Advanced Epitope Analysis for Improved Donor-Recipient-Matching

Matthias Niemann (PIRCHE AG)
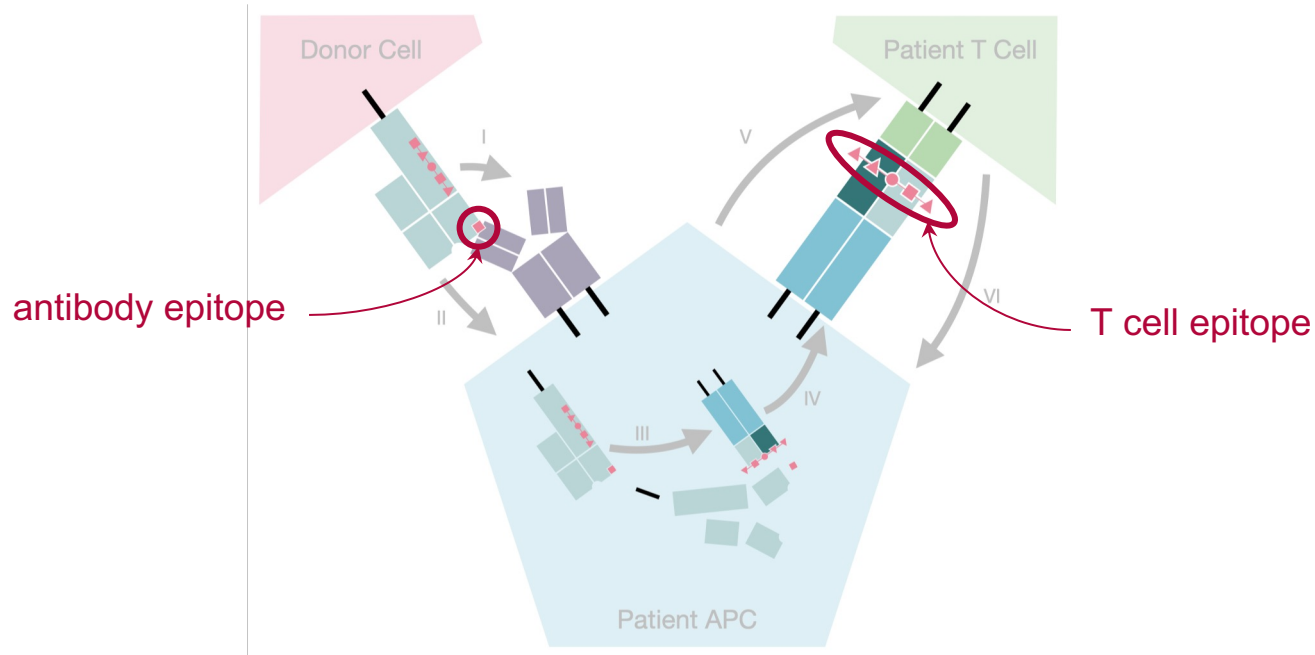
Histocompatibility improves graft survival

- Human leukocyte antigens (HLA) are
  - surface proteins
  - core element of human immune system
  - highly polymorphic

- HLA similarity between donor and recipient
  - reduces likelihood of identifying donor cell
  - lowers chances of immune response
  - improves graft survival

- …but what exactly is "compatible"?

Allo-HLA Recognition Crash Course

antibody epitope

T cell epitope

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Can we do better? (original plan)

- Implemented HLA Matchmaker as reference B-cell epitope matching

- Provide anonymized access to B- and T-cell epitope matching

- Explore in NephroCAGE cohort how to connect epitope matching algorithms

What we actually did…

- Implemented HLA Matchmaker as reference B-cell epitope matching

- Provide anonymized access to B- and T-cell epitope matching

- Connected SRTR as hypothesis-generating cohort
  - Time-independence of NephroCAGE cohort

- Integrated new predictors for antibody-accessibility
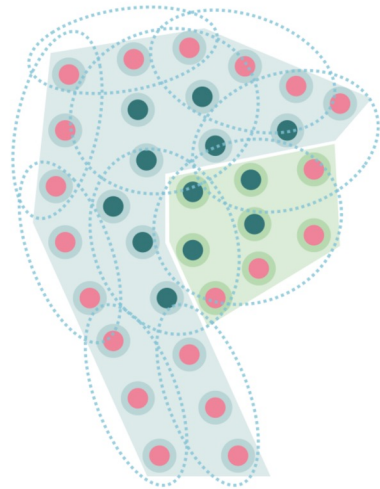 - Solvent accessible surface area
  - Localized ellipsoid protrusion

3rd Int'l NephroCAGE Symposium, Aug 2, 2023

Matthias Niemann,
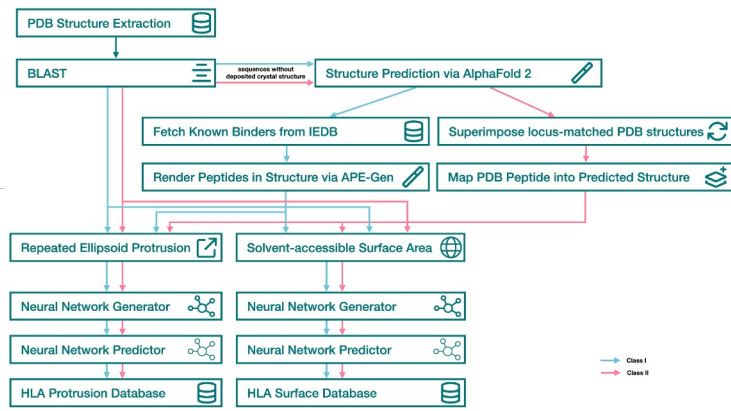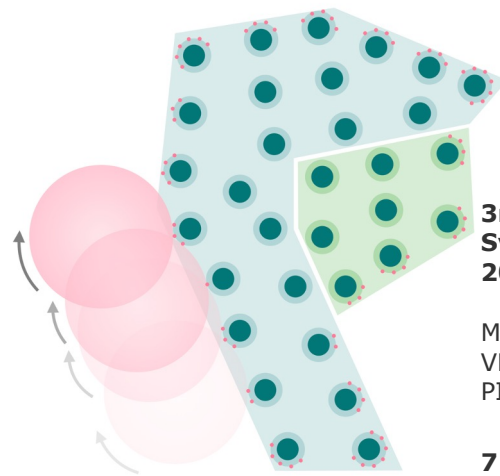VP Technology,
PIRCHE AG

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Snow: Protein-Specific Antibody Accessible Amino Acid Mismatches

Snowball

Snowflake

PDB Structure Extraction

BLAST → sequences without deposited crystal structure → Structure Prediction via AlphaFold 2

Fetch Known Binders from IEDB | Superimpose locus-matched PDB structures

Render Peptides in Structure via APE-Gen | Map PDB Peptide into Predicted Structure

Repeated Ellipsoid Protrusion | Solvent-accessible Surface Area

Neural Network Generator | Neural Network Generator

Neural Network Predictor | Neural Network Predictor

HLA Protrusion Database | HLA Surface Database

Class I
Class II

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Matthias Niemann, VP Technology, PIRCHE AG

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Niemann et al., in review.

Amino Acid Matching: Jack of all Trades

	A	B	C	D	E	F	G	H	I	J
Patient	A	B	C	D	E	F	G	H	I	J
Donor	A	B	**B**	D	**F**	F	G	H	**H**	J
Amino Acid Match			**B**		**F**				**H**	
B Cell Epitopes			**B**		**F**					
T Cell Epitopes					**F**				**H**	

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NEPHROCAGE

German-Canadian consortium on AI for improved kidney transplantation outcome
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Conclusion

- PIRCHE, Eplets, Snow and Amino Acid Matching are predictors of graft survival

- Multivariable models outperform univariable models

- Optimal configuration of predictors is dependent on combination
  - "Two specialists outperform one allrounder"

- Manuscript in review, manuscript in preparation

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