

# ***Autoimmunity in PIDD***

## ***Hematopoietic Cell Transplant in PIDD***



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## **Topics**

### **1. Autoimmunity**

#### **A. Theoretical**

#### **B. Practical**

### **2. Hematopoietic Cell Transplant (HCT)**

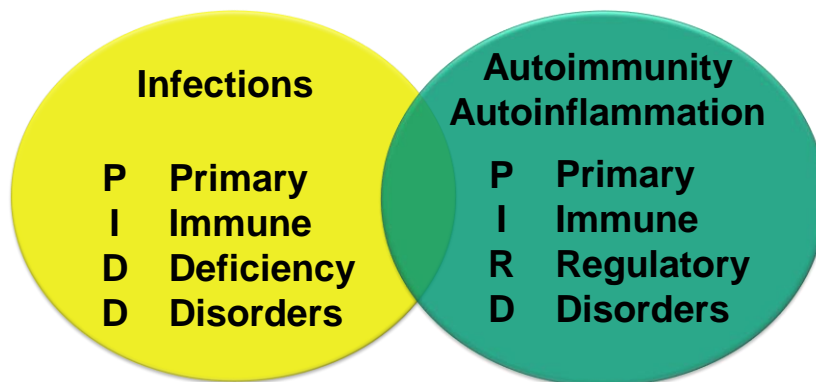
#### **A. Theoretical**

#### **B. Practical**

## Immune Dysregulation

A clinical disorder that occurs when normal mechanisms for maintaining immune homeostasis are either absent or are overcome/overwhelmed thus leading to an inappropriate immune response that causes damage to host cells in the form of autoimmunity or inflammation.

## Spectrum of Immune Defects



### PIDD:

- Infections Dominant
- May have autoimmunity/autoinflammation
  - CVID – Bowel, Lungs, Liver, Skin, etc.
  - CGD – Bowel, etc.
  - WAS – Vasculitis, etc.

### PIRD:

- Autoimmunity/Autoinflammation Dominant
- May have infections
  - STAT1-GOF – CMC, Mycobacteria
  - CGD – Bowel
  - WAS – Vasculitis, etc.

# Universe of PIRD Disorders

## Debris Defects

- Complement deficiency
- Phagocyte Defects
- Interferonopathies
  - DNase I
  - TREX1 Complex
  - IFIH1/MDA5
  - STING

## HLH

- SH2D1A, XIAP
- PRF1
- Degranulation Defects
  - MUNC13-4
  - RAB27A
  - LYST
- Signaling
  - ITK
  - MAGT1
  - STAT1-GOF

## Autoinflammatory

- TRAPS (TNFRSF1A, TNFRSF11A)
- CAPS (NLRP3)
- FMF (MEFV)
- CANDLE – Proteasome-opathies
- DADA2
- DIRA – IL-1 opathies

## Congenital Hypersensitivity Syndromes

- PGM3
- STAT5-GOF
- JAK1-GOF

## Treg-Opathies

- IPEX (FOXP3)
- IPEX-Like
  - CD25
  - STAT5B
  - hCTLA4
  - LRBA
  - STAT1-GOF
  - STAT3-GOF
  - IL10R1/2
  - Etc.

## IBD

- Infant Onset-IBD
- VEO-IBD
- EO-IBD

## Rheumatologic Dz

- JIA, SoJIA, Etc.
- Lupus
- Scleroderma

## Non-Malignant Lymphoproliferation

- ALPS (FAS, FASL, etc.)
- ALPS-Like/ALPS-U
  - STAT3-GOF
  - hCTLA4
  - PIK3CD/PIK3R1, etc.
  - RALD

# IPEX & IPEX-Like Genotyping

**IPEX:**

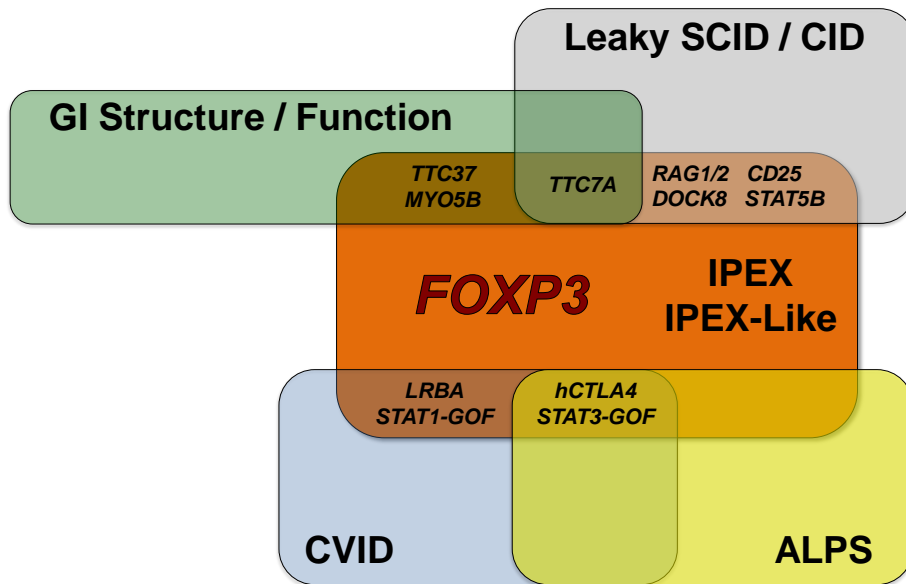
**FOXP3**

**IPEX-like:**

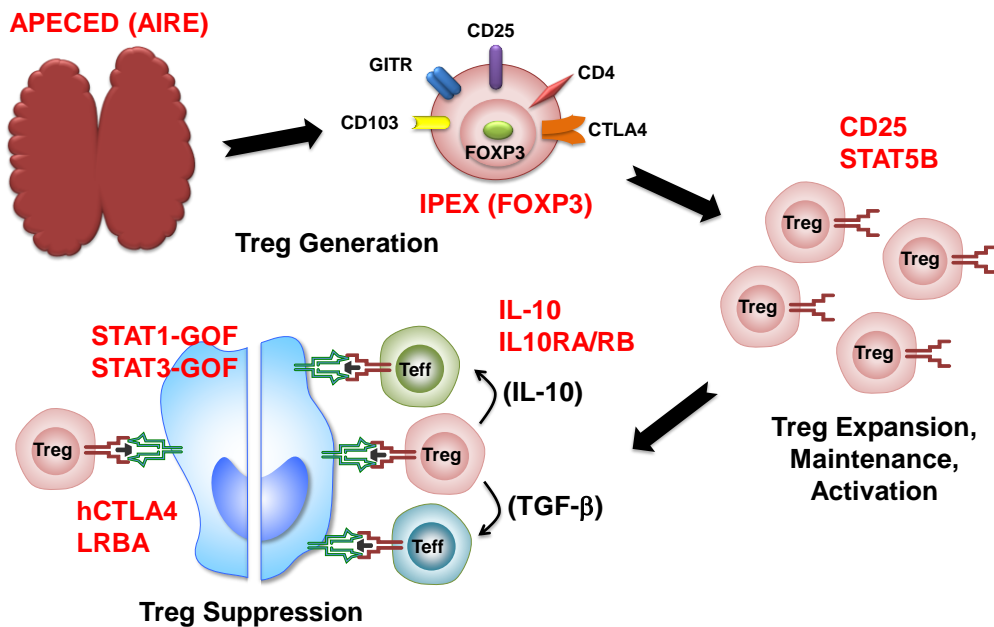
STAT1-GOF  
 STAT3-GOF  
 STAT5B  
 CTLA4 Haploinsufficiency  
 LRBA  
 CD25  
 TTC37  
 TTC7A  
 RAG1/2  
 DOCK8  
 IL10RA/RB  
 TNFAIP3  
 CARD11  
 MYO5B

34% of  
 patients in  
 IPEX-like  
 cohort

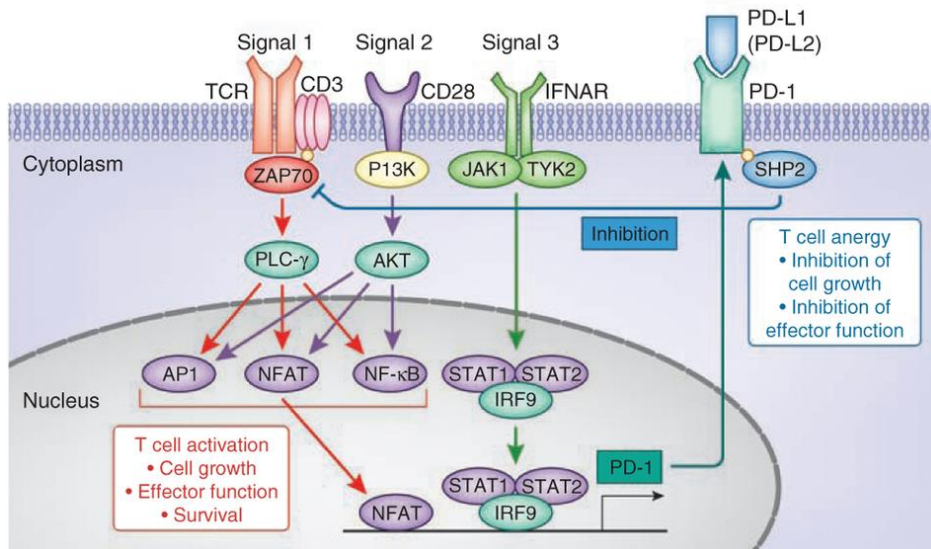
## Genotypic/Phenotypic Overlap



## Regulatory T Cell Axis



# Secondary Immune Dysregulation Checkpoint Inhibition



## Topics

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A. Theoretical

B. Practical

### 2. Hematopoietic Cell Transplant (HCT)

A. Theoretical

B. Practical

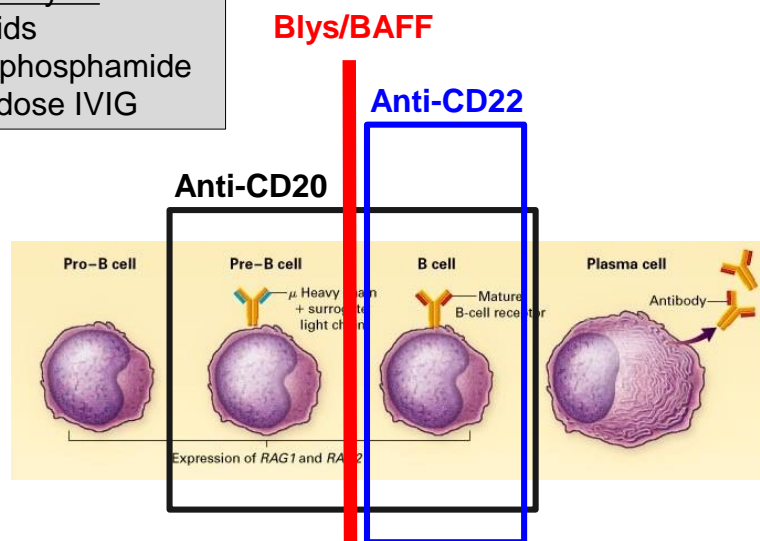
## Organ Involvement & Management

- **Heme** – AIHA, ITP, Autoimmune Neutropenia.
- **GI** – Enteropathy, Liver
- **Lungs** – LIP, Follicular bronchiolitis, Granulomas
- **Skin** – Eczema, Psoriasis, Pemphigus nodularis
- **Endocrine** – Thyroiditis, Type I DM, Other

## Comparison - B Cell Directed Therapy

Old Standby's :

- Steroids
- Cyclophosphamide
- High-dose IVIG



# Time to Response – Rituximab

Annals of Internal Medicine

123 Patients  
19 Studies

## Systematic Review: Efficacy and Safety of Rituximab for Adults with Idiopathic Thrombocytopenic Purpura

Donald M. Arnold, MD, MSc; Francesco Dentali, MD; Mark A. Crowther, MD, MSc; Ralph M. Meyer, MD; Richard J. Cook, PhD; Christopher Sigouin, MSc; Graeme A. Fraser, MD; Wendy Lim, MD, MSc; and John G. Kelton, MD

*Table 3.* Time to Response, Response Duration, and Follow-up of Patients with Idiopathic Thrombocytopenic Purpura Treated with Rituximab\*

Variable	Median	Interquartile Range	Range	Contributing Reports (Patients), n (n)
Time to response, wk	5.5	3.0–6.6	2.0–18.0	6 (123)
Response duration, mo	10.5	6.3–17.8	3.0–20.0	16 (252)
Follow-up, mo	9.5	6.0–21.3	2.0–25.0	10 (187)

*Ann Intern Med.* 2007;146:25-33.

# Time to Response – Rituximab

Acta Derm Venereol 2015; 95: 928–932

SPECIAL REPORT

578 Patients  
30 Studies

## Efficacy of Rituximab for Pemphigus: A Systematic Review and Meta-analysis of Different Regimens\*

Hsiao-Han WANG<sup>1</sup>, Che-Wei LIU<sup>2</sup>, Yu-Chuan LI<sup>1</sup> and Yu-Chen HUANG<sup>1</sup>

<sup>1</sup>Department of Dermatology, Wan Fang Hospital, Taipei Medical University, and <sup>2</sup>Department of Surgery, Cathay General Hospital, Taipei, Taiwan

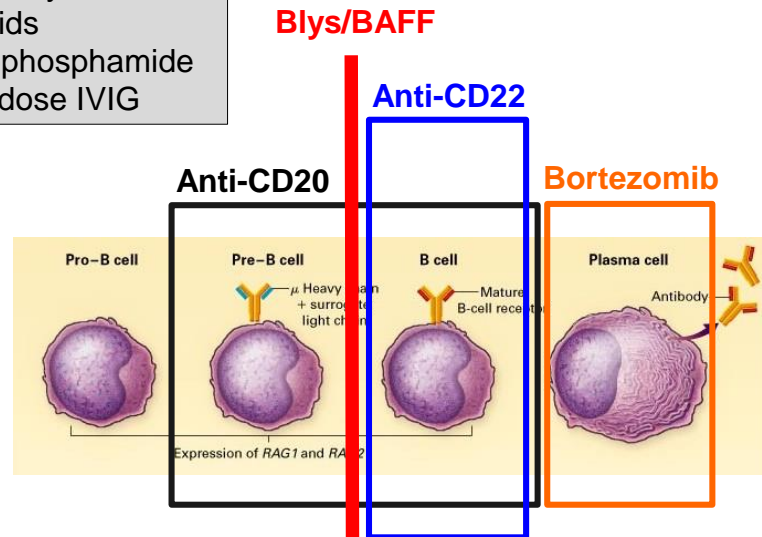
Table I. Key issues

1. Rituximab is efficacious and well-tolerated in patients with pemphigus.
2. Complete remission rate after 1 cycle of Rituximab was 76%. Mean time to complete remission was 5.8 months, complete remission duration 14.5 months and overall relapse rate 40%. Eighteen patients (3.3%) developed major adverse effects.
3. High-dose ( $\geq 2,000$  mg) Rituximab was associated with longer complete remission compared with low-dose Rituximab ( $<1,500$  mg).
4. No significant difference in time to complete remission, complete remission or relapse rates between the high-dose and low-dose Rituximab. No superiority of lymphoma protocol over rheumatoid arthritis in all outcomes.
5. Immunoadsorption-combined regimens resulted in the fastest control of disease before completion of Rituximab therapy.
6. Choice of optimal regimen may depend on the overall condition of the individual patient.

## Comparison - B Cell Directed Therapy

Old Standby's :

- Steroids
- Cyclophosphamide
- High-dose IVIG



## Bortezomib

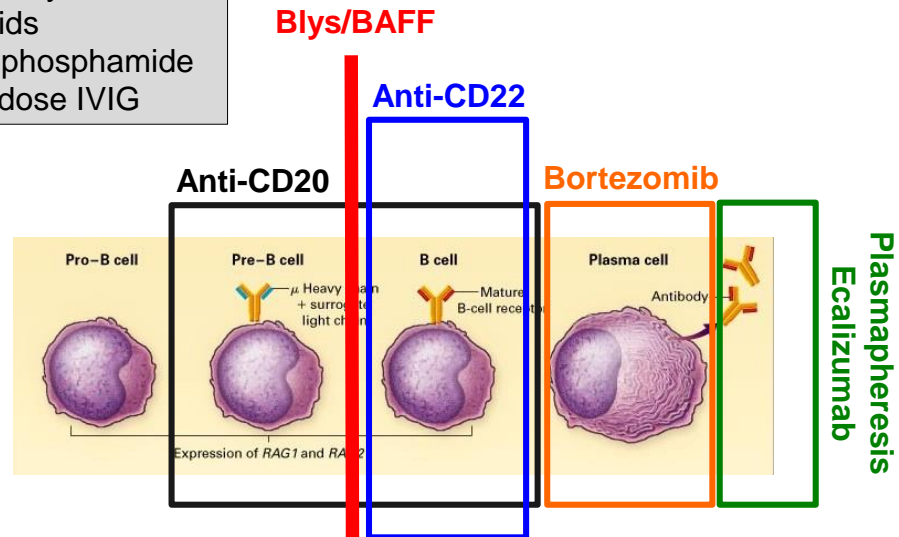
- An N-protected di-peptide with a boronic acid instead of carboxylic acid at C-term
- Given IV on days 1, 4, 8, and 11 of a 21 day cycle – 8 cycles for MM
- Short half-life: 9-15 hours
- Side effects: Peripheral neuropathy in 30%, myelosuppression (neutropenia, thrombocytopenia), Shingles.



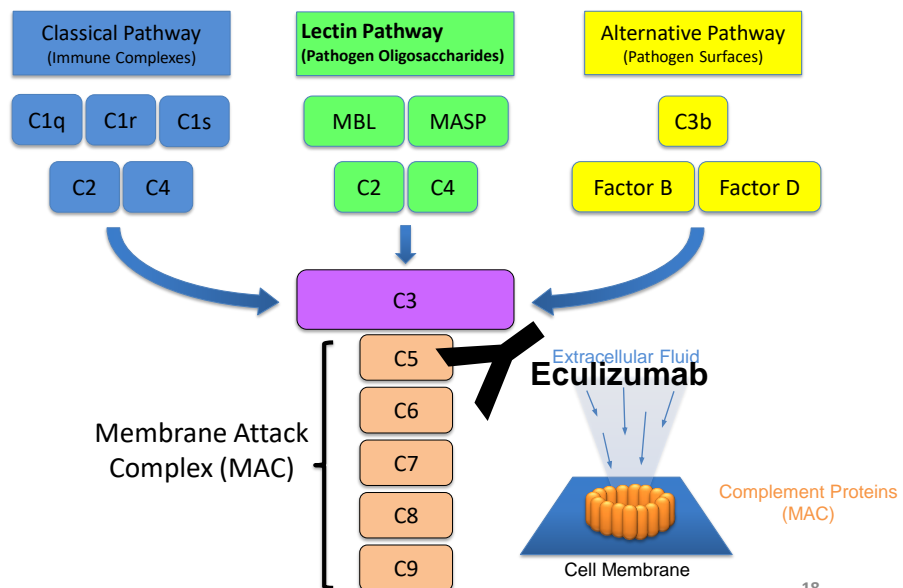
## Comparison - B Cell Directed Therapy

Old Standby's :

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## Treatment – MAC Inhibitors



18

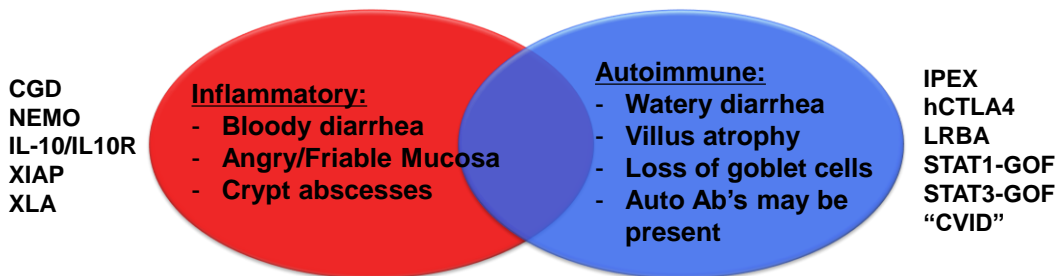
## Organ Involvement & Management

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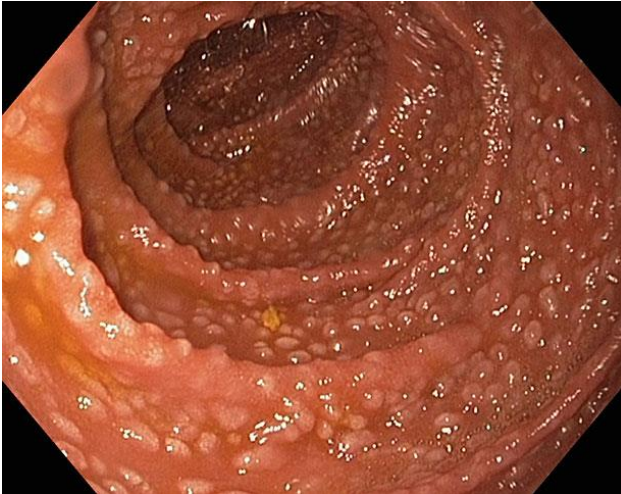
## General Management

Be aggressive about supportive care!!

Get tissue whenever possible – you learn a lot from the pathology – Inflammatory vs. Autoimmune.



## ***Nodular Lymphoid Hyperplasia***



- Watery diarrhea
- Often quite responsive to steroids – can use non-absorbable
- Responsive to Rapamycin

## **General Management (Cont.)**

### **Nutrition (Cont.):**

- Check nutrition labs early – Electrolytes,  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$ , Phos, Zinc, Micronutrients, Albumin, Pre-Albumin, AST/ALT, Clotting (Vit. K).
- You might need to enlist the help of a nutritionist – ask for consultation.
- Ask diet questions and try a change in diet (Cow- or soy-based formulas → partially digested or elemental formula).

## General Management (Cont.)

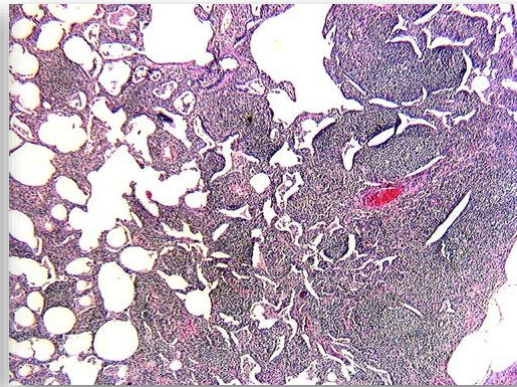
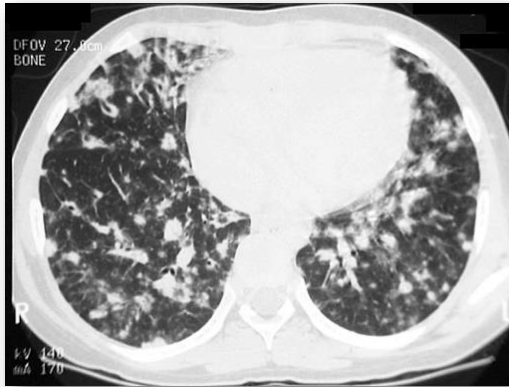
### Nutrition (Cont.):

- Some patients just don't tolerate oral feeds – profuse diarrhea or vomiting. Start TPN and put patient on full bowel rest if needed.
- If patients are severely malnourished, sometimes improving nutritional status alone with parenteral nutrition will allow them to re-grow villi and begin to absorb so enteral feeds can be re-started.

## *Organ Involvement & Management*

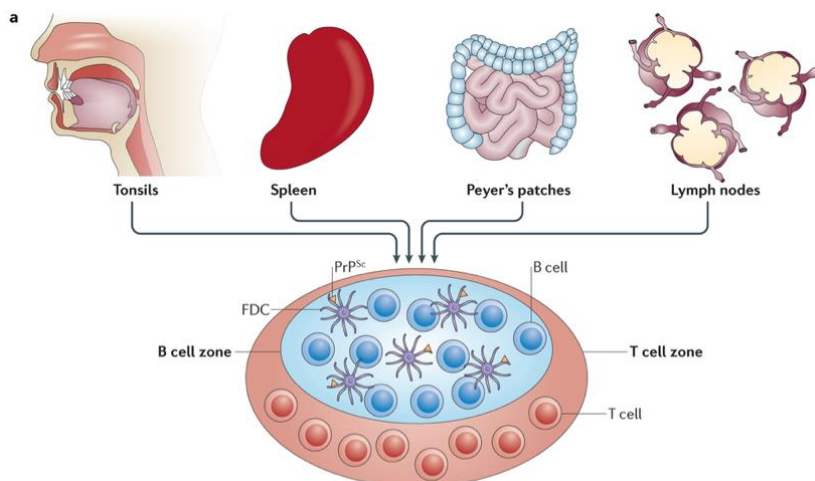
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## Follicular Bronchiolitis & Granulomas



**Light microscopy:** Expansion of alveolar septa by multifocal dense nodular and diffuse interstitial infiltrates composed of mature lymphocytes and plasma cells. Multiple lymphoid aggregates with active germinal centers also seen.

## Lymphoid Follicles



Adriano Aguzzi, Mario Nuvolone & Caihong Zhu  
*Nature Reviews Immunology* 13, 888–902 (2013)

# Rituximab in CVID GLILD

J Clin Immunol (2013) 33:30–39  
DOI 10.1007/s10875-012-9755-3

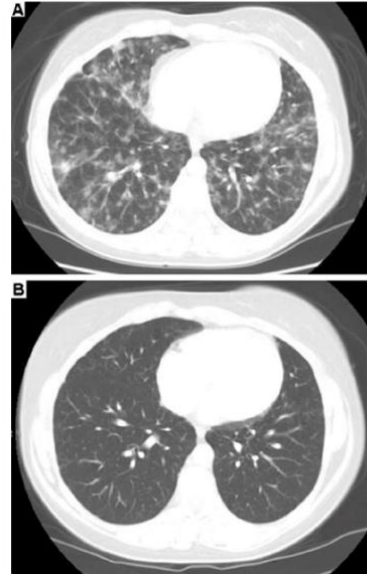
ORIGINAL RESEARCH

## Use of Combination Chemotherapy for Treatment of Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) in Patients with Common Variable Immunodeficiency (CVID)

Nicole M. Chase • James W. Verbsky • Mary K. Hintermeyer • Jill K. Waukau • Aoy Tomita-Mitchell • James T. Casper • Sumit Singh • Kaushik S. Shahir • William B. Tsot • Melodee L. Nugent • R. Nagarjun Rao • A. Craig Mackinnon • Lawrence R. Goodman • Pippa M. Simpson • John M. Routes

### Key Point:

- Lung biopsy is essential to make sure you know what you are dealing with
- Rituximab + Azathioprine



## Organ Systems

- Heme – AIHA, ITP, Autoimmune Neutropenia.
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## ***Common Skin Diseases***



## **Initial Management**

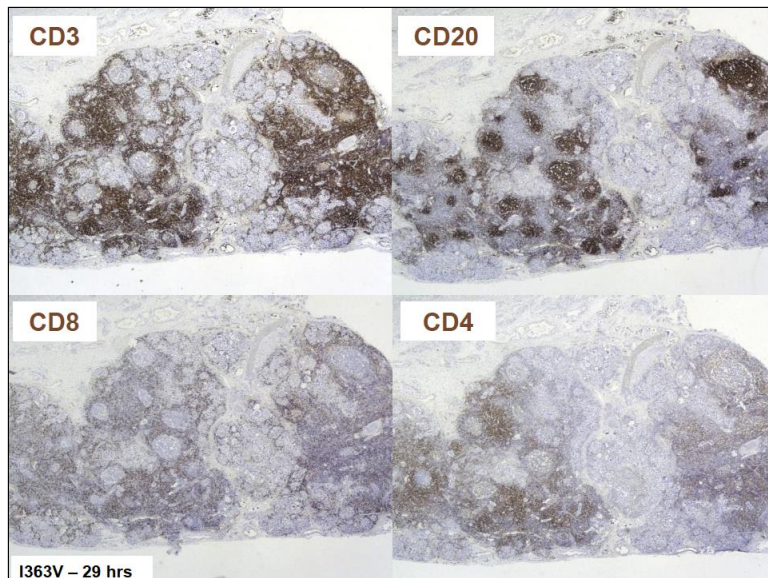
### **Aggressive Supportive Care:**

- **Nutritional support, Parenteral nutrition if needed**
- **Topical therapies – involve wound care/burn team if needed**
- **May need systemic therapy – Rituximab (Pemphigus), Others**

## Organ Systems

- **Heme** – AIHA, ITP, Autoimmune Neutropenia.
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## Follicular Inflammation – IPEX Pancreas





## Initial Management

### Aggressive Supportive Care:

- **Nutritional support, Parenteral nutrition if needed**
- **Insulin, Thyroid hormone, etc.**
- **Consider systemic therapies – Tacrolimus, Rapamycin, Rituximab, etc.**

## Targeted Treatments

### Immunosuppression –

*Seems counterintuitive/uncomfortable*

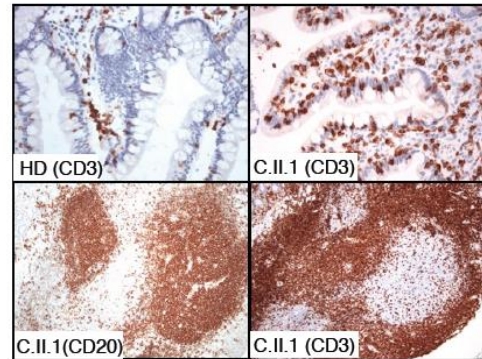
*Be as targeted as possible*

*Watch for side effects*

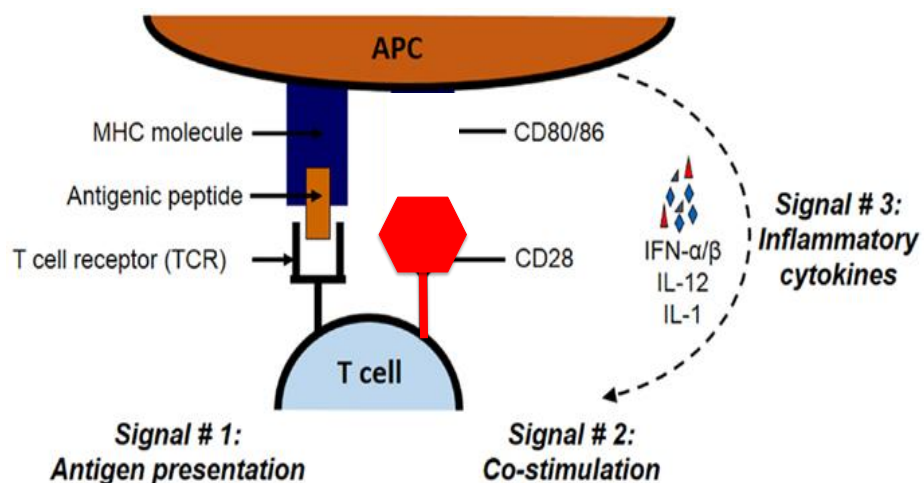
- Cyclosporine, FK506, Sirolimus (IPEX, CTLA4-h, etc.)
- CTLA4-Ig (LRBA, CTLA4-h)
- JAK inhibitors (STAT1-GOF, STAT3-GOF, Interferonopathies, etc.)
- PI3 Kinase Inhibitors (PIK3CD, PIK3R1 - ????)
- Others

# CTLA-4 Haploinsufficiency - Clinical Phenotype

Clinical manifestations	Frequency
Diarrhea/enteropathy	11/14 (78%)
Hypogammaglobulinemia	10/13 (76%)
Granulomatous lymphocytic interstitial lung disease	8/12 (66%)
Respiratory infections <sup>a</sup>	8/14 (57%)
Organ infiltration (bone marrow, kidney, brain, liver)	7/14 (50%)
Splenomegaly	6/12 (50%)
Autoimmune thrombocytopenia	5/14 (35%)
Autoimmune hemolytic anemia	4/14 (28%)
Lymphadenopathy	4/14 (28%)
Psoriasis and other skin diseases <sup>b</sup>	3/14 (21%)
Autoimmune thyroiditis	2/13 (15%)
Autoimmune arthritis	2/14 (14%)
Solid cancer	1/14 (7%)



## T cell Co-Stimulation – Signals 1,2,3



**A**

**■ = GOF Mutations**

STAT1α

NH2

134

CC

317

DNA-B

488

L

576

SH2

663

758

TA

930

COOH

175R,175S,180AG

192RnsA

A48T K201N K211R Q271P T288A

Y170N C174R A267V/K268I

D185H N202I R274W E320Q

G453H

L600P K637E K679P L706S

P586S

gY

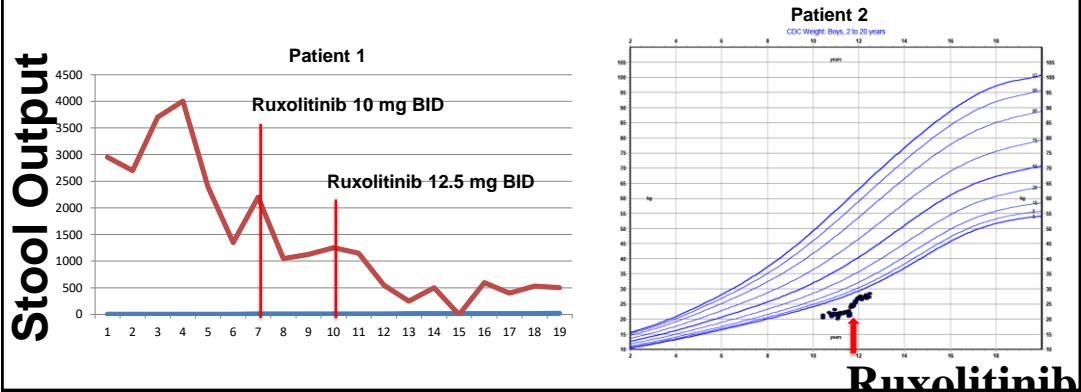
pS

Liu L et al., J Exp Med 208:1635-48 (2011)

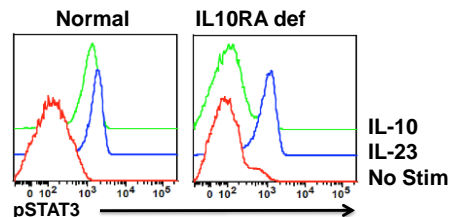
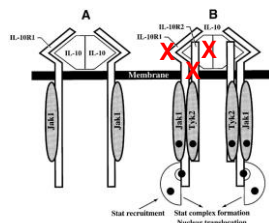
## STAT1-GOF Disease

### Treatment:

Jakafi (Ruxolitinib – JAK 1/2 inhibitor) highly effective in anecdotal cases. Not much pediatric dosing guidance. Usual adult dose is 20 mg po BID. Thrombocytopenia most common side effect. Risk for Herpes viral infections.



## *IL-10 Receptor Deficiency*



### IL10 Receptor Deficiency

- Mutations identified in both IL10R1 (2 patients) and IL10R2 (2 patients)
- Bone marrow transplantation effective
- Other immunosuppressants ineffective

### IL10 Deficiency

- 2 unrelated patients with a similar clinical phenotype but lacking mutations in IL10R1 or IL10R2
- Bone marrow transplantation effective

## BMT for IL-10 Receptor Deficiency



PRE



D+10



D+30



D+100

## Treatment of IL-10R Deficiency with IL-1 Blockade

Gastroenterology 2016;151:1100-1104

**Interleukin 1 $\beta$  Mediates Intestinal Inflammation in Mice and Patients With Interleukin 10 Receptor Deficiency**

Dror S. Shouval,<sup>1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219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## ***Summary***

- 1. Autoimmunity is the dominant feature of PIRDs and is common in PIDDs**
- 2. Need to treat autoimmunity and inflammation aggressively – Uncomfortable!**
- 3. If you can find a genetic defect – targeted therapies are available.**

## **Topics**

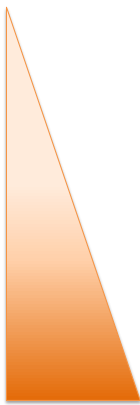
- 1. Autoimmunity**
  - A. Theoretical**
  - B. Practical**
- 2. Hematopoietic Cell Transplant (HCT)**
  - A. Theoretical**
  - B. Practical**

## Hematopoietic Cell Transplant – The 5 Key Things to Know

- Conditioning Regimen – Drugs, Radiation (TBI), Antibodies (ATG, Alemtuzumab, etc.)
- Donor Source – MRD, MUD, MMRD, Cord, etc.
- Graft Type – Bone marrow vs. PBSC
- Graft Manipulation – T cell depletion, CD34 selection, *in vivo* Cytosan, etc.
- GvHD Prophylaxis – Tacrolimus, Rapamycin, MTX, MMF, etc.

## Conditioning Regimens

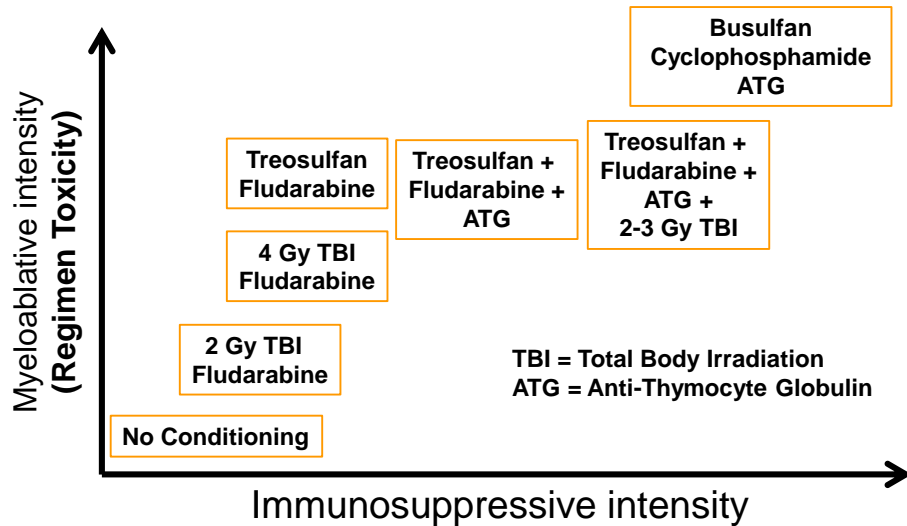
Side Effects & Risk for Infections



1. No Conditioning – mostly SCID
2. Minimal Intensity Conditioning (MIC)
3. Reduced Intensity Conditioning (RIC)
4. Myeloablative Conditioning (MAC)

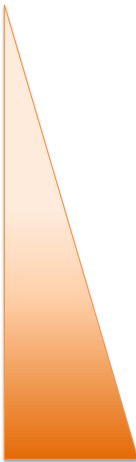
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## Conditioning Regimen Intensity



## Donor Source

Risk of GvHD and Graft Rejection



1. Matched Related Donor (MRD)\*
1. Matched Unrelated Donor (MUD)\*
2. Cord Blood Donor (Cord)  
\*\*Need more aggressive conditioning
3. Haploidentical Donor (Haplo / MMRD)

\*Bone Marrow vs. PBSC

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## Topics

### 1. Autoimmunity

- A. Theoretical
- B. Practical

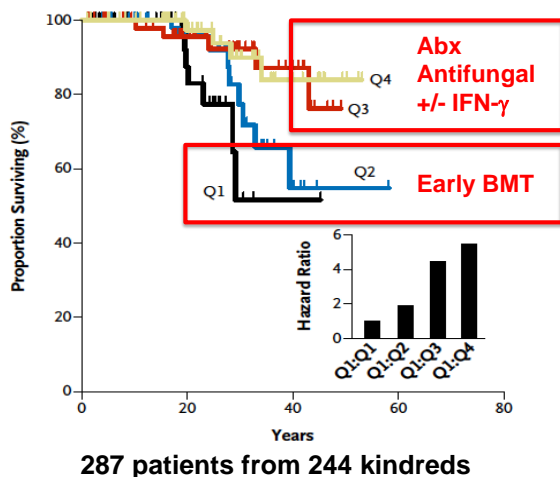
### 2. Hematopoietic Cell Transplant (HCT)

- A. Theoretical
- B. Practical**

## Transplant – Burning Questions

- **When do I transplant (Timing)?**
- **How do I transplant (Regimen)?**
- Disease and complication specific
- Changes with new data & experience
- Outcomes often poor to moderate in first experience & reports

## Timing of Transplant - CGD



### Residual NADPH Oxidase and Survival in Chronic Granulomatous Disease

Douglas B. Kuhns, Ph.D., W. Gregory Alvord, Ph.D., Theo Heller, M.B., Ch.B., Jordan J. Feld, M.D., M.P.H., Kristen M. Pike, M.S., Beatriz E. Marciano, M.D., Gulbu Uzel, M.D., Suk See DeRavin, M.D., Ph.D., Debra A. Long Priel, M.S., Benjamin P. Soule, M.D., Kol A. Zarembek, Ph.D., Harry L. Malech, M.D., Steven M. Holland, M.D., and John I. Gallin, M.D.

NEJM 363:2600-10 (2010)

## Timing of Transplant CGD CVID

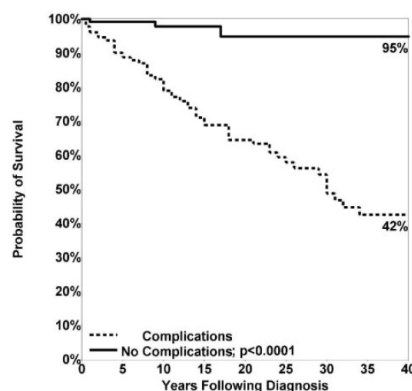
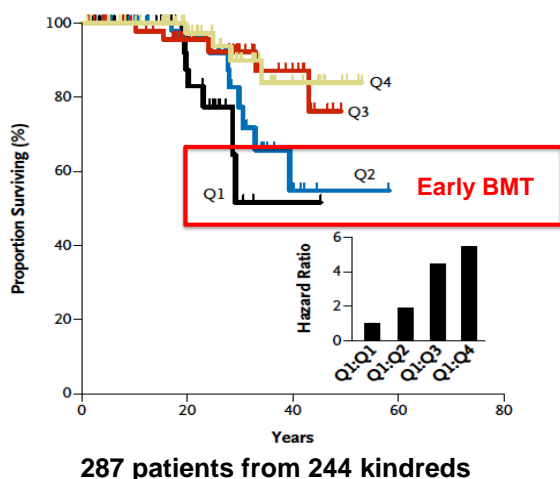


Figure 2. Kaplan-Meier curve for patients with and without noninfectious complications. Patients with noninfectious complications were significantly more likely to die than those with infections only ( $P < .0001$ ).

Morbidity and mortality in common variable immune deficiency over 4 decades

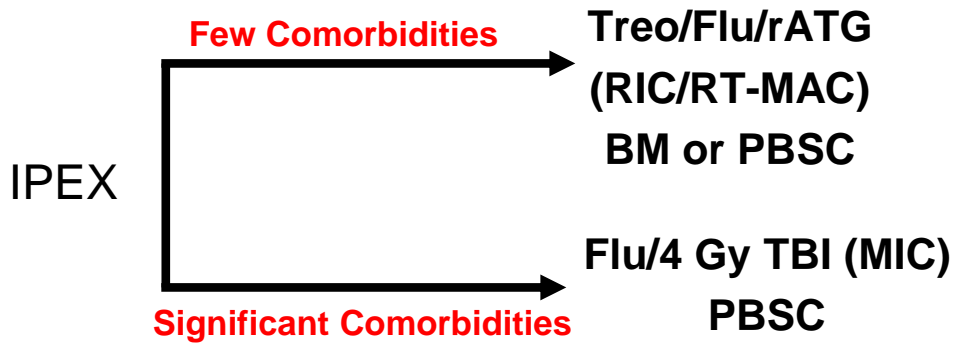
Elena S. Riederick,<sup>1,2</sup> Erin L. Mosher,<sup>2</sup> James H. Gribble,<sup>3</sup> and Charlotte Cunningham-Rundles<sup>1,2,4</sup>

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BLOOD, 16 FEBRUARY 2012 • VOLUME 119, NUMBER 7

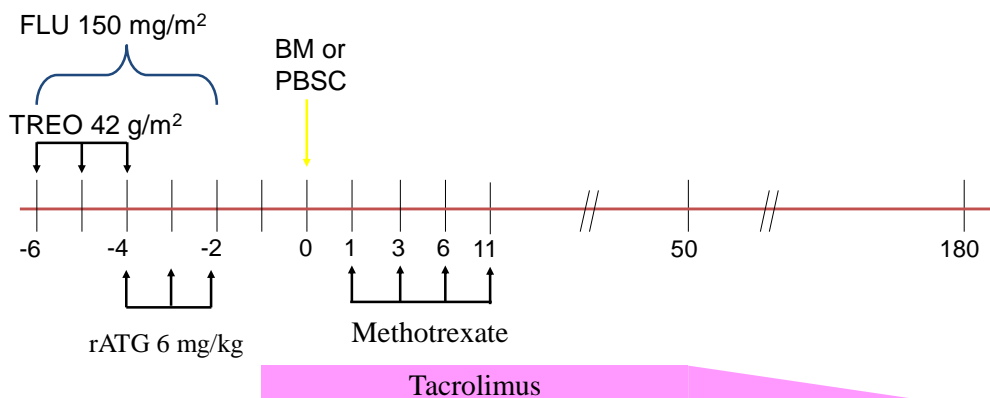
# Seattle Approach to IPEX HCT

Matched Related or Unrelated Donor



Alternative donor: Cord vs Haplo

## Conditioning Regimen U.S. Treosulfan Study: BM/PBSC



## IPEX - Treosulfan-Based HSCT (n=10)

Cell Source	% Chimerism		GVHD		Clinical Response	F/U (yrs)
	CD3	CD33	Acute	Chronic		
BM	100	100	-	-	Remission	>5
BM	100	100	II	-	Remission*	>5
BM	98	100	II	-	Remission*	>5
BM	100	100	-	-	Remission	>1.5
BM	100	100	-	-	Remission	>0.6
BM	93	100	-	-	Remission	>0.5
BM	32	8	-	-	Remission*	>4
BM	5	0	II	-	Rejection s/p 2 <sup>nd</sup> BMT	>7
DCB	96	100	III	+	Remission*	>4
CB	60	30	III	-	Remission	Died, 1

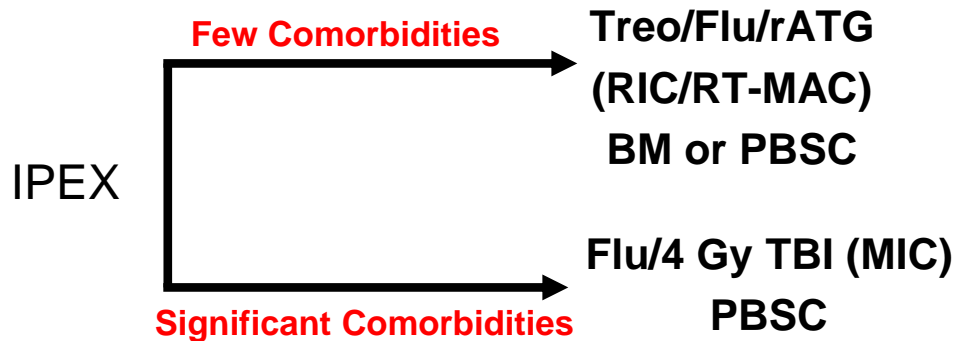
\* Persistent IDDM

## Conclusions: Treosulfan-Based Approach

- Well tolerated with low regimen related toxicity
  - 9/10 alive
- Successful engraftment
- Low incidence of severe acute & cGVHD
- Disease responses seen in majority of patients
  - Full donor chimerism is not required
- Late effects research needed

# Seattle Approach to IPEX HCT

**Matched Related or Unrelated Donor**



**Alternative donor: Cord vs Haplo**

## Nonmyeloablative Approach Flu/2-4 Gy TBI (n=5)

- IPEX (n=5)
- Median age 17 (range, 0.8-28) years
- Conditioning/Stem Cell Source:
  - Flu/2 Gy TBI: MRD Cord Blood (n=1)
  - Flu/4 Gy TBI: MRD BM (n=1), MURD PBSC (n=3)
- GVHD Prophylaxis:
  - CSP/MMF (n=4)
  - Sirolimus/MMF (n=1)

## Nonmyeloablative Approach Flu/2-4 Gy TBI (n=5)

Age (yrs)	Donor	% Chimerism		GVHD		Clinical Response	F/U (yrs)
		CD3	CD33	Acute	Chronic		
2	MRD Cord	1	84	N/A	N/A	Rejection s/p 2 <sup>nd</sup> BMT	>14
17	MRD BM	33	60	II	-	Remission*	>8
0.8	MUD PBSC	99	100	II	+	Remission*	>9
24	MUD PBSC	99	100	III	+	Remission	Died, 2.4 Norovirus
28	MUD PBSC	73	100	III	+	Remission*	>0.5

\* Persistent IDDM

Burroughs, et. al, BMT 2007 & JACI 2010

## Conclusions: Nonmyeloablative Approach

- Reasonable approach for high-risk patients unable to tolerate more aggressive conditioning
- Full donor chimerism not required for disease amelioration
- Low toxicity/mortality in high-risk patients
- GVHD remains a challenge

## HCT for CTLA4 Haploinsufficiency

- 8 patients (Newcastle & Seattle)
- Male: 5 Female: 3
- Age at transplant 10-32 years
- Mutation known in 1 patient at transplant
- MIC & RIC regimens
- 6 of 8 alive and well – disease in remission
- 2 deaths – DKA & GvHD

Slatter M et al., *J Allergy Clin Immunol* 138:615-19 (2016)

## HCT for STAT1-GOF

- 15 patients (Worldwide)
- Male: 9 Female: 6
- Age at transplant 1-33 years
- Mutation known in 1 patient at transplant
- RIC & MAC regimens
- MUD, MRD, and Cord donors
- 6 of 15 alive and well – disease in remission
- 8 of 15 with primary or secondary graft loss
- Death due to infections & HLH (2 pts). IPEX-like phenotype had best outcomes

Leiding J et al., *J Allergy Clin Immunol* in press (2017)

## HCT for STAT3-GOF

- 12 patients (Worldwide)
- Male: 5 Female: 7
- Age at transplant 1.5-20 years
- Mutation known in 3 patients at transplant
- RIC & Reduced toxicity MAC regimens
- 7 of 12 alive and well – disease in remission but no improvement in growth
- 5 deaths – Infections & GvHD

Forbes L et al., *Blood* submitted (2017)

## HCT for LRBA Deficiency

- 12 patients (European)
- Age at transplant 3-15 years
- Mutation known in 3 patients at transplant
- Various RIC regimens
- 8 of 12 alive – 3 in complete remission, 3 in good partial remission of IS, 2 in partial remission on IS.
- 4 deaths – All early (infections?)

Seidel M et al., *J Allergy Clin Immunol* in press (2017)



## **HCT for CVID**

- **25 patients (European)**
- **Age at transplant 8-50 years**
- **Mutation known in 3 patients at transplant**
- **RIC & MAC regimens**
- **Overall survival 48%, survival if transplant for lymphoma 83%.**
- **13 deaths – 9 infections, 2 cGvHD, 1 VOD, 1 lymphoma recurrence.**

Wehr C et al., *J Allergy Clin Immunol* 135:988-997 (2014)

## ***Summary***

- 1. Transplant is a viable option for many PIDD & PIRD disorders**
- 2. Timing of transplant remains a challenge for most diseases**
- 3. Many unanswered questions regarding best regimen, pre-transplant immune suppression, etc.**

# Acknowledgements

## **Torgerson Lab Core Team**

Stacey Rylaarsdam  
Jesus Lopez-Guisa  
Gesmar Segundo  
Sandro Perrazio  
Stephanie Anover  
David Hagin  
Sarah Baxter

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