FDA 2017 AMR Workshop

Consideration of Quantitative Use of HLA Antibody Assays

And

Summary of the 2017 ASHI/AST STAR workgroup meeting

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DISCLOSURE:

Dr Tambur is a full time employee of Northwestern University, Chicago, Illinois

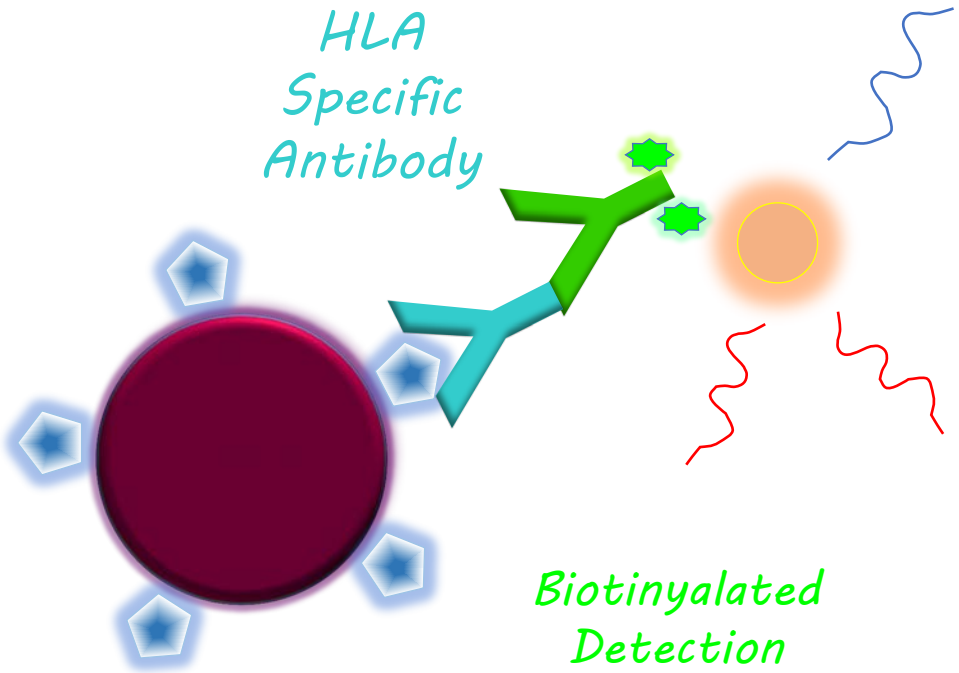
Dr Tambur is a consultant to Astellas and direct the core lab for the Astound clinical trial

Dr Tambur is a consultant to CSL Behring and received consultation fees

Why do we need to quantify?

Predict XM results	Immediate
Project response to treatment ?	Peri/post
Monitor response to treatment - desensitization	Peri/post
Diagnostic aid to Bx/clinical presentation	Post
Monitor response to treatment (rejection)	Post
Predict long term outcome	Future

What is REALISTIC to EXPECT from the Single Antigen Bead Assay

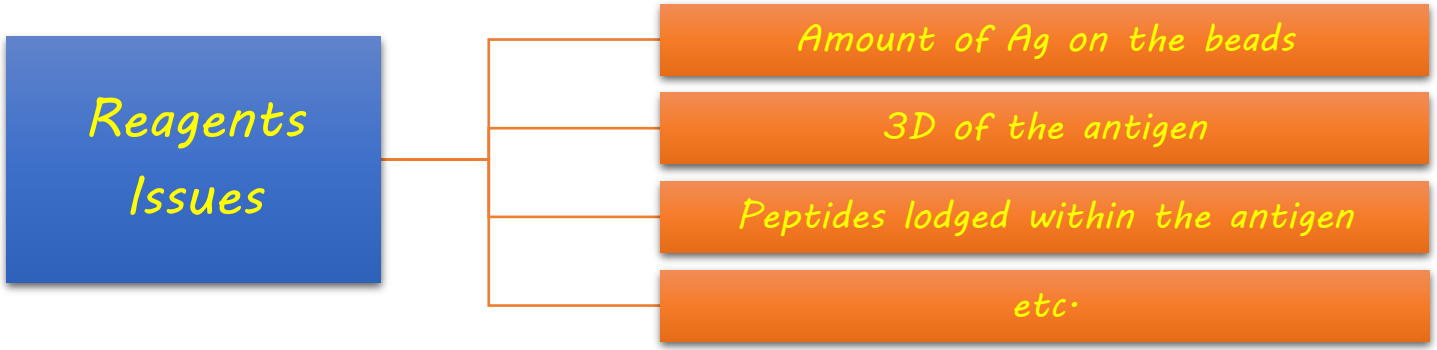


One molecule of fluorochrome binds to one molecule of antibody

Logical to assume the assay will be quantitative

~~MFI = antibody strength~~

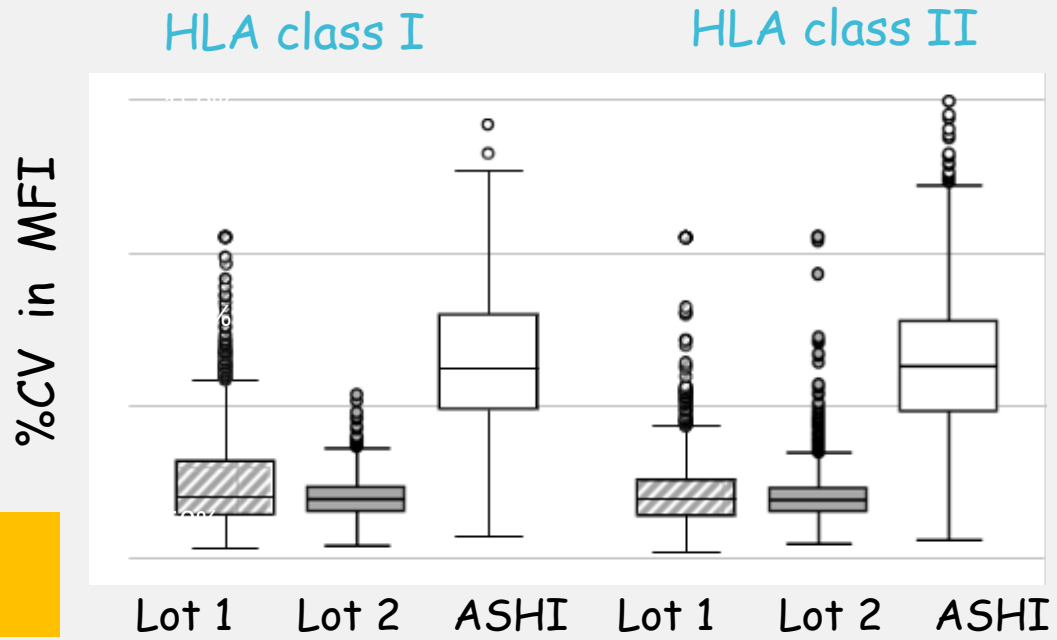
Why is it not working as expected ?



Why is it not working ?

Assay specific

- Small volume - - - 20% variability (CTOT trial)
- Automation? - - - did not seem to solve the issues



et al. Comprehensive assessment and Standardization of Solid-Phase ex- Bead Arrays for the Detection of Antibodies to HLA. **AJT 2013**

Serum specific

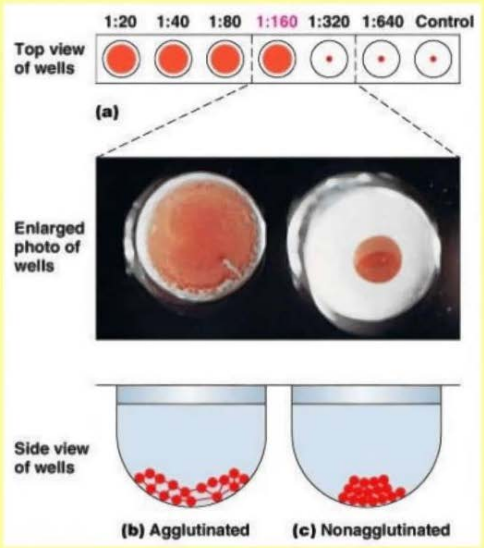
- Inhibition
- (Over)saturation
- Shared epitope phenomenon

Use of Titration Studies to Quantify Other Assays

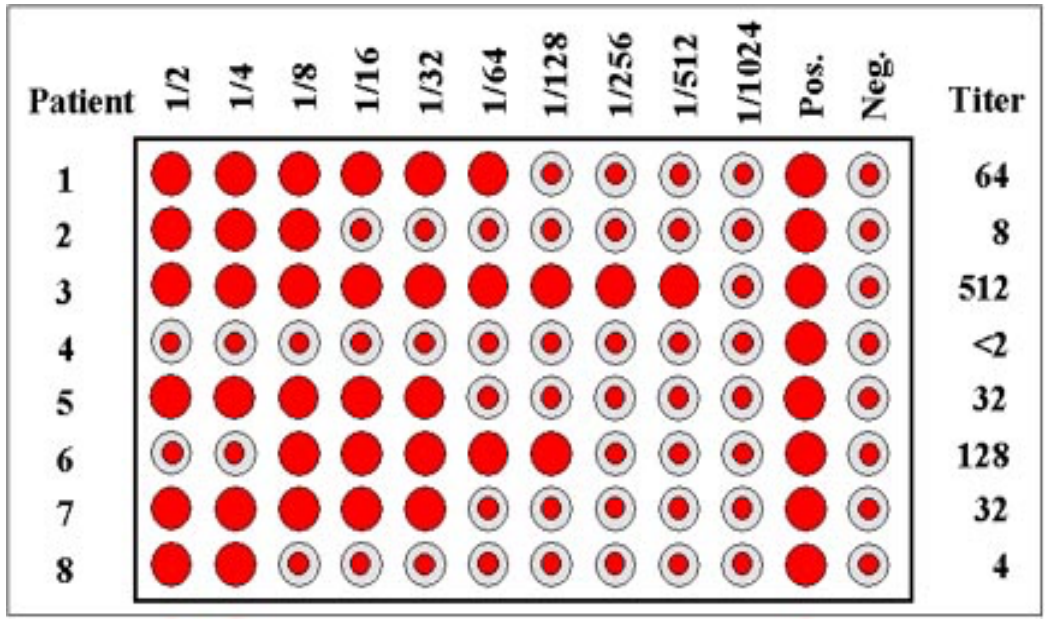
Agglutination assays to measure Antibodies to Blood Group Antigens
Antibodies to Autoantigens
Antibodies in response to vaccination

Antibody Titer

- Antibody titre is the concentration of antibodies against a particular antigen
- Serology test is usually done using micro well plate.
- So that the test sample can be done in a very small sample.

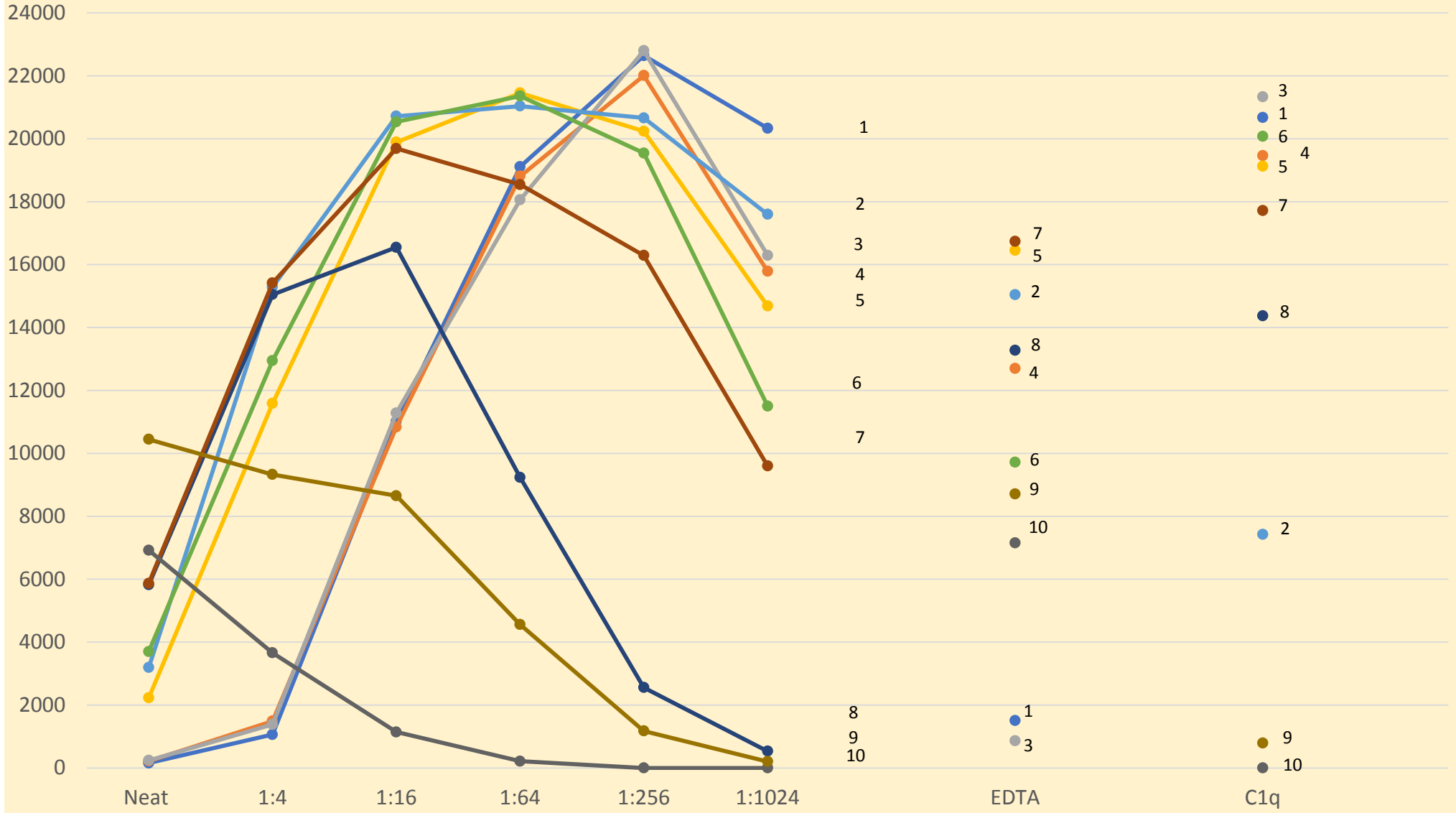


https://i.ytimg.com/vi/otyp7xoVmSk/maxresdefault.jpg



http://www.microbiologybook.org/mayer/ab-ag-rx.htm

Titration dilutes inhibitory factors



Labor intensive and expensive approach to remove inhibition

Titration reveals (over)saturation

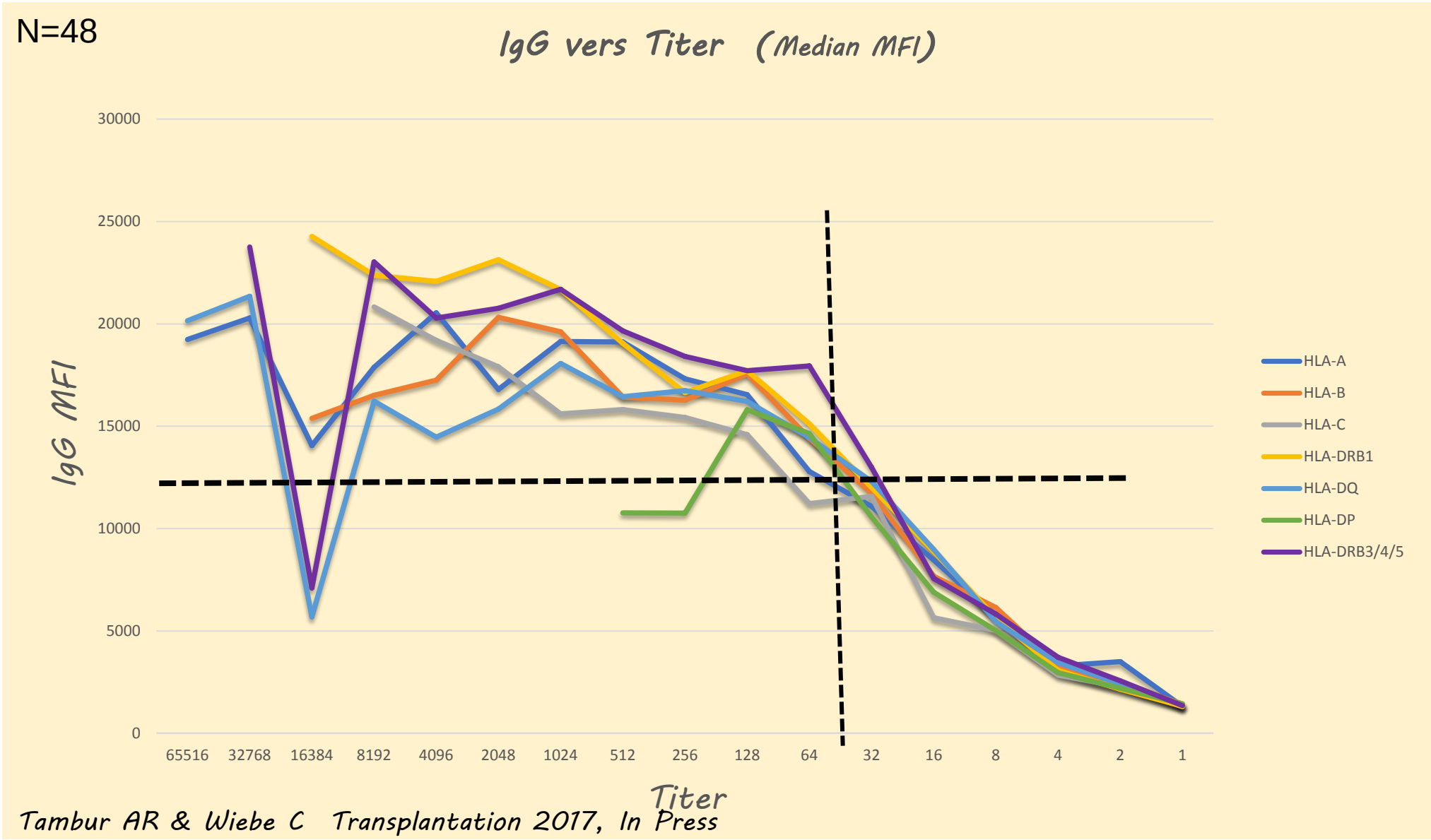
Titer	65516	32768	16384	8192	4096	2048	1024	512	256	128	64	32	16	8	4	2	1	N
Median IgG MFI																		
A	19232	20281	14052	17873	20532	16789	19132	19115	17307	16540	12786	11078	8459	5746	3288	3496	1307	595
B			15381	16508	17241	20314	19607	16429	16266	17548	14404	11723	7668	6132	3302	2424	1425	1146
C				20826	19193	17899	15601	15808	15420	14584	11215	11567	5633	5020	2837	2273	1294	268
DRB1			24272	22366	22068	23131	21672	19041	16641	17709	15110	11994	8871	5632	3068	2150	1311	585
DQ	20155	21339	5685	16218	14460	15835	18060	16443	16735	16208	14443	12296	8975	5445	3443	2414	1391	717
DP								10765	10747	15802	14639	10563	6880	5012	2956	2192	1433	369
DRB345		23754	7100	23027	20288	20762	21684	19648	18409	17705	17936	12982	7556	5814	3699	2553	1345	133

Tambur AR & Wiebe C Transplantation 2017, In Press

Critical information that is not appreciated otherwise

SIMILAR DATA OBTAINED FOR C1q ASSY

Is there an added value to titration studies over MFI?



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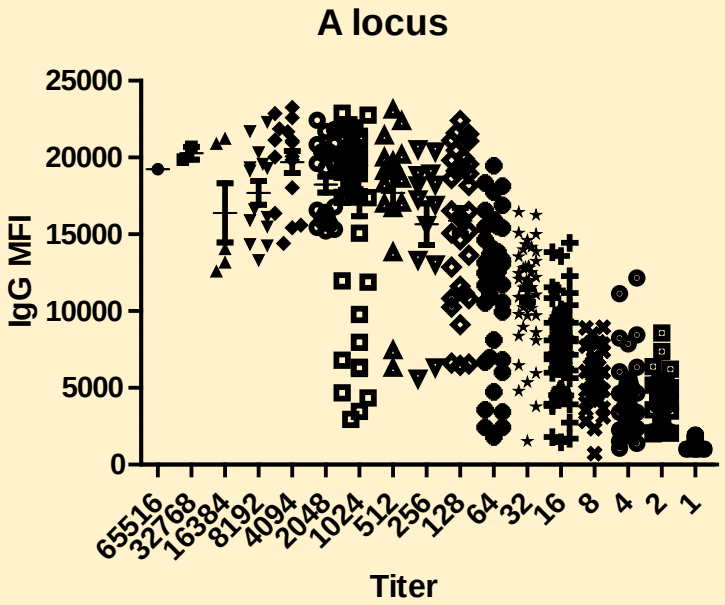
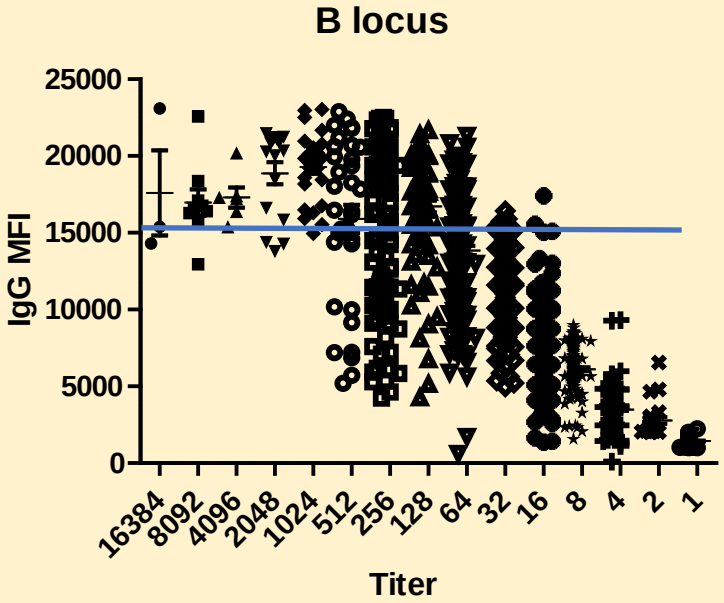
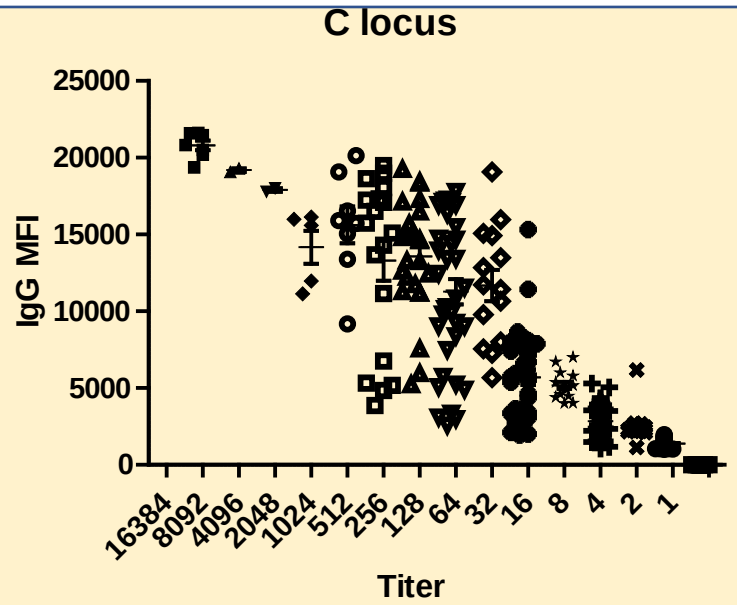
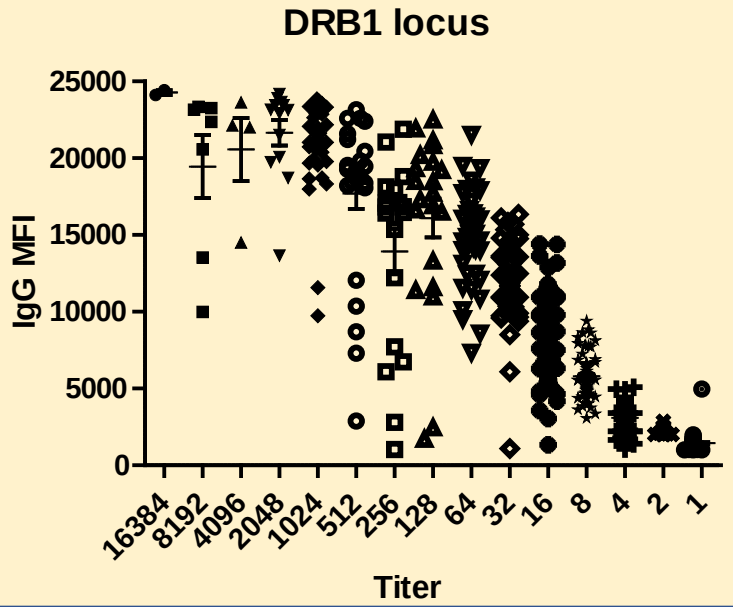
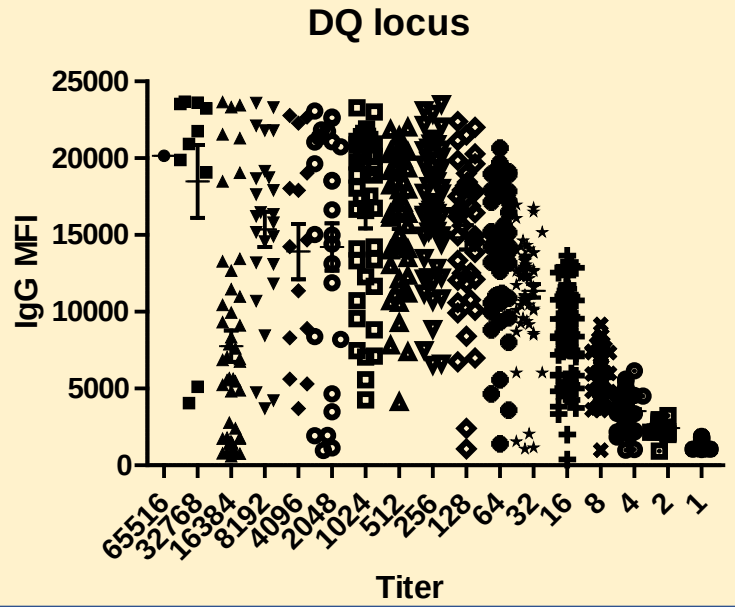
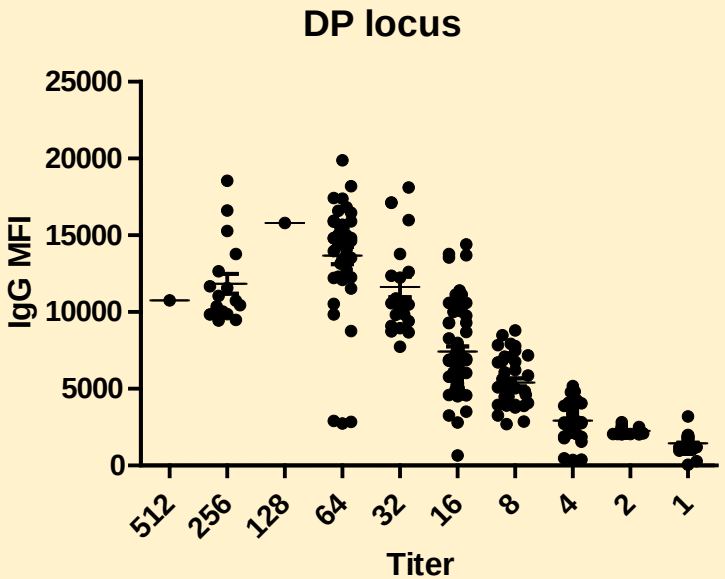






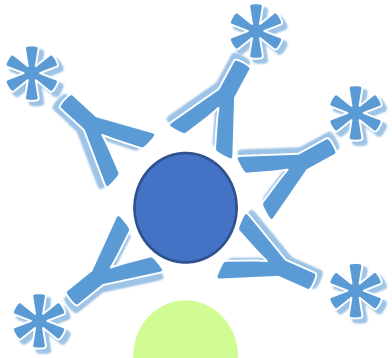






Tambur AR & Wiebe C Transplantation 2017, In Press

Titration DOSE NOT resolve phenomenon of low MFI value/bead due to "Shared Epitope" recognition



MFI

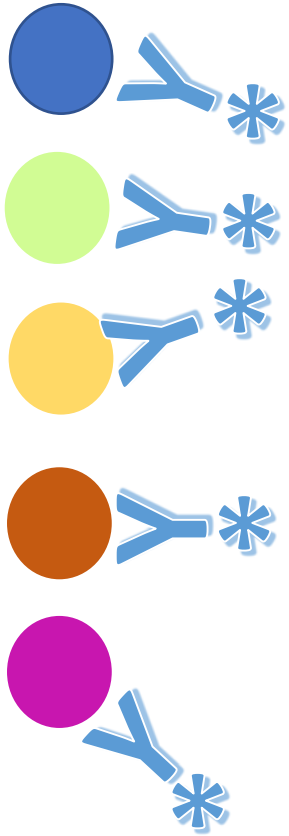
5000

0

0

0

0



MFI

1000

1000

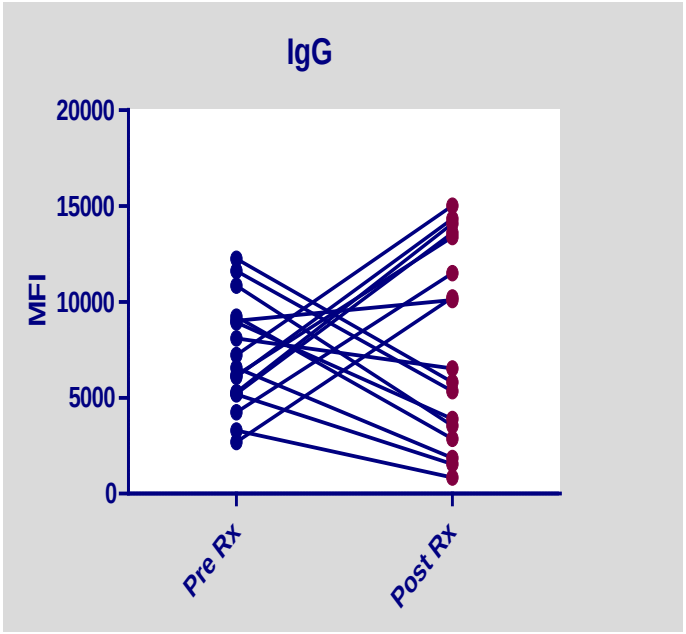
1000

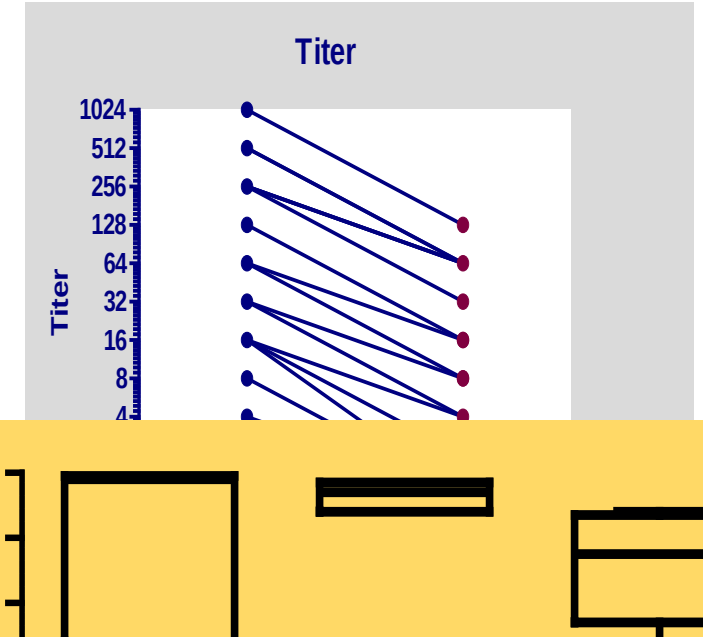
1000

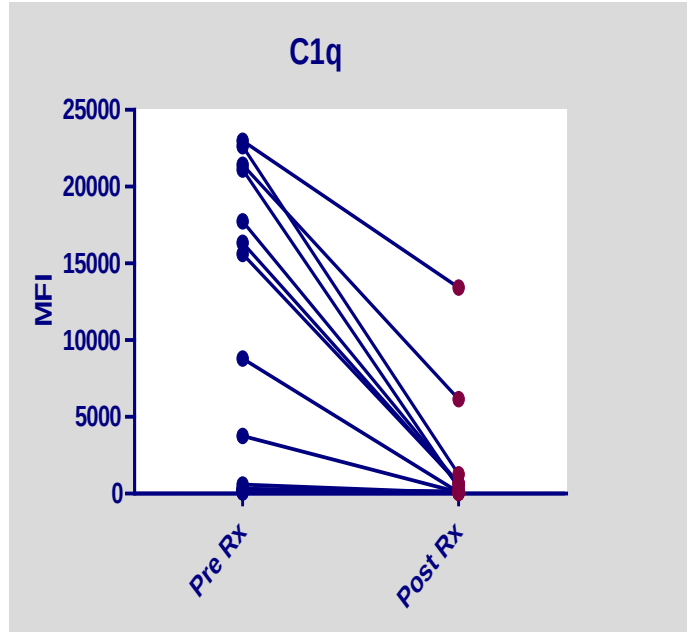
1000

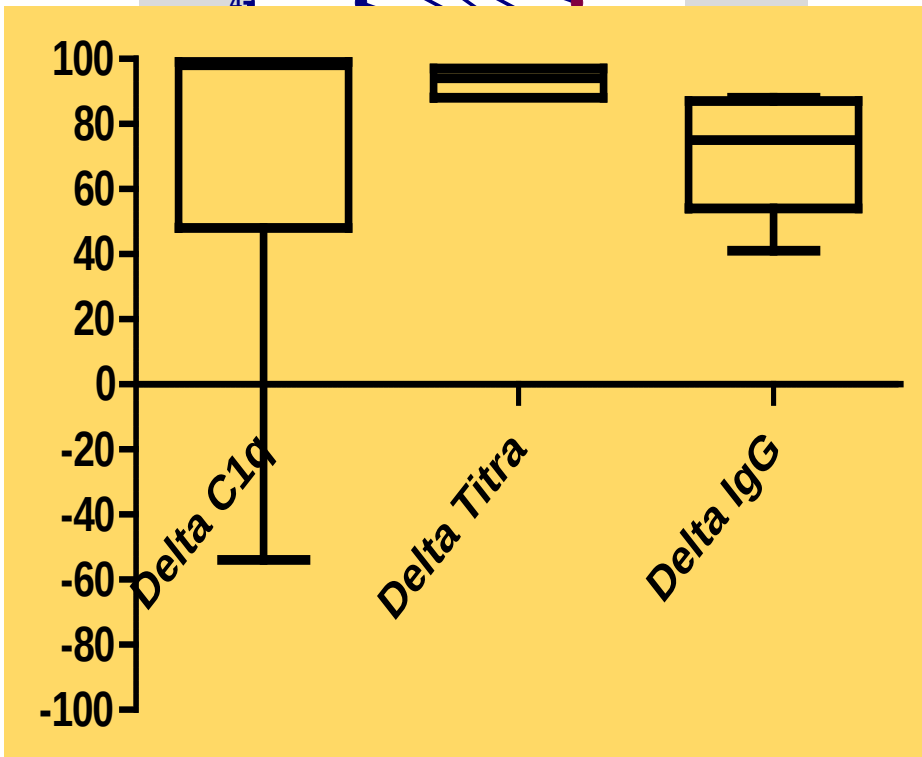
Requires other approaches to resolve

Titration studies provide better tool to monitor antibody response to treatment



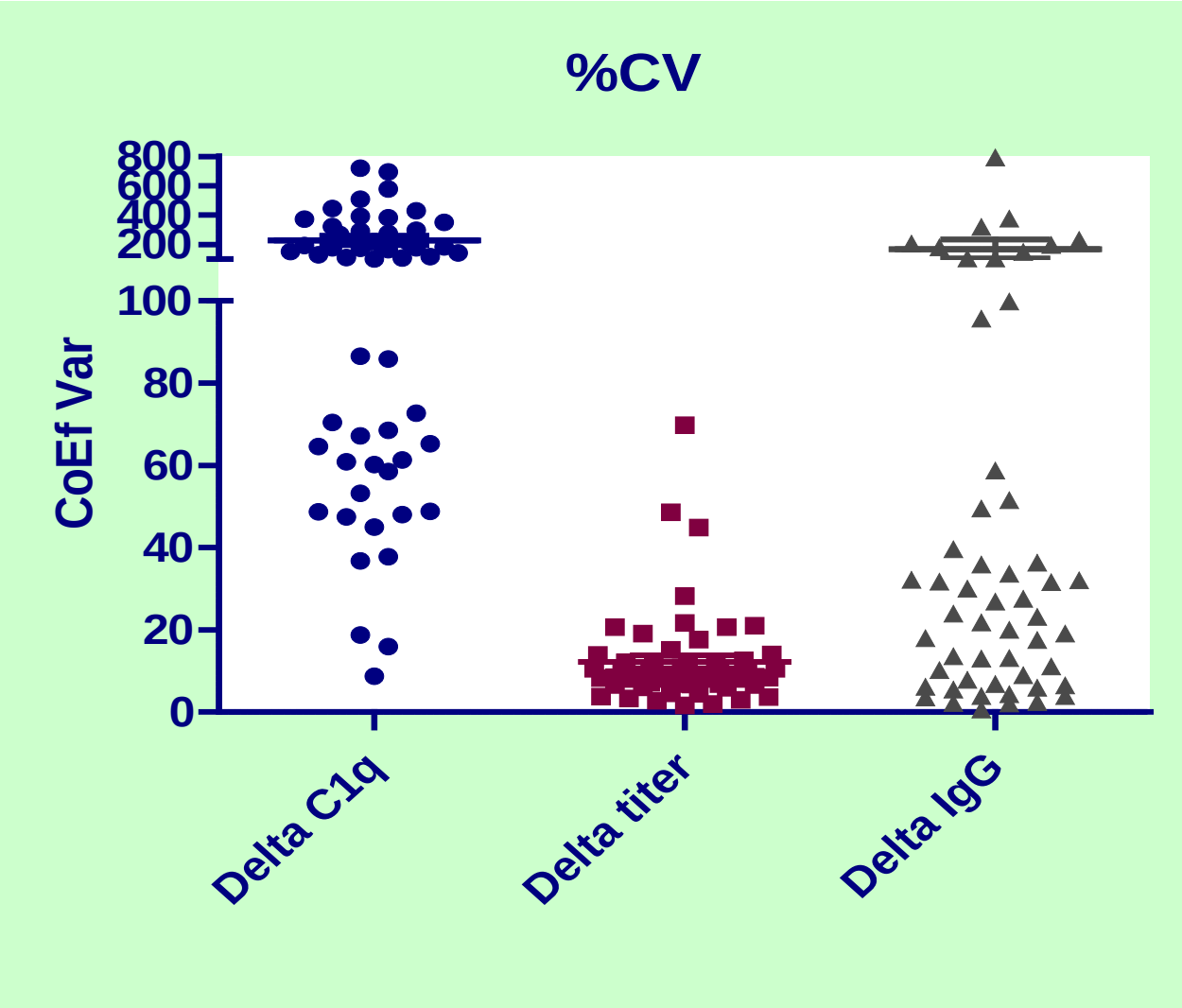






Tambur A et al· Human Immunology 2016

Titration studies provide better tool to monitor antibody response to treatment

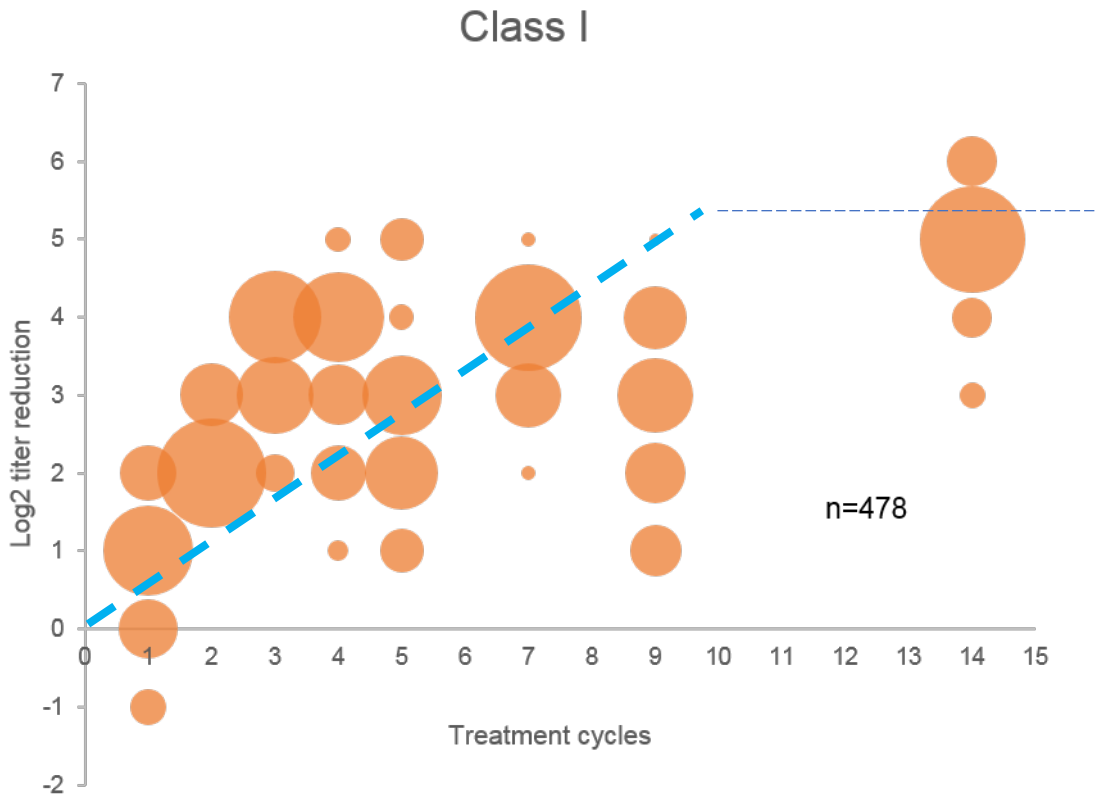


Tambur A et al· Human Immunology 2016

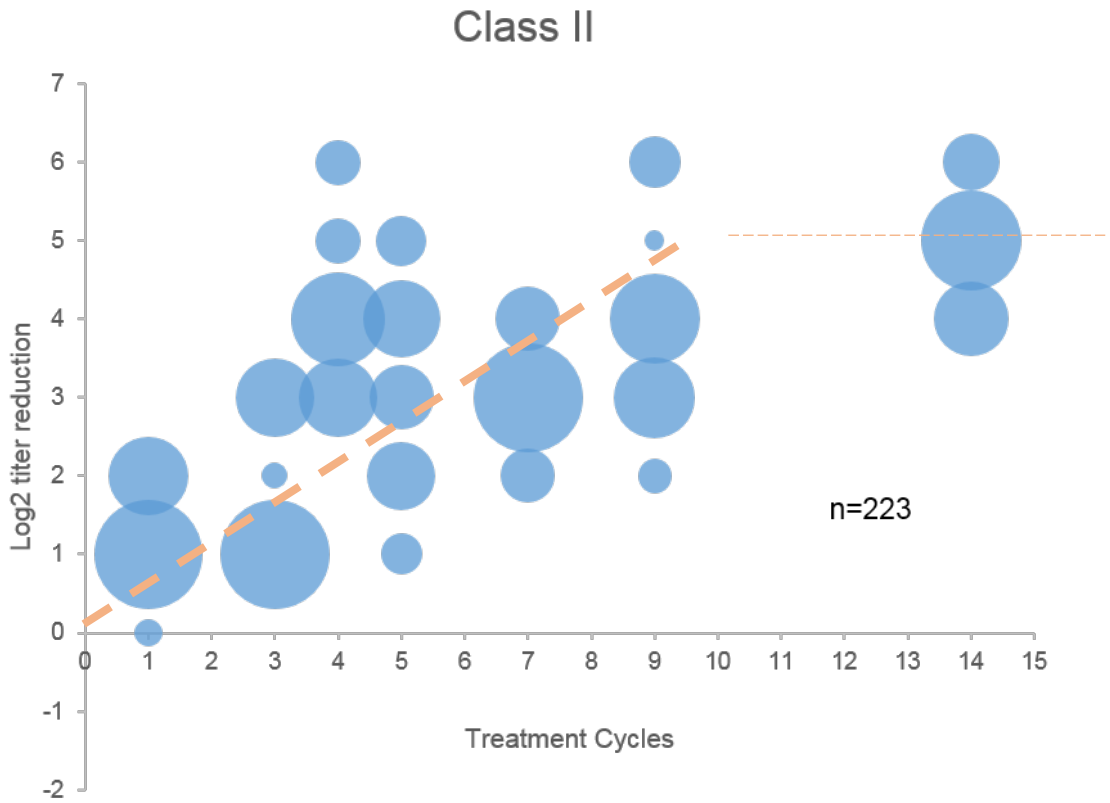
Decision Making/Monitoring of Responses to Ab Removal Rx

	IgG				C1q				Titer			
	Pre-RX	Pre-TX	Post-TX	F/U Post	C1q	C1q	C1q	C1q				
	76487-1	76487-2	76487-3	76847-4	76487-1	76487-2	76487-3	76847-4	76487-1T	76487-2T	76487-3T	76847-4T
A*01:01	19232	21117	21724	22158	20565	16975	14106	17649	32768+	4096	4096	4096
A*23:01	19874	20702	21007	21905	18232	17839	14857	16548	32768	1024	512	1024
A*24:02	20688	21455	21421	22093	19853	17759	14557	16372	32768	1024	1024	1024
A*24:03	20905	21811	20565	21884	19052	18521	14141	16253	16384	512	256	512
A*36:01	21233	22293	21760	21812	22414	19613	15186	18130	16384	1024	512	512
A*11:02	20329	21464	15973	15871	20791	17153	1692	1122	8192	256	32	32
A*29:01	22310	21038	19491	21713	21092	15719	12107	14089	8192	256	64	128
A*03:01	22866	20822	11834	12784	20674	13816	512	289	4096	128	32	32
A*11:01	21867	21280	14475	14625	20523	15590	785	599	4096	256	32	32
A*30:02	22435	16080	9650	10606	21495	1156	24	26	2048	64	16	16
B*82:01	14275	9723	10075	10552	8758	120	399	279	2048	64	64	128
A*25:01	21119	15438	7465	7188	19658	67	6	15	1024	32	8	8
A*74:01	21858	14871	2135	2099	22149	72	9	6	1024	64	2	2
A*33:03	21808	12197	1323	1266	17497	43	28	29	1024	32	1	1
B*44:03	22888	5211	8607	8890	20100	16	9	11	512	8	16	16
B*49:01	22408	6272	5225	5768	21291	17	12	17	512	8	8	1
B*57:01	21795	10012	10160	12410	19182	32	17	20	512	16	16	16
B*44:02	19542	2967	5606	6086	10603	32	20	23	256	4	8	8
B*45:01	20084	3276	6282	7647	13809	24	12	16	256	4	8	16
B*53:01	19922	5461	5086	6636	14613	23	16	23	256	8	8	4
B*59:01	20935	4876	3991	4303	14656	29	19	25	256	8	4	4
B*13:01	18066	3275	1417	1175	11456	36	31	33	256	4	1	1
B*47:01	15083	6966	1681	1296	2780	24	12	19	128	16	1	1
B*51:01	20892	3154	2816	2818	14576	27	17	17	128	4	4	1
C*07:02	5939	1471	1462	1052	76	48	50	43	128	4	4	1
B*07:02	9302	2388	2031	2629	40	16	5	13	64	4	2	4
C*05:01	8003	1960	580	599	432	36	30	33	32	4	1	1
A*68:02	13598	916	341	395	2765	25	7	14	16	1	1	1
B*27:08	5588	919	899	1283	31	16	9	11	16	4	1	1
B*42:01	4219	858	548	714	37	18	9	18	8	1	1	1
B*55:01	5244	516	546	591	32	22	13	20	8	1	1	1
A*02:06	1392	620	317	434	25	12	5	10	4	1	1	1

Correlation Between Antibody Titer and Response to PP/IVIg



Rounds	1	2	3	4	5	7	9	14
# Beads	51	24	11	74	51	84	133	50



Rounds	1	3	4	5	7	9	14
# Beads	24	28	28	45	32	49	17

D Pinelli et al, abstract accepted for ATC 2017

N=26 Pts

20 patients for Class I 17 patients for Class II (NW/JH)

Remediation…
Moving forward

Provide vendors resources of patient samples to enable QC / improvement of assays

- Adjust our expectation from the assay
- Do not use strict MFI as cutoff
- Use additional tools to assess presence and strength of antibodies

SENSITIZATION IN TRANSPLANTATION: ASSESSMENT OF RISK (STAR)

NORTH AMERICAN 2017 WORKING GROUP

Co-Chair	*Peter Nickerson*
Steering Committee	*Frans Claas; Ron Gill; Denis Glotz; Jon Kobashigawa; Michael Mengel; Peter Nickerson; Parmjeet Randhawa; Steve Woodle*
Group Leads	*Frans Claas; Trish Campbell; Sandy Feng; Howie Gebel; Annette Jackson; Kathryn Tinckam; Roz Mannon; Elaine Reed*
Administrative Support	*Victoria Converse; Anthony Celenza*
Stakeholders	*FDA; NIH; UNOS*

Goals

- Establishing criteria to assess whether immune memory exists, how much risk that memory represents, and practice guidelines to manage the risk before and after transplant
- Establishing criteria to assess a patient as immunologically naïve, how much risk a given donor represents, and practice guidelines for management both before and after transplant

Guiding Principles

- Biologically driven based on scientific data
- Focused on state-of-the-art clinical diagnostics
- Clinical practice recommendations based on “GRADE” and Strength of evidence

Deliverables

1. **Primer/Technical**
    - Definition of terms
    - Overview of clinical laboratory diagnostics and their strengths and limitations

2. **Definition of Immunologically Naïve vs. Memory – Biologic Basis**
    - Class I and Class II – which genetic loci are relevant?
    - What clinical diagnostic tools are available and required?
    - What quality assessment is required for these tools to be valid?
    - Future basic science and diagnostic needs?

Deliverables

SENSITIZATION IN TRANSPLANTATION: ASSESSMENT OF RISK (STAR)
NORTH AMERICAN 2017 WORKING GROUP

3. **Immunologic Memory – clinical application**
    - Pre-transplant assessment/management – risk stratification/desensitization
        - Class I vs. Class II
        - Determination of antibody attributes that have clinical impact
    - Peri-operative assessment/management
    - Post-transplant diagnostic monitoring
    - Post-treatment ABMR diagnostic monitoring
    - Future needs?

4. **Immunologically Naïve – clinical application**
    - Post-transplant diagnostic monitoring based on risk stratification
    - Post-treatment ABMR diagnostic monitoring
    - Future needs?

Recommendations for HLA testing to support clinical decision making in solid organ transplantation

- ***Donor and Recipient HLA typing***

  1. **Should be "comprehensive"** requiring information regarding all major HLA loci – HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1/DQB1, and -DPA1/DPB1

  2. **Should be performed using molecular methods** and, at least for antigens with more than one allele common in the donor population, should be given at high-resolution (e.g. resolving to at least CWD alleles)

Recommendations for HLA testing to support clinical decision making in solid organ transplantation

- ***Patient HLA antibody assessment***

1. **Should be performed by a solid phase assay and should include information regarding all major HLA loci – HLA-A, -B, -C, -DRB1, -DRB3/4/5, -DQA1/DQB1, -DPA1/DPB1.** Antibody information should be captured at the **allele level** (*in fact, the software provided by the manufacturer already provides the information at the allelic level, in addition to the serologic level that is currently used*)

2. **Measures to remove inhibition must be put in place.** Verified methods include EDTA (25/60mM) and/or titration studies. Other methods such as dialysis, DTT treatment or heat-inactivation have been reported but should be further verified.

3. **Mechanism should be put in place to detect phenomenon of potential "epitope sharing"** (such as stacking of antibodies against members of a known CREG). Methods to test for this hypothesis should be sought when possible (e.g., performing surrogate XM if possible), or as minimal practice alert the clinicians of the potential presence of such phenomenon. In such instances one cannot rely on the use of vXM and physical/lymphocyte XM must be performed.

Why is it not working ?

HLA is complicated (expensive), so we tend to over-simplify things

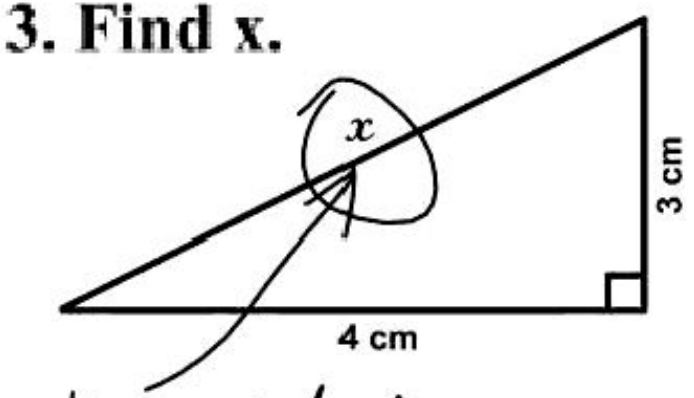
Solving equation by one Blondie:

$$\frac{1}{n}\sin x = ?$$

$$\frac{1}{n}\sin x =$$

$$six = 6$$

3. Find x.



Here it is

Allele Level Antibodies

Composition of HLA-DQ specific ... [part of this heading is hidden behind the overlapping title]

Frequency of HLA-DQ Alleles in among NU donors

Allele Level Typing	Serologic Typing
NC	
PC	
DRB1*01:01,-,-,-,-,-,-,-,-,-,-	DR1
DRB1*01:02,-,-,-,-,-,-,-,-,-,-	DR1
DRB1*01:03,-,-,-,-,-,-,-,-,-,-	DR1
DRB1*03:01,-,-,-,-,-,-,-,-,-,-	DR17
DRB1*03:02,-,-,-,-,-,-,-,-,-,-	DR18
DRB1*04:01,-,-,-,-,-,-,-,-,-,-	DR4
DRB1*04:02,-,-,-,-,-,-,-,-,-,-	DR4
DRB1*04:03,-,-,-,-,-,-,-,-,-,-	DR4
DRB1*04:04,-,-,-,-,-,-,-,-,-,-	DR4
DRB1*04:05,-,-,-,-,-,-,-,-,-,-	DR4
DRB1*07:01,-,-,-,-,-,-,-,-,-,-	DR7
DRB1*08:01,-,-,-,-,-,-,-,-,-,-	DR8
DRB1*09:01,-,-,-,-,-,-,-,-,-,-	DR9
DRB1*09:02,-,-,-,-,-,-,-,-,-,-	DR9
DRB1*10:01,-,-,-,-,-,-,-,-,-,-	DR10
DRB1*11:01,-,-,-,-,-,-,-,-,-,-	DR11
DRB1*11:04,-,-,-,-,-,-,-,-,-,-	DR11
DRB1*12:01,-,-,-,-,-,-,-,-,-,-	DR12
DRB1*12:02,-,-,-,-,-,-,-,-,-,-	DR12
DRB1*13:01,-,-,-,-,-,-,-,-,-,-	DR13
DRB1*13:03,-,-,-,-,-,-,-,-,-,-	DR13
DRB1*14:01,-,-,-,-,-,-,-,-,-,-	DR14
DRB1*14:02,-,-,-,-,-,-,-,-,-,-	DR14
DRB1*14:54,-,-,-,-,-,-,-,-,-,-	DR14
DRB1*15:01,-,-,-,-,-,-,-,-,-,-	DR15
DRB1*15:02,-,-,-,-,-,-,-,-,-,-	DR15
DRB1*15:03,-,-,-,-,-,-,-,-,-,-	DR15
DRB1*16:01,-,-,-,-,-,-,-,-,-,-	DR16
DRB1*16:02,-,-,-,-,-,-,-,-,-,-	DR16
-,-,DRB3*01:01,-,-,-,-,-,-,-,-	DR52
-,-,DRB3*02:02,-,-,-,-,-,-,-,-	DR52
-,-,DRB3*03:01,-,-,-,-,-,-,-,-	DR52
-,-,DRB4*01:01,-,-,-,-,-,-,-,-	DR53
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-,-,-,-,DQA1*01:03,-,DQB1*06:03,-,-,-,-,-	DQ6
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-,-,-,-,DQA1*02:01,-,DQB1*03:01,-,-,-,-,-	DQ7
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-,-,-,-,-,-,-,-,DPA1*01:03,-,DPB1*02:01,-	DP2
-,-,-,-,-,-,-,-,DPA1*01:03,-,DPB1*03:01,-	DP3
-,-,-,-,-,-,-,-,DPA1*01:05,-,DPB1*03:01,-	DP3
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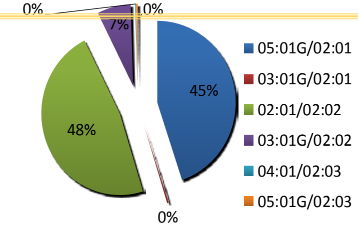
-,-,-,-,-,-,-,-,DPA1*01:05,-,DPB1*28:01,-	DP28
-,-,-,-,-,-,-,-,DPA1*04:01,-,DPB1*28:01,-	DP28

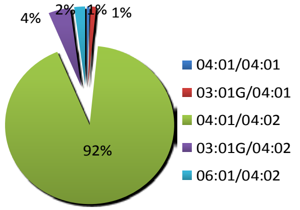
95 Alleles
42 Antigens

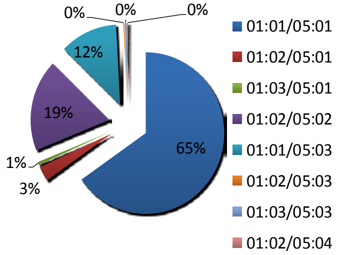
DQα	DQβ	Serologic equivalent
DQA1*02:01	DQB1*02:01	DQ2
DQA1*03:01	DQB1*02:01	DQ2
DQA1*04:01	DQB1*02:01	DQ2
DQA1*05:01	DQB1*02:01	DQ2
DQA1*02:01	DQB1*02:02	DQ2
DQA1*03:02	DQB1*02:02	DQ2
DQA1*05:01	DQB1*02:02	DQ2
DQA1*02:01	DQB1*04:01	DQ4
DQA1*03:03	DQB1*04:01	DQ4
DQA1*04:01	DQB1*04:01	DQ4
DQA1*02:01	DQA1*04:02	DQ4
DQA1*04:01	DQB1*04:02	DQ4
DQA1*06:01	DQB1*04:02	DQ4
DQA1*01:01	DQB1*05:01	DQ5
DQA1*01:02	DQB1*05:01	DQ5
DQA1*01:02	DQB1*05:02	DQ5
DQA1*01:04	DQB1*05:03	DQ5
DQA1*02:01	DQB1*05:03	DQ5
DQA1*01:03	DQB1*06:01	DQ6
DQA1*01:04	DQB1*06:01	DQ6
DQA1*02:01	DQB1*06:01	DQ6
DQA1*05:01	DQB1*06:01	DQ6
DQA1*01:01	DQB1*06:02	DQ6
DQA1*01:02	DQB1*06:02	DQ6
DQA1*01:03	DQB1*06:03	DQ6
DQA1*01:02	DQB1*06:04	DQ6
DQA1*01:02	DQB1*06:09	DQ6
DQA1*02:01	DQB1*03:01	DQ7
DQA1*03:01	DQB1*03:01	DQ7
DQA1*03:02	DQB1*03:01	DQ7
DQA1*05:01	DQB1*03:01	DQ7
DQA1*05:03	DQB1*03:01	DQ7
DQA1*05:05	DQB1*03:01	DQ7
DQA1*06:01	DQB1*03:01	DQ7
DQA1*01:01	DQB1*03:02	DQ8
DQA1*02:01	DQB1*03:02	DQ8
DQA1*03:01	DQB1*03:02	DQ8
DQA1*03:02	DQB1*03:02	DQ8
DQA1*02:01	DQB1*03:03	DQ9
DQA1*03:01	DQB1*03:03	DQ9
DQA1*03:02	DQB1*03:03	DQ9
DQA1*04:01	DQB1*03:03	DQ9
DQA1*06:01	DQB1*03:03	DQ9

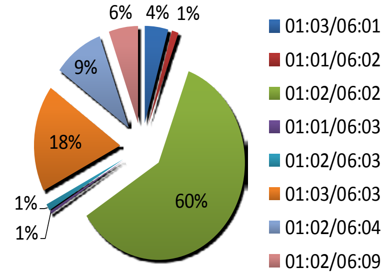
43 Alleles
7 Antigens

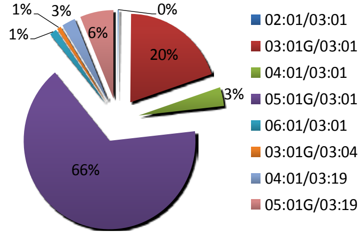
Tambur et al
Transplantation
2013;95:635

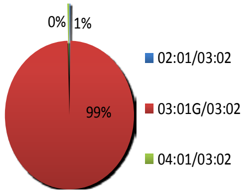


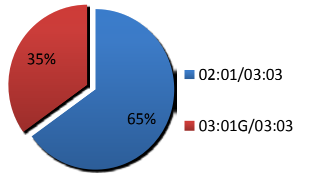












Tambur et al Transplantation 2013;96:1065

DRB1	DQB1	EUR rank	AFA rank	API rank	HIS rank
1301	0603	5	15	16	9
1301	0605	63	NA	93	NA
1301	0604	66	45	NA	NA
1301	0303	68	28	NA	68
1301	0501	69	27	NA	53
1301	0602	76	73	NA	NA
1301	0609	79	34	NA	NA
1301	0301g	NA	74	NA	NA
1301	0302	NA	NA	NA	81
1301	0608	NA	36	NA	67
1301	0611	NA	NA	NA	92
1302	0604	11	19	24	11
1302	0609	23	13	21	35
1302	0501	61	21	NA	44
1302	0603	64	NA	NA	NA
1302	0602	97	NA	NA	NA
1302	0301g	NA	101	NA	NA
1302	0502	NA	41	NA	72
1302	0503	NA	NA	NA	73
1302	0605	NA	86	83	NA
1303	0301g	18	17	89	26
1303	0502	102	NA	NA	NA
1303	0201g	NA	18	NA	49
1303	0302	NA	79	NA	NA
1303	0402	NA	91	NA	58
1303	0609	NA	81	NA	NA
1304	0301g	78	24	NA	34
1304	0302	NA	102	NA	NA
1305	0301g	29	NA	NA	47
1309	0603	NA	NA	NA	75

I don't have high resolution typing but I can impute...

Donor typed as DR13 DQ6

Which allele of DQ6 is DSA?

What is the donor is part EUR part AFA?

And somehow we know the HR typing for the DRB1?

Is it the
DRB1*13:02 w DQB1*06:04

or
DRB1*13:02 w DQB1*06:09

New End-Points for New Generation Clinical Trials - DSA?

Make Sure DSAs are Measured Appropriately

- ❑ HR typing of donors (at least "for cause") for all HLA loci
- ❑ Assigned Abs based on HR (provided with the kits)
- ❑ Determine whether SAB-kit indeed includes reagents to test DSA
- ❑ Remove potential inhibitory factors from serum
- ❑ Account for potential "Shared-Epitope" reactions
- ❑ MFI should not be used as a strict cut-off value
- ❑ Monitoring efficacy of treatment is best done by dilution studies

SENSITIZATION IN TRANSPLANTATION: ASSESSMENT OF RISK (STAR)

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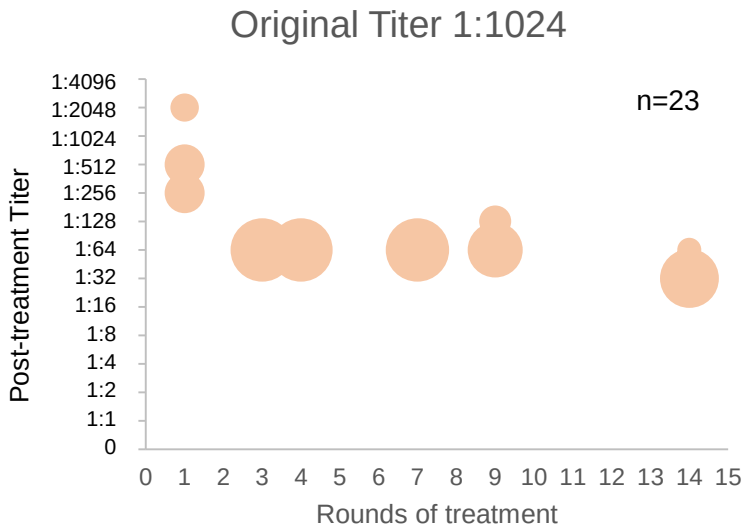
& Laurinda Jaffe
in Memory of
Paul Terasaki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Post-treatment Titer
1:4096
1:2048
1:1024
1:512
1:256
1:128
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1:8
1:4
1:2
1:1
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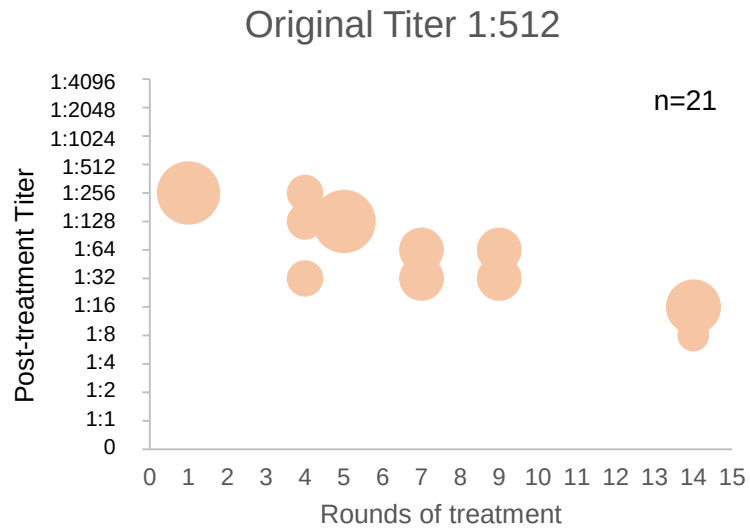
Rounds of treatment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1:128
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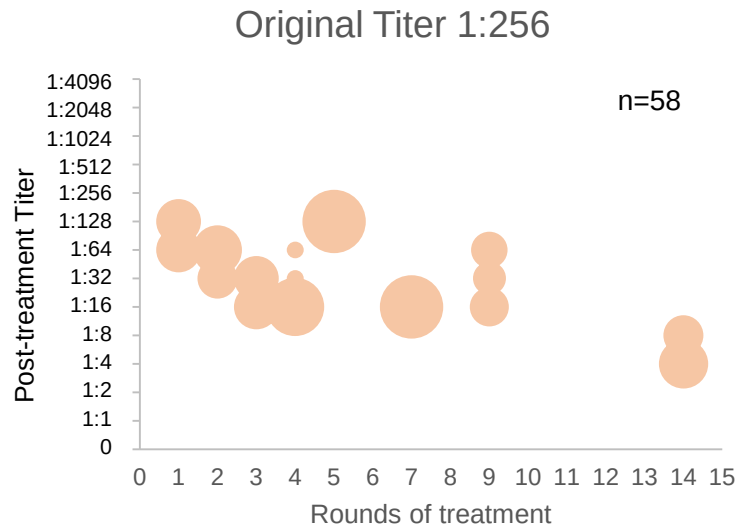
1:8
1:4
1:2
1:1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Rounds of treatment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1:256
1:128
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1:8
1:4
1:2
1:1
0
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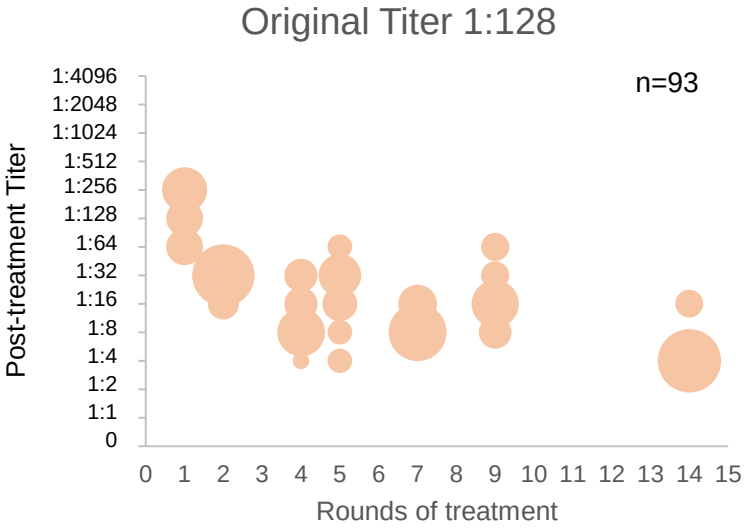
Rounds of treatment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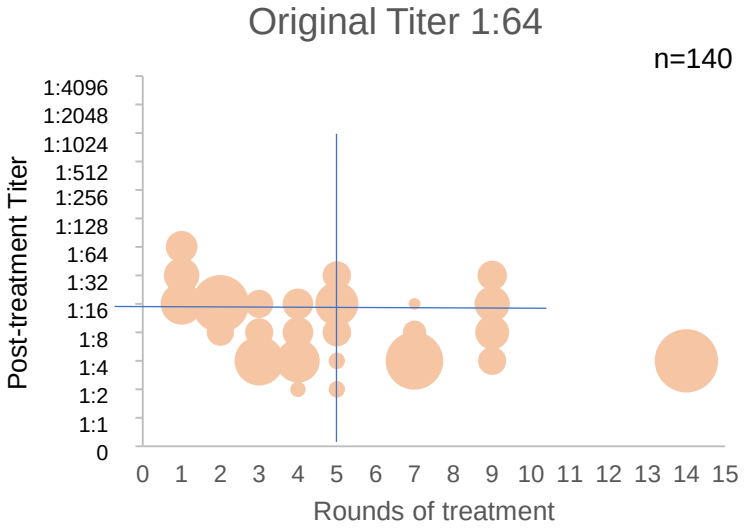
Rounds of treatment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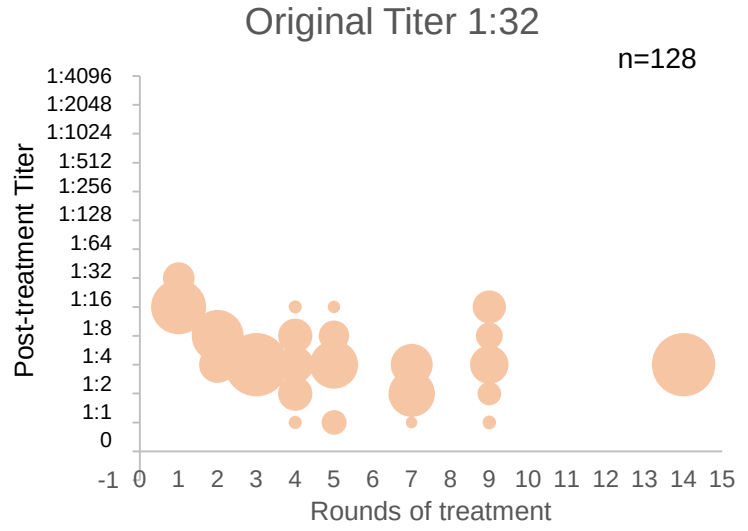
Rounds of treatment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1:128
1:64
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1:4
1:2
1:1
0
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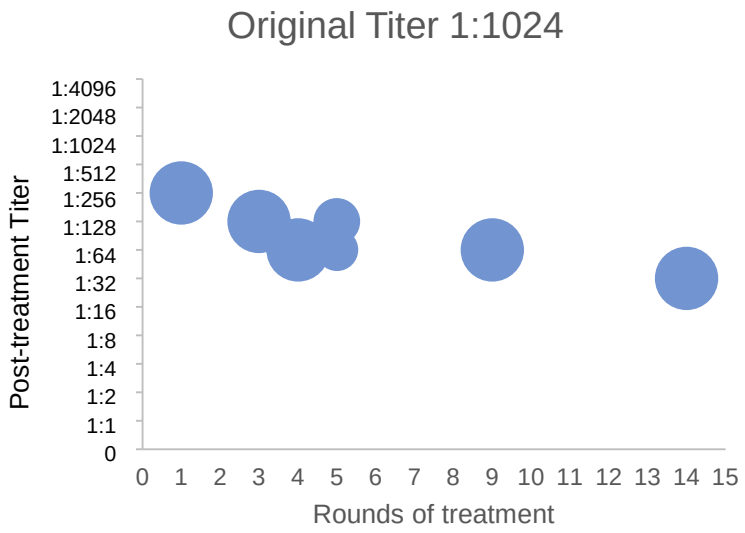
Rounds of treatment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Post-treatment Titer
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1:256
1:128
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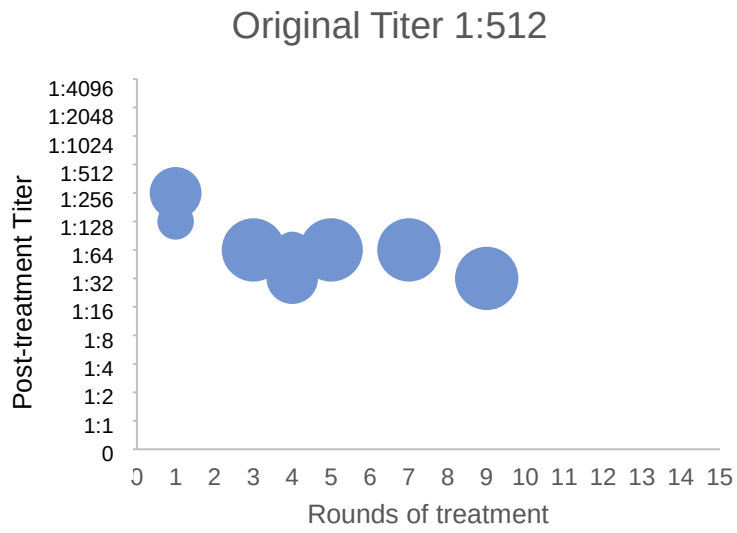
Rounds of treatment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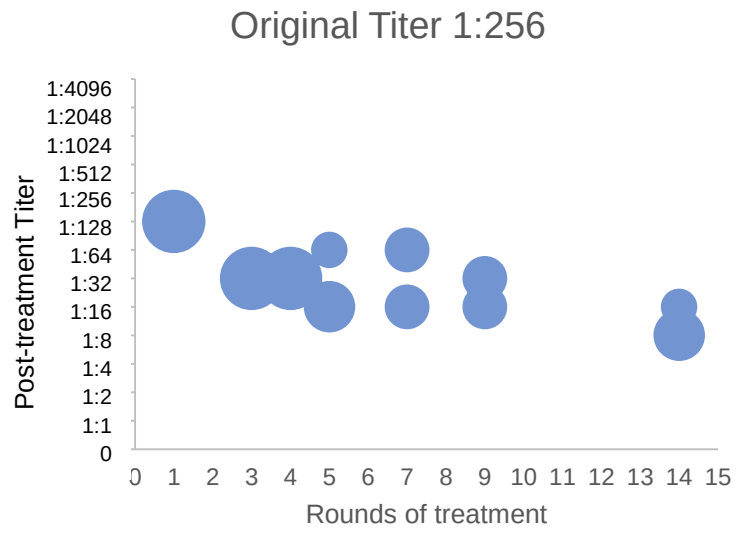
Rounds of treatment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1:1
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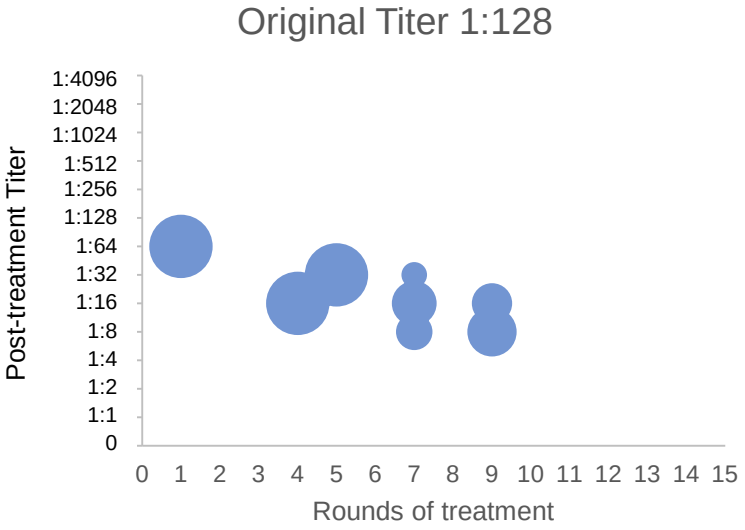
Rounds of treatment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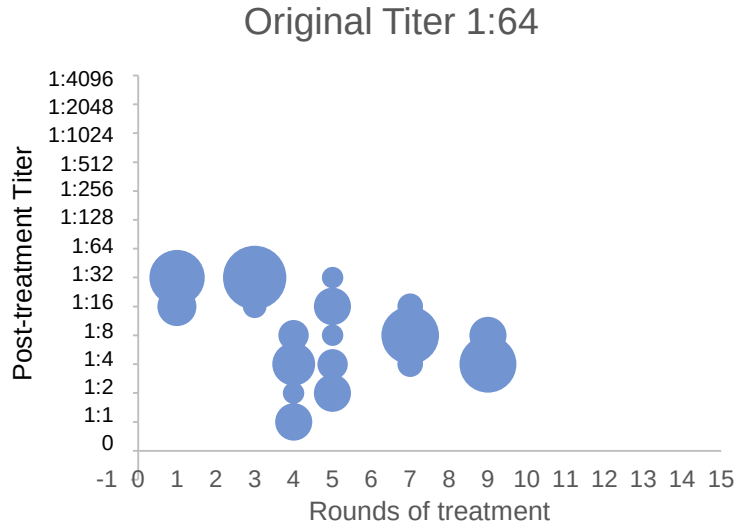
Rounds of treatment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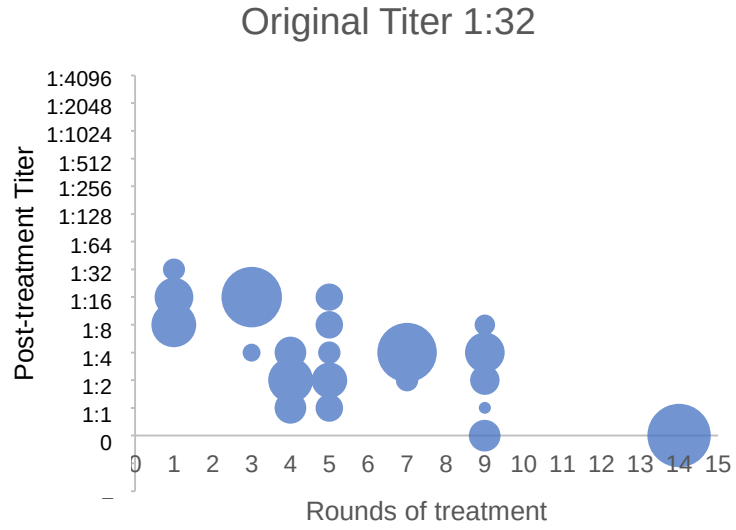
Rounds of treatment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0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Rounds of treatment