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Immunosuppression-Free Kidney Transplantation: Advancing New Treatments by Building on Our Past Foundations

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The development of solid organ and bone marrow transplantation has been considered among the most important medical advances in the last half of the 20th century. Solid organ and bone marrow transplant programs at the University of Wisconsin School of Medicine and Public Health (SMPH) and UW Health started more than 50 years ago. Since then, our solid organ transplant program has performed over 16,000 transplants, making it the largest such program in the Midwest and one of the largest and most successful in the nation. The underpinnings of both programs are their scientific accomplishments in immunology and their highly collaborative, innovative approach. A recent example is the endeavor to perform kidney transplants without the lifelong need for antirejection medications, referred to as immunological tolerance.

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Numerous UW-Madison faculty members stand out in laying the foundation for new clinical studies in this field. For instance, Ray D. Owen, PhD, a geneticist who made fundamental discoveries in the 1940s on the effect of mixing of immune cells in animals, paved a pathway toward understanding immune tolerance. And in the 1960s, Fritz Bach, MD, an assistant professor of genetics and medicine, was among the first to perform a successful bone marrow transplant between siblings to cure an immunodeficiency disorder. Previously, bone marrow transplants had worked only between identical twins. However, a few years earlier, Dr Bach had developed a matching test that could determine whether donor and recipient cells would be good matches to permit a safe, effective bone marrow transplant. The test—called the Mixed Leukocyte Culture (MLC)—opened the door to the first successful bone marrow transplants between sibling donors. Today, bone marrow and hematopoietic cell transplants are completed in tens of thousands of patients all over the world for leukemia and other hematological malignancies. In addition, the pool of donors has expanded from family donors to unrelated donors, about 20 million worldwide. UW-Madison is one of only two centers in Wisconsin that are performing these "allogeneic" bone marrow transplants.

> The discovery of immune chimerism and its link to immunological tolerance observed by pioneering investigators at UW-Madison several decades ago are transforming organ and bone marrow transplantation.

The success in providing a long life for a solid organ transplant recipient depends on avoiding transplant rejection. There are two ways to avoid immune rejection of a transplanted organ:

- Through perfect tissue matching between identical twins, an uncommon situation in which the recipient and donor share the same tissue HLA and other antigens. In this case, no immunosuppressive drugs are required because all HLA antigens match, and there is no destructive immune response that needs to be suppressed. The next best matching situations are between

HLA-identical siblings and between siblings who share one HLA allele, called a haplomatch. HLA-matched transplants, nevertheless, still require immunosuppression due to the existence of numerous minor transplantation antigens.

- Through the use of drugs that suppress the recipient's immune response, thereby preventing organ rejection. Immunosuppressive medications—which are required for the rest of the patient's life—prevent a destructive allo-immune event and allow the transplanted organ to survive despite differences in HLA and/or minor antigens between the recipient and the donor. These drugs have revolutionized the field of transplantation and saved hundreds of thousands of lives that otherwise would have been lost due to failure of a vital organ. Unfortunately, all available immunosuppressive drugs increase susceptibility to infection and have other side effects that often cause severe morbidity.

The ability to perform solid organ transplants without the life-long need for immunosuppression requires the induction of transplant-specific tolerance in the recipient. The UW Health and SMPH solid organ and bone marrow transplant programs are putting their combined efforts into new basic science and clinical research studies that aim to produce immunological tolerance in kidney transplant recipients, thus eliminating the need for anti-rejection medications. This approach requires creation in the recipient of a dual immune system consisting of the patient's own and that of the organ donor. The coexistence of dual immune systems is called "immune chimerism."

The UW Health clinical tolerance induction protocol involves a combined kidney and hematopoietic cell transplant between sibling donor and recipient pairs. The new program is led collaboratively by two of the authors, Drs Dixon B. Kaufman and Peiman Hematti. This team-oriented clinical research program also involves collaborators in the Department of Human Oncology, including Kristin Bradley, MD, and the Division of Transplantation's Clinical Trials Unit.

Such tolerance-induction studies using combined kidney and bone marrow transplantation strategies were initiated in October 2018 and are being conducted in two groups of living-related kidney transplant patients: (1) recipients of an HLA-identical kidney transplant between siblings and (2) recipients of a living donor transplant that is matched among two and five HLA antigens.

The discovery of immune chimerism and its link to immunological tolerance observed by pioneering investigators at UW-Madison several decades ago are transforming organ and bone marrow transplantation. Building on the past, we look forward to the future impact of the current, exciting clinical studies of immunosuppression-free transplantation.

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