PIRCHE
New Standards in Transplantation

The PIRCHE® technology: Predicting HLA epitopes being indirectly recognized improves donor selection in various transplantation settings

University Medical Center (UMC) Utrecht has developed a new method to select permissible mismatches. This technology applies to hematopoietic stem cell transplantation, solid organ transplantation, and other domains improving graft acceptance and therapy effectiveness.

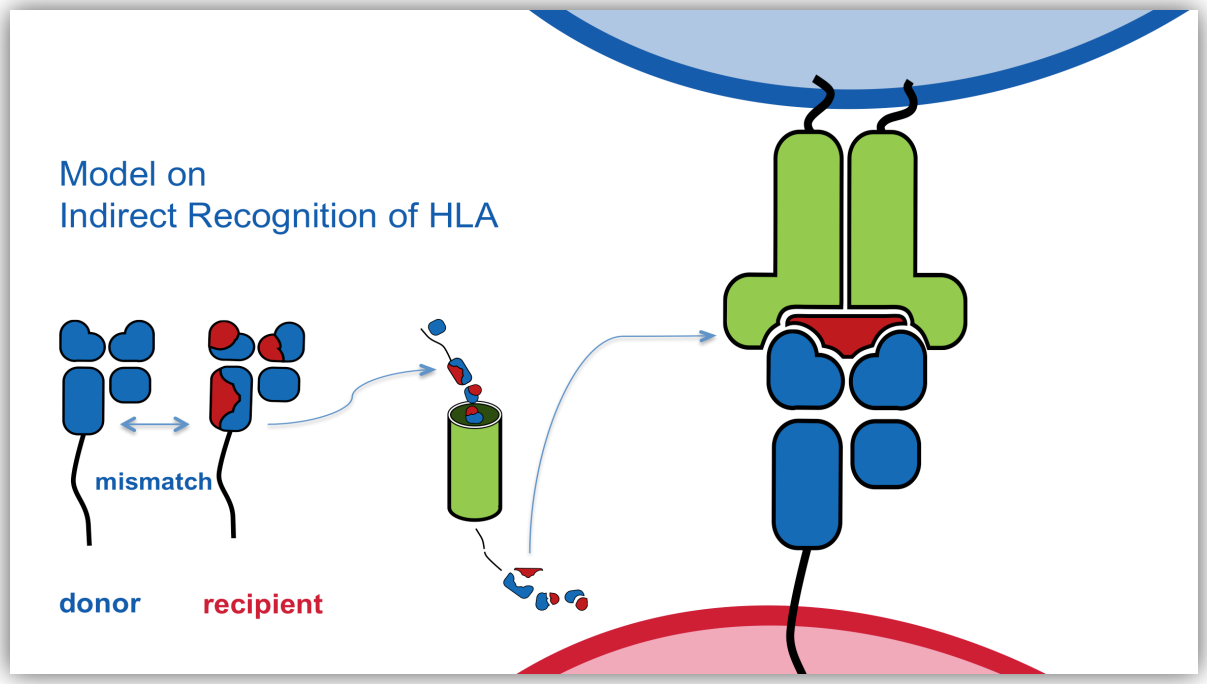

Fig. 1: Mismatched donor and recipient HLA molecules, red parts representing the mismatch between both (left). HLA protein is processed by proteasomes (green tube) within the cell (mid). Peptides are presented on shared (HSCT), respectively all (SOT) HLA molecules, being recognized by donor (HSCT) respectively patient (SOT) T-cells leading to T-cell induced alloreactivity – the indirect pathway. Figure kindly provided by Dr. Eric Spierings, UMC Utrecht.

The new technology named PIRCHE® forecasts T-cell related immune responses against HLA derived peptides after transplantation[3]. In contrast to existing technologies, the indirect pathway of allorecognition is in focus. This takes another important functional aspect of HLA molecules into account: HLAs load peptides into their characteristic binding grooves to present it to the antigen-peptide-specific receptors of T-cells.

In transplantation, mismatched HLA proteins are introduced to the immune system. When being processed by enzymes or the proteasome, peptides are derived that are unknown to the T-cells, making them a potential target for immune responses (Fig. 1). The technology of PIRCHE® predicts

these peptides (i.e. PIRCHEs) only by using the HLA typing of patient and donor. The number of PIRCHEs presented on HLA class-I and -II are called PIRCHE-I and -II.

Matching with PIRCHE® was shown to be a significant and independent parameter in various transplantation settings beyond classic HLA matching technologies and modern epitopes matching algorithms.

Kidney Transplantation

In the setting of kidney transplantation, the biggest market of solid organ transplantation (SOT), PIRCHE® was found to be correlated with the development of de novo donor specific antibodies (DSA)[3]. Patients transplanted with a donor organ having a high PIRCHE-II score are more likely to develop immunogenic HLA-antibodies, an indicator for complicated and expensive graft rejections. As the technology can already be applied when preparing a transplantation, PIRCHE® allows to reduce risk of post transplant complications as early as possible.

To confirm the earlier proof-of-concept, two retrospective, independent, European studies with over 7000 patients were initiated. Not only the PIRCHE® score was in alignment with the earlier finding of predicting de novo DSA development, but also had a significant impact on graft survival.

The technology behind PIRCHE® allows identifying high-risk transplantations (e.g. retrospectively), but also assists in defining permissible mismatches (e.g. prospectively). This makes PIRCHE® an effective tool to improve the process of donor selection.

Hematopoietic Stem Cell Transplantation

Transplantation of allogeneic hematopoietic stem cells (HSCT) is an evolving therapy that has become an increasingly attractive therapeutic option. Alloreactivity after HSCT has a major impact on clinical outcome. The pathological effect of alloreactivity is reflected by graft-versus-host disease (GVHD). The risk of acute GVHD is dependent on the level of matching human leukocyte antigen (HLA) alleles for the loci HLA-A, HLA-B, HLA-C, HLA-DRB1, and HLA-DQB1. The optimal transplant is a full match for all five HLA loci, a 10/10 match. Recipients of matched-unrelated HSCT have a 24% reduced cumulative incidence of severe acute GVHD and a better overall survival compared to recipients of single HLA mismatched donors[1]. However, in 40% of the cases a single HLA mismatch, a 9/10 match, is the best available option[2].

Both, PIRCHE-I and -II are highly correlated to clinical measures of alloreactivity, such as acute GVHD and transplant related mortality[4,5,6]. PIRCHE® may help to predict the patient's risk of developing graft-versus-host disease and allows selecting the best permissible mismatch carrying HSCT for a better outcome of the patient.

Beyond Kidney and Stem Cells

New studies show, that the mechanism introduced by PIRCHE® also describes formation of child-specific HLA antibodies during pregnancy[7]. This suggests the concept of PIRCHE® is universal.

Backed by these findings, PIRCHE AG collaborates with UMC Utrecht and additional partners to explore prediction of platelet transfusion refractoriness by PIRCHE®.

PIRCHE AG, together with UMC Utrecht, constantly aims on entering new domains and developing PIRCHE® further, bringing the technology's benefits to various domains[8].

PIRCHE® can be accessed via a web-based matching service, making it

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continuously available worldwide at any time.

For more information please contact us at:

info@pirche.com

References

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7. K. Geneugelijk, G. Hönger, H.W.M. van Deutekom, C. Keşmir, I. Hösli, S. Schaub and E. Spierings. “Predicted Indirectly Recognizable HLA Epitopes Presented by HLA-DRB1 Are Related to HLA Antibody Formation During Pregnancy.“ American Journal of Transplantation 2015; XX: 1-11.
8. The University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands (UMCU) has filed a patent application on the prediction of an alloimmune response against mismatched HLA, PIRCHE AG is holding an exclusive license to the intellectual property covering the PIRCHE® method.