller: The intent of a clinical trial is to assess how a subject responds to an intervention. That intervention can be walking up a flight of steps, a device, a drug, a drug and a device, a diagnosis, and behavior. It is simply a means to study a perturbation of a system with some knowledge of the control of the system. And that control can take many forms. It can be merely an observation that is anecdotal: "Grandma walks better now that she swims in the pool." The types of trials that we would all love to see conducted are what are called "randomized controlled trials." They are oftentimes treated as the gold standard, referred to as a placebo-control trial, to remove any sense of hypothesis-based bias in the design of that trial.

A natural history study is merely observational -- to collect data on subjects over time and merely being an astute observer, without interfering in the collection of the data. So an optimal observational trial would be one in which the participant acts as if they were invisible to the observer and the data collected would have zero impact on how the participant was behaving. Problems occur when the observers and the participants are interrelated, and the natural history that is being collected does not truly reflect what goes on in the disease.

In summary, a natural history study gathers an understanding of how a disease evolves over time; a clinical study strives to understand how an intervention impacts a subject enrolled in a study.

Q: How has EPI-743 helped patients specifically?

Dr. Miller: Our principal investigators and advisors as well as regulators would agree that we have seen unambiguous signs of clinical benefit. I think the general impression of the clinical investigators who have conducted the studies is that clinical benefit has ranged on virtually all organ systems in a variety of clinical settings.
The one we have most recently focused on is built upon a body of data that has been obtained at the Children's Hospital of Philadelphia looking at the morbidity associated with Leigh syndrome, in particular around hospitalization and severity of disease. They have conducted an extensive review on mitochondrial disease, how it progresses, and the association with hospitalizations and morbidity or unfortunate outcomes associated with the disease. What we have observed in our Leigh syndrome trial in the States, as

well as in Europe and Japan, is an unequivocal reduction of hospitalizations associated with those patients who have been in the treatment arms of the trial. I think that we are prepared to say that we are meeting an analogous level of evidentiary requirement.

Q: How does compassionate use work in a rare community for these drugs that are not quite through the FDA yet?

Dr. Miller: The FDA has multiple vehicles where patients can gain access to drugs prior to FDA approval. They include compassionate use, in some cases, expanded access programs as opposed to individuals being granted access on a case-by-case basis. There are also vehicles such as treatment INDs that can be a modicum of reimbursement to companies as they are making the drug available for clinical testing.

So, I think the general question is how can you gain access to a drug prior to it being approved.

If the question is more to the point, is there an expanded access compassionate program that is open right now for EPI-743, the answer is no. We enrolled numerous subjects, close to 100, in the expanded access compassionate use in the 2009 IND. At this point, we simply do not have sufficient drug to be enrolling subjects further into that study. Certainly, we are beginning to get more clarity on drug synthesis and availability for commercial use production; we would anticipate that being a significant part of the approval process.

Q: What is the best way to obtain a copy of the study results when they are available.

Dr. Miller: The classic way is through peer-reviewed publications. We are working right now with our principal investigators in drafting the summaries of these collective experiences. The clinical studies in each of these conditions have fairly lengthy "extension periods," which I think are critical to the full evaluation to gain a proper perspective on the treatment or absence of a treatment effect. One of the questions we have been asked is, 'If a clinical trial lasts 6 months, why isn't there a study report in 61/2 months?' Then we would have a caution, which is while the placebo portion of a clinical trial can last 6 months, the extension phase of trial can run an additional one or two years. The desire we have is to not issue out premature data, but to have a completed data set that we can generate as was envisioned in the design of these trials. In each of these circumstances we will do what is industry standard and customary, which is to submit the results for peer review publication.

In closing, Dr. Miller noted that there is a whole shop of people who feel as passionate as he and Dr. Klein do. We are yet again reminded how important the work is that we all undertaking. With regard to the FDA, I think we are all in this boat together and we are standing on the shoulders of giants. We are very cognizant that EPI-743 is not the best drug that this company will produce, but we are very cognizant that we have to start with a first drug and that we will learn and iterate and become smarter each time. Many more people will come into this field to work on the work that we have set in motion. So, I

think that it is a virtuous cycle that we are looking to get started with getting 743 access more broadly into the patient community, which we are ready to champion and we certainly can't do it without the full support of all of the stakeholders in the community.

Additional Reading

BioElectron's website

EPI-743 for Metabolism or Mitochondrial Disorders

Clinical Trials in Mitochondrial Disease: An Update on EPI-743 and RP103

Edison Pharmaceuticals Announces Positive Results from Phase 2 Placebo-Controlled EPI- 743 Leigh Syndrome Trial

EPI-743 reverses the progression of the pediatric mitochondrial disease--genetically defined Leigh Syndrome.