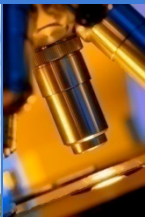


Complement Activation in Type 1 Diabetes: Analysis of Pancreatic Tissue from nPOD Cases

Patrick Rowe

January 16, 2012



Indirect Evidence for a Role of Complement Activation in Beta Cell Destruction

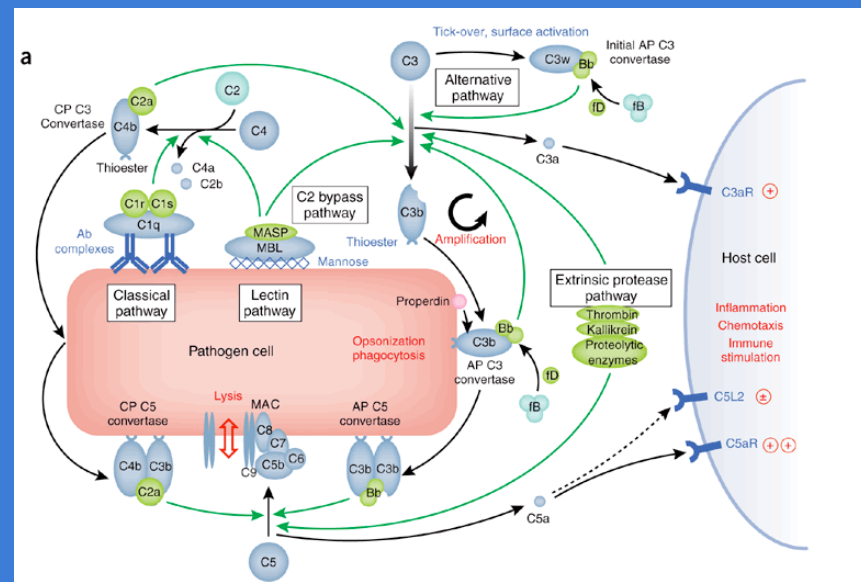
- IgG and complement deposited in islets from new-onset T1D patient

N Engl J Med 1985; 313:353-360

- CF-ICA titers increase in the pre-onset period
- CF-ICA titers decrease more rapidly after onset than traditional ICA

Lancet.1980 Mar 29;1(8170):668-72

Diabetologia (1994) 37:388-393



Nature Biotechnology 25, 1265 - 1275 (2007)



nPOD
Network for Pancreatic Organ
Donors with Diabetes



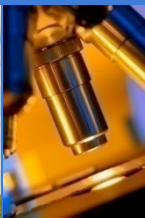
Study Design

Donor groups

- No diabetes (n=11, age 32.1±5.5 yrs, BMI 26.8±1.4 kg/m²)
- No diabetes, islet autoantibody-positive (n=10, age 33.4±5.8 yrs, BMI 25.7±1.7 kg/m²)
- Type 1 diabetes (n=11, age 22.1±2.2 yrs, duration 10.3±2.0 yrs, BMI 24.2±1.3 kg/m², 63% aab+)
- Type 2 diabetes (n=8, age 53.4±4.1 yrs, duration 5.5±2.8 yrs, BMI 35.1±2.0 kg/m², 25% aab+)

IHC analysis of C4d antigen on frozen pancreas sections

- anti-human C4d mouse monoclonal antibody, clone 10-11 (cat# 2222-8004, AbD Serotec) 1:8000 dilution
- C4d staining scored by board-certified pathologist blinded to donor groups
- Aperio software used to quantify C4d staining on digital slides

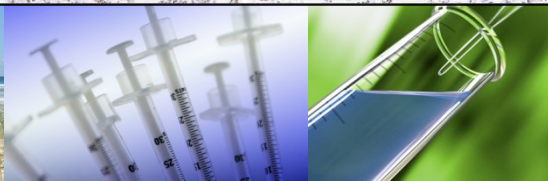
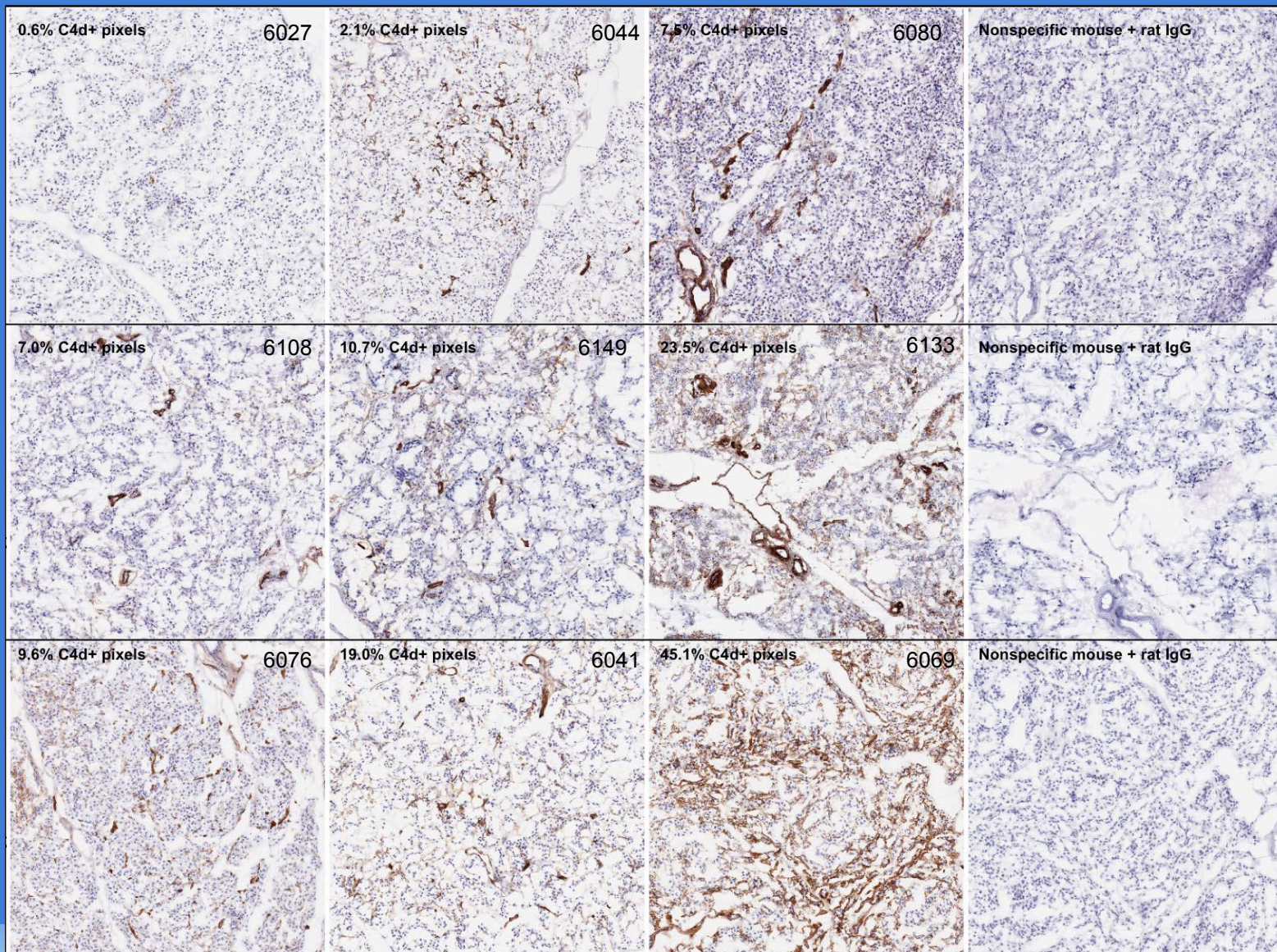


C4d localizes to blood vessels

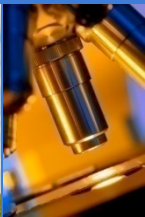
No diabetes

Type 2 diabetes

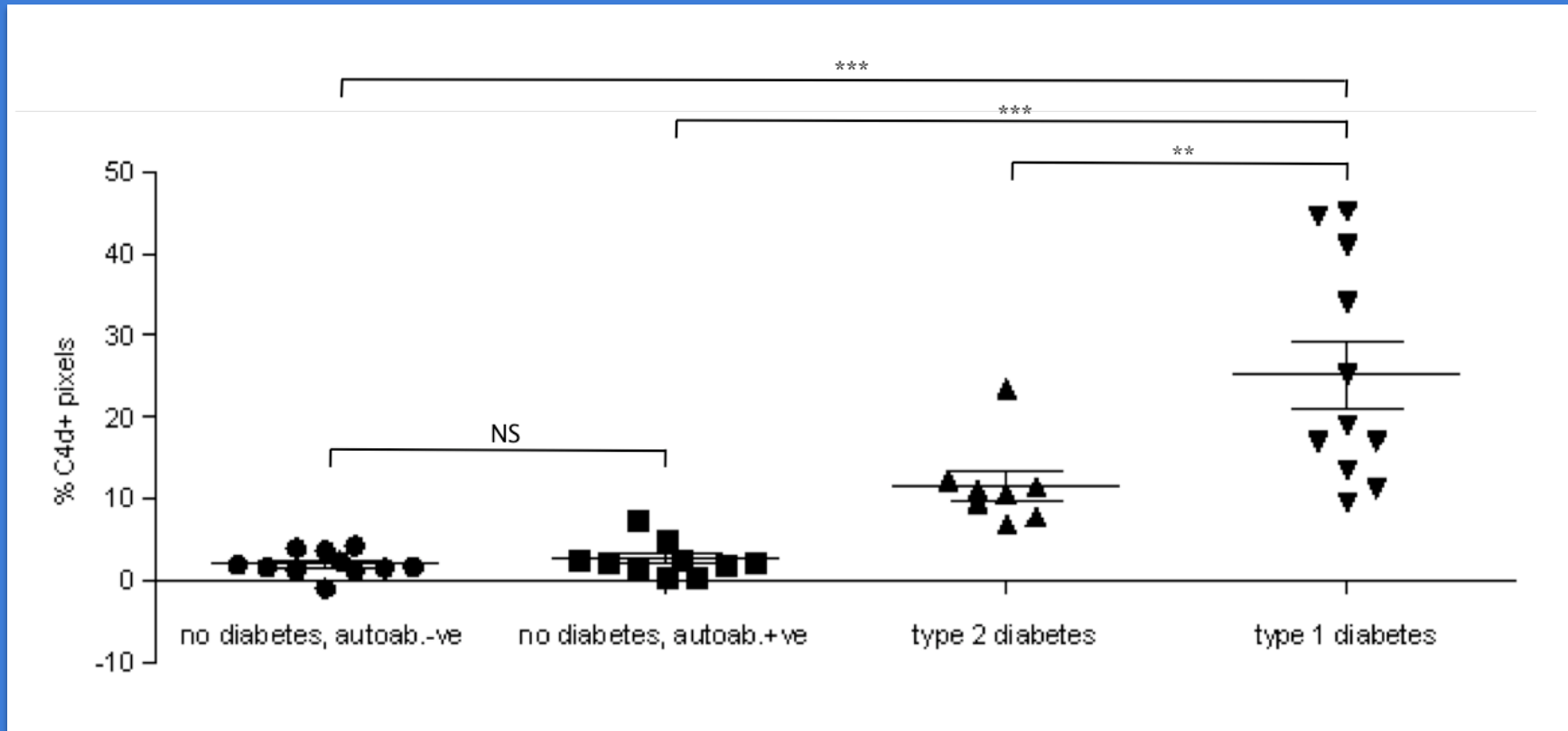
Type 1 diabetes



npod
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More C4d antigen in pancreatic sections from patients with type 1 diabetes

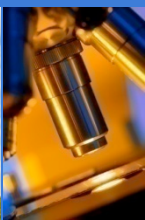


Overall group effect $p < 0.0001$ (one-way ANOVA)

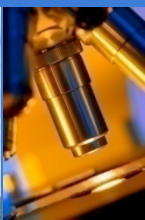
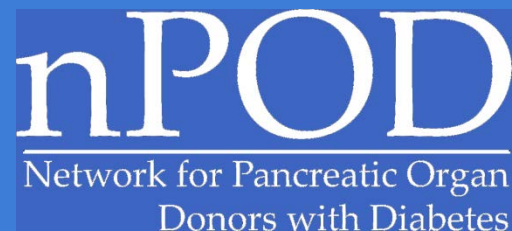
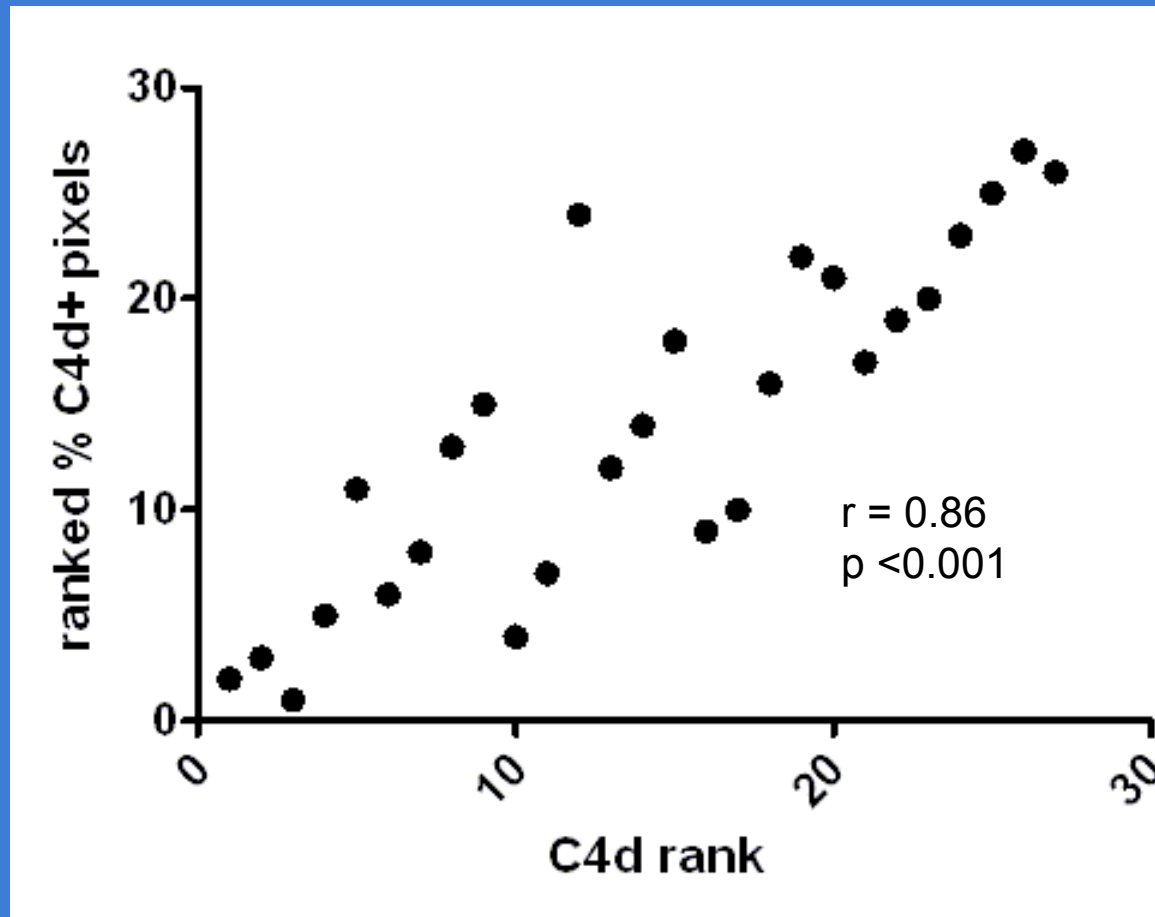
Group pairs ** = $p < 0.01$, *** = $p < 0.001$ (Bonferroni post test)



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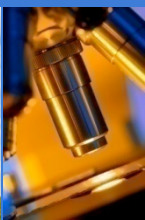


Agreement between pathologist-ranked and image analysis quantified C4d antigen density



Conclusions

- C4d reactivity is primarily restricted to blood vessel endothelium and vascular basement membrane extracellular matrix
- Greater C4d antigen in pancreata from patients with type 1 diabetes
- Patients with type 2 diabetes have an intermediate level of C4d antigen deposition
- The presence of islet autoantibodies in nondiabetic individuals is not associated with elevated pancreatic C4d deposition
- Is complement activation within the pancreas related to hyperglycemia in general and/or intensive care conditions?



Acknowledgements

Molecular Pathology & Immunology Core

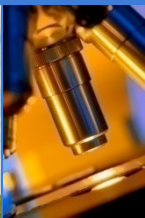
- Martha Campbell-Thompson
- Li Zhang
- Ann Dongtao Fu
- Robert Pietras
- Maria Fernanda Martino
- Emily Montgomery

Byron Croker

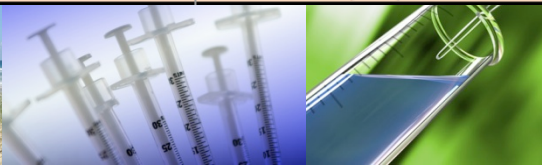
Elaine Dooley

Clive Wasserfall

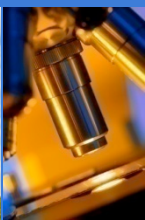
Mark Atkinson



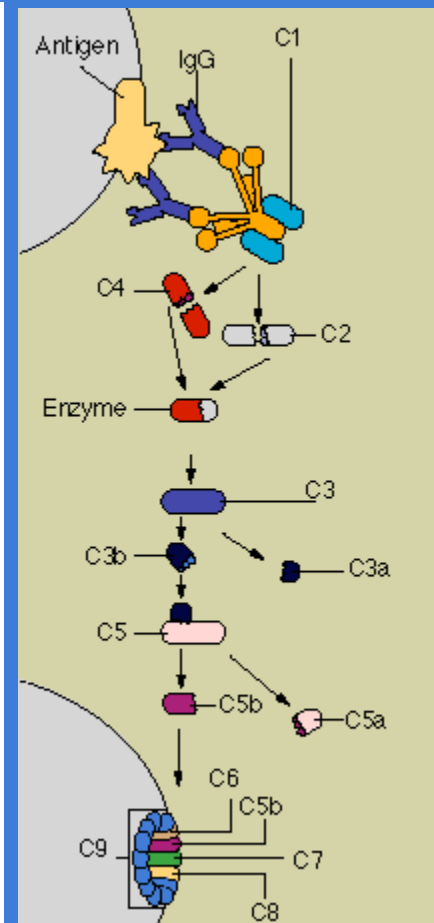
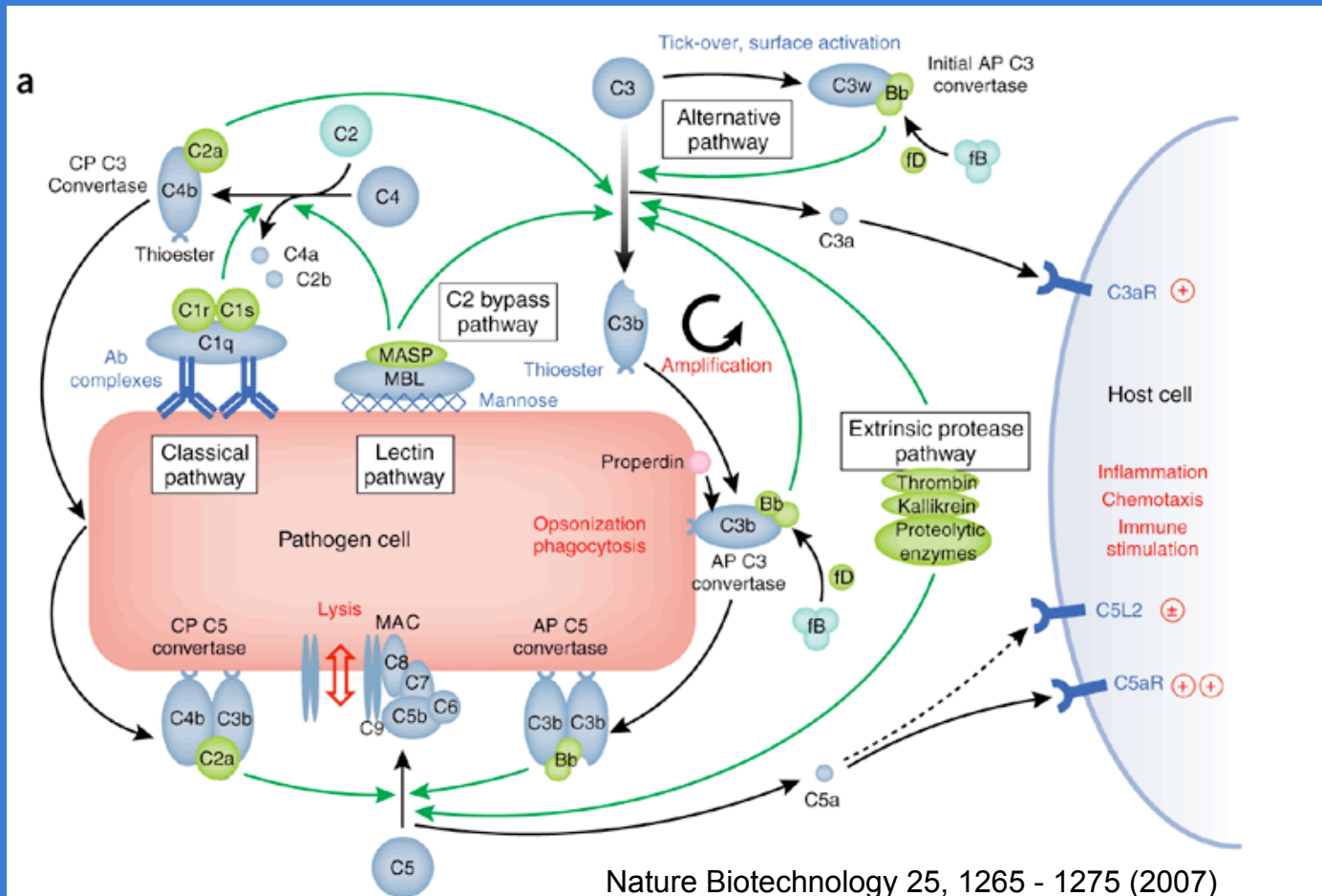
nPOD ID#	C4d stain run	Group	C4d	IgG	C4d-IgG	x100
6080-02 panH	May 2011 (1st)	AAB	0.079921	0.004827	0.0751	7.509
6156	12/13/2011 (2nd)	AAB	0.051742	0.000070	0.0517	5.167
6147	12/13/2011 (2nd)	AAB	0.027910	0.000058	0.0279	2.785
6090-02 panH	May 2011 (1st)	AAB	0.028807	0.002674	0.0261	2.613
6167	12/13/2011 (2nd)	AAB	0.024960	0.000040	0.0249	2.492
6154	12/13/2011 (2nd)	AAB	0.024805	0.000179	0.0246	2.463
6044-02 panH	May 2011 (1st)	AAB	0.024720	0.003969	0.0208	2.075
6151	12/13/2011 (2nd)	AAB	0.015513	0.000111	0.0154	1.540
6123-05 panH	May 2011 (1st)	AAB	0.007942	0.001829	0.0061	0.611
6027-02 panH	May 2011 (1st)	AAB	0.006977	0.001060	0.0059	0.592
6020-02panT	May 2011 (1st)	no diab	0.049154	0.005801	0.0434	4.335
6060-02 panH	May 2011 (1st)	no diab	0.042856	0.002529	0.0403	4.033
6019-06 panH	May 2011 (1st)	no diab	0.038483	0.000915	0.0376	3.757
6007-06 panT	May 2011 (1st)	no diab	0.026558	0.001602	0.0250	2.496
6053-06panOth	May 2011 (1st)	no diab	0.021149	0.000761	0.0204	2.039
6015-05 panH	May 2011 (1st)	no diab	0.017955	0.000139	0.0178	1.782
6055-02 panH	May 2011 (1st)	no diab	0.017732	0.000303	0.0174	1.743
6012-05 panH	May 2011 (1st)	no diab	0.016955	0.000821	0.0161	1.613
6024-06 panH	May 2011 (1st)	no diab	0.013400	0.000297	0.0131	1.310
6057-03 panH	May 2011 (1st)	no diab	0.015472	0.002815	0.0127	1.266
6075-03 panB	May 2011 (1st)	no diab	0.007576	0.016528	-0.0090	-0.895
6069-02 panH	May 2011 (1st)	T1D	0.451892	0.001118	0.4508	45.077
6061-02panH	May 2011 (1st)	T1D	0.451779	0.005968	0.4458	44.581
6038-02 panH	May 2011 (1st)	T1D	0.410458	0.000552	0.4099	40.991
6062-02 panT	May 2011 (1st)	T1D	0.341435	0.001145	0.3403	34.029
6064-02panB	May 2011 (1st)	T1D	0.254770	0.001852	0.2529	25.292
6041-02 panH	May 2011 (1st)	T1D	0.191505	0.001336	0.1902	19.017
6046 panB	May 2011 (1st)	T1D	0.171418	0.000610	0.1708	17.081
6070-02panB	May 2011 (1st)	T1D	0.172389	0.001723	0.1707	17.067
6051-02panB	May 2011 (1st)	T1D	0.135581	0.000503	0.1351	13.508
6052-04panB	May 2011 (1st)	T1D	0.114823	0.001641	0.1132	11.318
6076-04panT	May 2011 (1st)	T1D	0.097035	0.000890	0.0961	9.614
6133	12/13/2011 (2nd)	T2D	0.235688	0.000374	0.2353	23.531
6114	12/13/2011 (2nd)	T2D	0.124213	0.000324	0.1239	12.389
6109	12/13/2011 (2nd)	T2D	0.114721	0.000046	0.1147	11.468
6157	12/13/2011 (2nd)	T2D	0.112143	0.000076	0.1121	11.207
6149	12/13/2011 (2nd)	T2D	0.107310	0.000210	0.1071	10.710
6124	12/13/2011 (2nd)	T2D	0.096450	0.000180	0.0963	9.627
6132	12/13/2011 (2nd)	T2D	0.079234	0.000073	0.0792	7.916
6108	12/13/2011 (2nd)	T2D	0.070627	0.000249	0.0704	7.038



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Complement activation cascade



<http://www.cancer.gov/>



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