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INNOVATIONacademy

A Patient Specific Approach To HLA Antibody Incompatible Renal Transplantation.

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Renal Transplantation:

- Kidney transplantation is the gold standard treatment for patients with end stage renal disease.
- Dialysis is a temporary option - associated with significant morbidity and mortality.
- Life expectancy on dialysis is 4 – 20 years.
- Additionally it is expensive and time consuming.
- Donors may be living or deceased.
- Half life of transplanted kidneys from living donors is 15.3 years and deceased is 11.9 years.
- 1st successful transplant in 1954.
- Still evolving and learning.

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Graft Rejection:

- Main cause of graft loss is 'rejection'.
- Immediate to years later.
- Immune reaction generated to differences between donor and recipient HLA molecules.
- HLA molecules are responsible for presentation of antigen to activate the immune system.
- The most diverse genetic system in the Human genome.
- HLA class I on all nucleated cells, HLA class II on specialised cells including renal endothelium.
- In organ transplantation the donor HLA antigens become the targets of the recipient immune system.
- Highly immunogenic.
- HLA matching helps but is not always possible.
- Immunosupression reduces the response, but not always 100% effective.

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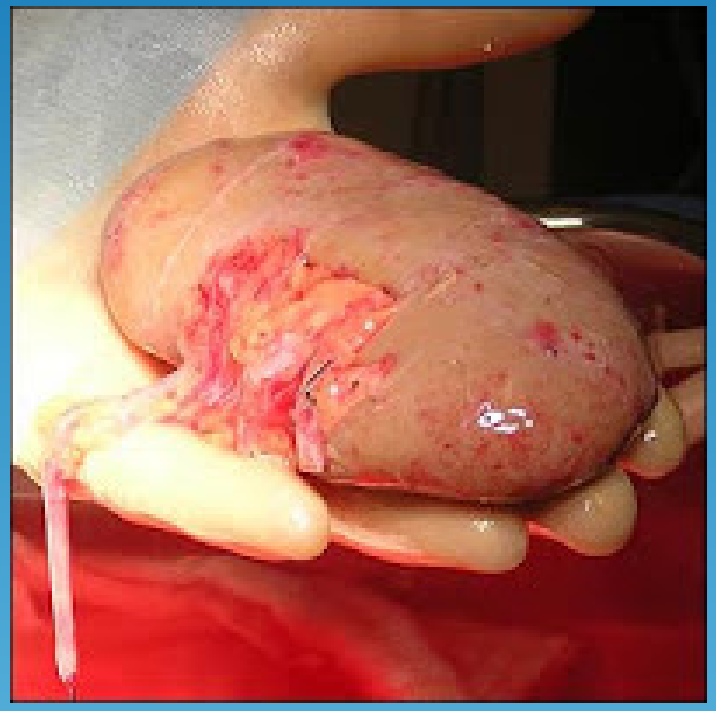
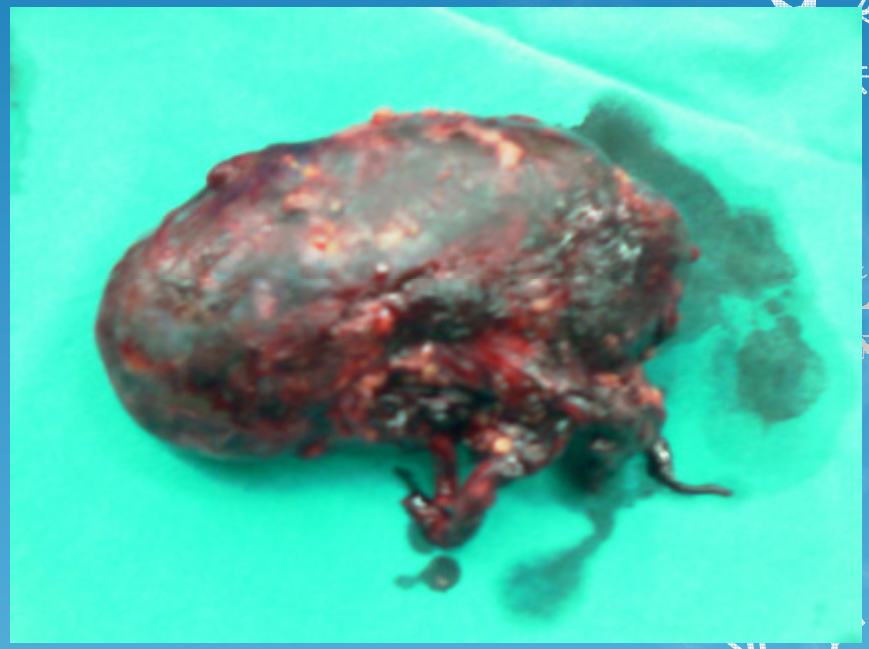
HLA specific Antibody:

- Antibody specific to non-self HLA.
- Generated through exposure via – transplantation, blood transfusion and pregnancy (also naturally occurring)
- In 1969 Patel and Terasaki linked preformed donor HLA specific antibody with hyperacute rejection (DSA)
- Since also associated with acute and chronic rejection.
- Much of CTL work devoted to identification of HLA specific antibody.
- Information used to avoid donors to which antibody is formed.
- Hyperacute rejection is now very rare!

Hyperacute Rejection:





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Methods of Antibody Detection:

- At Guys CTL we use Flow Crossmatching and Luminex bead technology.
- Both are highly sensitive.
- Flow crossmatching detects antibody in recipient serum binding to donor lymphocytes – detected by flow cytometry.
- Luminex Bead technology detected antibody in recipient serum binding to micro particles coated in known HLA antigens.
- Both give a fluorescence readout – Relative median Fluorescence (RMF) for crossmatch and Median fluorescence intensity (MFI) for Luminex.
- For both the larger the value potentially the greater the Antibody level.
- Cut-off values calculated locally to assign negative and positive results.
- A positive crossmatch is generally a contraindication to transplantation.

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Sensitised Patients:

- Patients who produce HLA specific antibody are referred to as 'sensitised'.
- A measure of sensitisation is the 'calculated reaction frequency' or %cRF.
- Calculates the % of deceased donors in the past 10000 with which we would expect a positive crossmatch.
- 0% cRF being unsensitised and 100% cRF being highly sensitised.
- Greater the %cRF the longer the wait for transplant
- In UK – 0% cRF wait 788 days, >85% cRF wait 2232 days.
- In US only 6.5% of HS patients transplanted annually compared to >20% of unsensitised patients.
- HLA specific antibody is a major barrier to transplantation.

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Transplanting the highly sensitised patient:

- Few offers of deceased donor organs.
- 25% of our assessed potential living donor pairs are antibody incompatible.
- 3 options available –
  - Wait for an offer.
  - Paired exchange.
  - HLA antibody incompatible (HLAi) transplant.
- HLAi transplant – transplantation following removal of antibody to a level deemed safe to Tx without the risk of hyperacute rejection.
- Removal can involve – PEX/DFPP/IA, IVIg, rituximab plus IS and induction therapy.

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HLAi transplantation:

- Become a more viable and popular option in past 10-15 years.
- Marfo et.al. reviewed all published cases between 2000-2010.
- 725 patients, 86% graft survival at 2 years
- Acute TCMR in 36% and acute AMR in 28%
- Varied outcomes and no clear indication of risk.
- GT started attempting HLAi from 2005.

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Titre Flow Crossmatch

- 1st few patients embarked on Ab removal with no clear endpoint.
- Most centre reports show similar ad hoc approach.
- Antibodies do not always reduce.
- Difficult to plan and expensive.
- Introduced the 'Test DFPP'.
- HLA antibody incompatible patients treated with a single DFPP with samples taken pre and post.
- Samples titred and crossmatched against potential donor.

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Titre Flow Crossmatch:

- Pre and post samples diluted to 1:32 and 1:16.
- Crossmatched against cells from potential donor.
- Reduction in titre and RMF at neat assessed.
- If reduction observed then estimated number of DFPP required pre transplant to achieve a negative crossmatch calculated.
- Allows efficient planning and screens out patients in whom it would not be possible to reduce the Ab.

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Titre Flow Crossmatch Study:

- 117 titre XM with DFPP and 34 without included in study.
- 31 went on to be transplanted following Ab removal.
- To date no patients assessed by titre XM as being suitable for Ab removal have tried and failed.

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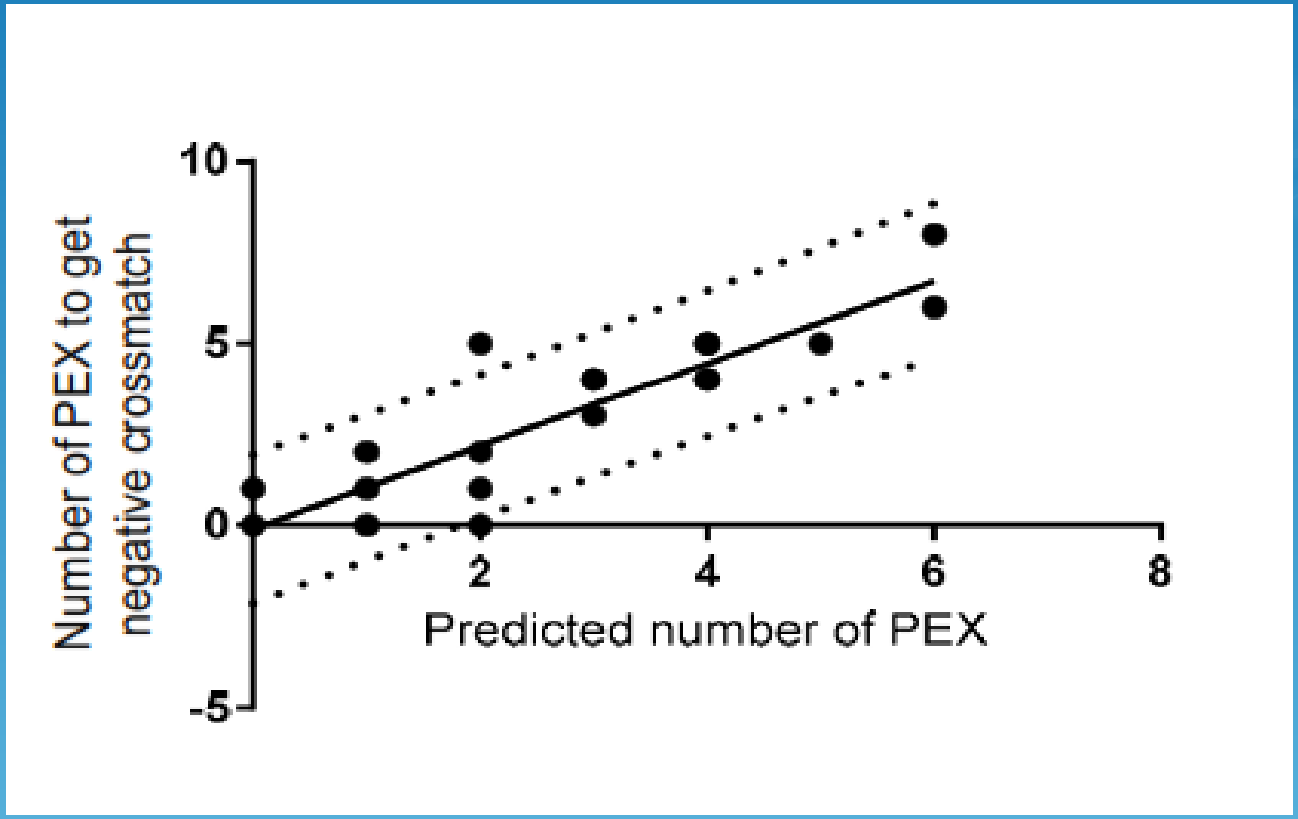
Predictive?



- R^2 = 0.87 (p=<0.0001)

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Do we need the DFPP?

- Can the starting titre predict the amount of Ab removal required?

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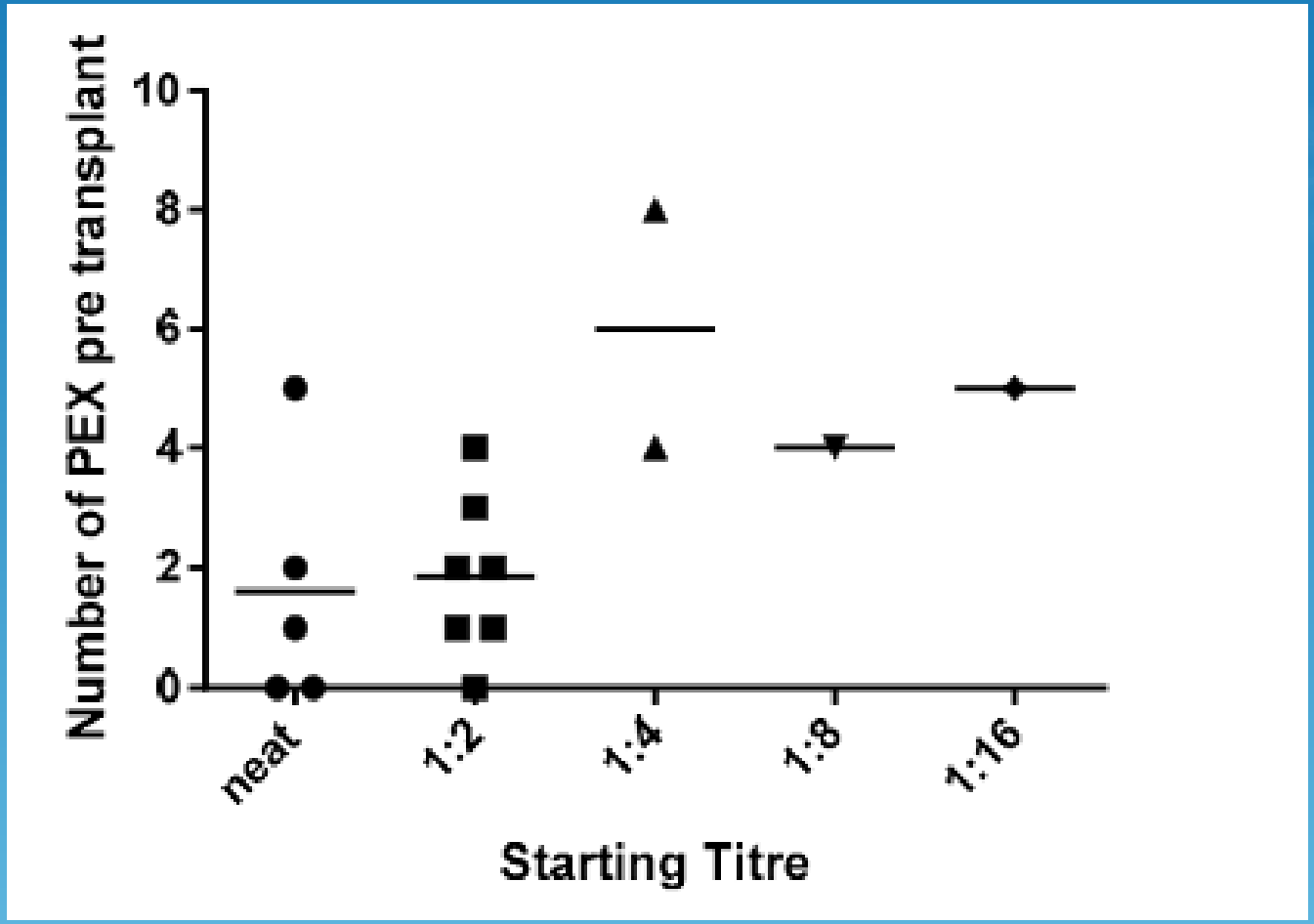
T cell starting titre:



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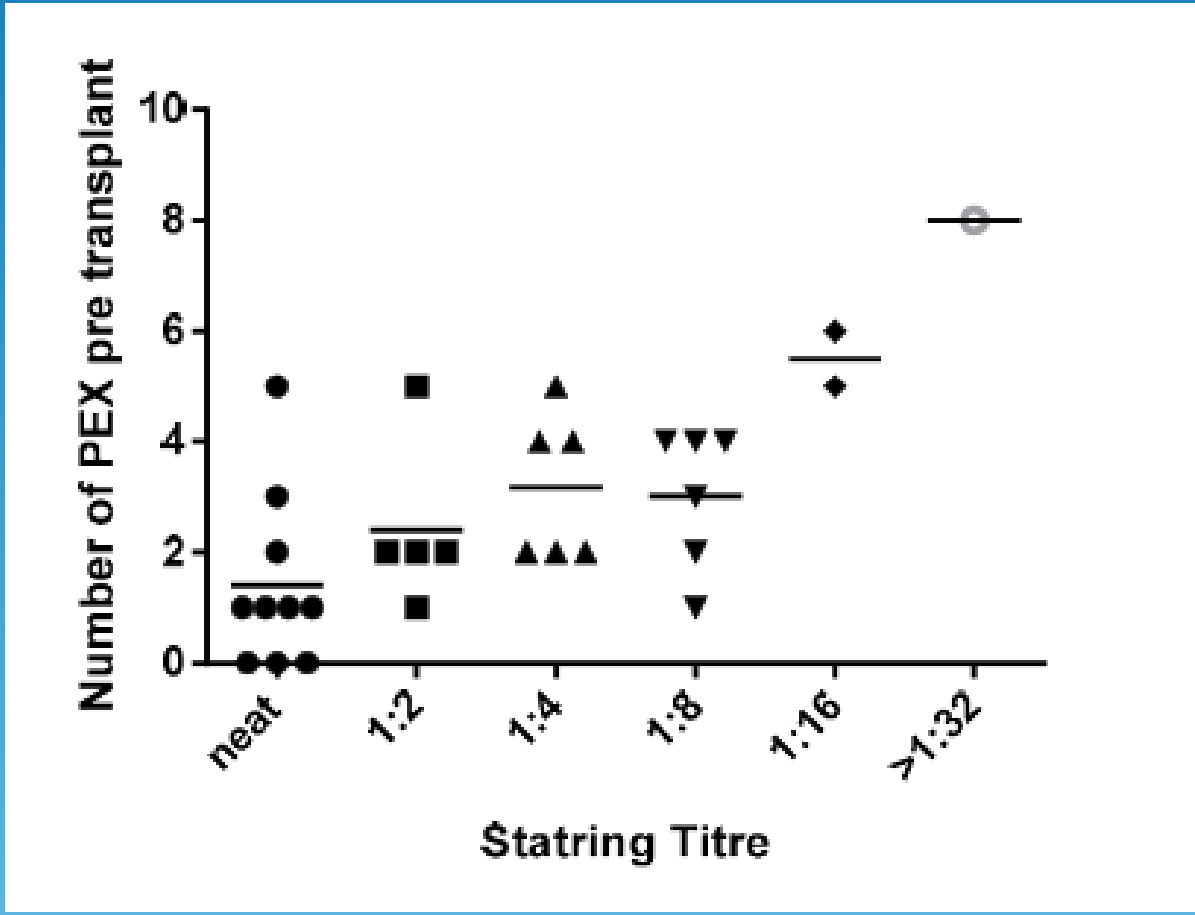
B cell starting titre:



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Do we need a crossmatch?

- Could single antigen bead MFI values be equally predictive?
- Do bead MFI values correlate with XM RMF values?
- Pre and Post sera from 68 patients receiving a test DFPP and titre XM were also tested using single antigen Luminex beads.
- Total of 136 values to compare.
- Initially compared total DSA MFI vs RMF at neat.

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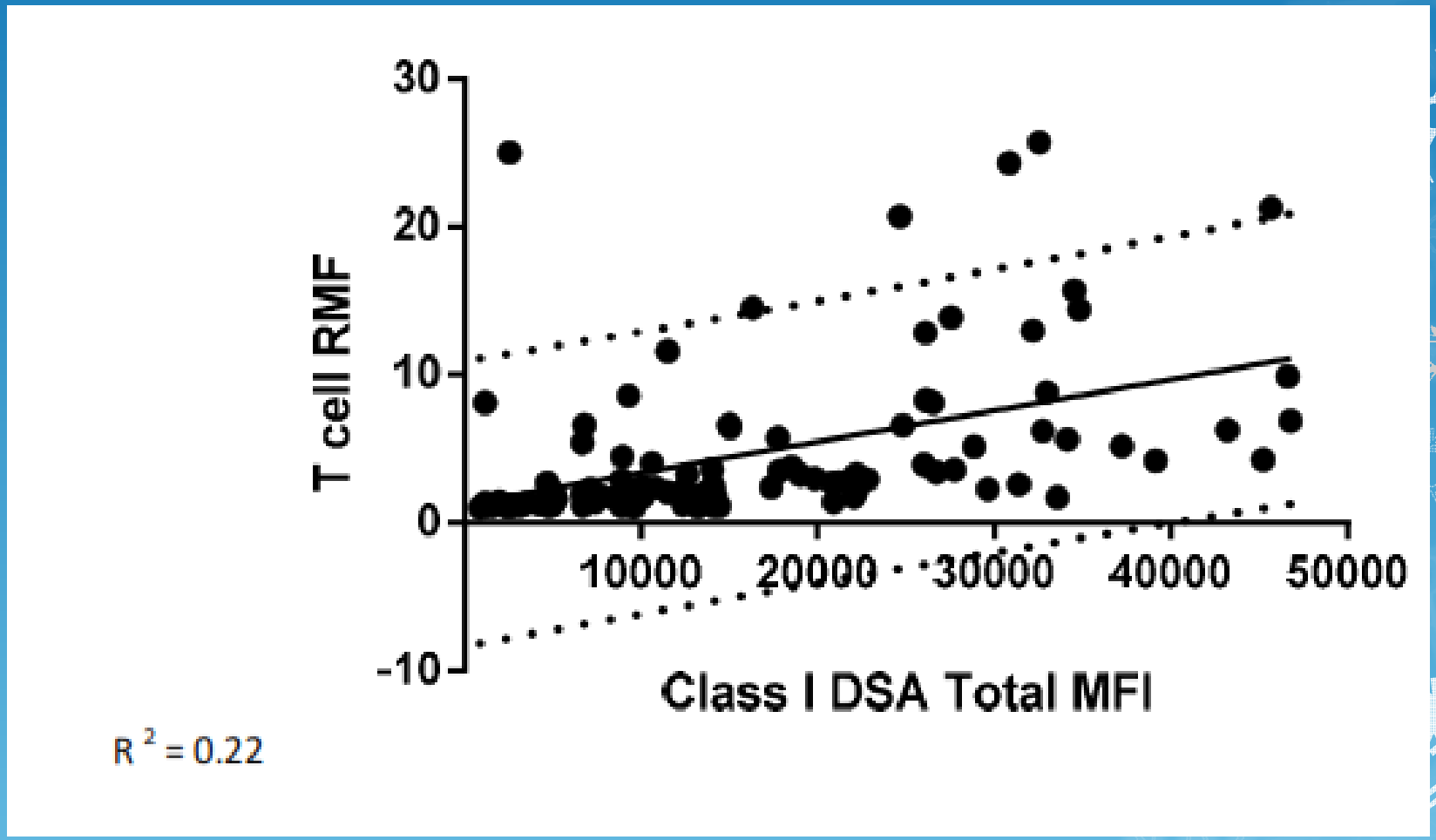
T cell RMF vs total CI DSA MFI



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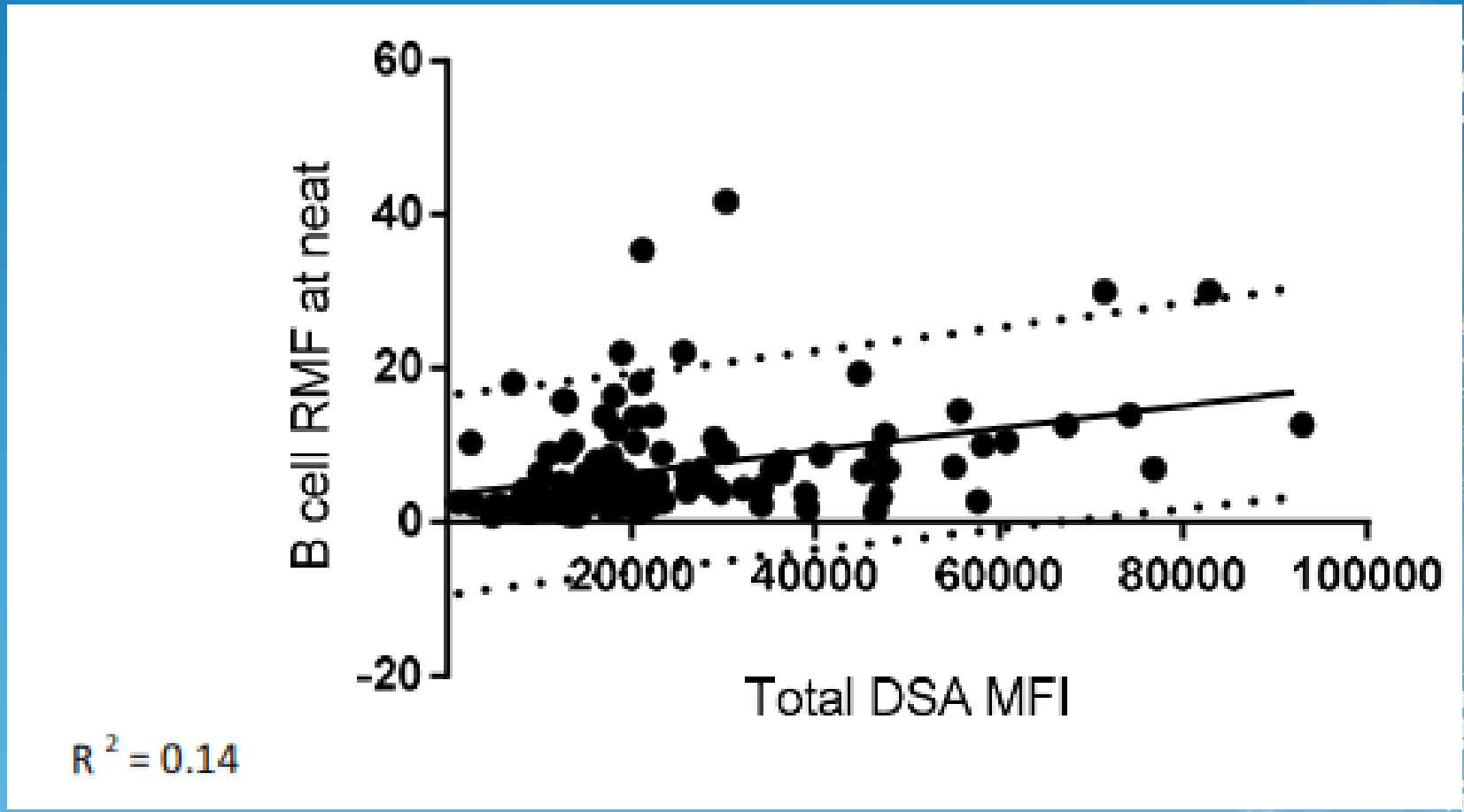
B cell RMF vs total CI+II DSA MFI



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Beads vs XM

- Can’t accurately predict RMF from MFI
- Can we predict a positive XM?
- Compared total DSA MFI values between positive and negative XMs.

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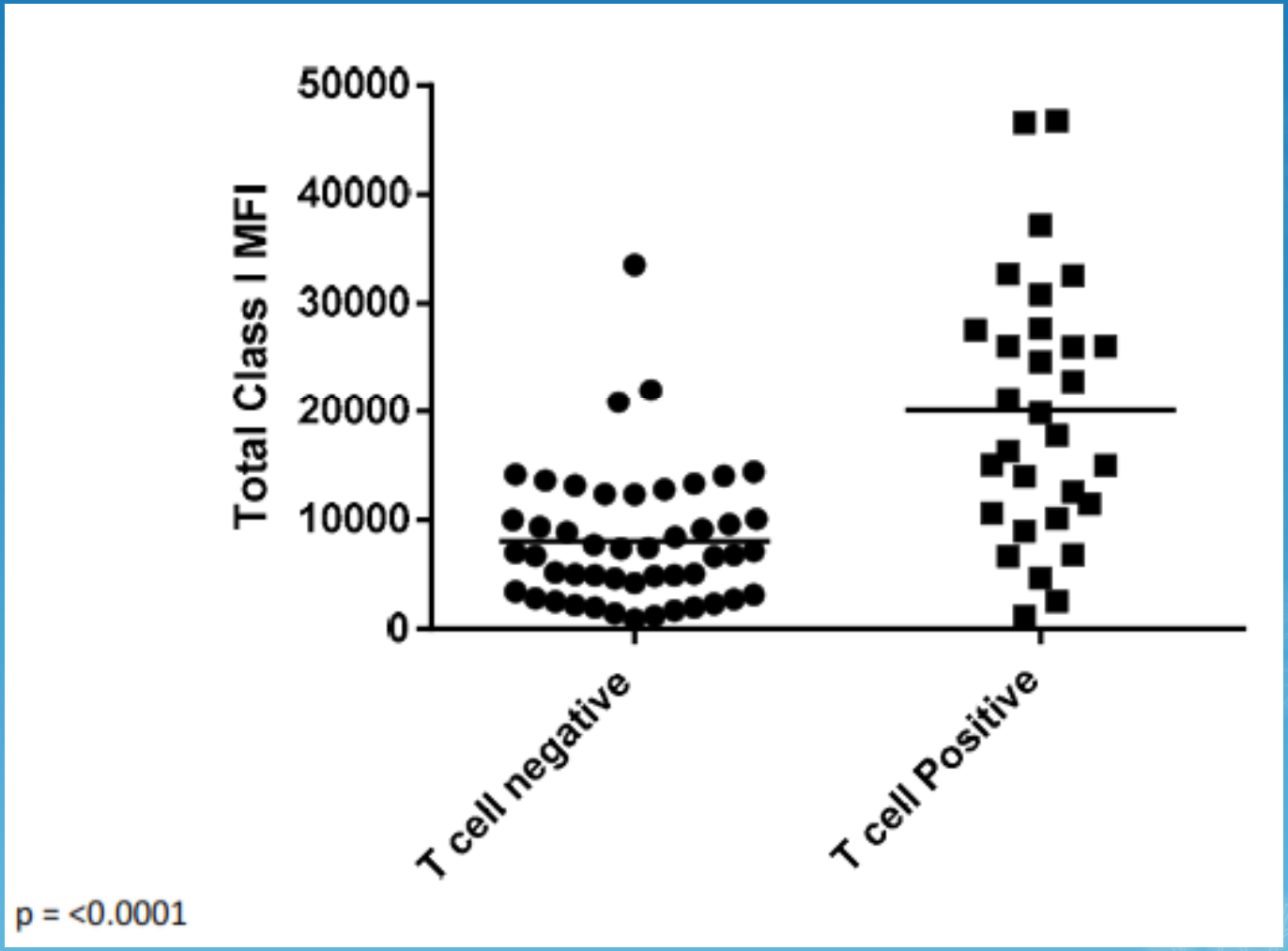
Total CI DSA MFI vs T cell XM result



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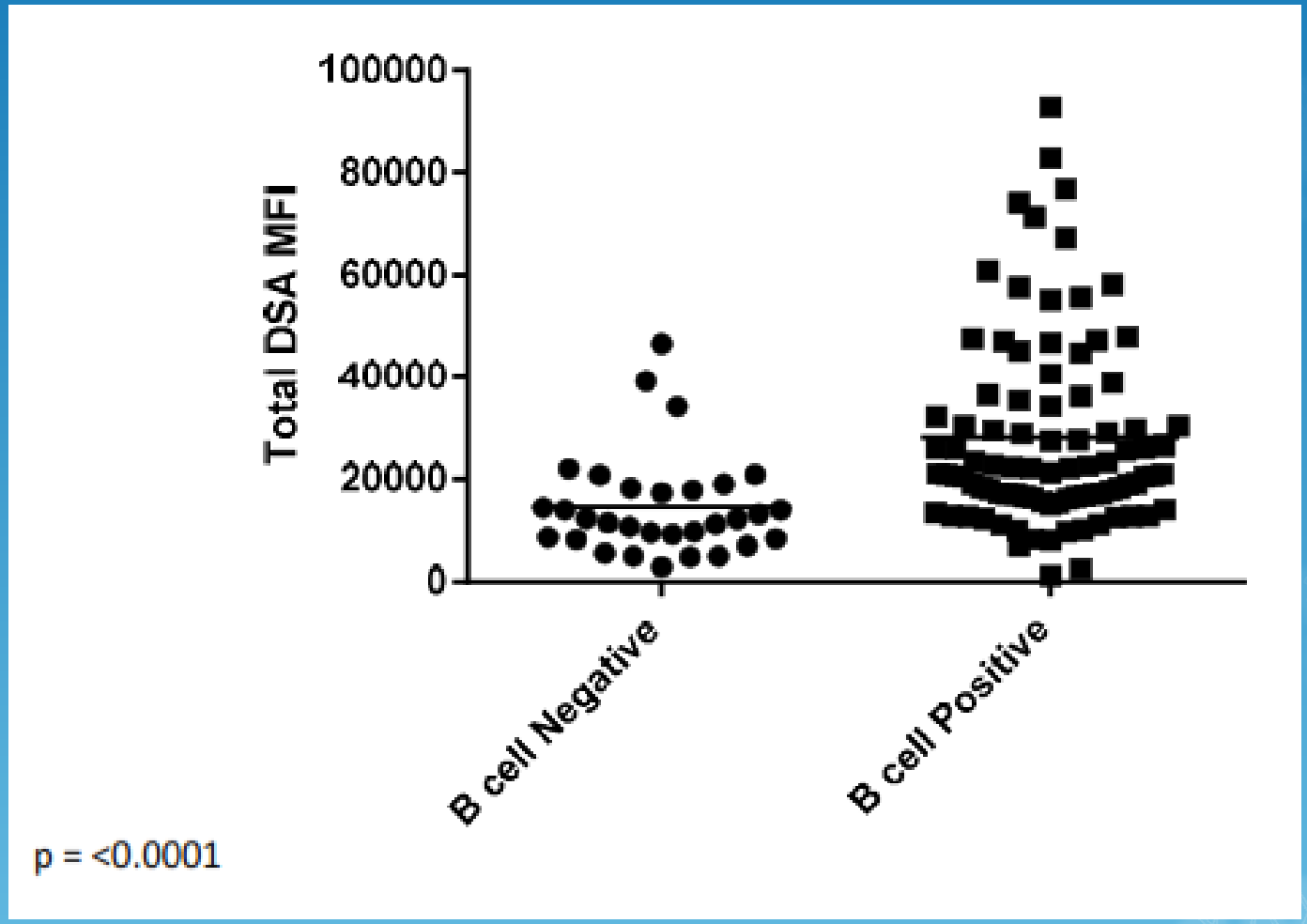
Total CI+II DSA MFI vs B cell XM result.



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Conclusion:

- Titre XM pre and post test DFPP was a good predictive indicator as to how much DFPP would be needed pre transplant.
- Starting titre pre DFPP did not alone predict amount of Ab removal required.
- Bead DSA MFI values did not predict RMF and positive XM with enough certainty to replace the FXM assessment.

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A Unique Approach:

- As a unit we have developed a unique approach to transplanting these patients.
- Fortnightly MDM to discuss all the highly sensitised patients.
- Patients identified as potential candidates with living donors are offered a test PEX and titre XM.
- If a direct transplant is deemed possible they are offered the choice of remaining in the paired scheme or proceeding directly to transplant.
- If a direct transplant is deemed unlikely they remain on call for a deceased donor and in the paired scheme.
- New potential donors can be reassessed on stored test PEX samples.

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Now and the Future:

- Our success has led to many referrals from across the UK and abroad.
- Have recently extended our programme to include HLA antibody incompatible stem cell transplantation.
- Become the national antibody referral centre for the HLAi haploidentical stem cell transplant trial.
- Further data is being collected regarding antibody strength and outcomes.
- This will allow the real risk of rejection and graft failure to be given to the patient and the donor.
- Currently only adult patients – but a number of paediatric patients in work up.

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Thank you!

- Clinical Lead – Nizam Mamode
- Ab removal – Irmen Generalao
- Lab Staff – Chloe Martin, Kamla Reddi, Sarah Blears, Flavia Namananga, Susan Wallace.
- Bob Vaughan

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