

For patients with rare diseases,  
the unknowns are unending,  
the diagnoses difficult,  
and the treatments often non-existent.  
But research is bringing new hope.

# DESPERATELY SEEKING ANSWERS

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Coping with a life-threatening disease is never easy. But if only 100 people worldwide have the disease, everything from getting a diagnosis to finding a treatment becomes much more difficult.

People with rare diseases can find themselves trapped in an endless maze of doctors' visits, diagnostic procedures and treatments that don't work. The financial and emotional costs can be devastating as they continue to get sicker, but no one knows why and nothing seems to help.

The sad fact is that there are no treatments for most rare diseases. According to the National Institutes of Health, FDA-approved treatments exist for only about 200 of 6,800 rare diseases, which are defined as diseases affecting fewer than 200,000 Americans.

While the number of people with any single rare disease is small, the big picture tells a different story. In the U.S. alone, at least 25 million people — or nearly 8 percent of the population — are affected by some type of rare disease.

Thanks to recent scientific advances, researchers now realize that even common killers like cancer, diabetes or cardiovascular disease are not single entities, but rather clusters of rare diseases with related symptoms. For this reason, many U-M scientists believe that research on rare diseases could lead to important insights into how to diagnose and treat common diseases. Therapies developed to treat rare diseases today could turn out to be the blockbuster drugs of tomorrow.

The U-M Medical School has a history of achievement in all aspects of rare disease research from laboratory science to clinical care. U-M scientists have identified the genetic and metabolic defects associated with rare disorders like cystic fibrosis, Crohn's disease, Hirschsprung's disease, and hereditary spastic paraplegia. Patients with Wilson's disease and follicular non-Hodgkin's lymphoma are benefiting today from new drugs and diagnostic tools developed and tested in U-M labs and clinics.

The future began to look brighter for people with rare diseases when Congress passed the Orphan Drug Act in 1983. It provided tax credits and market incentives for pharmaceutical companies, which made it profitable to develop and test new drugs for small numbers of patients.

Since 1983, the FDA has approved 350 of these so-called "niche drugs" to treat patients with 200 rare diseases, and others are currently being tested in clinical trials. One of them was developed by James Shayman, M.D., and his colleagues in the U-M Medical School.

Shayman studies lysosomal storage diseases, a group of 42 related disorders with one thing in common: Cells and body tissues are damaged by fatty substances that build up to toxic levels in lysosomes, which process cellular waste. For reasons scientists don't understand, different types of these diseases attack different organs in the body.

"People with Gaucher disease, for instance, develop massive enlargement of the spleen and liver, severe bone disease

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and significant anemia," explains Shayman, a U-M professor of internal medicine and of pharmacology. "Patients with Fabry disease have renal failure and neuropathy. In infants born with Tay-Sachs disease, fatty substances destroy nerve cells and tissue in the brain."

Until recently, there were no treatments for lysosomal storage diseases, but that changed in 1991 when the FDA approved the first treatment for the most common type of Gaucher disease — an enzyme replacement therapy called Cerezyme® that must be injected or given by infusion. A year's supply costs between \$250,000 and \$300,000.

"Worldwide, there are about 4,000 to 5,000 patients currently treated for Gaucher disease with enzyme replacement therapy," says Shayman. "The annual cost to treat those patients is \$1.2 billion."

Since 1988, Shayman has been working on a different approach to the defective enzyme problem in lysosomal storage diseases, an approach suggested by his Medical School



James Shayman

collaborator Norman Radin, Ph.D., who has since retired and lives in California.

Instead of trying to replace the enzyme that lysosomes need to degrade a toxic fatty material, Radin said, what if they limited the amount of the toxic material in the first place?

Shayman and Radin developed a novel class of drug compounds that blocked the activity of an enzyme responsible for production of the toxic fatty material. After proving that their experimental drug prevented disease in laboratory mice, they patented the technology. The University licensed these



Matthias Kretzler

drugs to Genzyme (the same pharmaceutical company that makes Cerezyme) in October 2000, and the company began testing one version called eliglustat tartrate in clinical trials.

Because eliglustat is an oral medication, Shayman says it will be much less expensive than current therapies. But what

really excites him is that the drug also prevents the accumulation of a related fatty material that affects people with another lysosomal storage disorder called Fabry disease. It also appears to block the progression of some types of diabetes and polycystic kidney disease in research animals.

Three worldwide phase 3 trials of eliglustat are now underway in patients with Gaucher disease. If results continue to be positive, Shayman hopes to see his drug on the market within the next few years.

“It’s been 38 years since Norm Radin first proposed the concept of synthesis inhibition for lysosomal storage diseases, and now it’s been proven clinically,” Shayman says. “When I started in research, I never imagined that I would develop a drug and see it used clinically.”

**R**esearch on rare diseases took a big step forward in 2001 when Congress established the Office of Rare Disease Research within the National Institutes of Health. The goal was to create a system of research networks that would bring scientists, clinicians and patients with rare diseases together under one central umbrella. Since then, NIH has established 19 research networks. One of them, the Nephrotic Syndrome Study Network or NEPTUNE, is directed by Matthias Kretzler, M.D., a professor of internal medicine.

Kretzler studies rare diseases that affect the kidney and cause a condition called nephrotic syndrome. These diseases can be deadly, especially the most severe form called focal segmental glomerulosclerosis, or FSGS.

“FSGS is a disease that progresses rapidly,” Kretzler explains. “It’s devastating for patients, because adults and children with FSGS can reach end-stage kidney disease — meaning total loss of kidney function — after only one or two years.”

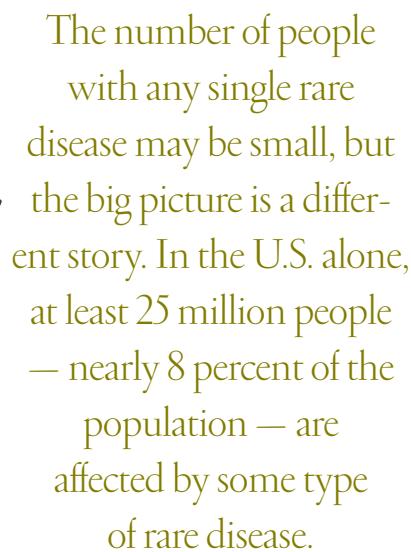
Except for a few rare genetic diseases, researchers don’t know exactly what causes FSGS or other nephrotic syndrome diseases, but Kretzler says they all involve damage to octopus-shaped filtration cells called podocytes, which line millions of tiny blood vessels called glomeruli in human kidneys.

“Podocytes are very sensitive to genetic mutations or environmental challenges from toxins, hormones, diabetes or hypertension,” says Kretzler. “When podocytes are damaged, proteins like albumin start to appear in urine — one of the earliest warning signs of kidney disease.”

When Kretzler joined the U-M Medical School in 2005, his first goal was to establish a multi-institutional clinical research network for the study of nephrotic syndrome similar to a network he had created in Europe. “Michigan

had a strong program in basic scientific research and a long-standing association with a private, patient-interest group called the NephCure Foundation to facilitate this research,” he says.

But clinical research was a different story, Kretzler discovered. Because nephrotic syndrome diseases are so rare, it was difficult for any single institution to find enough patients for a clinical research study. Research programs were scattered across multiple institutions, and each investigator had a different research protocol. Patient records and tissue samples from one study weren’t available to other researchers. There was no established research infrastructure



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available to support scientists working to find causes and develop treatments for these diseases.

So a team of investigators in nephrology set about creating an infrastructure at Michigan. Combining funding from the Medical School, NephCure, the U-M Office of the Vice President for Research and a fund Shayman established to support rare disease research, Kretzler started a small, multi-center translational research study of nephrotic syndrome diseases. Data from this pilot study helped the Michigan team receive, in 2009, a \$6.25 million grant from the NIH Office of Rare Disease Research to establish NEPTUNE.

Today, NEPTUNE has trained researchers at 15 participating institutions across North America. Since October 2010, 52 patients have enrolled in the clinical cohort study.

# RARE CARE

Sometimes the most difficult part of having a rare disease is finding a doctor who can tell you what's wrong. This is particularly true if the symptoms are vague and non-specific, as is the case with a rare disorder called pulmonary arterial hypertension that affects just 15 to 30 people per million.

"Our typical patient is a woman in her 40s or 50s who comes with a two-to-three-year history of shortness of breath that has been slowly progressive," says Vallerie McLaughlin, M.D., professor of internal medicine and director of the Health System's Pulmonary Hypertension Program. "Patients often get shuffled from one doctor to another before someone clues into the diagnosis.

"The most common symptoms are shortness of breath, lightheadedness and swelling in the legs," McLaughlin adds. "When doctors see a patient with those symptoms, there are about 50 things that pop into their head before pulmonary arterial hypertension does."

Pulmonary hypertension is high blood pressure in the lungs. Common varieties are caused by chronic lung, blood or heart disorders. But in the rare form of the disease called pulmonary arterial hypertension, the problem doesn't start in the heart. It starts in cells that line the blood vessels in the lungs.

For unknown reasons, these cells proliferate and thicken. This narrows the opening within pulmonary blood vessels and forces the heart's right ventricle to push harder



Vallerie McLaughlin

and harder to get blood through the lungs. Patients develop shortness of breath, because not enough oxygenated blood reaches the rest of the body. Eventually, the right ventricle can enlarge and fail.

Delayed diagnosis, while common, is a serious problem, because early treatment is important, according to McLaughlin. “When patients present with shortness of breath, it’s not early disease; it’s advanced disease,” she says. “The sooner we can get to patients, the better chance we have of stopping or reversing the changes in their pulmonary vasculature.”

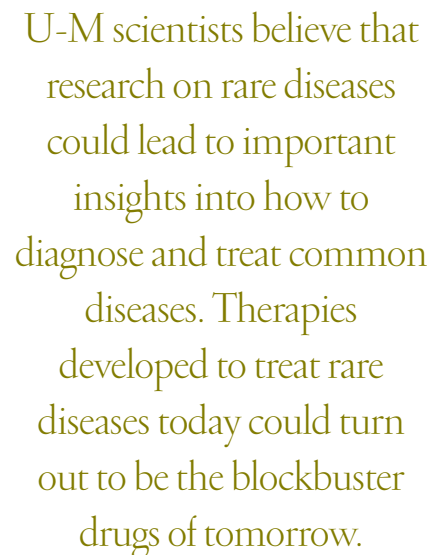
Before 1995, there was no treatment for pulmonary arterial hypertension, but now there are several alternatives available. Even though most patients can be treated, PAH is still a life-altering disease, according to McLaughlin.

“It’s not like they have high cholesterol and you just give them a pill,” McLaughlin says. “Just being on the therapy is a total lifestyle change.”

Early in the disease process, patients can take oral medications, but some require frequent dosing adjustments and regular blood tests. Patients with advanced disease require continuous medication administered through a permanently implanted catheter. The last option for patients who don’t improve with medical therapy is lung transplantation.

McLaughlin stresses the importance of patient education and having nurses available to answer questions from PAH patients. But sometimes nothing helps as much as talking to another patient with the same disease. Support groups are especially important for people with rare diseases. Whether in-person or online, having someone who understands what you are going through can be an important part of treatment.

“You can let the disease get you or you can fight back,” McLaughlin says. “Sometimes bonding with another patient helps you fight back.” —SP



U-M scientists believe that research on rare diseases could lead to important insights into how to diagnose and treat common diseases. Therapies developed to treat rare diseases today could turn out to be the blockbuster drugs of tomorrow.

More than 750 patients with nephrotic syndrome have signed up for a patient registry maintained by the NIH Office of Rare Disease Research.

“This collaborative network allows us to address one of the key challenges of rare disease research — the difficulty of identifying patients for studies,” says Kretzler.

Biopsied kidney tissue, blood and urine samples from patients enrolled in NEPTUNE are stored in a central biobank. Researchers at one institution complete genomic analyses of all tissue samples. Another institution analyzes proteins present in the samples. Detailed clinical information on patients is collected at each study visit and entered in a central database. Statisticians analyze all this information for clues that could help researchers discover what causes the cell damage and scarring associated with nephrotic syndrome diseases.

“While the specific diseases leading to FSGS are rare, the basic mechanism leading to loss of podocytes and scarring are probably the same between FSGS and other glomerular kidney diseases,” says Kretzler. “So if we can understand FSGS, there’s a real chance we could help patients with all glomerular diseases.”

Kretzler and Shayman are just two of the many U-M investigators whose research is making it possible for more people to live with rare diseases, instead of dying from them. With millions of patients still waiting for an effective treatment, however, much work remains to be done. [M]