n the past few decades, organ transplantation has gone from experimental to routine. In the United States alone, more than 20,000 heart, liver, and kidney transplants are performed every year. But for transplant recipients, one prospect has remained unchanged: a lifetime of taking powerful drugs to suppress the immune system, a treatment that can have serious side effects. Researchers have long sought ways to induce the immune system to tolerate a transplant without blunting the body’s entire defenses, but so far, they have had limited success.

They face formidable challenges. Although immune tolerance can occur—in rare cases, transplant recipients who stop taking immunosuppressants have not rejected their foreign organs—researchers don’t have a clear picture of what is happening at the molecular and cellular levels to allow this to happen. Tinkering with the immune system is also a bit like tinkering with a mechanical watch: Fiddle with one part, and you may disrupt the whole mechanism. And there is a big roadblock to testing drugs designed to induce tolerance: It is hard to know if they work unless immunosuppressant drugs are withdrawn, and that would risk rejection of the transplant. But if researchers can figure out how to train the immune system to tolerate transplants, the knowledge could have implications for the treatment of autoimmune diseases, which also result from unwanted immune attack—in these cases on some of the body’s own tissues.

A report in Science 60 years ago fired the starting gun in the race to induce transplant tolerance—a race that has turned into a marathon. Ray Owen of the University of Wisconsin, Madison, reported that fraternal twin cattle sometimes share a placenta and are born with each other’s red blood cells, a state referred to as mixed chimerism. The cattle tolerated the foreign cells with no apparent problems.

A few years later, Peter Medawar and his team at the University of Birmingham, U.K., showed that fraternal twin cattle with mixed chimerism readily accept skin grafts from each other. Medawar did not immediately appreciate the link to Owen’s work, but when he saw the connection, he decided to inject fetal mice in utero with tissue from mice of a different strain. In a publication in Nature in 1953, the researchers showed that, after birth, some of these mice tolerated skin grafts from different strains. This influential experiment led many to devote their careers to transplantation and also raised hopes that the work would lead to cures for autoimmune diseases.

Immunologists, many of them working with mice, have since spelled out several detailed mechanisms behind tolerance. The immune system can, for example, dispatch “regulatory” cells that suppress immune attacks against self. Or the system can force harmful immune cells to commit suicide or to go into a dysfunctional stupor called anergy. Researchers indeed now know fine details about the genes, receptors, and cell-to-cell communications that drive these processes.

Yet it’s one matter to unravel how the immune system works and another to figure out safe ways to manipulate it. Transplant researchers are pursuing three main strategies to induce tolerance. One builds on Medawar’s experiments by trying to exploit chimerism. Researchers infuse the patient with the organ donor’s bone marrow in hopes that the donor’s immune cells will teach the host to tolerate the transplant; donor immune cells that come along with the transplanted organ also, some contend, can teach tolerance. A second strategy uses drugs to train T cells to become anergic or commit suicide when they see the foreign antigens on the transplanted tissue. The third approach turns up production of T regulatory cells, which prevent specific immune cells from copying themselves and can also suppress rejection by secreting biochemicals called cytokines that direct the immune orchestra to change its tune.

All these strategies face a common problem: It is maddeningly difficult to judge whether the approach has failed or succeeded because there are no reliable “biomarkers” that indicate whether a person has become tolerant to a transplant. So the way to assess tolerance is to stop drug treatment, which puts the patient at risk of rejecting the organ. Similarly, ethical concerns often require researchers to test drugs aimed at inducing tolerance in concert with immunosuppressive therapy. This, in turn, can undermine the drugs’ effectiveness because they need a fully functioning immune system to do their job.

If researchers can complete their 50-year quest to induce immune tolerance safely and selectively, the prospects for hundreds of thousands of transplant recipients would be greatly improved, and so, too, might the prospects for controlling autoimmune diseases.

—Jon Cohen