Transplant Immunology

Josh Levitsky, MD, MS
Professor of Medicine
Division of Gastroenterology and Hepatology
Northwestern University Feinberg School of Medicine

Transplant Immunology

- Innate and Adaptive Immune System
- Immune Response
- Tolerance

Main Concepts

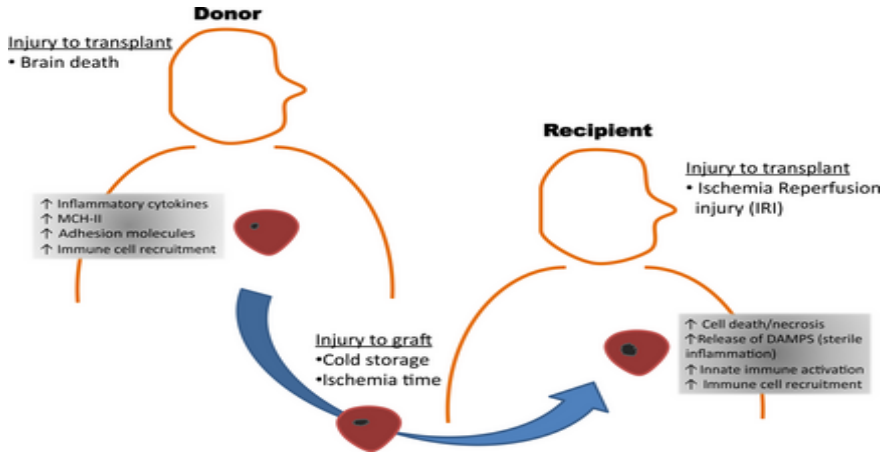
- Innate immune activation at transplant (APC) stimulates adaptive immunity (T/B cells) which promotes alloreactivity over tolerance
- Histocompatibility genes give rise to MHC
  - MHC genes encode alloantigens known as HLAs (cell surface) {Class I and II}
  - MHC's role is to present fragments of foreign antigens as complexes {Class II}
  - MHC are membrane associated and present to antigen-specific T Cells
- Deletion of alloreactive lymphocyte clones is a critical step in the development of long term liver transplant tolerance

Good Review: Rosen HR. Gastroenterology May 2008, 134 (6): 1789-1801

Immune Cells

- Innate (first line of defense, no memory, same response each time, non-specific)
  - Polys (PMNs, eos, baso)
  - Monocyte/Macrophage
  - NK (NKT)
  - DC
- Adaptive (effector, helper, memory; increased response every time, specific)
  - Lymphocytes
    - Cellular Immunity
      - CD4+ T helper (class II MHC)
      - CD8+ T cytotoxic (class I MHC)
    - Humoral Immunity
      - B cells
      - Plasma Cells

Inflammatory triggers of acute rejection of organ allografts



Immunological Reviews
Volume 258, Issue 1, pages 132-144, 11 FEB 2014 DOI: 10.1111/imr.12146
http://onlinelibrary.wiley.com/doi/10.1111/imr.12146/full#imr12146-fig-0001

Types of Immune Response

- **Hyperacute** (preformed ABO Abs)
- **Acute** (T cell-mediated (TCMR); HLA Abs may add insult to injury)
- **Chronic**: fibrosis + vasculopathy – mix of TCMR/AMR

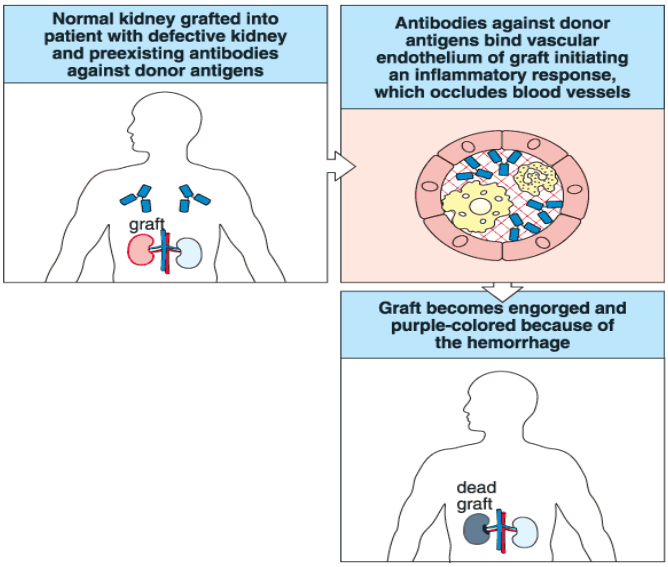


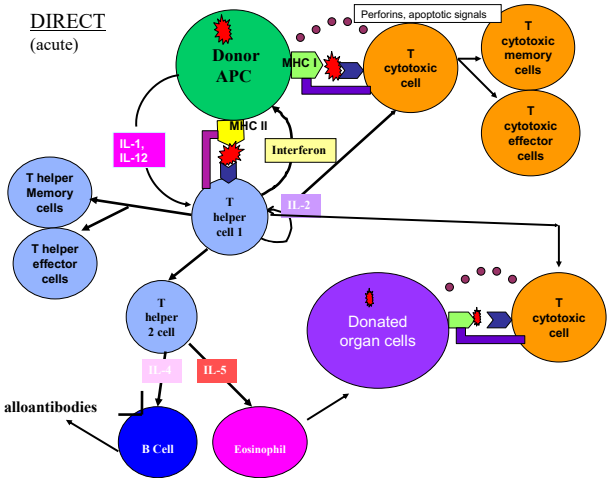
Fig 13.27 © 2001 Garland Science

Hyperacute Rejection

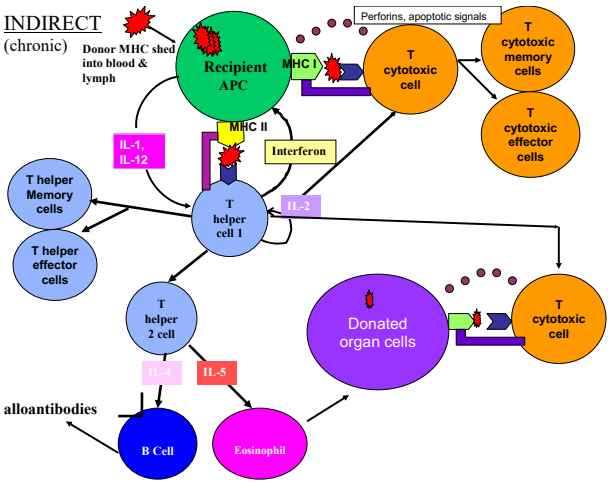
Preformed antibodies exist if graft is not ABO-matched; alloantibodies can be generated during previous blood transfusions, previous transplantation, or pregnancy

Desensitization protocols work if needed (PP, IVIG, rituximab +/- splenectomy

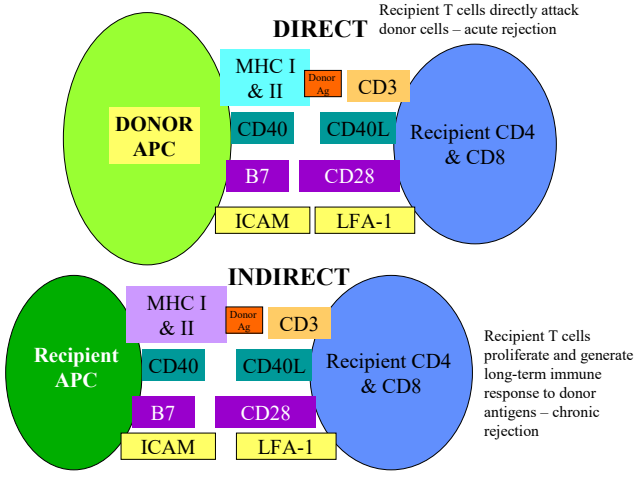
Early Direct pathway of Allorecognition

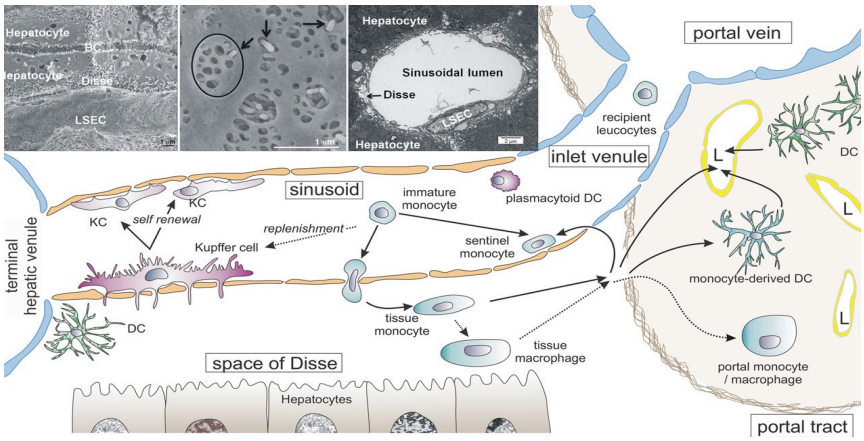


Late Indirect Pathway of Allorecognition

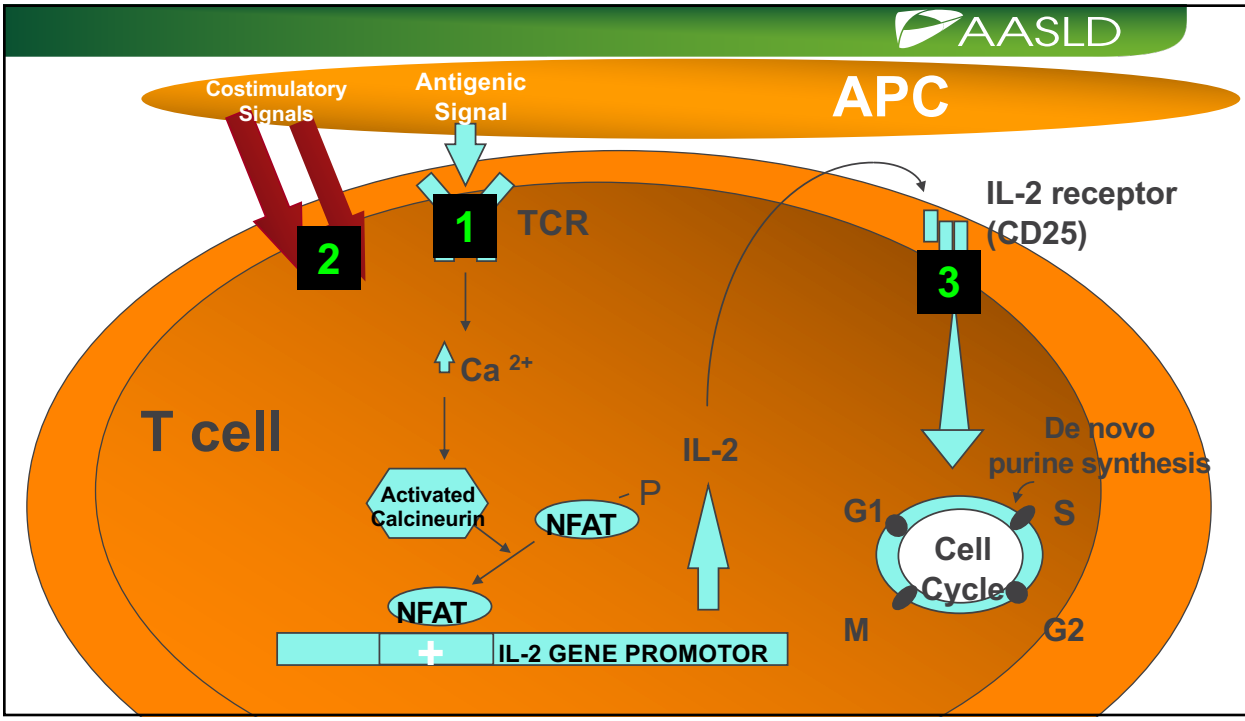


Side by Side Comparison

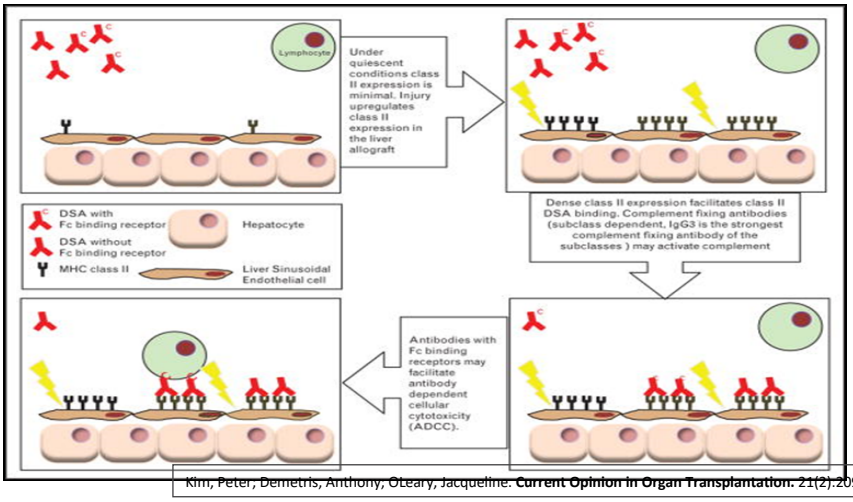




Demetris et al. Liver Immune Microanatomy AJT 2016



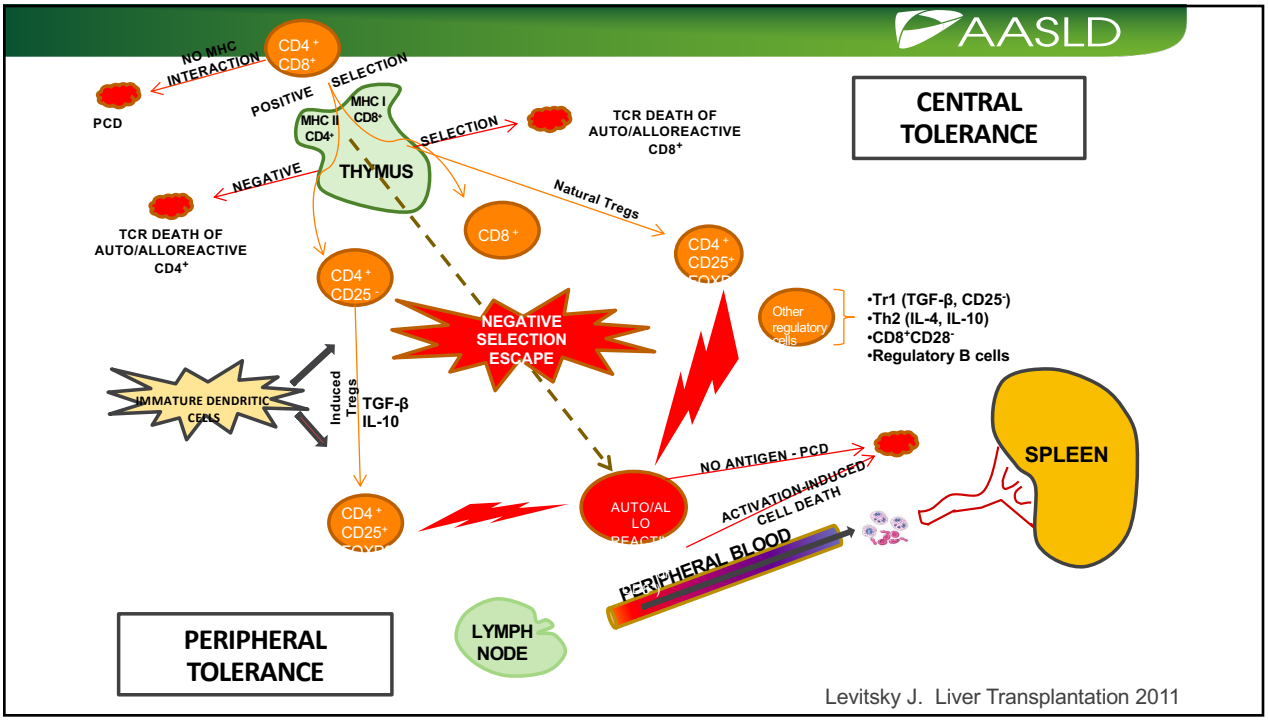
Liver allograft antibody-mediated rejection and the role of the 'two-hit hypothesis'



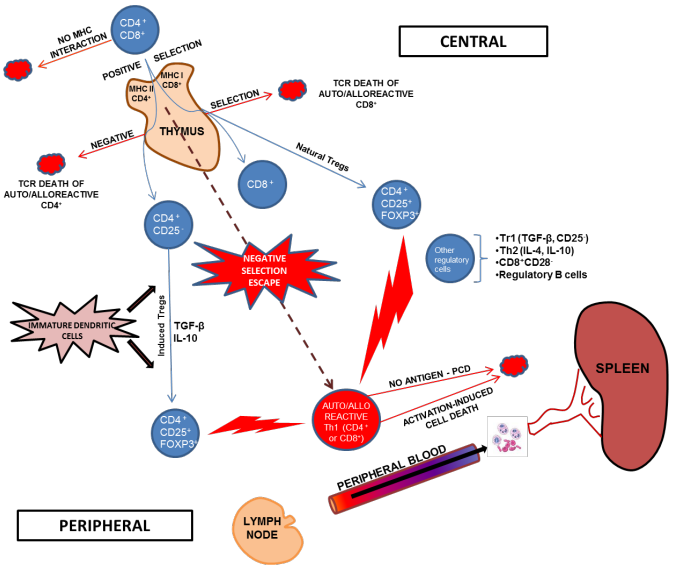
Kim, Peter, Demetris, Anthony, OLeary, Jacqueline. **Current Opinion in Organ Transplantation.** 21(2):209-218, April 2016.

Tolerance

- Immunological Tolerance: Absence of immune reactivity toward specific antigens but preservation of immunity against foreign antigens, in the absence of ongoing IS
- Operational tolerance: clinical circumstance in which graft function is stable without rejection in the absence of IS
- Prope (almost) tolerance: Minimal IS with stable graft function ("as little as possible without rejection")



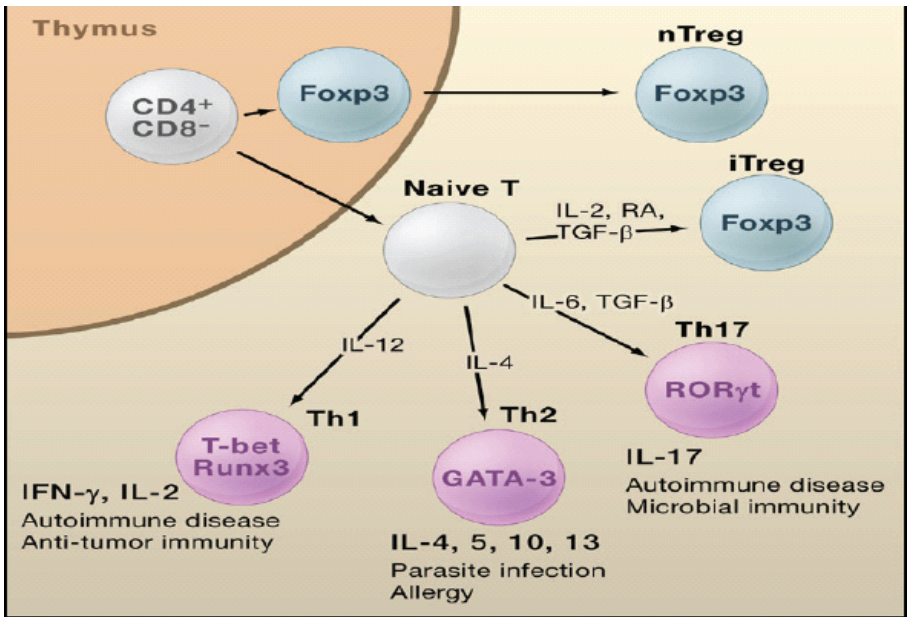
Levitsky J. Liver Transplantation 2011



Levitsky J. Liver Transplantation 2011

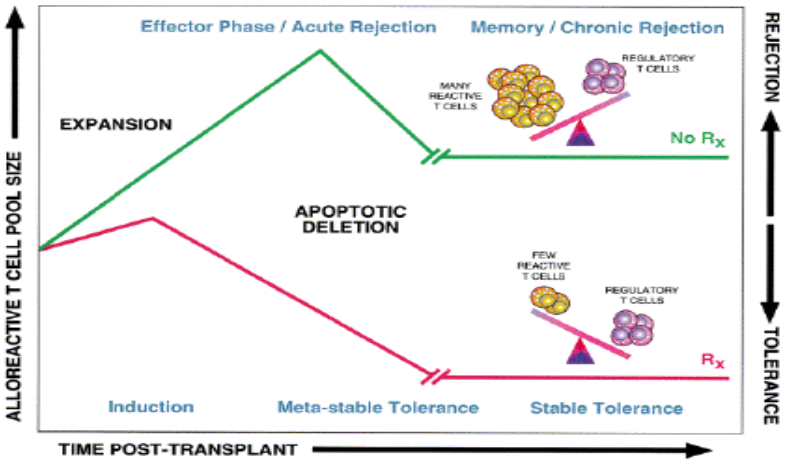
Regulatory T cells (Tregs)

- Naturally produced in the thymus and induced in the periphery to control effector responses to auto- and allo-antigens
- Require TCR interaction and IL-2 for proliferation
- Characteristically express:
  - High levels of CD25 (IL2 receptor)
  - Low CD127 (IL7 receptor)
  - FOXP3
  - TSDR (demethylated)



AASLD

The Balance of Teff/Tregs Determines Outcome



Turka/Strom/Sayegh 2007

AASLD

CLINICAL

- ✓ Lower relevance of acute rejection
- ✓ Rare chronic rejection
- ✓ Lower immunosuppression required
- ✓ Regulatory effect of combined liver-other organ
- ✓ Less significance of HLA match

IMMUNOLOGIC

- ✓ Large cellular compartment
  - Hematopoietic regulators (γδ T, NK/NKT cells, pDC)
  - Dilutional mass effect
- ✓ Regulatory proteins/cytokines
- ✓ Alloantibody dissolution
- ✓ Mixed hematopoietic microchimerism

Why Consider IS Withdrawal in Liver vs. Other Organ Recipients?

Levitsky J. Liver Transplantation 2011

AASLD

Published Immunosuppression Withdrawal Studies

Table 1
Published immunosuppression withdrawal studies (≥10 subjects enrolled).

Center (# subjects)	Adult or Pediatric	DD or LD LT	HCV+ included?	Age at LT or study (years)	Time from LT to Weaning (years)	Biopsy: Pre-/Post-Withdrawal		Tolerant* N (%)
						Pre	Post	
Single Center								
Pittsburgh (n = 95) [22]	Both	DD	Y	–	8.4 ± 4.7	Y	N	18 (19%)
London (n = 18) [23]	Adult	DD	Y	40.2 ± 12.7	7 (5 −1 1)			2 (11%)
Kyoto (n = 115) [24]	Pediatric	LD	–	–	> 2 per protocol	N	N	49 (42%)
Murcia (n = 20) [26,71]	Adult	DD	N	47.7 ± 9.5	3.4 ± 2.2	Y	N	8 (40%)
Rome (n = 34) [27,28]	Adult	DD	Y (only)	62 ± 5.9	5.3 ± 1.7	Y	Y	7 (20%)
New Orleans (n = 18) [29]	Adult	DD	Y	–	> 0.5 per protocol	N	N	1 (6%)
Winnipeg^ (n = 26) [30]	Adult	DD	–	53.7 ± 14.1	4.6 ± 1.8	Y	Y	11 (42%)
Miami^^ (n = 104) [32]	Adult	DD	Y	48.7 ± 3.2	4.1 ± 0.3	N	N	23 (22%)
Sapporo# (n = 10) [37]	Adult	LD	N	55.2 ± 6.1	> 0.5 per protocol	Y	Y	7 (70%)
Pamplona (n = 24) [35]	Adult	DD	N	65 (60–70)	9.3 (6–13.3)	Y	N	15 (63%)
Taipei (n = 16) [36]	Pediatric	Both	Y	4.0 ± 4.8	7.8 ± 5.4	Y	Y	5 (31%)
Palo Alto~ (n = 38) [72]	Pediatric	Both	N	1.8 ± 2.8	2.9 ± 3.5	N	N	17 (45%)
Multi-Center								
U.S. (n = 20) [33,38]	Pediatric	LD	N	8.5 (IQR 6.4–10.7)	7.9 (IQR 5.9–12)	Y	Y	12 (60%)
Spain (n = 102) [34,70]	Adult	DD	Y	47 ± 10	8.7 ± 3.9	Y	Y	41 (40%)

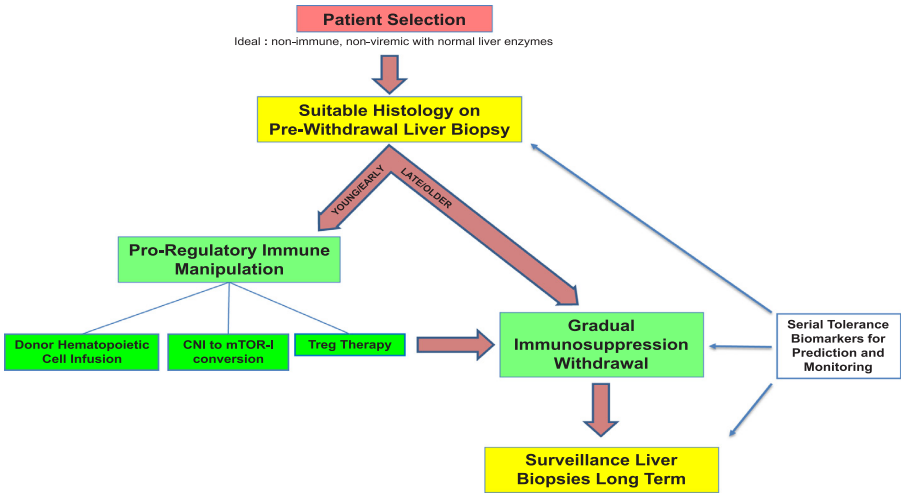
Levitsky, Feng. Human Immunol 2018
Newton, Levitsky. Current Immunol Reports 2016

AASLD

Tolerance in LT

- In very select groups, can achieve tolerance in >50% with simple weaning
- Factors associated with IS withdrawal success
  - Late withdrawal in older recipients
  - Less inflammation and lower C4d on pre-withdrawal bx
- What can we learn?
  - Biopsies are important pre- and post-weaning
  - Do this late, but not too late when the impact of IS has already occurred

Algorithm for achieving tolerance after LT



Levitsky, Feng. Human Immunol 2018

Thanks