Research Changes Lives

For half a century, immunologists at Seattle Children's have worked to understand — and find the genetic causes of — primary immune deficiency diseases. Their pioneering work is advancing treatments and closing in on a cure.

Dr. Troy Torgerson's lab at Seattle Children's is one of only a few in the nation that can analyze proteins made by genes to determine whether children like 2-year-old Michael Vogel — and many adults — have primary immune deficiency diseases.

Michael Vogel runs through his house screaming with delight, his 4-year-old cousin fast on his trail. At age 2, he is a social butterfly who loves to roughhouse and show off new skills with a flourish of his hand and a proud "ta-da!"

Michael's antics give no hint to his fragile condition.

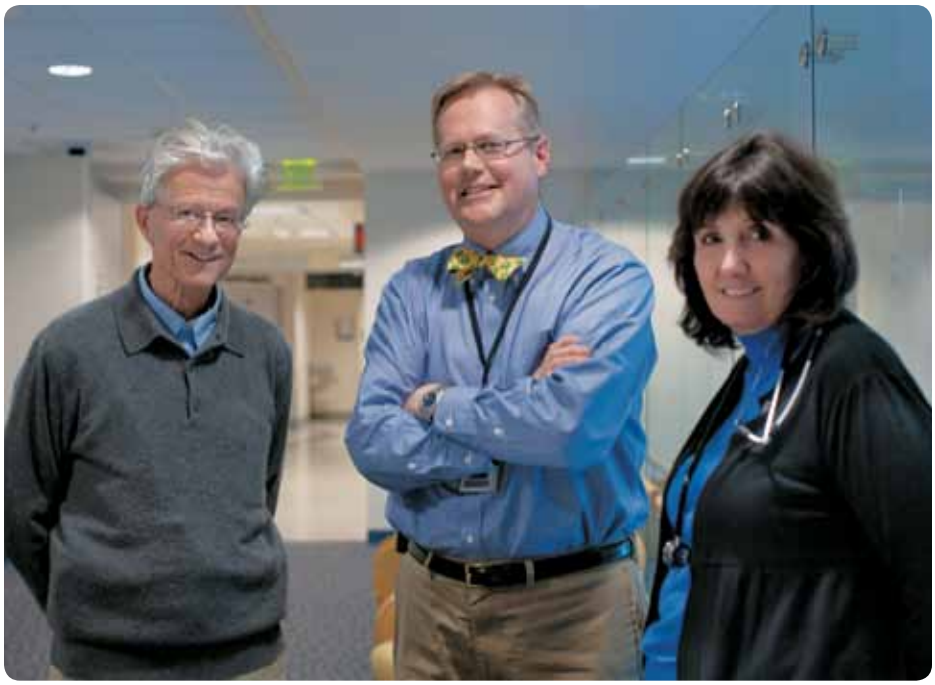
Out of the 30,000-plus genes in his body, one has a defect that stops his immune system from functioning normally, making him susceptible to severe infections. That gene, called STAT3, is one of about 160 genes that researchers have linked to deficiencies in the human immune system. In Michael's case, the mutation in his STAT3 gene causes him to have a rare condition known as hyper-IgE syndrome.

Immunologists at Seattle Children's have been studying inherited and congenital conditions such as hyper-IgE syndrome for more than 50 years. They're called primary immune deficiency diseases (PIDD), and experts believe they affect at least one in every 500 people.

Immune deficiencies are characterized by unexplained patterns of recurring illness. The diseases that fall under this umbrella range from the severe — like the "boy in the plastic bubble" — to those that are merely annoying, like a lifetime of chronic

1 in 500

people are affected by a primary immune deficiency disease.



Drs. Hans Ochs (left) and Troy Torgerson touch base with nurse practitioner Kathey Mohan at Seattle Children's Immunology Clinic. Ochs' national leadership studying primary immune deficiencies at the molecular level earned him the first endowed chair funded by the Jeffrey Modell Foundation, an organization dedicated to finding the causes and cures for primary immune deficiency diseases.

low-grade sinus infections. Although PIDD can strike at any age, the most extreme of these diseases are typically found in infants and toddlers.

A family legacy

Michael is the third generation in his family to carry the defect in the gene that causes hyper-IgE syndrome. His grandmother, Roganna Barnes, has the same genetic defect and remembers her childhood as a dark time spent in sickness and isolation. Repeated pneumonias kept her out of school, and she endured many surgeries at Children's to drain abscesses in her ears so she wouldn't go deaf.

In 1966, when Barnes was 9, Children's immunologist Dr. Ralph Wedgwood and his colleagues described her unusual mixture of symptoms in the medical journal *The Lancet*, and named her condition "Job's syndrome" for the boils that covered her body like the biblical character Job.

Wedgwood recognized that children with these puzzling symptoms were different. He suspected that their immune systems might not be able to fight infections normally, so he treated them aggressively with antibiotic and antifungal medications to protect them from infections. This allowed Barnes and others like her to grow into adulthood and have children of their own.

Wedgwood's leadership in studying new treatments such as immunoglobulin replacement therapy — which uses blood plasma pooled from thousands of people to replace antibodies that are missing in many immune-deficient patients — cemented his reputation as one of the pioneers of pediatric immunology and began the legacy that has put Children's at the forefront of immune deficiency research.

Unraveling the mystery

By the late 1970s, Barnes' symptoms improved somewhat — though still plagued by frequent problems, she did not seem to get as many severe skin or lung infections.

Unfortunately, her son David Vogel wasn't as lucky. As a teenager in the mid-1990s, his health worsened. Vogel's lungs developed cysts where staph bacteria thrived, and he was plagued by frequent bouts of pneumonia. Despite aggressive treatment, Vogel fought frequent dips in his health that left him unable to finish college or hold down a job for long.

In 2007, Drs. Troy Torgerson, Hans Ochs and members of their labs, together with two other groups, found the defect in the STAT3 gene that causes hyper-IgE syndrome. Their study — published in the *New England Journal of Medicine* — came out four decades after Wedgwood's original description of the disease. Since the discovery, they've confirmed the STAT3 gene mutations in about 40 people who they suspected had hyper-IgE syndrome.

Identifying these gene mutations provides patients with concrete

> “Immunology research is a priority at Seattle Children’s because immunity — the body’s ability to fight infection and disease — influences almost every medical illness.”
>
> — Vicki Modell, co-founder of the Jeffrey Modell Foundation, an organization dedicated to finding the causes and cures for primary immune deficiency diseases.

diagnoses and opens the opportunity for early, aggressive treatment. It also holds great promise for advancing current therapies.

“We can now take the mutations found in the STAT3 gene, study them in cells and figure out how they cause disease,” says Torgerson. “We can see how the mutation affects the immune system, and more precisely target therapies to the specific clinical features of the disorder.”

Sadly, Vogel never had the opportunity to benefit from new therapies that might emerge from the discovery at Children’s. He succumbed to hyper-IgE syndrome at the age of 29.

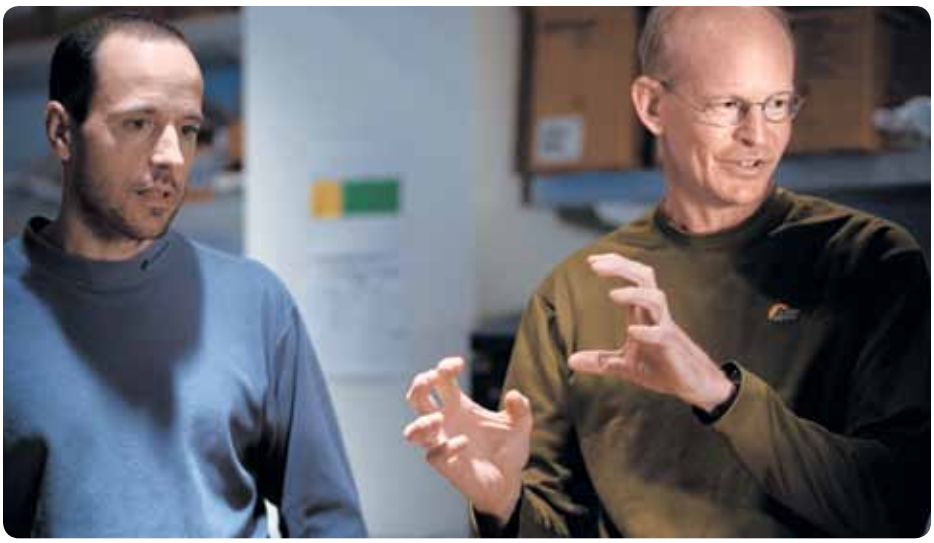
The outlook for his son is different. Born just before Torgerson and Ochs discovered the STAT3 gene defect in his family, Michael developed pneumonia at 3 months of age.

Thanks to the early genetic diagnosis from a test developed in Torgerson and Ochs' lab, Michael has had the benefit of immunoglobulin replacement therapy and prophylactic antibiotics to reduce bacteria in his body and prevent infections from causing serious damage to his lungs. But all this medical management is still just a control measure — and immunologists at Children’s are intent on a cure.

Harnessing the future, today

Children’s is unique among pediatric immunology centers, and our other clinics, because we diagnose and treat children and adults with immune system disorders. Watching people contend with these diseases over time — Barnes has known some of the immunologists here for more than 40 years — inspires clinicians to develop the next generation of therapies.

Currently, Children’s researchers are working on two solutions to put an end to PIDD.



Drs. Andy Scharenberg (left) and Dave Rawlings are working to cure single-gene diseases of the immune system by developing customized proteins that can find defective gene sequences in cells, then cut out and repair them.

Bone marrow transplant can be a lifesaving option for patients affected by the most severe immune deficiencies. But current protocols were developed for patients with cancer and include high amounts of chemotherapy and radiation. Torgerson and Dr. Suzanne Skoda-Smith work in a unique partnership with bone marrow transplant specialists Drs. Lauri Burroughs and Anne Woolfrey to customize transplant protocols for PIDD sufferers to make them less toxic and more likely to be accepted by the patient's body. The team expects to publish the results of some of their new protocols within the next two years.

Drs. Andy Scharenberg and Dave Rawlings are developing ways to correct the gene defects that cause PIDD. Their work — to develop customized proteins that can find defective gene sequences in cells, then cut out and repair them — sounds like the stuff of science fiction. But, based on early successes, the team believes human trials for gene repair are less than a decade away. ■

Jennifer Goldberg (with her kids Clara and Tate) knew she had a role to play in finding a cure for her son's immune disorder, even if she wasn't a researcher. She now leads Children's Gift of Immunity Guild and is a member of the Guild Association Board of Trustees.

Becoming Part of the Solution

When Jennifer Goldberg says her son Tate is one in a million, she's not joking. Four hours after birth, he had a skin rash that wouldn't go away. Pneumonia and enlarged lymph nodes followed. After visiting her pediatrician at least 15 times in one month, she and Tate were referred to Seattle Children's, where she met Dr. Hans Ochs, an internationally known immunologist.

"It took only a day after meeting Dr. Ochs to find out that my son had chronic granulomatous disease," remembers Goldberg.

Only one in every 1 million children has this immune disorder. Most experience a serious, life-threatening infection every four years. Tate, now 8, hasn't been hospitalized since he was an infant. Goldberg credits the excellent care he's received at Children's for keeping him healthy, and she's passionate about supporting the researchers here who she hopes will find a cure for her son.

After a talk by Dr. Andy Scharenberg about the promise of gene therapy in 2004, Goldberg overheard him say that he was building a specialized microscope because his lab didn't have the money to buy one.

"I knew in that moment that I had a role to play," she says.

Today, Goldberg is president of Children's Gift of Immunity Guild, a growing group of 200 supporters committed to funding the future of pediatric immunology — one microscope at a time.