# Lymphedema medication brings hope

## Exciting potential for a new pharmaceutical solution.

Please enjoy this extended version of our interview with Dr. Stanley Rockson, published in *Pathways* Fall 2017. We have published this edition online only, for our readers interested in taking a more in-depth look at Dr. Rockson's research process and findings. In this article, we offer over 1000 words not printed in *Pathways.*

*Dr. Anna Towers and Anna Kennedy recently sat with Dr. Stanley Rockson at the International Lymphedema Framework conference in Italy to learn about the new clinical trial currently underway for an exciting potential new pharmaceutical solution to lymphedema. The purpose of this interview was to help our readers understand what the drug is intended to do, what the implications are for clinical practice and when we can realistically expect the drug approved for general use.*

***Anna:*** *A recent article published in "Science Translational Medicine" created a lot of buzz within the lymphedema community. Not only did the article provide hope for a pharmaceutical solution to lymphedema, but it surprised many people by describing lymphedema as an inflammatory process, rather than a "broken plumbing" issue.*

**Dr. Rockson:** It has taken a long, 15 to 18-year journey to get to the findings of the current study. When I began looking for drug treatments for lymphedema, it became apparent to me that it was unlikely that we would be able to rebuild the "broken plumbing" seen in lymphedema patients. In lymphedema, the plumbing is of such a fine and microscopic nature. The idea that we could undo the damage through growth factors and such seemed did not seem promising.

It occurred to me that in many diseases, the difference between somebody who is prone to the disease and somebody who has the disease has to do with how adaptable their tissues are to the underlying problem. The tissues, and eventually the organs, express the disease. Many people have latent diseases and don't even know they have a problem. An example is heart failure. When we treat heart failure, we use medications that effectively make people asymptomatic. The medications don't make the heart stronger; they just put the disease into a latent stage.

To pursue my idea, the first thing we needed to understand was: what is lymphatically diseased tissue doing, what is it expressing and how is it responding to the flow problem? Remember that for every woman who develops lymphedema after breast cancer, three other women don't, despite having the same loss of lymph nodes, radiation therapy etc.

I decided to use a technique called transcriptional profiling to look at the tissues. Transcriptional profiling allows us to see what the tissues are expressing and responding to. By looking at the RNA expression of cells, we can understand how the genetic blueprint is being expressed.

Using transcriptional profiling, we compared mice with lymphedema to normal mice and to mice that had surgery but didn't have lymphedema. We found an extraordinary profile of inflammation. Almost everything we could detect in the skin of the lymphedema mouse had to do with inflammation and the

immune response. This was somewhat of a surprise in that era (approx. 1996), since until then, people were thinking of lymphedema predominantly in terms of flow issues.

We repeated this work with human lymphedema patients. Although we found other expression pathways that were important (such as vascular growth factors, fat metabolism and fibrosis), again the predominant picture was inflammation.  thought it would be important to think about whether we could treat the inflammatory response of the skin to make the lymphedema go into a latent phase.

Again, we went back to the mouse model and I chose a medication, semi-empirically, based on the patterns that we saw in the profiles of RNA expression. I chose a nonsteroidal anti-inflammatory that has two pathways through which it reduces inflammation. The first of those pathways involves an enzyme called cyclooxygenase. That's the pathway that most anti-inflammatories work on (Aspirin, Aleve, Advil, Motrin or Ibuprofen). They all impair the cyclooxygenase process. We took a drug that does all of that, *plus* it works on another pathway called five lipoxygenase (5LO).

We know that the products of the 5LO enzyme have a profound capacity to create inflammation. Upon using this drug in the mouse model, not only did the lymphedema resolve, but when we looked at the skin and the tissues under the microscope, they also normalized. Everything that we can see in untreated lymphedema, as a pathological representation of the disease, went away. These results not only gave us hope that lymphedema could be treated medically, but challenged the notion that the structural changes of lymphedema are irreversible.

We have completed a clinical trial of about 120 patients, in which we saw a 97% response rate to the same drug we used in the mice. We conducted the trail such that, after the initial observation of the first 60 patients, we did a placebo control double blind component. Of course, the placebo patients did not respond, but the treated patients did. Again, we looked at the skin under the microscope and saw a dramatic improvement in the structural components of lymphedema.

I started to wonder: is this a very non-specific anti-inflammatory response, or could a lymphedema patient go down to the corner drugstore and buy an anti-inflammatory, such as ibuprofen? Alternatively, was it targeting the other pathway, (5LO), that yielded benefits?

We began a further investigation and returned to the animal model (we always ping-pong back from the human to the animal models), where we began to look at other drugs. For example, we looked at ibuprofen and found that it did not make the lymphedema better; it seemed to make it worse. That suggested to us that 5LO and the inflammatory mediators it creates, called leukotrienes, are the key components in lymphedema.

Both inflammatory pathways, Cyclooxygenase and 5LO, use prostaglandins to make inflammatory mediators. Cyclooxygenase makes thromboxane, but we clearly identified that that is not the issue in lymphedema. We began to focus on leukotrienes, the mediator created by 5LO. The 5LO pathway has three sub-pathways, in which it basically creates leukotrienes A, B and C. Leukotriene C is the pathway that’s involved in asthma (up until our work, the major area in which drug therapy is targeted to the 5LO pathway is in asthma, an airway disease.) When we tried drugs that target leukotriene C, they were not beneficial for lymphedema.

One of my colleagues at Stanford was interested in the leukotriene B pathway in another vascular disease and pulmonary hypertension. We began to think, well maybe that's where the action is, maybe

there is a more universal effect from the leukotriene B pathway on endothelial cells. That's where we decided to direct our research. We realized that, if we inhibit 5LO, which is the parent molecule, or we inhibit the downstream pathway that leads to the production of leukotriene B4, we can get the same effect, only the latter is much more potent.

Not only have we localized a mechanism that might be prone to clinical applicability, but we've also learned a lot about the lymphedema mechanism itself. We figured out, by working on the pathway and doing experiments in tissue culture, in animals, in molecular form, that what seems to happen in lymphedema is that once this pathway is turned on, it blocks the lymphatic repair process. Leukotriene B4 actively inhibits the VEGF R3 pathway and the Notch pathways, which are both central mechanisms whereby lymphatic vessels repair themselves. It appears that if we can block the production of leukotriene B4 with a specific drug, we can restore the ability of the lymphatic system to repair itself, mitigate the damage and allow the tissues to begin to heal.

***Dr. Towers:*** *What is the name of this drug and are there any known side effects?*

**Dr. Rockson:** The drug that we tested on animals, and in the laboratory, is a drug that's been in active clinical use in Japan for about 35 years. In its generic form, it is called Bestatin, but the trade name is Ubenimex. Ubenimex, or Bestatin, has been used for over 30 years to treat forms of leukemia in Japan, a completely different action of leukotriene antagonism. Many thousands of humans have been treated quite safely with this drug. It has no identifiable toxicity, and its side effect profile is as clean as any drug can be. In Japan, it has been used in the long term without incident.

We published an article in "*Science Translational Medicine*" earlier this year. A start-up pharmaceutical company, called Eiger, licensed the intellectual property from my scientific work and licensed the drug from the Japanese manufacturer. They now have the license to conduct a human clinical trial.

***Dr. Towers:*** *Please tell us about the current clinical trial.*

**Dr. Rockson:** Our current Phase 2 clinical trial was launched last July. We will be enrolling 45 patients with lower limb lymphedema (both secondary and primary). For the moment, we have chosen not to include congenital lymphedema patients.

The four trial sites are in Stanford, California; Columbus, Ohio; Orlando, Florida and Sydney, Australia. Enrollment is over half complete at this point. We plan to complete enrollment by December. Ideally, the last patient in would complete the trial by the third quarter of 2018, and we will report on the results shortly thereafter.

The end points we are using are: a change in skin thickness, volume, bioimpedance (assessing a tissues ability to resist the flow of an electrical current, to measure body composition), histology (microscopic tissue structures) and quality-of-life measures. We've created a quality-of-life score that's derived from Vaughan Keeley's, but more specifically streamlined for the purposes of this study.

***Anna:*** *Can you share what you've seen in the study so far?*

**Dr. Rockson:** So far, we are very excited. Of course, since it's a double blinded placebo trail, I'm blinded to the identity of the patients I've enrolled. We have upwards of 30 patients in queue at my site right now, with a number who have already completed the entire protocol. A subset of patients is improving, and we can only assume they are not in the placebo group.

***Dr. Towers:*** *Do you think that it might be possible to target people, for example those who have just completed breast cancer surgery, and use this drug to prevent lymphedema?*

**Dr. Rockson:** Absolutely. Testing the notion that what can be reversed can also be prevented makes sense on paper, and I am interested in looking at that. As I have mentioned, we are blocking the production of an inflammatory molecule called Leukotriene B4. Leukotriene B4 has a bimodal mechanism. Like all things in the body, it has a use: at low levels in the tissues, it promotes wound repair. This means that we would not want to initiate treatment in patients, who are for example, pre-sentinel nod biopsy or pre-axillary lymph node dissection, but perhaps it could be implemented after radiation therapy, when the wound healing requirements are minimized. Timing will be important.

I would also like to understand more about the pharmacokinetics of Bestatin. Is treating lymphedema like an on-off switch, where, if you turn it off long enough and you get enough repair, you could eliminate use of the drug? I would expect this to be the case. The theory is that once you repair the vasculature, it will be self-sustaining.

***Dr. Towers:*** *Theoretically, if you have a lymphangiogenic stimulus with this drug, what makes you think that it would not increase the rate of cancer recurrence?*

**Dr. Rockson:** There are two reasons. Number one: we know of Ubenimex's 30-year track history as a cancer therapeutic. Although there is not an existing database to tell us what happens to lymphedema in its use, we have strong evidence to suggest that it's not pro-neoplastic, it's anti-neoplastic, at least in the settings in which it has been used (neoplastic meaning an uncontrolled growth of tissue). Beyond that, I wouldn't call this drug pro-lymphangiogenic. It reverses the inhibition of lymphatic repair that exists in untreated lymphedema.

***Anna:*** *Eventually, do you see this drug being effective at different stages of lymphedema?*

**Dr. Rockson:** Yes. In the forerunner study that led to the discovery of this drug, I had patients that had had lymphedema for as long as six decades who responded. This idea that the tissue changes of lymphedema are irreversible is being challenged. For a long time, people thought you must catch lymphedema in time so you don't end up frozen with it forever. Maybe we can do something for all people: people who are at risk and hopefully people who are at various stages of the disease. I'm hoping that the human trial replicates what we've seen in animals and in the forerunner trial to date. I'd like to believe it will.

***Anna:*** *How do you plan to continue with this research after the trial has concluded?*

**Dr. Rockson:** Of course, if we get positive results, the sponsor will be predisposed to continue further studies. We first need to learn more about dosing, duration of treatment, treatment protocols and maintenance protocols. Many subpopulations will then need to be looked at.

In the future, we need to look at the breast-cancer population, as they are not being addressed in the current trial. We are not currently including arm lymphedema for the purposes of homogeneity and being able to report to the FDA. I am also very interested in the potential to use this drug to treat head and neck lymphedema, which is really a profound problem with few solutions. Eventually, we will want to look at congenital lymphedema.

We are also planning a study wholly devoted to primary lymphedema. That study is envisioned to be a two-centre trial at Stanford and St. George's Hospital in London. We're hoping to launch that as this first trial is being concluded.

***Dr. Towers:*** *How long before this drug might be FDA approved and readily available?*

**Dr. Rockson:** If plans go smoothly and there are no impediments along the way, we're probably looking at a three to five-year process. At some point, the pharmaceutical company is going to require data for the FDA on long-term use. That's going to be another investigational mode in which patients will have the opportunity to participate, if they can't do so now.

***Anna:*** *Many of our Pathways readers are not only patients or health care providers, but also advocates for advancing lymphedema care. How can we help promote participation in clinical trials and contribute to the greater knowledge?*

**Dr. Rockson:** Now that we have an exciting prospect, one of the obstacles in the lymphedema community is that the patient population is generally very naïve to the process of clinical trial conduct. This community has almost given up hope, in a way, that science would give them answers. Now answers can come, but it requires the placebo control mechanism. For or individuals who have the disease and are selected to participate in the trial, but end up as recipients of the placebo rather than the drug, their participation is still very important. This trial is a path to the acquisition of the knowledge that one day creates the answer.

Comparatively, people often line up for cancer therapeutic trials because they have other option. While everybody acknowledges that lymphedema is a life changer, it's still predominantly a morbid, but not fatal, condition, so there is a limit to what patients are willing to do. We need the patient base to be supportive of clinical trials if they want the answers they are looking for. We need to invigorate the lymphedema community to understand that now that this exciting development and other things are beginning to happen, it's part of their societal responsibility, to themselves and to their community, to get involved.

***Anna:*** *How much attention has this development garnered beyond the lymphedema community?*

**Dr. Rockson:** The response has been overwhelming. According to their website tracking, within one week of publication, our paper was ranked in the top 2% of all manuscripts that "Science Translational Medicine" has ever published.

You can read the Stanford press release about this research at www.med.stanford. edu. Learn more about the ULTRA clinical trial by emailing rockson@stanford.edu, or visit www.eigerl.com. You can also visit www.lymphaticnetwork.org to learn more about clinical trials.