



Investigating Misfiring Marrow

Seattle Children's meets the varied medical needs of bone marrow failure patients with a range of specialized care and ongoing research to find a cure.

Bone marrow failure is considered a rare disease, but don't try telling that to Dr. Akiko Shimamura. Since she started the Bone Marrow Failure Program at Seattle Children's in 2007, growing numbers of patients are being referred to the program for diagnosis and treatment.

Bone marrow failure is not just one disease. It's a group of nonmalignant but life-threatening syndromes that can be inherited or acquired. "On its own, each disorder is rare, but when you pool them all together, they're really not so rare at all," Shimamura says.

Every month, 16 to 20 children with congenital neutropenia, aplastic anemia or some other form of bone marrow failure come to Shimamura's program, which is one of just a handful nationwide and the only one of its kind in the region.

Caring for children with bone marrow failure is complex. It requires a wide range of medical specialists who are able to address the many complications associated with each syndrome. Expertise with bone marrow transplants is also needed, as it's the only known cure for patients with diseases causing bone marrow failure.

"Children's has everything it takes to have an outstanding bone marrow failure program," Shimamura says. "All of the expert care that patients and their families need is available here."

It helps that Shimamura and others at Children's are actively studying what



(Above) Dr. Akiko Shimamura studies the molecular pathways within the body's cells that lead to bone marrow failure.

(Left) Jayne Johnson, 16, is among the first generation of kids with severe chronic neutropenia to live past infancy thanks to a medicine that was newly approved when she was diagnosed in 1994.

causes bone marrow failure and striving to improve treatment. "Because we're constantly working to learn more, we can offer patients advanced diagnostic testing and therapies that aren't available everywhere," Shimamura says.

That's the case for Jayne Johnson. The 16-year-old from Kent was diagnosed with congenital neutropenia as a toddler, putting her in constant danger of potentially fatal bacterial

infections and requiring repeated trips to the hospital. Now, she's looking forward to the possibility of beating the disease, thanks to a new approach to bone marrow transplant being explored by Dr. Lauri Burroughs, a bone marrow transplant expert at Children's.

"I'm super excited about getting a transplant," Jayne says. "If I have a good outcome, it means I won't have neutropenia anymore."



(Above) Dr. Akiko Shimamura helps Jayne Johnson manage her illness and look ahead to a brighter future.

(Left) Dr. Lauri Burroughs is working to make bone marrow transplants safer for patients with bone marrow failure and immune deficiency diseases.

“By using less intense regimens, we can offer transplants sooner.”

— Bone marrow transplant expert Dr. Lauri Burroughs

Too few blood cells

Bone marrow failure means the marrow inside the bones isn't making enough of one or more of the kinds of blood cells the body needs — white blood cells to fight infection, red blood cells to carry oxygen, or platelets to make the blood clot and stop bleeding.

If the marrow fails to make enough white blood cells, children are at higher risk of infection and may get sick more often. If it makes too few red blood cells, children may tire easily and become pale and dizzy. If it makes too few platelets, children may bruise or bleed easily.

Each type of bone marrow failure involves one or more of these defects. Patients with congenital neutropenia, for example, don't produce enough white blood cells, while those with aplastic anemia don't produce enough of all three types of blood cells.

All children with bone marrow failure remain at risk for various complications

associated with their syndrome, which range from organ failure to leukemia to solid-tumor cancers.

Although medications and transfusions can help many children cope with bone marrow failure, severe cases can lead to fatal infections and bleeding. “Even without our help, some children do OK for a long time, but when things go bad, they really go bad,” Shimamura says. “If we see them early enough, we can manage their disease and begin treatment promptly when the chances of success are highest. If not, by the time we do see them, they often do poorly.”

Catch-22

The only known cure for bone marrow failure is a successful bone marrow transplant, but the rigorous nature of current transplant protocols often presents higher risks for these patients because of their underlying health problems.

It's a catch-22. “If you wait too long,” says Shimamura, “you miss the best opportunity for a successful transplant before severe medical complications or leukemias develop. But if you go too early, you risk giving a transplant to a child who may not have needed one. A significant percentage of patients will need a transplant at some point in their lifetime, but the challenge is determining who will or won't.”

Jayne is a good example of that dilemma. Her disease has been successfully managed for a long time, but recently the daily injections she's been taking to boost her white blood count stopped working well and starting causing debilitating side effects. “It's really affected my quality of life because I've been in the hospital a lot with infections,” she says. “I also have a lot of bone pain and have to lie down a lot.”

Jayne's ticket to health may be a potentially safer type of bone marrow transplant being explored by Burroughs, who does research at the Fred Hutchinson Cancer Research Center.

Expanding transplant options

Bone marrow transplants were originally developed to treat leukemia, a cancer of the blood. Like bone marrow failure, leukemia is a disorder

of the marrow, but instead of producing too few of one or more kinds of blood cells, it produces too many.

The standard regimens used to prepare leukemia patients for transplant rely on powerful doses of drugs and/or radiation to destroy both the cancer and the old marrow. But high doses can be difficult to tolerate, especially for the elderly and people with additional health problems, so the Hutchinson Center began developing less intense alternatives for cancer patients.

Burroughs wondered how those alternatives might work with other types of patients who would also have difficulty tolerating high doses of drugs and radiation. She is currently conducting four clinical trials for children with nonmalignant disorders, such as immune deficiency diseases and bone marrow failure. Each trial is using a regimen adapted from low-intensity protocols that were developed for leukemia patients.

The hope is that the less intense regimens will make transplants a safer option for patients with immune deficiencies and bone marrow failure.

“Often they aren’t considered for transplant until their disease is so advanced because the standard regimens are too risky, but by that time they’re so sick that the risks are even greater,” Burroughs says. “By using less intense regimens, we can offer transplants sooner, when patients are in a better position to handle them, and to patients who may have been too sick to receive the standard regimens.”

That gives people like Jayne a better shot at a brighter future. She’s looking forward to playing basketball and taking her two dogs, Taffy and Tyrone, for walks again — activities she’s had to give up because of chronic pain. “There are still risks with a transplant, but there are so many rewards,” Jayne says.

Early results from one of the low-intensity trials look promising. A group of patients with immune deficiency experienced a 90% success rate with one of the less intense regimens.

“There’s still a long way to go, but I think this could have a huge impact,” Burroughs says. ■

Exploring Molecular Pathways



Jim and Marjorie Ghiglione

Research funding is scarce for rare diseases such as bone marrow failure, so contributions from private donors are important to advancing treatment. After losing their daughter, Carla, to aplastic anemia more than 40 years ago, Jim and Marjorie Ghiglione created an endowment at Children’s to support research aimed at preventing, treating and eliminating the disease.

“We would love to see doctors be able to detect aplastic anemia early and head it off before it results in the catastrophic outcomes we still see today,” says Jim Ghiglione.

Dr. Akiko Shimamura is working on just that. She is looking for the molecular pathways within the body’s cells — including the genetic mutations — that lead to bone marrow failure. “Once you find a pathway, you can use it to diagnose the disease and develop therapies to stop it,” says Shimamura, who recently published a paper about a novel molecular pathway that might be targeted with drugs to treat Shwachman-Diamond syndrome, a rare disease that affects the pancreas, bone marrow and bones.

Although the population of bone marrow failure patients is small, Shimamura’s research has broad implications. “These syndromes are closely linked to leukemia, solid tumor cancers and other diseases,” Shimamura says, “so whatever we learn about the pathways leading to bone marrow failure can also help us understand other pathways, such as ones leading to breast cancer.”