nmdp BioTherapies℠
FIND CURES. SAVE LIVES.

The historical HLA learning curve:
How recognizing the necessity for HLA matching could bring more therapies to market, faster

HLA matching improves allogeneic outcomes

Human leukocyte antigens, or HLAs, are proteins found on the surface of most human cells. Everyone has a particular HLA profile inherited from their parents, half from the mother, and half from the father. These proteins play an important role in modulating immune response, as immune cells use HLAs to identify one's own cells from invading microbes and viruses. A properly functioning immune system will attack that which doesn't match the body's HLA profile.

This immune response has several important implications for the development of allogeneic cellular therapies and transplant, including:

- graft-versus-host-disease (GVHD), where the donor cells attack the patient's cells because they do not match the "self" HLA pattern.
- Graft rejection, where the patient's immune system attacks the transplanted donor cells, leading to graft failure.

Due to these potential after-effects the identification of HLA type has played a critical role in matching donors with patients in need of life-saving hematopoietic stem cell transplants (HSCT). When the first transplants were conducted in the 1950s, the rate of transplant success was low, but improved dramatically once consideration of HLA type became part of the transplant process.

History repeats itself: HLA matching improves cord blood transplant outcomes

Similarly, the use of cord blood as a donor cell source was another important innovation in the field of transplant, as it made it possible for a patient without a family match to find a donor source. There has been a lot of debate as to the level of matching required when using cord blood as a donor source, but recent research indicates that HLA matched cord blood can lead to faster engraftment times and a lower risk of GVHD.[1]

Will history repeat itself once again? An expert opinion on relevance for cell therapies

Martin Maiers, MS
Vice President of Biomedical Informatics CIBMTR® (a research collaboration between the Medical College of Wisconsin® and NMDP℠)

As the next generation of therapies are developed, HLA matching could play an important role in a number of leading-edge therapeutics and cellular therapies.

"In the next 10 years, HLA matching may become one of the most important aspects of precision medicine and will play an essential role in drug development," said Martin Maiers, MS, Vice President of Biomedical Informatics, CIBMTR® (a research collaboration between the Medical College of Wisconsin® and NMDP℠). "The role of HLA matching today is limited to particular procedures and treatments, like bone marrow transplant."

The implications for HLA matching are enormous, not only in the development of cellular therapies, but also across the field of drug development. Some cancer drugs that are currently being developed by pharmaceutical companies have a component that corresponds to HLA type, Maiers explained. "Organizations who are creating these

drugs may be able to use information about HLA type even when developing these non-cell-based therapies," Maiers said. For example, a recent paper published in Nature Medicine[2] demonstrated that HLA type plays a role in the efficacy some cancer therapies, like immune checkpoint inhibitors, have in treating disease.

In another modality, natural killer (NK) cells used in combination with monoclonal antibodies have shown promise recently as an approach to treating diseases like lymphoma. NK therapies have been described as an "off-the-shelf" therapy, in that they don't require matching with a patient, but it's possible that matching NK cells could lead to better outcomes for patients as well. One consideration with "universal" therapies relates to graft rejection. Donor-specific anti-HLA antibodies (DSA) have shown increased risk for graft failure in both solid organ and HSCT.[3] This has potential to impact the efficacy of newer cell therapies where there is some indication that persistence of these cells is critical to avoiding relapse.

Though the region of the genome that codes for HLA type is well-characterized, determining HLA type remains a complex process with many unknowns. As the importance of HLA grows in relation to the development of new therapies, one of our primary objectives at NMDP BioTherapies℠ is providing historical data and search algorithms to ensure patients receive the therapies with the most probability for success. "Finding an HLA match is a probabilistic system and our goal is to manage uncertainty when it comes to HLA matching," Maiers said. "As genomic sequencing technologies become more accurate and more affordable, we will be able to gain an even more precise indication of a person's HLA type."

In the future, HLA will likely play a larger role in the development and administration of cancer therapies. At NMDP BioTherapies℠, our partnership with CIBMTR helps to provide therapy developers with the evidence-based resources necessary to navigate, and ultimately reduce, the uncertainties associated with HLA matching as they develop new allogeneic cellular therapies.

About NMDP BioTherapies

NMDP BioTherapies is dedicated to accelerating patient access to life-saving cell and gene therapies by providing high-quality cellular source material from the NMDP Registry℠, the world's most diverse registry of more than 7 million potential blood stem cell donors. Through established relationships with apheresis, marrow collection, and transplant centers worldwide, the organization develops, onboards, trains, and manages expansive collection networks to advance cell therapies. NMDP BioTherapies uses a proven infrastructure consisting of regulatory compliance and managed logistics experts and cell therapy supply chain case managers to successfully transport and deliver regulatory-compliant life-saving therapies across the globe. Through CIBMTR, NMDP extends services beyond the cell therapy supply chain to include long-term follow-up tracking for FDA-approved CAR-T therapies.

For more information, follow NMDP BioTherapies on LinkedIn or Twitter.

REFERENCES

1. Jason Dehn, Stephen Spellman, Carolyn K. Hurley, Bronwen E. Shaw, Juliet N. Barker, Linda J. Burns, Dennis L. Confer, Mary Eapen, Marcelo Fernandez-Vina, Robert Hartzman, Martin Maiers, Susana R. Marino, Carlheinz Mueller, Miguel-Angel Perales, Raja Rajalingam, Joseph Pidala; Selection of unrelated donors and cord blood units for hematopoietic cell transplantation: guidelines from the NMDP/CIBMTR. Blood 2019; 134 (12): 924–934. doi: https://doi.org/10.1182/blood.2019001212
2. Chowell, D., Krishna, C., Pierini, F. et al. Evolutionary divergence of HLA class I genotype impacts efficacy of cancer immunotherapy. Nat Med 25, 1715–1720 (2019). https://doi.org/10.1038/s41591-019-0639-4
3. Ciurea, Stefan O.; de Lima, Marcos; Cano, Pedro; Korbling, Martin; Giralt, Sergio; Shpall, Elizabeth J.; Wang, Xuemei; Thall, Peter F.; Champlin, Richard E.; Fernandez-Vina, Marcelo; High Risk of Graft Failure in Patients With Anti-HLA Antibodies Undergoing Haploidentical Stem-Cell Transplantation. Transplantation: October 27th, 2009 - Volume 88 - Issue 8 - p 1019-1024. doi: 10.1097/TP.0b013e3181b9d710

