Lowe Syndrome International Workshop Summary

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Over many years, basic research has led to a much greater scientific understanding of the disturbances in the internal workings, the biochemical pathways, in Lowe Syndrome. The Lowe syndrome gene makes an enzyme in the cell, called a "phosphatase" that removes a molecule of phosphate from a fatty substance in cell membranes called phosphatidylinositol [4,5] bisphosphate. Loss of this enzyme results in having too much phosphatidylinositol [4,5] bisphosphate and not enough of other related substances. This imbalance interferes with many processes in the cells. Understanding the biochemical abnormalities has given scientists clues on how one might manipulate these pathways with chemicals or drugs in order to rebalance the levels of these substances to improve or correct the defective functioning. This research has also provided the tools needed to test whether a particular chemical or drug can reverse the disturbances caused by loss of the Lowe syndrome gene. These tools include cells, whose appearance or behavior is abnormal when the Lowe syndrome gene is defective, and animal models (flies, fish, mice) in which certain processes, such as kidney function, are abnormal when there is a defective Lowe syndrome gene.

Recently, scientists in five different countries have made much progress in finding chemicals and drugs that, in part or nearly completely, restore normal function in cells and animals lacking the Lowe syndrome gene. The Lowe Syndrome Association (LSA) leadership decided it was time to host an international scientific meeting to allow scientists to compare

notes and share the work they are doing on finding chemicals or drugs to treat abnormal kidney function in Lowe Syndrome. As an unintended, but welcome, side-effect of the COVID-19 pandemic, the meeting had to be held by videoconferencing, thereby greatly reducing the cost of holding such a meeting.

On December 2nd and 3rd 2020, the Lowe Syndrome Association and the Centre of Excellence in Commercialization and Research (IRICOR) at the University of Montreal in Canada, joined forces to host a virtual International Workshop focused on reviewing and sharing information on progress that has been made just in the past few years in developing drug therapies for Lowe Syndrome. The meeting was organized by Jeri Kubicki from the LSA and Alix Molinier from IRICOR.

The meeting was attended by members of LSA leadership and Board (Jeri Kubicki , Cori Langert-DeGori and Lisa Waldbaum), representatives of IRICOR (Alix Molinier Violetta Dimitriadou), speakers from five countries (listed below along with select members of their research team), members of the LSA Medical and Science Board (Drs. Eileen Brewer, Robert Nussbaum, Sharon Suchy, Yang Sun), and Dr. Francesco Emma, a physician and research expert on renal tubular disorders from Rome, Italy. Dr. Tiina Urv representing the Rare Disease Clinical Research Unit at National Center for Advancing Clinical Translational Science (NCATS) at NIH gave advice on how to launch clinical trials for rare diseases.

Speakers (Alphabetical Order) were:

Dr. Claudio Aguilar, Purdue University, Indiana

Dr. Eileen Brewer, Baylor College of Medicine, Houston TX

Dr. Sebastien Carreno, Montreal, Quebec, Canada

Dr. Antonella De Matteis, TIGEM, Naples Italy and Leopoldo Staiano, a scientist in her group

Dr. Olivier Devuyst, ITINERARE Consortium, University of Zurich Switzerland and Dr. Marine Berquez from his lab.

Dr. Jenny Gallop, Cambridge University, UK and Jonathan Gadsby from her lab

Dr. Herb Lachman, Albert Einstein, New York and Jesse Barnes, a student in his lab

The Workshop began with an overview given by Dr. Brewer of the clinical features of Lowe Syndrome, with emphasis on the kidney problems. Drs. Aguilar, Carreno, De Matteis, Devuyst, and Gallop then described different cells and animals in which they could see clear differences in the internal functioning of cells in culture and abnormal kidney function in different kinds of animals when the Lowe Syndrome gene is defective, compared to what they see when the gene is normal. Each scientist then used different approaches to look for chemicals or drugs that would reverse the changes seen in cells or animals with a defective Lowe syndrome gene and make them look more like normal cells or their kidneys function more like normal kidneys. Six different compounds have been found. Three of them are already approved for use as drug therapies for other diseases – studying their impact on Lowe Syndrome is what is known as “re-purposing” an already approved drug. Re-purposing greatly streamlines clinical trials since much of the work around dose levels, mode of administration (oral or by injection) and whether the drugs have serious side-effects have already been done and the drug is approved for use for other diseases (none of which bear any relationship to Lowe syndrome). That said, these drugs have primarily been tested in adults only versus children (pediatric use). A fourth very promising compound is in late clinical trials now, not yet approved, but has already been shown not to cause bad side effects. Two additional

compounds are not approved drugs but one of them appears to act to correct the defect in Lowe syndrome by the same mechanism, through the same pathway, as one of the approved drugs. This corroborative evidence strengthens the conclusion that drugs or chemicals working on this pathway have the potential to reverse the abnormalities seen in kidney tubular cells from patients with Lowe Syndrome. Being able to improve or correct the defective function of the kidney tubular cells in Lowe syndrome would be a first, very early step, in developing drug therapy for the kidney abnormalities in Lowe Syndrome.

Dr. Lachman spoke about his work on another critically important area of Lowe syndrome, the brain. With funding from the LSA, Dr. Lachman has developed cells called "induced pluripotent stem" cells, known as iPS cells from three Lowe syndrome patient cells and a number of normal control cells. These iPS cells can be induced in culture to become nervous system cells, and he can demonstrate clear changes in these cells when the Lowe syndrome gene is defective. These cells can now be tested for whether the same compounds and drugs that appear to reverse the abnormalities in kidney cells will also work in nervous system cells. Finding drugs that can reverse the abnormalities in nerve cells would be a first step towards developing drug therapies for some of the neurological problems in Lowe syndrome.

The final session of the meeting focused on how to launch small clinical trials for some of the already approved drugs to determine if they can improve the kidney function of Lowe syndrome patients. In the US, there are challenges with organizing such trials, funding them, obtaining the necessary regulatory approvals, and, very importantly, identifying clinical researchers willing to lead such efforts. Funding and advice is available from the NIH but the

funding cycle is very long and may have to wait until 2025, with no guarantee of success. Dr. Urv emphasized the importance of natural history studies and patient registries to have collections of data that clearly delineate the abnormalities in Lowe syndrome patients so that any intervention, such as a drug treatment, can be understood either as being successful or not. There was strong advice to establish partnerships beyond just Lowe syndrome when looking to launch trials, for example with already existing clinical trials of conditions related to Lowe syndrome, such as cystinosis or Dent2 disease, which is due to particular changes in the same gene as is defective in Lowe Syndrome. Drs. Emma and Devuyst made a strong case for the European Research Networks (ERNs), of which one is dedicated to kidney disease (ERKnet), operating in 28 countries, across 80 expert centers for kidney disease (www.erknet.org). Clinical trials can be funded by the European community.

The meeting adjourned with a heightened sense of optimism that the scientific community has collected enough data to justify proposing a clinical trial of some of the already or soon-to-be-approved drugs. This is by no means to say that a treatment for Lowe syndrome is imminent – there is much work to be done to figure out if these clues from cells in culture or model organisms really translate to potential therapies. Much more work needs to be done but we have moved one step closer to finding treatment.

How can the Lowe Syndrome Community help advance treatment efforts?

1. **Join the patient registry.** We need as complete a clinical picture as possible of the boys and men in this country with Lowe Syndrome to further efforts to find treatments. Please complete a patient registry and update it annually or when any significant change occurs in your child with Lowe Syndrome. The link to the registry can be found at the bottom of the

Lowe Syndrome Association webpage: http://lowesyndrome.org or here: https://cordsconnect.sanfordresearch.org/BayaPES/sf/screeningForm?id=SFSFL

2. **Share the name of your nephrologist.** We want to engage with them to develop an informal network of clinicians interested in renal tubular dysfunction who may possibly be willing to participate in clinical trials. Send the name and contact information to Jeri Kubicki at jgkubicki@gmail.com.

From the very beginning, the parents and their children with Lowe Syndrome have been essential to all of the progress that has already been made in understanding this disease, finding the gene responsible, providing the samples used to study what goes wrong inside the cells and tissues in Lowe Syndrome, and fundraising to raise awareness and fund research. It is time to take the next step: continue your essential participation in moving therapies forward. We thank you for your commitment to this important effort!

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