

LAM Publications in New England Journal of Medicine (NEJM)

The roadmap that the LAM Foundation has charted to find an effective treatment for our disease is simple: gene, protein, pathway, target, trials, therapy. The first step began in 1995 as the "Journey of a Thousand Miles", and was achieved in 2000 with Dr. Elizabeth Henske's discovery of the importance of tuberous sclerosis genes in LAM. Dr. Vera Krymskaya then showed us in 2003 that the cellular pathway that was affected in tuberous sclerosis was also relevant to LAM and that LAM cells responded to rapamycin. Drs. Ray Yeung and David Kwiatkowski demonstrated that tumors in mice and rats with tuberous sclerosis shrunk on rapamycin, and based on his laboratory data, Dr. Richard Lamb from England first uttered the heretical suggestion that we might treat LAM patients with rapamycin. The discoveries of these LAM Foundation-funded scientists, and those of countless other partners in the tuberous sclerosis and Drosophila biology fields, has now brought our destination into focus.

The January edition of the New England Journal of Medicine (NEJM), the most prestigious of medical journals, published the first prospective study of a drug treatment for LAM in history. The LAM Foundation was an active partner in patient recruitment and was the first to offer peer-reviewed support for the trial, which played a pivotal role in attracting additional funding from federal agencies. The results of the trial confirm the predictions from ten years of LAM Foundation funded cell and animal model experiments in the laboratory; that therapy which aims to replace the function of the missing tuberous sclerosis proteins in LAM has promise in the treatment of the disease.

The primary purpose of the NEJM study was to determine if sirolimus could quiet the cellular chaos that tuberous sclerosis DNA mutations caused in the organs of patients with LAM or tuberous sclerosis. The most measurable of endpoints was chosen to assess the sirolimus response, the size of kidney angiomyolipomas (AML). The idea was that if AML size could be reduced with the drug that perhaps other disease manifestations such as LAM would respond similarly. Sirolimus treatment resulted in a 50% reduction in AML tumor size over the first year of treatment; a truly remarkable result. But the biggest surprise was that over the same period the lung function improved by approximately 10% in the patients who had LAM, during a period in which a 2.5-5% loss of lung function was expected. Although kidney tumors started to grow again and lung function improvements waned somewhat after the drug was stopped, the resounding message is that we have confirmed the promise of a drug and a molecular target developed in the laboratory.

This does not mean that sirolimus is recommended as a treatment for women with LAM at this point. Treatment only makes sense if the risks outweigh the benefits and we don't have a clear answer to that question. There were side effects in this trial, including mouth ulcers, elevations in cholesterol and hospitalizations for pneumonia, mouth ulcers, diarrhea, cellulitis and palpitations. Pulmonary function tests are effort dependent, and the psychological effect of being on the drug might have affected the results. Furthermore, a smaller trial from England reported in this issue of the Journal had no effect on lung function, albeit in only three patients. So we need a larger trial designed to keep us honest - one in which neither the doctor nor the patient knows if the drug is on board when testing is done and interpreted. This is the only way to prove if sirolimus can help patients with LAM. This is why the Foundation launched the Multicenter International LAM Efficacy of Sirolimus Trial, named MILES to reflect our continuing journey on the path to effective treatment.

Another major focus for The LAM Foundation has been to improve the ability of the medical community to make the diagnosis of LAM. A letter published by Drs. Lisa Young, Yoshikazu Inoue and Frank McCormack, in the same issue of NEJM, reports that a blood protein called VEGF-D levels may be useful to distinguish LAM from other diseases that produce cysts on CT scans and to predict the presence or absence of LAM in women with tuberous sclerosis. The

availability of a simple blood test to assist with the diagnosis of LAM could potentially reduce the need for lung biopsy and perhaps facilitate clinical trials in the future.

An editorial by Drs. Elahna Paul and Elizabeth Thiele, also in this issue of the NEJM, expresses enthusiasm and caution in the interpretation of all three studies. We could not agree more.