Eledon Pharmaceuticals

R&D Day 2022

Transplantation | Autoimmunity | ALS

April 28, 2022

Forward-Looking Statements

This presentation contains forward-looking statements that involves substantial risks and uncertainties. Any statements about the company's future expectations, plans and prospects, including statements about its strategy, future operations, development of its product candidates, and other statements containing the words "believes," "anticipates," "plans," "expects," "estimates," "intends," "predicts," "projects," "targets," "could," "may," and similar expressions, constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, although not all forward-looking statements include such identifying words. Forward-looking statements include, but are not limited to statements regarding: expectations regarding the timing for the commencement and completion of product development or clinical trials; the rate and degree of market acceptance and clinical utility of the company's products; the company's commercialization, marketing and manufacturing capabilities and strategy; the company's intellectual property position and strategy; the company's ability to identify additional products or product candidates with significant commercial potential; the company's estimates regarding expenses, future revenue, capital requirements and needs for additional financing; developments relating to the company's competitors and industry; and the impact of government laws and regulations.

Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: the ability to develop commercially viable product formulations; the sufficiency of the company's cash resources; the ability to obtain necessary regulatory and ethics approvals to commence additional clinical trials; whether data from early clinical trials will be indicative of the data that will be obtained from future clinical trials; whether the results of clinical trials will warrant submission for regulatory approval of any investigational product; whether any such submission will receive approval from the United States Food and Drug Administration or equivalent foreign regulatory agencies and, if we are able to obtain such approval for an investigational product, whether it will be successfully distributed and marketed. These risks and uncertainties, as well as other risks and uncertainties that could cause the company's actual results to differ significantly from the forward-looking statements contained herein, are discussed in our annual report on Form 10-K for the year ended December 31, 2021, and other filings with the SEC which can be found at www.sec.gov. Any forward-looking statements contained in this presentation speak only as of the date hereof and not of any future date, and the company expressly disclaims any intent to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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Today's Speakers

David-Alexandre C. Gros, MD
Chief Executive Officer

Steven Perrin, PhD
President & Chief Scientific Officer

Jonathan Barratt, MBChB (Hons), PhD, FRCP
Mayer Professor of Renal Medicine and Honorary Consultant Nephrologist, University of Leicester

Stanley H. Appel, MD
Chair of Neurology and Co-Director, Houston Methodist Neurological Institute
Distinguished Endowed Chair for the Treatment and Research of ALS, Houston Methodist Research Institute

Flavio Vincenti, MD
Professor of Clinical Medicine and Surgery, University of California San Francisco

Piotr Witkowski, MD, PhD
Associate Professor of Surgery and Director of Pancreatic and Islet Transplant Program, University of Chicago

Jeff Bornstein, MD
Chief Medical Officer

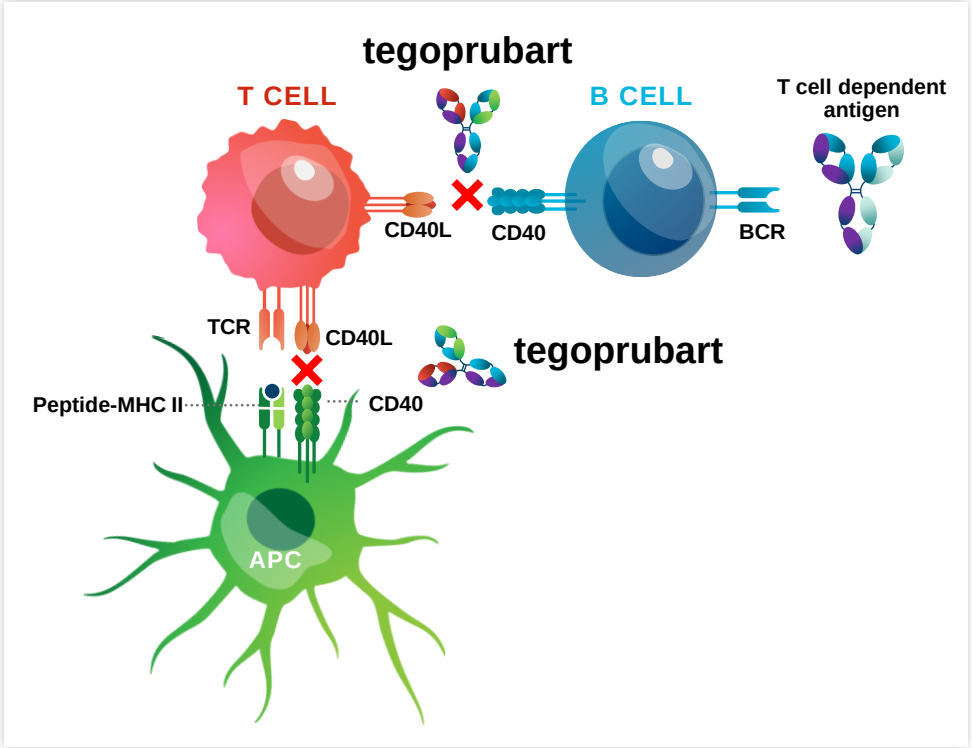
Overview of Tegoprubart

Steven Perrin, PhD

President and Chief Scientific Officer
Eledon Pharmaceuticals

Mechanism Overview of CD40L Inflammatory Signaling

- Interaction of CD40 with CD40L on immune cells **mediates activation of the co-stimulatory immune pathway**, controlling "cross talk" between the adaptive and innate immune systems
- Maximal activation of inflammatory system is a 3-step process requiring co-stimulatory signaling
  - **Step 1:** Major histocompatibility complexes (MHC) and CD3/TCR engagement
  - **Step 2:** CD40 and CD40L binding resulting in cell division and clonal expansion
  - **Step 3:** Pro-inflammatory response by polarized T cells expressing inflammatory chemokines and cytokines
- Blocking CD40L shifts polarization from pro-inflammatory signaling to T cell anergy, apoptosis, and polarization to a Treg environment
  - Blocking CD40L thus **does not generally result in lymphopenia** often seen with immunosuppressive agents



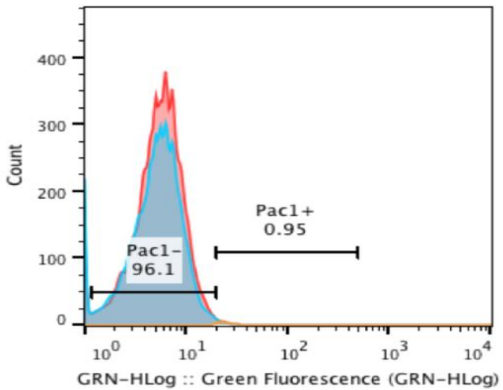
Tegoprubart: Potential Best-in-Class Anti-CD40/CD40L Antibody

Targeting CD40 Ligand vs. CD40 Receptor		IgG1 vs. fusion protein, pegylated FAB or IgG4
CD40L and CD40	**CD40L only**	
Targeting both anti-CD40L and anti-CD40 inhibits B cell polarization and class switching, as well as inhibits the pro-inflammatory polarization of $CD4^+$ Helper T cells	✓ Blocking anti-CD40L also inhibits CD11 costimulatory receptors on antigen presenting cells, thus blocking the pro-inflammatory polarization of $CD8^+$ Cytotoxic T cells	✓ Up to over 2x times longer half-life
	✓ Blocking CD40L also polarizes $CD4^+$ lymphocytes to $FoxP3^+$ Regulatory T cells (Tregs), thus creating a potentially more tolerogenic environment	✓ Manufacturing advantages
	✓ CD40L is more selectively expressed, providing the potential for additional safety and PK/PD/dosing advantages	✓ Less anti-drug antibodies

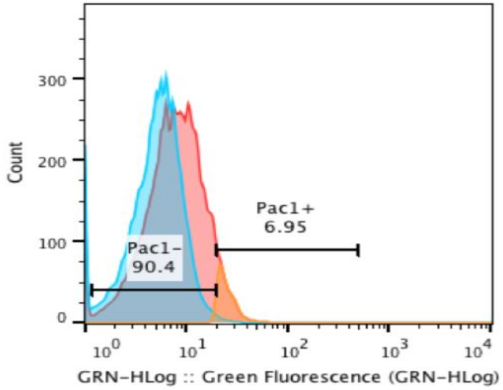
Note: Potential advantages versus selected other CD40/CD40L clinical programs; not based on head-to-head studies. Differences versus any individual competitive program may vary.

Tegoprubart Demonstrates Absence of Platelet Activation vs. 5c8

Tegoprubart



5c8



Tegoprubart binds CD40L on platelets but **compared to 5c8 no longer activates human platelets** as determined by PAC1 expression (orange) on the surface of platelets measured by FACS

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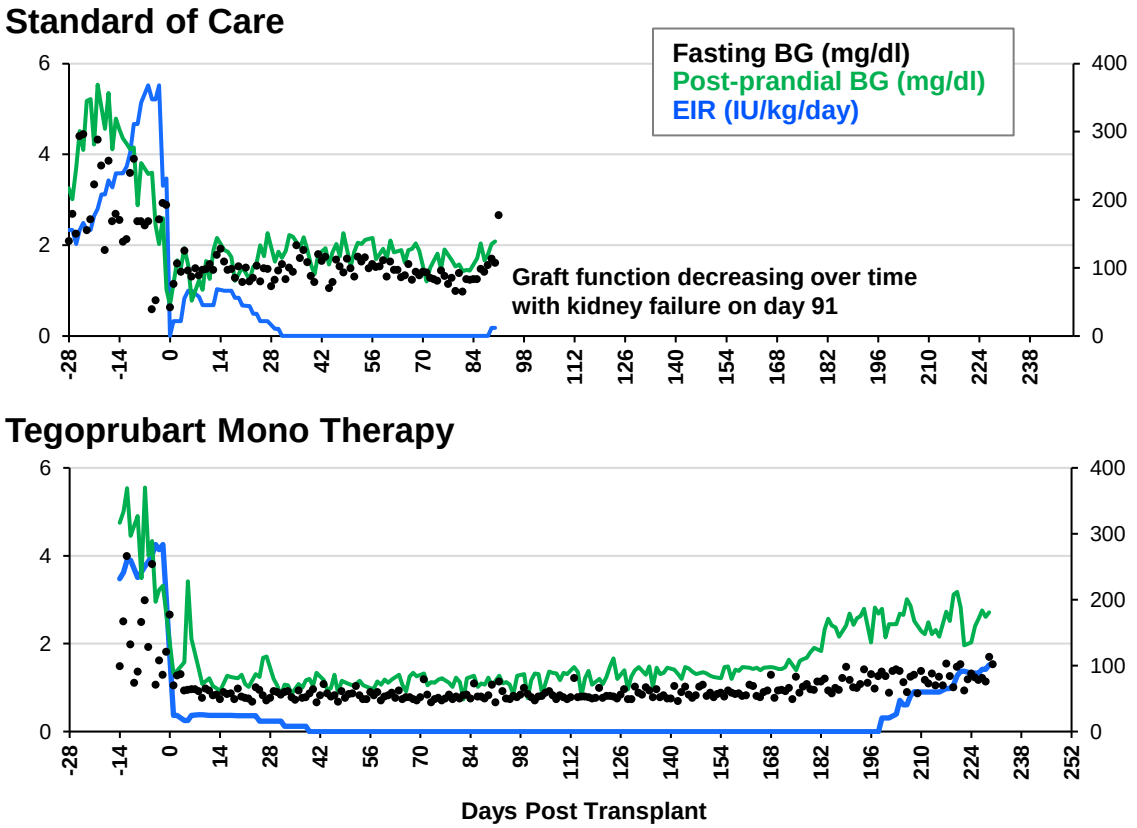
Tegoprubart Phase 1a/1b Single Ascending Dose Trial Completed in Healthy Subjects and ALS Patients

Healthy Volunteers or ALS Patients Receiving Either tegoprubart (mg/kg, IV) or Placebo

Subjects	Healthy	Healthy	ALS	Healthy	Healthy	Healthy	Tego-prubart	Placebo
Dose (mg/kg)	0.5	1	**1**	2	4	8	NA	NA
n=	6	3	**3**	3	3	6	24	8
Number of Subjects (%) Experiencing TEAEs by Maximum Toxicity Grade								
Grade 1 (% Subjects Experiencing Events)	3 (50.0%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	1 (33.3%)	1 (16.7%)	11 (45.8%)	5 (62.5%)
Grade 2 (% Subjects Experiencing Events)	–	–	1 (33.3%)	–	–	1 (16.7%)	2 (8.3%)	–
Grade 3	–	–	–	–	–	–	–	–
Grade 4	–	–	–	–	–	–	–	–
Grade 5	–	–	–	–	–	–	–	–

Non-Human Primate Islet Cell Transplant Model: SOC Versus Tegoprubart Blood Glucose Stabilization



In animals whose islet cells were ablated to induce T1D and who then underwent islet cell transplantation, **tegoprubart provided for better blood glucose level stabilization and less drug related animal morbidity and mortality** than standard of care

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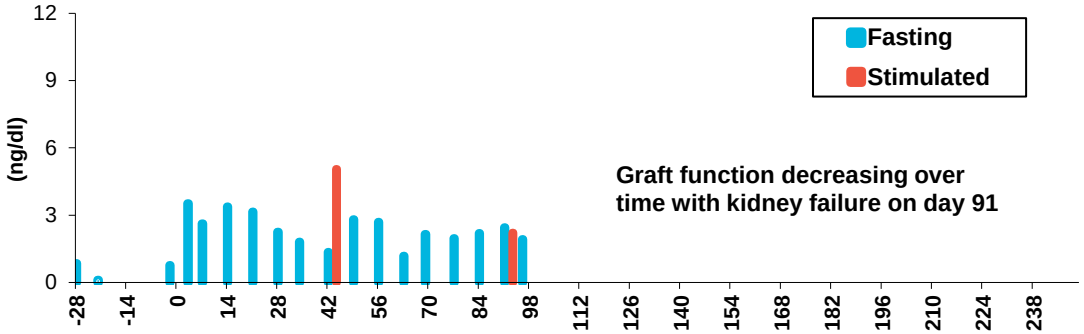
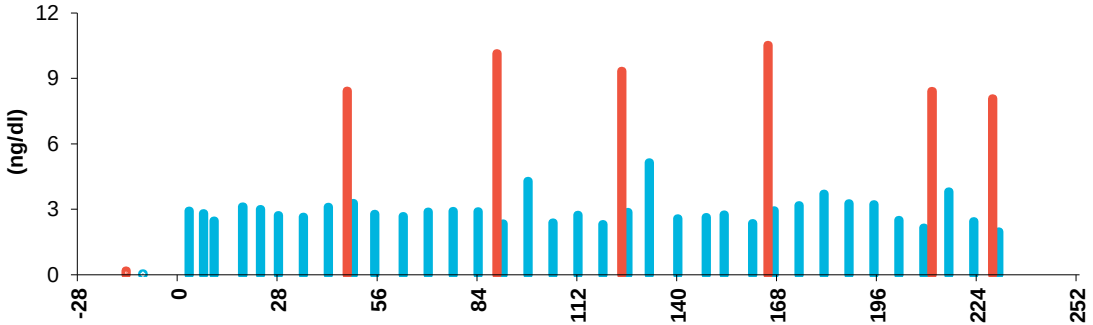
Non-Human Primate Islet Cell Transplant Model: SOC Versus Tegoprubart C-peptide Levels

Standard of Care



Tegoprubart Mono Therapy



- C-peptide levels are a surrogate biomarker of insulin production, islet cell viability and function
- In response to meal stimulation, functioning islets produce more insulin and thus C-peptide
- **Animals receiving tegoprubart showed better islet cell function than those receiving standard of care**

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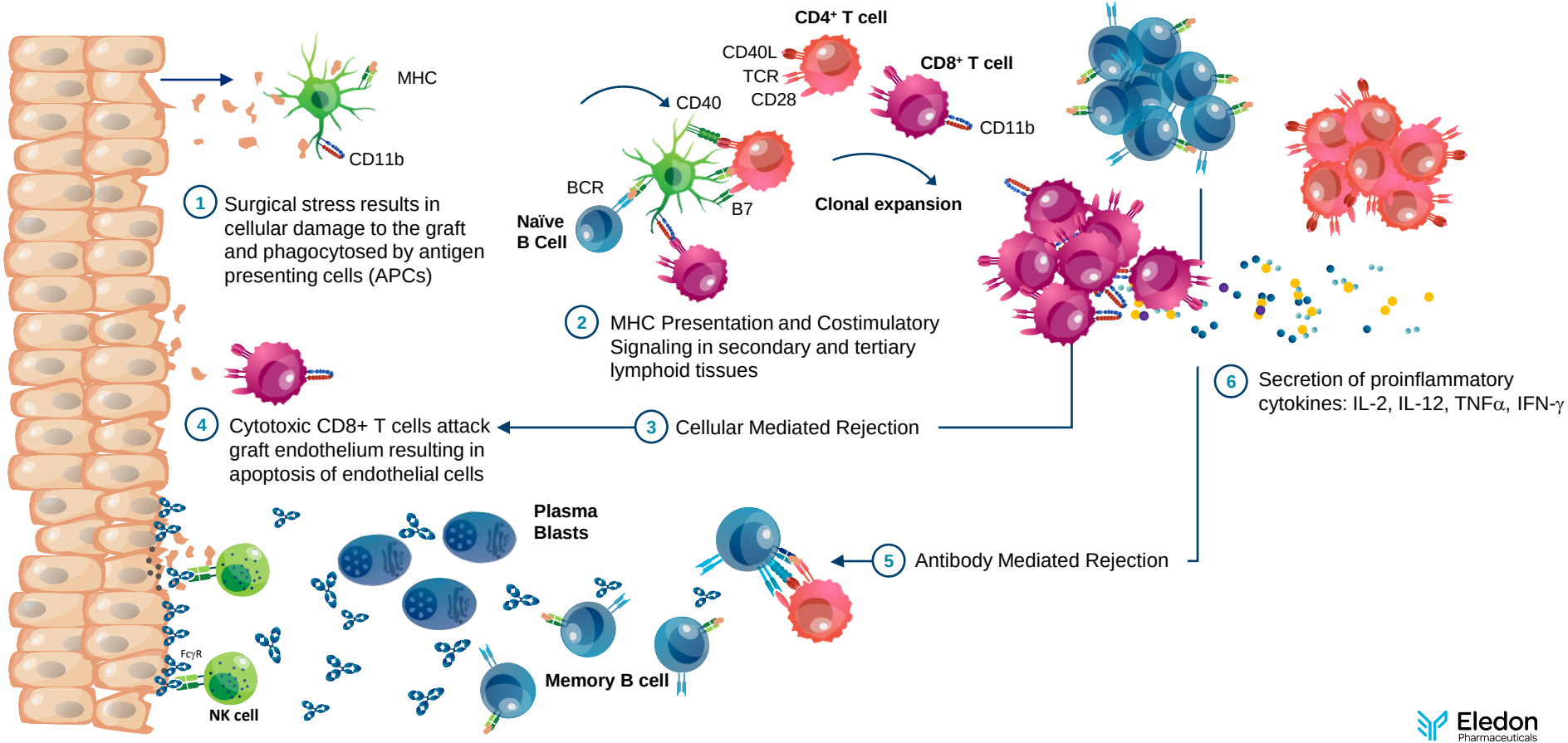
Pathophysiology of Transplant Rejection



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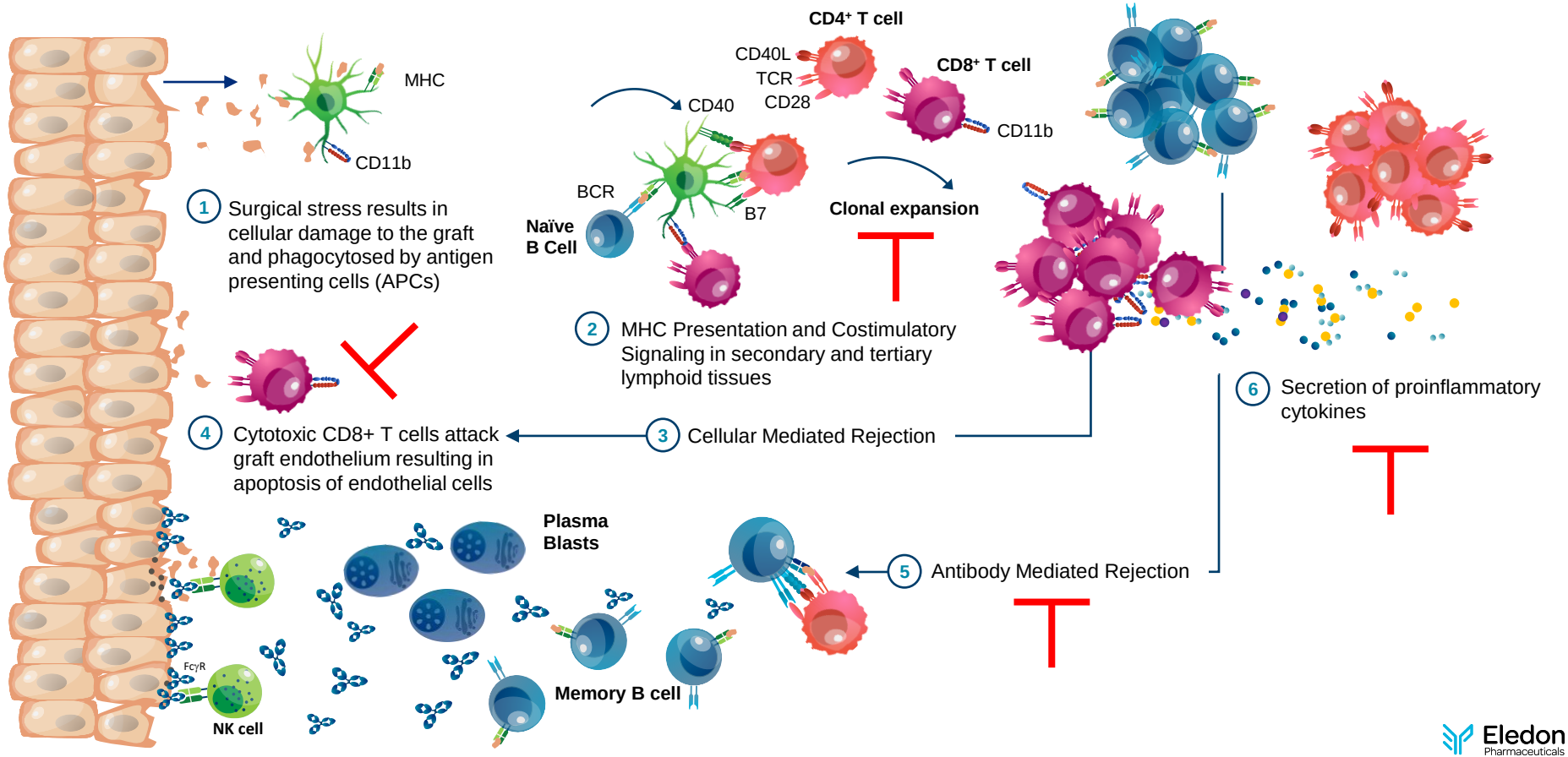
Anti-CD40L in the Prevention of Transplant Rejection



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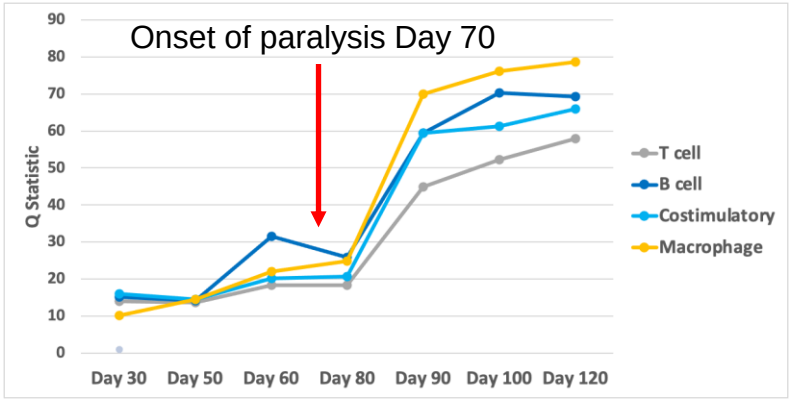
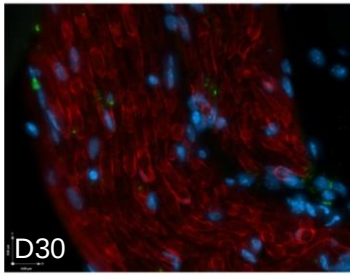
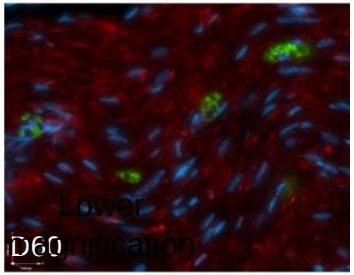
Inflammatory Pathways are Activated in the Periphery in ALS Animal Models

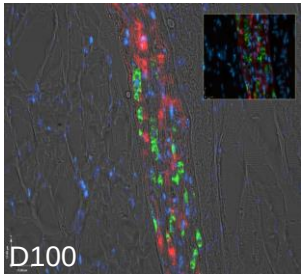
Activation of Inflammatory Pathway in ALS Rodent Skeletal Model

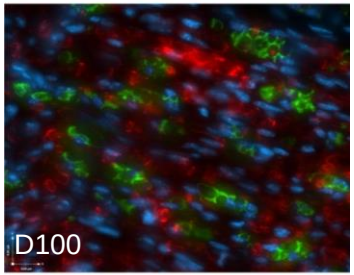


- Macrophages accumulate on peripheral nerves in skeletal muscle
- Staining shows Myelin (Red), Macrophages (Green), and Nuclei (Blue)









Source: Lincecum, 2010.

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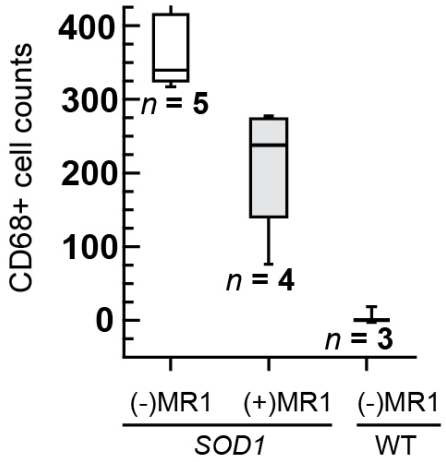
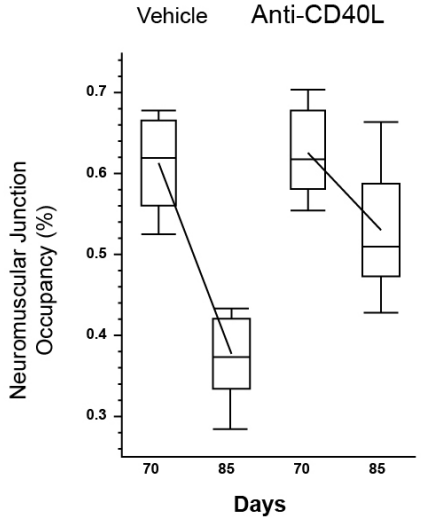
Anti-CD40L Historical Antibody Improves Motor Neuron Survival & Decreases Inflammation in Peripheral Nerves of ALS Mice

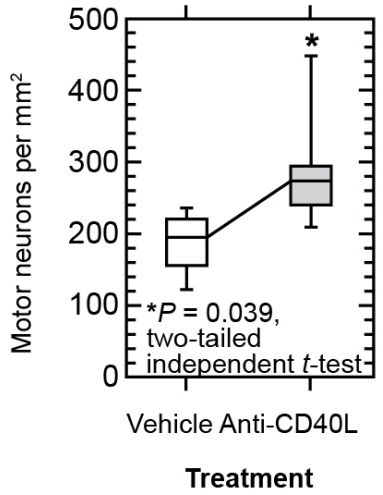
Anti-CD40L (MR1) treatment reduces macrophage infiltrate and "attack" of denervated peripheral nerves in skeletal muscle



Anti-CD40L treatment reduces macrophage infiltrate resulting in increased neuromuscular junction occupancy



Anti-CD40L treatment reduces neuroinflammation in the spinal cord resulting in improved motor neuron survival



Source: Lincecum, 2010.

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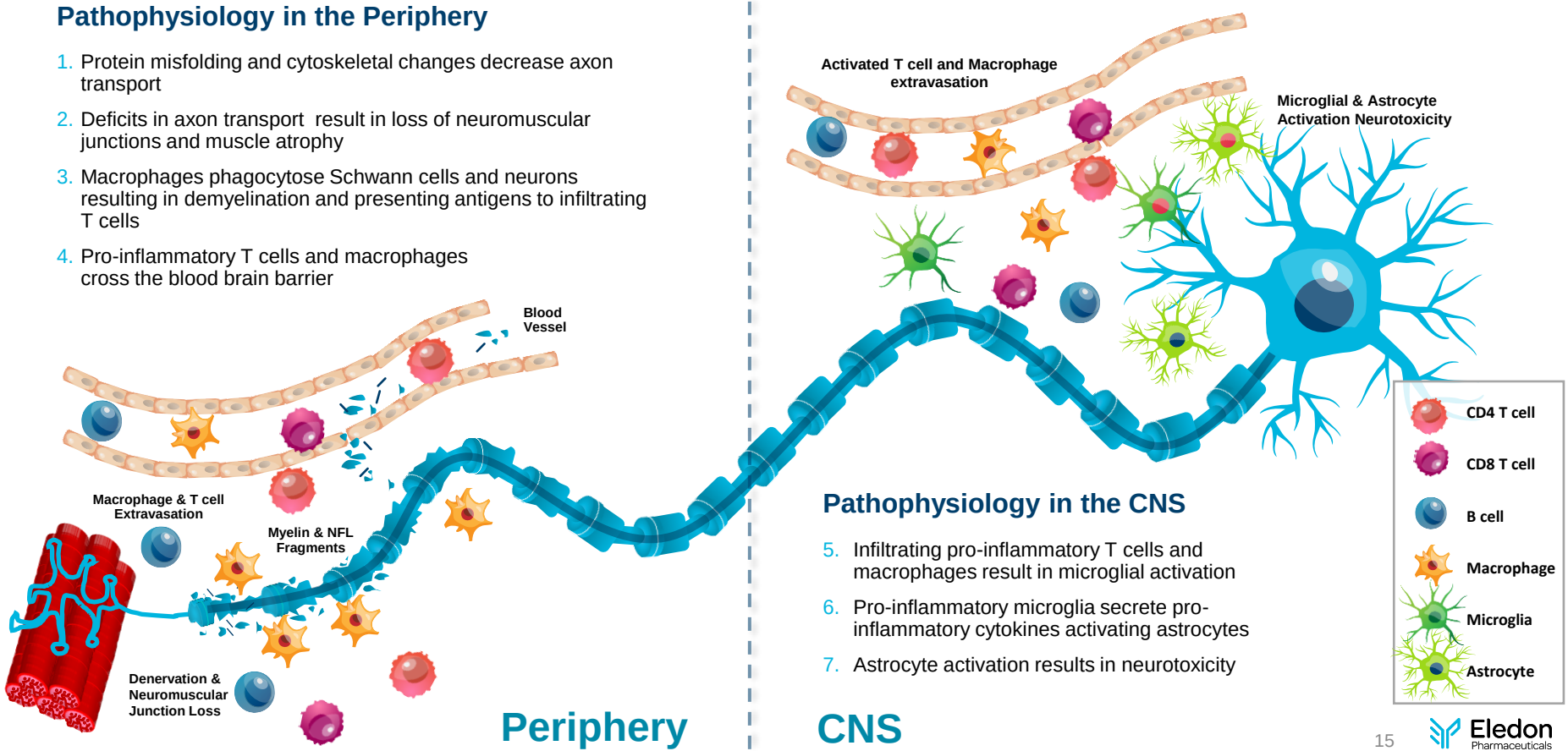
Pathophysiology of Amyotrophic Lateral Sclerosis

Pathophysiology in the Periphery

1. Protein misfolding and cytoskeletal changes decrease axon transport
2. Deficits in axon transport result in loss of neuromuscular junctions and muscle atrophy
3. Macrophages phagocytose Schwann cells and neurons resulting in demyelination and presenting antigens to infiltrating T cells
4. Pro-inflammatory T cells and macrophages cross the blood brain barrier



Pathophysiology in the CNS

5. Infiltrating pro-inflammatory T cells and macrophages result in microglial activation
6. Pro-inflammatory microglia secrete pro-inflammatory cytokines activating astrocytes
7. Astrocyte activation results in neurotoxicity

Periphery **CNS**

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Anti-CD40L for the Treatment of ALS

Pathophysiology in the Periphery

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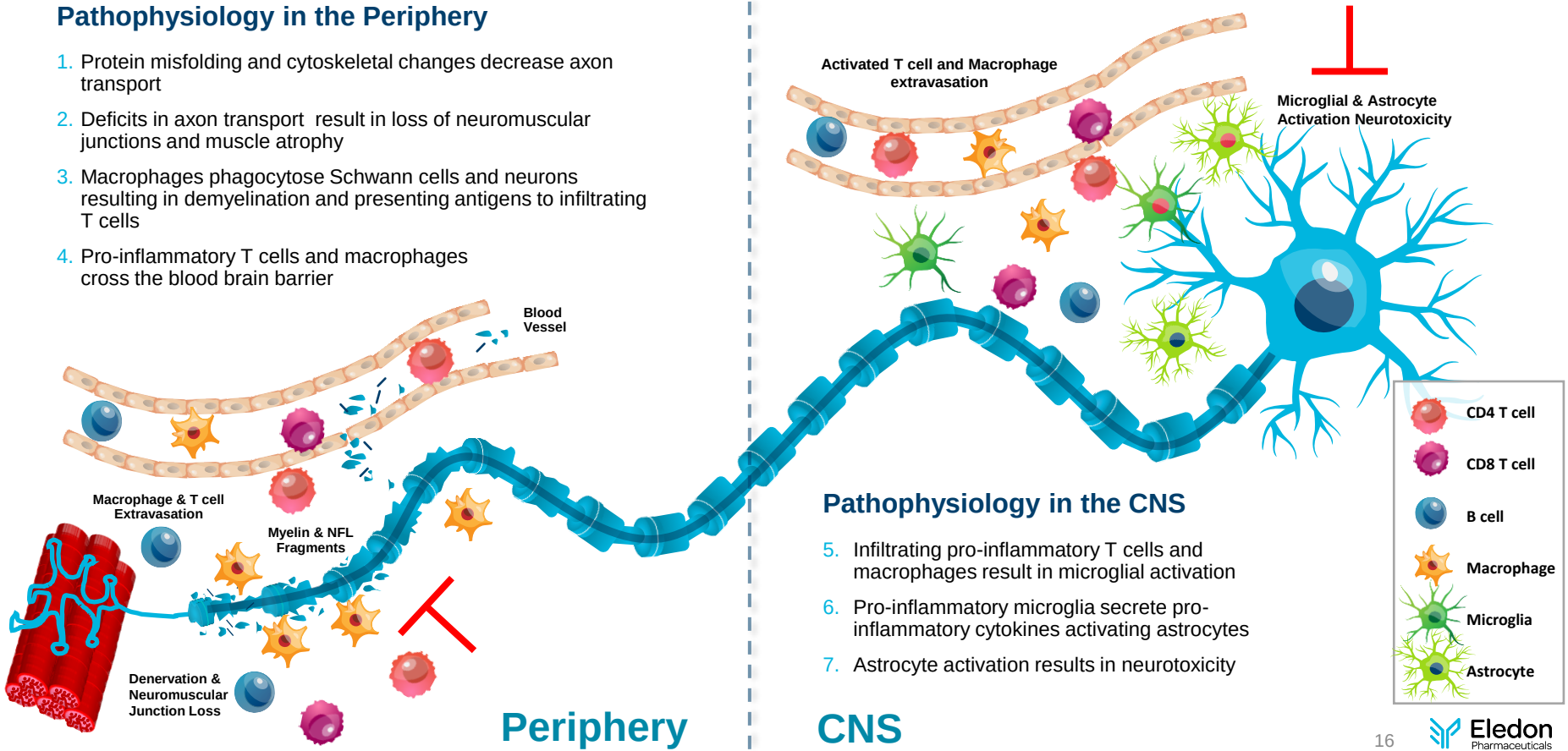

Pathophysiology in the CNS

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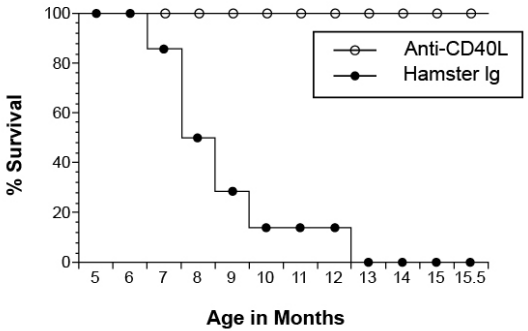
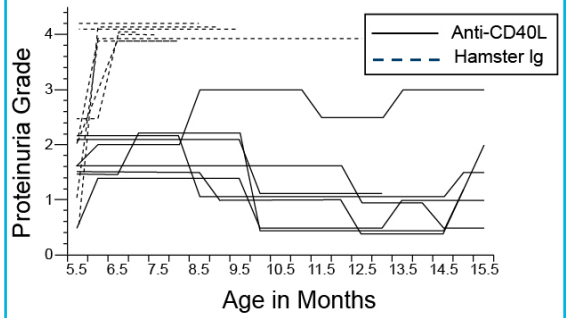
Blocking CD40L Ameliorates Glomerulosclerosis and Proteinuria in Historical Autoimmune Nephritis Rodent Models

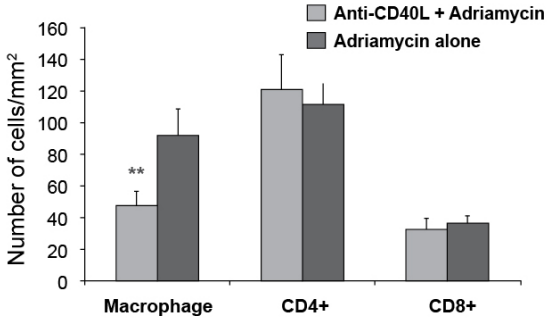
Blocking CD40L improved survival in a Lupus Nephritis mouse model



Blocking CD40L improved proteinuria in a Lupus Nephritis mouse model



Treatment with anti-CD40L reduced tissue damage and macrophage infiltration in Adriamycin induced glomerulosclerosis mouse model



Source: Kalled, 1999.

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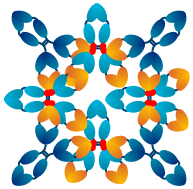
Pathophysiology of IgA Nephropathy

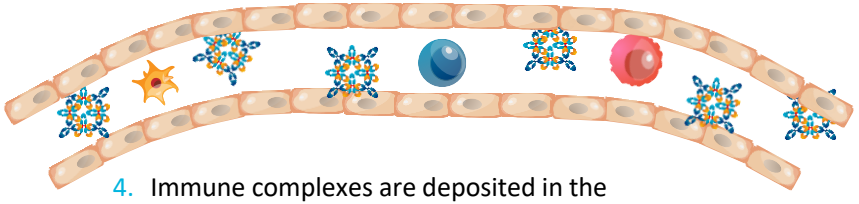
Production and Pathophysiology of galactose deficient IgA

1. Deficiencies in galactosyltransferase enzymes results in production of improperly galactosylated IgA in the hinge regions (Gd-IgA1)
2. Gd-IgA1 is recognized as “foreign” by antigen presenting cells and antibodies to Gd-IgA1 are produced in the mucosal germinal centers

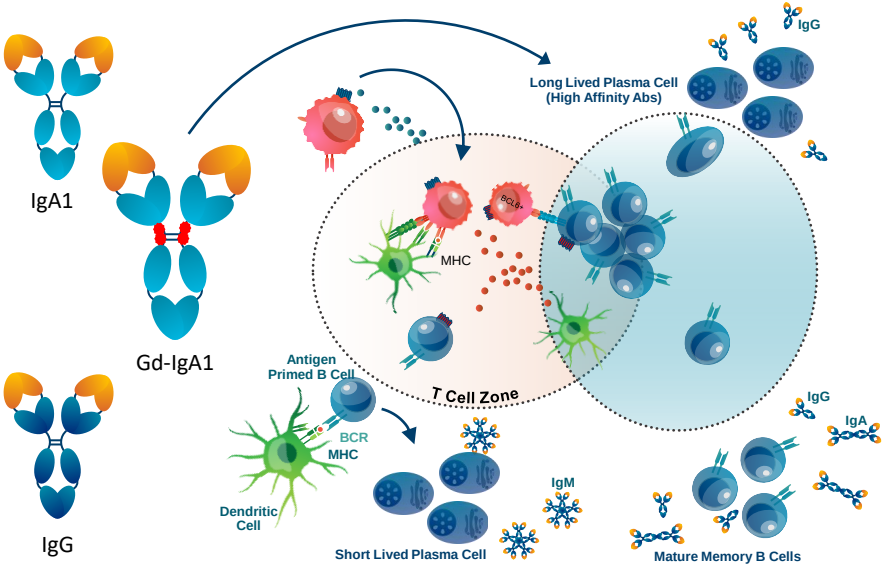


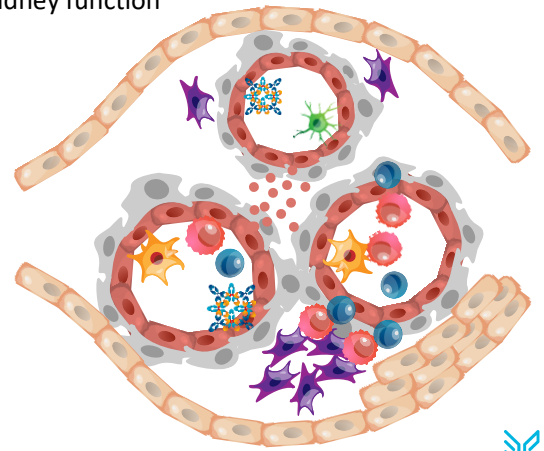
3. Antibodies to Gd-IgA1 form immune complexes in circulation

Immune Complexes in Circulation



4. Immune complexes are deposited in the mesangium of the kidney resulting in focal damage and production of pro-inflammatory cytokines
5. Chronic induction of inflammatory signaling results in immune cell infiltration, fibrosis and loss of kidney function





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Anti-CD40L Targeted Mechanism in IgA Nephropathy

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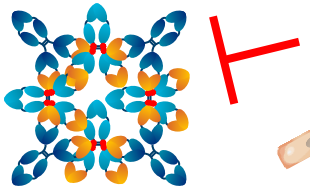

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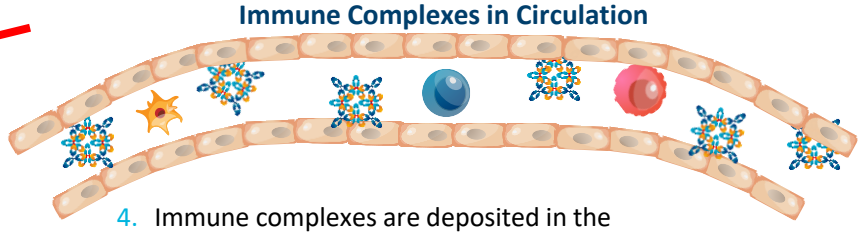

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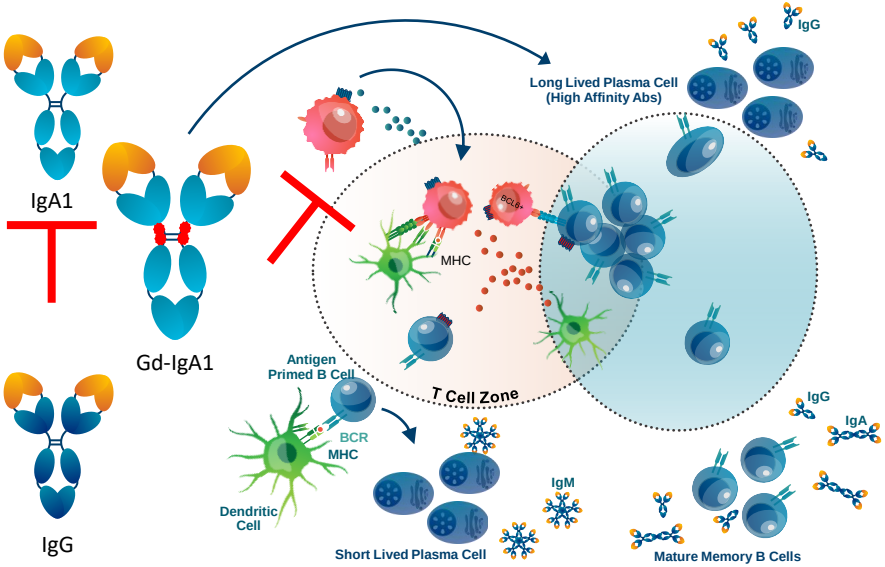

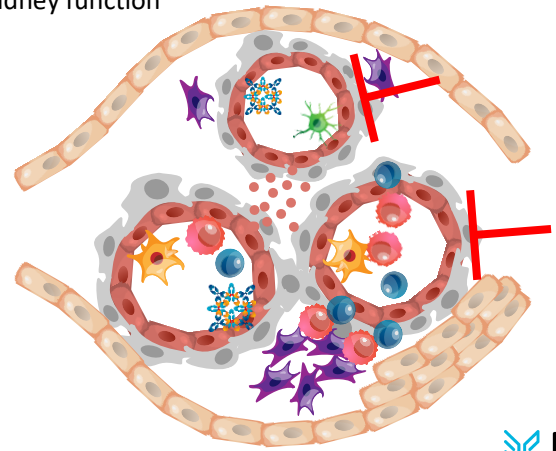

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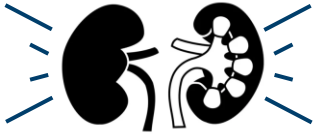
IgA Nephropathy (IgAN)

Jonathan Barratt, MBChB (Hons), PhD, FRCP

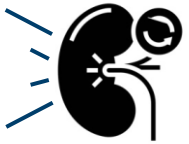
Mayer Professor of Renal Medicine
Honorary Consultant Nephrologist
University of Leicester

IgAN: Natural History

- Average age at diagnosis between 20 and 40 years old
- Often initially asymptomatic or mildly symptomatic (hematuria, proteinuria)



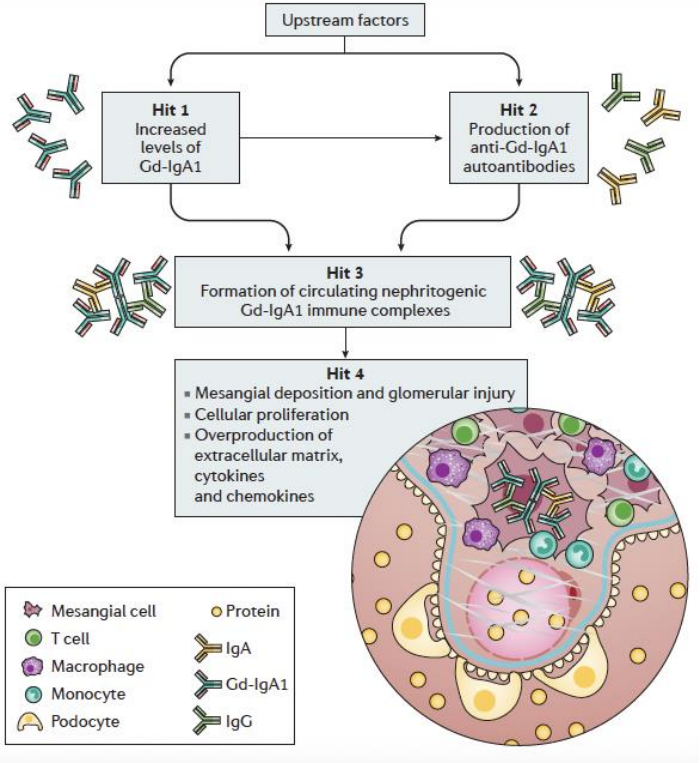
- Variable progression:
  - Overall, up to 30% progress to ESRD
  - In patients with significant proteinuria, 30-40% progress to ESRD within 20 years of diagnosis
  - May lead to kidney transplant since patients are generally young with few other comorbidities



- Recurrent glomerulonephritis is a significant cause of graft loss in kidney transplant patients
  - Reported recurrence rate of ~30% after kidney transplantation

Source: Glassrock, 2019; Schena, 2018; Moroni 2019.

IgAN: Pathophysiology

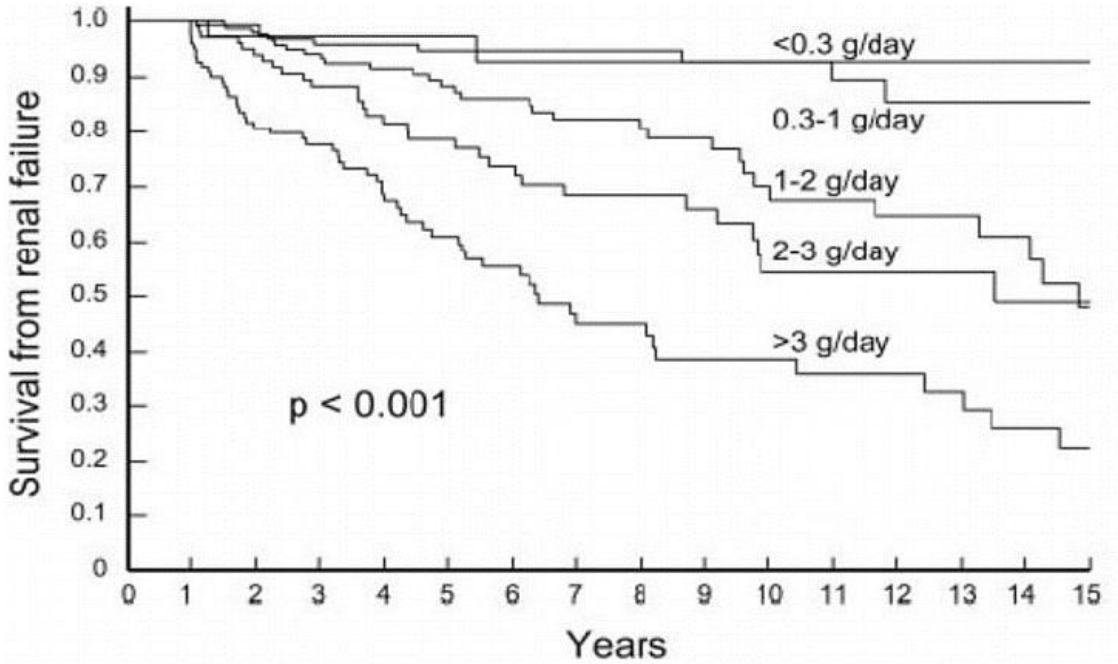


Proteinuria Results & is a Key Biomarker

- Blood cells and large proteins cannot normally leave the glomerulus capillaries and cross the glomerular basement membrane
- In CKD, proteins leak through the compromised glomerular filtration barrier and get reabsorbed by epithelial cells on the proximal tubule
- Vicious cycle results:
  - Excess resorption of filtered protein leads to inflammation and fibrosis, which in turn further damages the filtration barrier
  - Nephron loss during CKD progression results in elevated single nephron GFR in the remaining nephrons, which causes glomerular and tubular damage, and further advances glomerular barrier injury

Source: Lai, 2016.

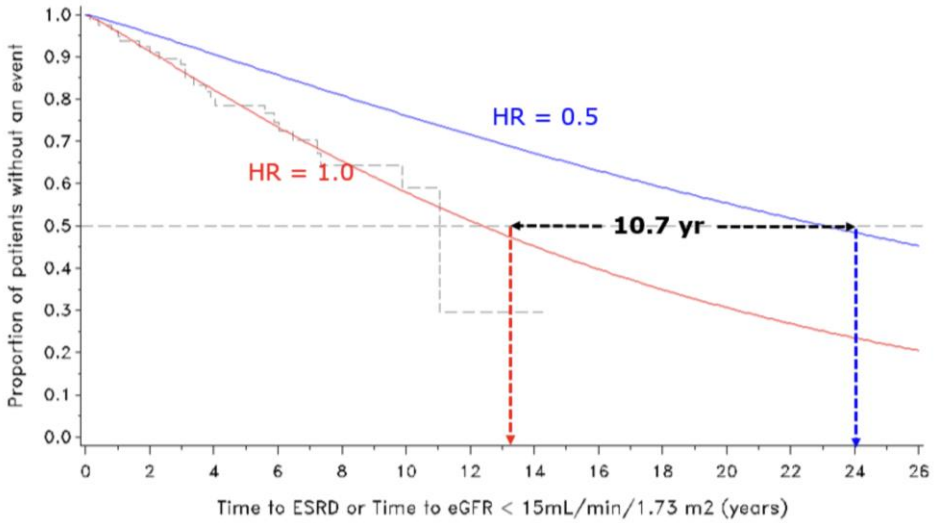
Proteinuria is the Leading Predictor of Progression to ESRD in IgAN



Source: Reich, 2007.

Proteinuria Reduction Important Treatment Target to Delay Disease Progression and Time To ESRD

Kaplan Meier Plot & Weibull Fit Analysis: Leicester IgAN Patients



- Hazzard ratio (HR) of 1.0 represents no treatment effect on proteinuria from baseline vs. a HR of 0.5 representing a 30% treatment effect
- **Since mean age at diagnosis is under 40 y.o., delaying ESRD by 10 or even 20 years will still lead to many patients ultimately developing ESRD in their lifetime**

Source: Barratt.

IgAN Current Standard of Care (SoC)

- **Non-specific treatment** including:
  - Control blood pressure
  - ACEi / ARBs
  - Corticosteroids / other immunosuppression
  - Tonsillectomy

SoC including ACE/ARBs reduces proteinuria to below 0.5 g/d in 30% to 50% of people with IgAN

- **One FDA approved therapy:** TARPEYO™ (budesonide)
  - Accelerated approval based on reduction in urine protein
  - Reasonable safety profile; some evidence of systemic steroid effects

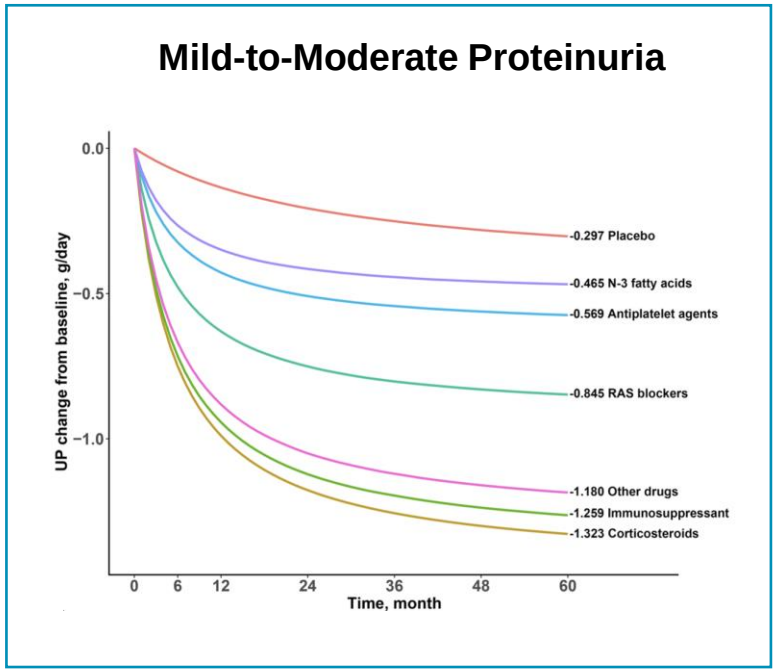
Table 2: Analysis of the primary efficacy endpoint at 9 months in Phase 3 Study Nef-301

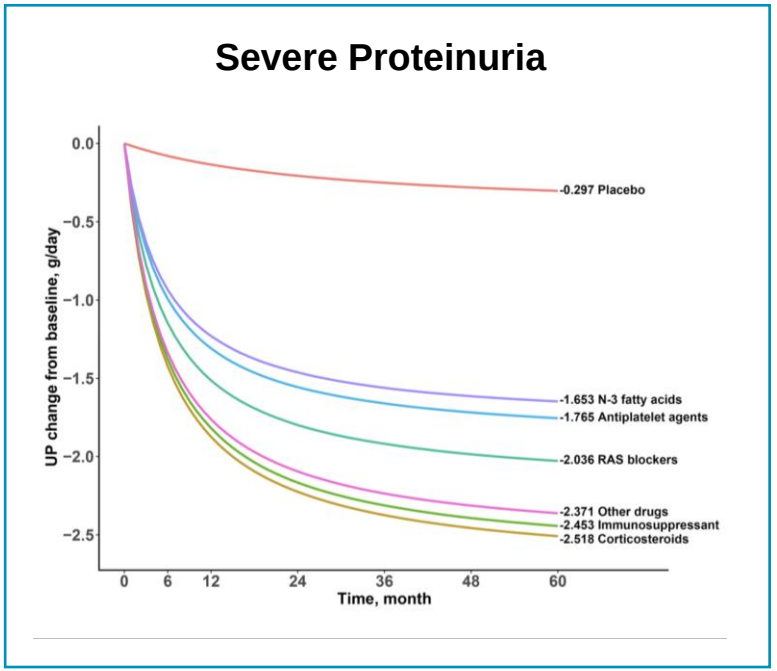
Primary Endpoint: UPCR g/g [a]	TARPEYO 16 mg (N=97)	Placebo (N=102)
Percentage reduction from baseline (Adjusted for baseline) [b]	34%	5%
TARPEYO 16 mg versus Placebo : Percentage reduction (95% CI) [c]; 2-sided p-value	31% (16% to 42%); p=0.0001	

Source: Bagchi, 2021; Li, 2013.

Efficacy of Steroids vs. Immunosuppressants vs. RAS Blockers

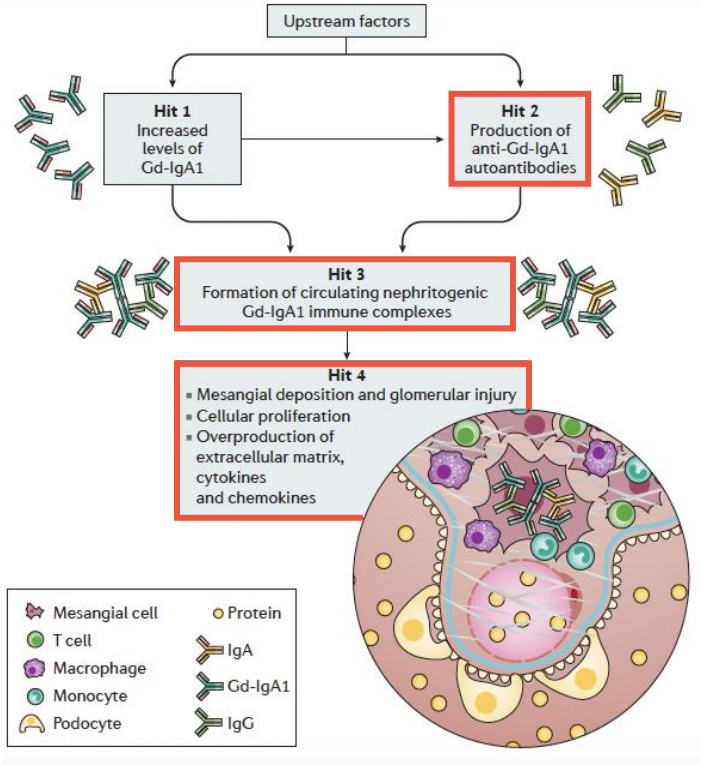
Meta-analysis of Typical Time-Effect Curves for IgAN Therapies vs. Placebo





Source: Yu, 2022.

Tegoprubart May Impact Multiple Steps in IgAN Pathogenesis



- Current Standard of Care and other drugs in development generally aim to either reduce production of antibodies or reduce the leakage of antibodies and subsequent tissue damage by decreasing local blood pressure (i.e., either Hits #2 or #4)
- **Tegoprubart has the potential to hit at the root of the pathophysiology by reducing production of IgA autoantibodies and thus the immune complex formation (i.e., Hits #2, #3 and #4)**

Source: Lai, 2016

Anti-CD40L (MR1) Improves Renal Pathology & Function in an Adriamycin Rodent Model of Glomerulosclerosis

Pathologic Markers of Disease Severity at Day 42

[a]$P < 0.001$ compared to group 2 [b]$P < 0.01$ compared to groups 1 and 2	Normal (group 1)	Adriamycin alone (group 2)	MR1 + adriamycin (group 3)
Glomerular changes			
Glomerular surface area μm^2	3292 ± 569	2463 ± 630	3142 ± 675^a
Glomerular sclerosis %	0	30.2 ± 7.2	20.1 ± 4.7^b
Number of nuclei per glomerulus	32.5 ± 5.7	21.8 ± 4.3	30.9 ± 4.9^a
Tubulointerstitial changes			
Tubular diameter μm	37.3 ± 5.7	66.3 ± 13.7	42.5 ± 6.9^b
Tubular cell height μm	18.2 ± 1.9	11 ± 1.8	16.3 ± 1.7^b
Interstitial volume %	1.3 ± 0.7	26.2 ± 4.9	13.9 ± 5.1^b

Functional Markers of Disease Severity at Day 42

[a]$P < 0.01$ vs. group 2 [b]$P < 0.05$ vs. both groups 1 and 2	Normal (group 1)	Adriamycin alone (group 2)	MR1 + adriamycin (group 3)
Body weight *g*	24.4 ± 1.6	18.6 ± 1.8	20.6 ± 3.0
Serum creatinine *mmol/L*	23.6 ± 3.2	51.4 ± 4.4	29.5 ± 6.7^b
Serum albumin *g/L*	27.6 ± 3.1	23.7 ± 3.1	23.1 ± 1.4
Urinary protein *mg/24 hours*	0.7 ± 0.2	4.3 ± 0.8	1.8 ± 0.6^b
Urinary protein creatinine *mg/mmol*	0.3 ± 0.2	3.3 ± 0.8	1.4 ± 0.6^b
Creatinine clearance *μL/min*	82 ± 4	35 ± 2	75 ± 4^a

Source: Kairaitis, 2003.

Summary

- Pathophysiology associated with IgA nephropathy is the result of IgA containing immune complex formation and deposition in the kidney resulting in immune cell infiltration and chronic kidney damage
- Current standard of care with ACE/ARB therapies and Tarpeyo are effective in a subset of patients with IgAN but many patients will continue to have progressive disease and be at risk of ESRD
- Non-specific immunosuppressant treatments has demonstrated impact on clinical outcomes associated with IgAN
- Additional treatment modalities directly targeting the pathophysiology of autoantibody formation and immune complex formation need to be investigated
- Blocking CD40L function with tegoprubart may lead to improved clinical outcomes by protecting the kidneys via reducing Gd-IgA1 levels, decreasing autoantibody production, reducing immune complex formation, and decreasing glomerular inflammation

Amyotrophic Lateral Sclerosis (ALS)

Stanley H. Appel, M.D.

Chair of Neurology and Co-Director, Houston Methodist Neurological Institute

Distinguished Endowed Chair for the Treatment and Research of ALS, Houston Methodist Research Institute

ALS Natural History

- **US incidence of ~5,000 diagnosed cases per year with a prevalence over 30,000**
  - Globally, more than 600,000 people are living with ALS
  - Onset typically occurs in middle adulthood with an average age at diagnosis of 55 although it can occur as early as in the twenties
  - Only 5-10% of cases are considered familial (genetic)
- **Etiology has not been completely elucidated however genetics suggest deficiencies in RNA processing leading to protein misfolding, neuroinflammation, axonopathy, muscle atrophy, and motor neuron death**
- **Disease onset and rate of progression is heterogeneous but invariably progressive**
  - Symptom onset is focal in nature and usually in the arms or legs
  - As ALS progresses, muscle weakness and atrophy spreads to other body regions
  - Individuals typically develop difficulty - thus requiring external assistance - with walking, swallowing (dysphagia), speaking (dysarthria), and breathing (dyspnea) in 3-5 years post onset
  - Average life expectancy after diagnosis is two to five years, but some patients may live decades

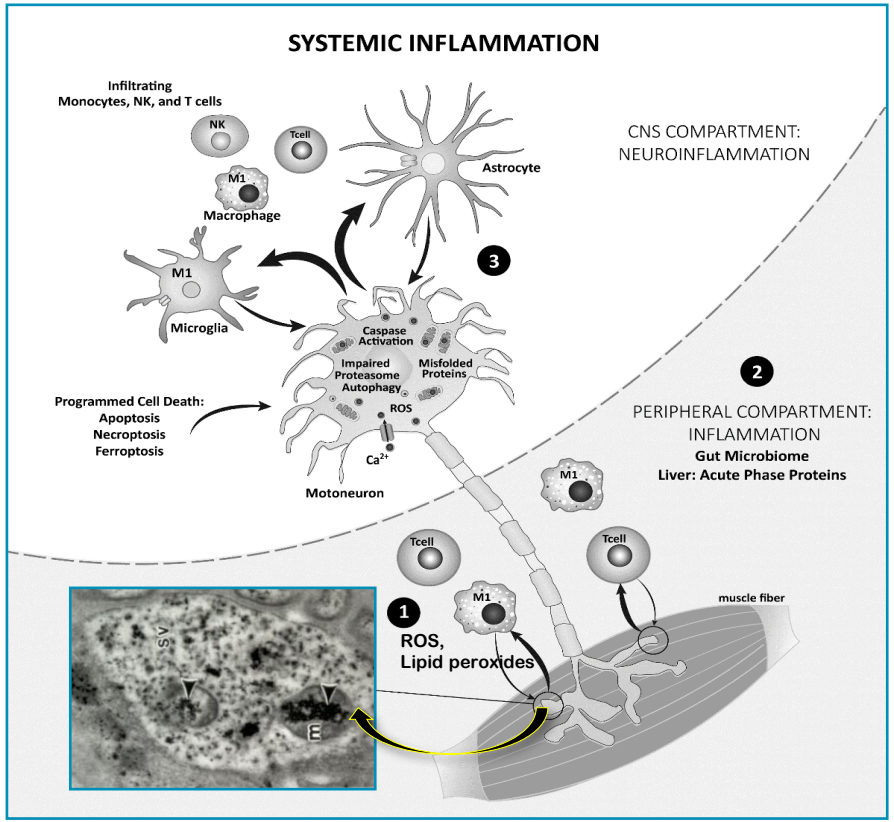
ALS Current State of the Art

- **2 US FDA approved therapies but average life expectancy remains only two to five years after diagnosis**
  - **Riluzole:** Approved globally in the 1990s and became generic in the US in 2013
  - **Edaravone:** Approved in Japan and the US in 2017, but not approved in Europe

- **In recent years, ALS has had a robust clinical development pipeline**
  - Antisense and gene therapy approaches are focusing on genetic forms of the disease
  - Other investigational treatments are focusing on immune system activation, mitochondrial function, muscle function, cell stress, and other pathophysiologies associated with neurodegeneration

- **Established US regulatory pathway with change in ALS FRS as primary endpoint**
  - Survival and biomarkers including regarding target engagement and neuronal health also important
  - Global regulatory agencies recognize the significant unmet need

Systemic and CNS Neuroinflammation Promote Neurodegeneration

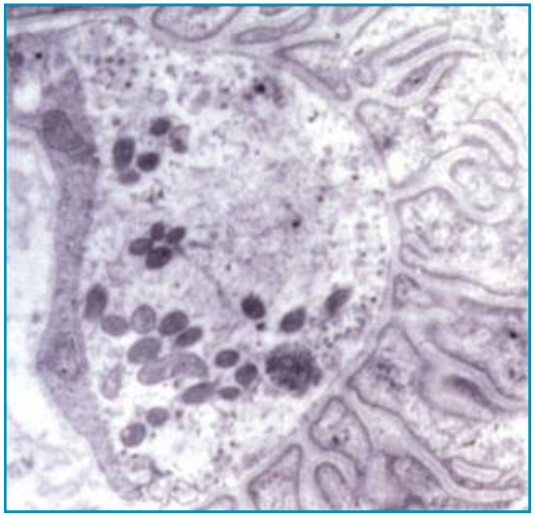


Source: Appel SH.

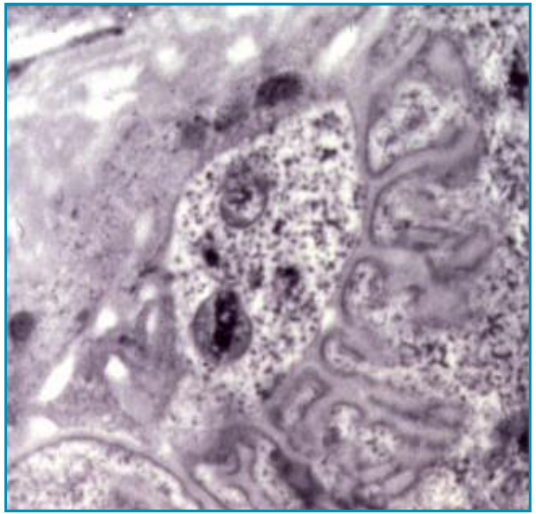
HOUSTON Methodist NEUROLOGICAL INSTITUTE

Ultrastructure of Neuromuscular Junctions in ALS (1 of 2)

Control



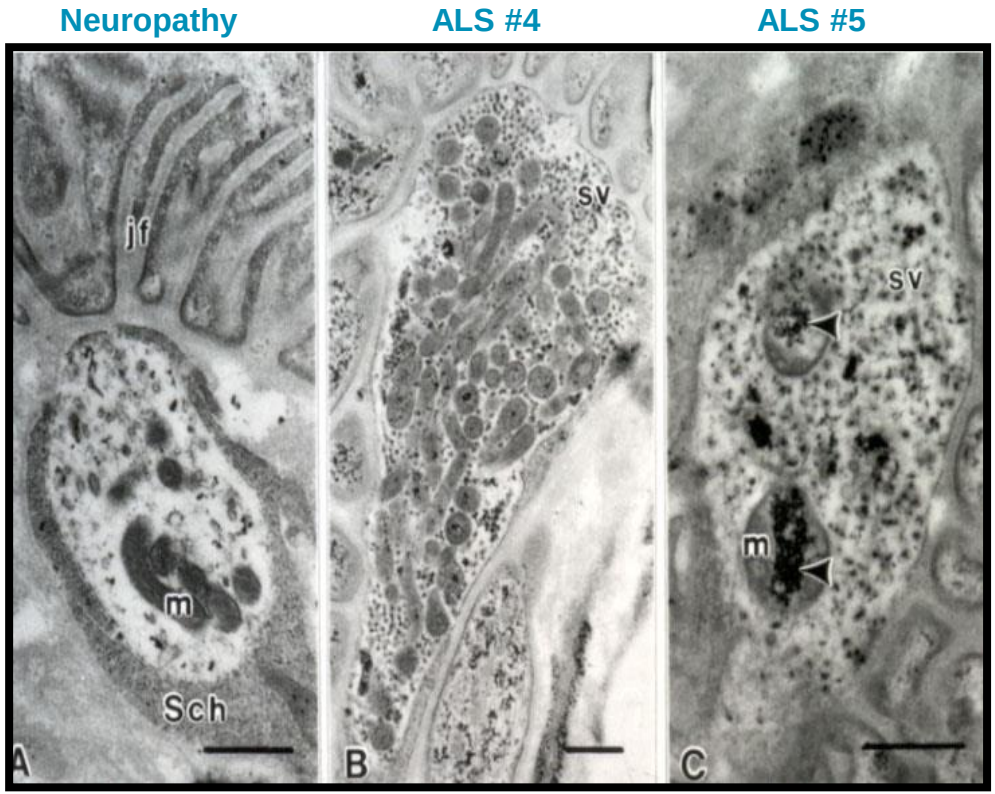
ALS #5



ALS motor nerve terminals contain significantly increased calcium, altered mitochondria, and increased vesicles

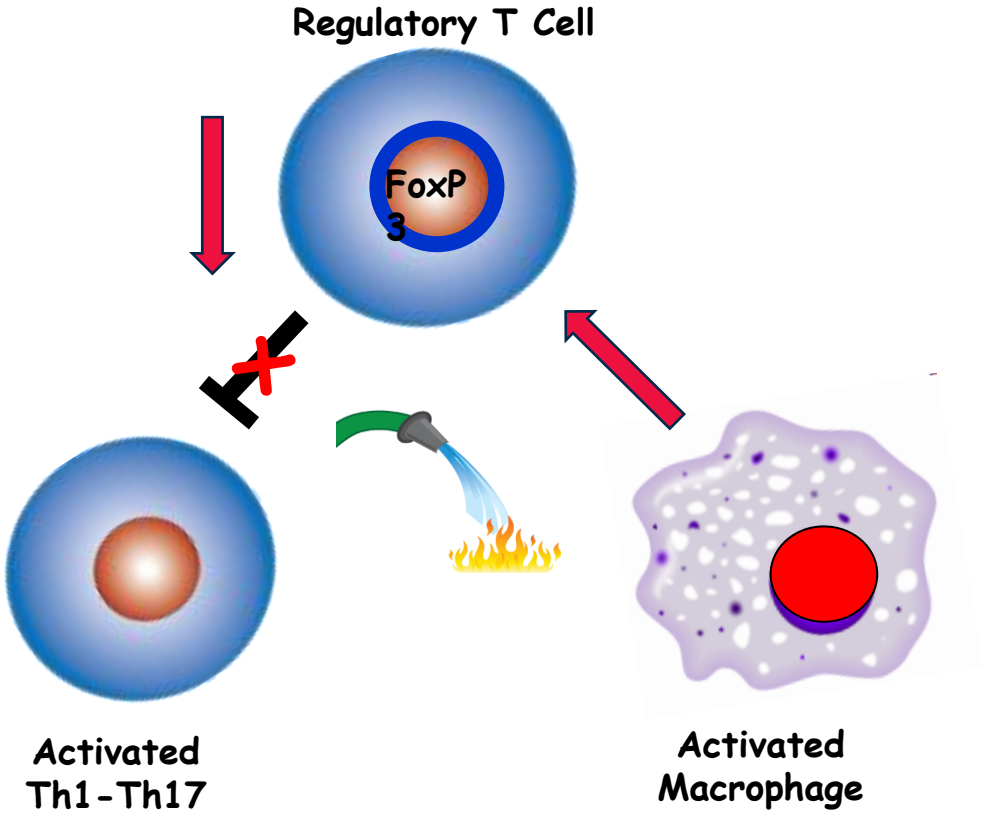
Source: Siklos L…Appel SH, 1996.

Ultrastructure of Neuromuscular Junctions in ALS (2 of 2)



Source: Siklos L…Appel SH, 1996.

Regulatory T Cells Suppress Neuroinflammation



Modulation of Pro-Inflammatory Signaling in Rodent Models Ameliorates Pathophysiologies Associated with Neurodegeneration

Figure A

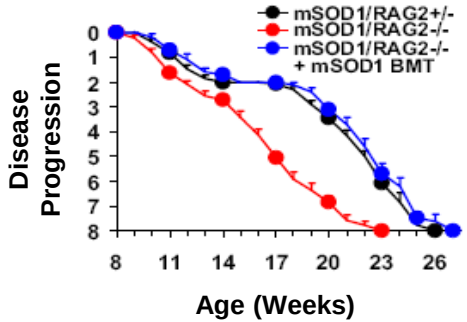
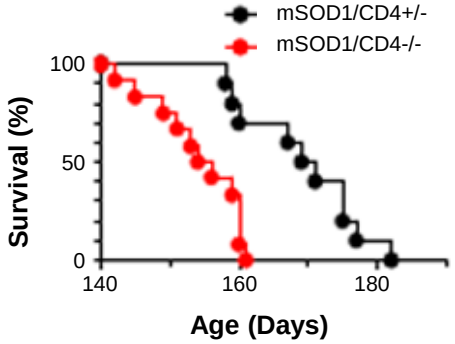


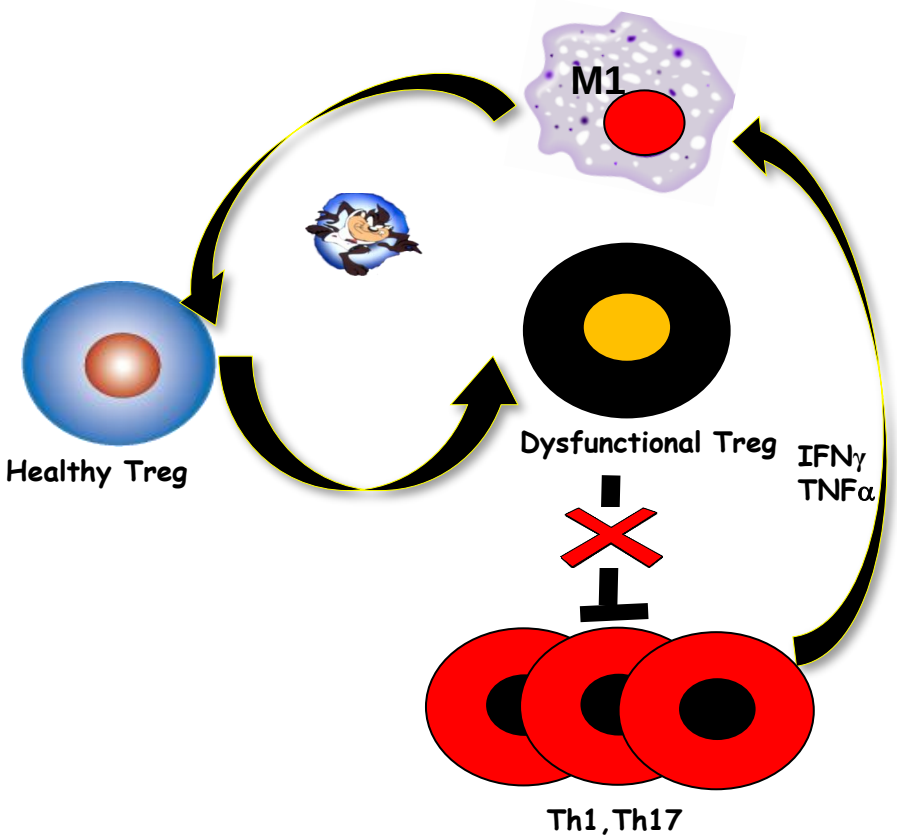
Figure B



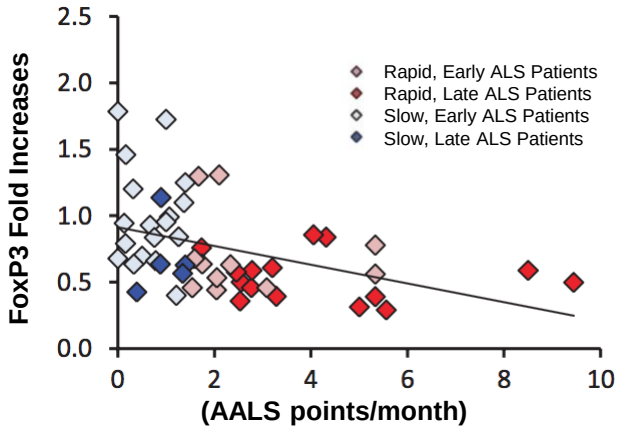
- **Genetic crossing of lymphocyte depleted RAG2$^{-/-}$ mice (Figure A) or CD4$^{-/-}$ mice (Figure B) into SOD1 ALS mice exacerbates disease progression suggesting a neuroprotective effect of CD4+ T cells in neurodegeneration**
- **Transplanting Regulatory T lymphocytes, suppresses neuroinflammation and prolongs survival by 88%**

Source: Beers, 2006; McGeachy, 2005.

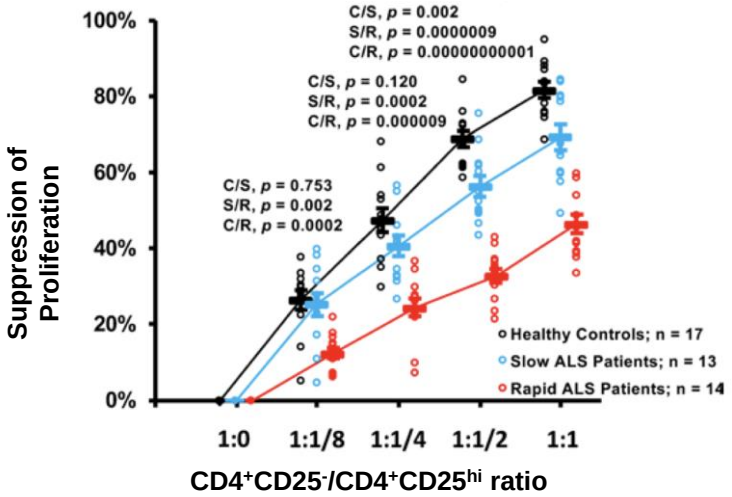
Treg Dysfunction Occurs in ALS, Alzheimer's Disease, and Parkinson's Disease



Treg Activity is Prognostic of Disease Progression in ALS



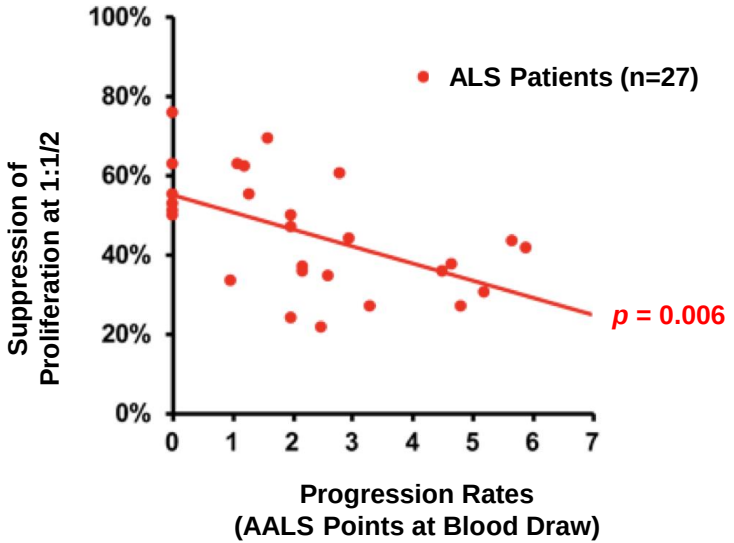
FoxP3 T lymphocyte levels correlate with ALS disease progression with high levels of FoxP3 predicting slower disease progression (p<0.005)

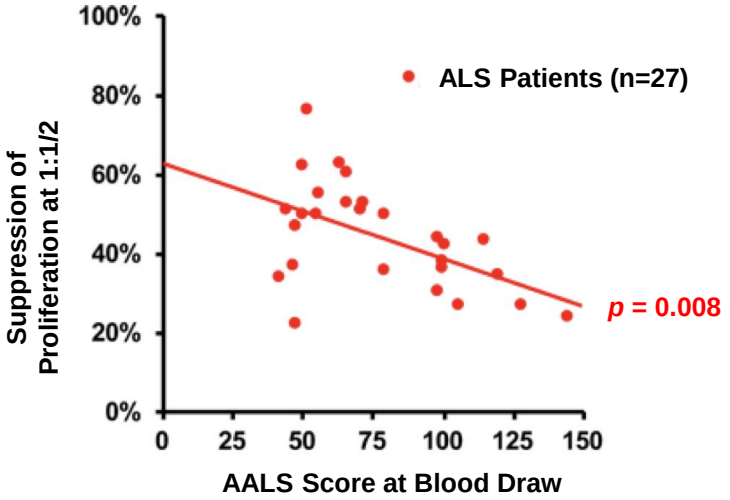


Loss of FoxP3 expression in Tregs from ALS patients results in lower suppressive function

Source: Henkel J…Appel SH, 2013; Beers D…Appel, SH 2017.

Tregs Influence ALS Burden, Progression Rate and Survival





Tregs are dysfunctional in ALS, with less suppressive function associated with greater ALS burden and faster disease progression

Source: Henkel J…Appel SH, 2013; Beers D…Appel, SH 2017.

Inflammatory Biomarkers & Neurofilament Light Chain Levels are Elevated in Serum of Patients with ALS

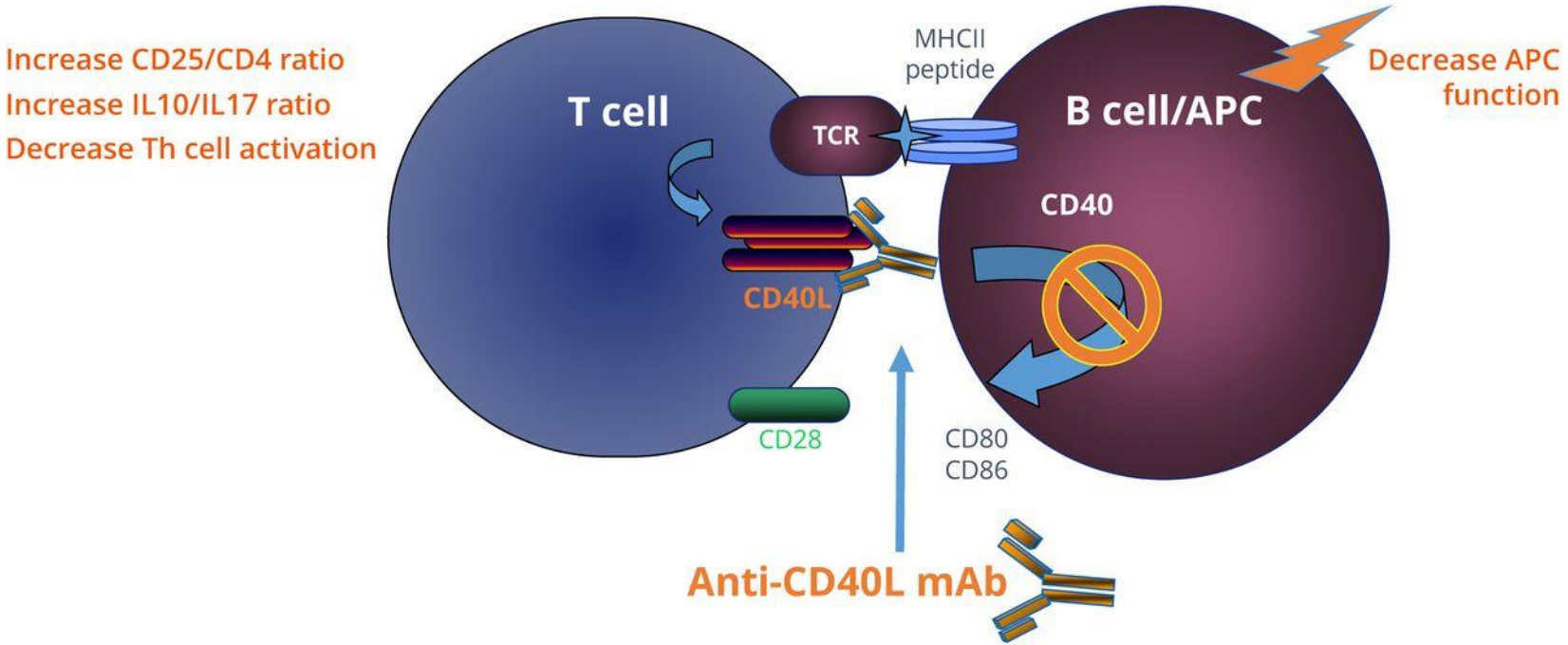
Serum Biomarker Levels: ALS Patients vs. Controls

Serum	Ctrl (n = 94)	ALS (n = 60)	*p* value
Nf-L (pg/ml)	30.20 ± 23.41	512.4 ± 417.4	**< 0.0001**
VCAM-1 (ng/ml)	647 ± 181	891 ± 366	**< 0.0001**
ICAM-1 (ng/ml)	485 ± 120	750 ± 297	**< 0.0001**
VEGF (pg/ml)	199.1 ± 232.5	150.0 ± 77.23	0.523
Eotaxin (pg/ml)	242.4 ± 143.3	284.5 ± 104.6	0.134
MCP-1 (pg/ml)	256.9 ± 96.94	373.8 ± 169.1	**< 0.0001**
IP-10 (pg/ml)	384.7 ± 289.5	640.2 ± 320.4	**< 0.0001**
IL-17a (pg/ml)	0.68 ± 0.53	1.38 ± 1.48	**< 0.0001**
TNF-α (pg/ml)	1.76 ± 0.72	4.99 ± 7.85	**< 0.0001**
IL-2 (pg/ml)	N.A	0.40 ± 0.41	
IL-10 (pg/ml)	0.29 ± 0.34	0.51 ± 0.19	**< 0.0001**
IL-8 (pg/ml)	106.1 ± 186.5	172.3 ± 354.9	0.395
IL-6 (pg/ml)	0.58 ± 0.58	2.0 ± 2.6	**< 0.0001**
IL-1β (pg/ml)	N.A	0.47 ± 0.73	
IFN-γ (pg/ml)	5.31 ± 5.22	2.96 ± 2.25	**< 0.0001**

- **Levels of both inflammatory biomarkers and Nf-L levels, have been found to be:**
  - i. **Elevated in ALS patients vs. controls across multiple studies, and**
  - ii. **Correlated with disease progression**

Source: Brodovitch, 2021.

Costimulatory Interaction of CD40/CD40L is Involved in T Cell Activation and the Pathogenesis of Neuroinflammatory Diseases



Source: Fadul, 2021.

Summary

- Neuroinflammation is increasingly recognized as an important mediator of disease progression in ALS patients and is characterized by reactive central nervous system microglia and astroglia, together with infiltrating peripheral monocytes and lymphocytes
  - Pro-inflammatory polarization and increased expression of pro-inflammatory cytokines (e.g., TNF-a, MCP-1, IL-1, IL-6, IL-17, En-raged, and others) have been demonstrated in ALS
  - Loss of Treg function correlates with poor disease outcomes in ALS
  - Elevated inflammatory biomarker levels have been found in ALS patients vs. controls across multiple studies, and have demonstrated correlation with disease progression
  - Neurofilament light chain levels in circulation are elevated in ALS and have demonstrated correlation with disease progression and survival

- Costimulatory interaction of CD40/CD40L is involved in T cell activation and the pathogenesis of neuroinflammatory diseases including ALS

- Reductions in pro-inflammatory cytokines, pro-inflammatory chemokines, and Nf-L levels in circulation, as well as ALSFRS/ALSFRS slope changes, may individually correlate with ultimate clinical benefit in ALS

UCSF Transplant Surgery
Department of Surgery

Kidney Transplantation

Flavio Vincenti, MD

Professor of Clinical Medicine and Surgery
Endowed Chair in Kidney Transplantation
University of California San Francisco

Kidney Transplantation Overview

Unmet Need

- Calcineurin inhibitors (CNIs) – cyclosporin and tacrolimus – revolutionized the field of transplantation, allowing transplant medicine to grow across transplant types, and providing meaningful treatment to thousands of people
- CNIs provide excellent 1 year patient and graft outcomes, but:
  - They are less effective against long term antibody mediated rejection
  - They are nephrotoxic and slowly harm the graft over time
  - They are associated with significant adverse effects including post-transplant new onset diabetes, tremors, infections, and hair loss
- ~5,000 Americans per year on the transplant waiting list die without getting a transplant

Co-Stimulatory Blockade Experience To Date

- Co-stimulatory blockers have demonstrated efficacy in the prevention of allograft rejection
- Belatacept is approved for use as an alternative to CNIs
  - Limited use due to black box warnings and mixed 1 year efficacy data
- Targeting CD40L may be a mechanistically more desirable approach than blocking CD80/86

Clear Clinical Regulatory Pathway

- Demonstrate non-inferiority to tacrolimus at 1 year
  - Look for superiority in terms of safety at 1 year, and superiority in terms of rejection and organ survival over the longer term

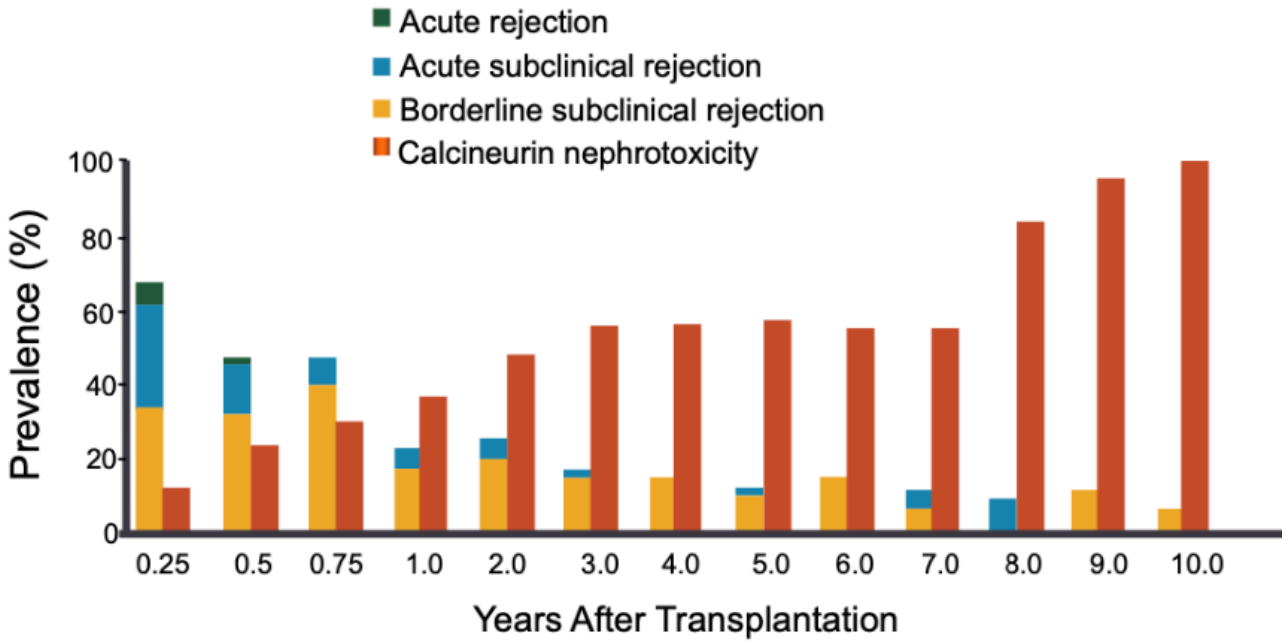
CNIs Have Been Associated with a Range of Short-Term Toxicities when used in Kidney Transplantation

Adverse Event (6 months post transplant)	Cyclosporin (n=336)	Tacrolimus (n=346)
NODAT / Impaired Fasting Glucose	26.0%	33.6%
Any renal impairment	23.1%	23.7%
Tremor	14.8%	21.7%
Any serious infection	24.4%	19.4%
Hypertension	13.9%	15.0%
Hirsutism / Hypertrichosis	8.9%	0.6%
Alopecia	1.2%	3.2%

Incidence of CNI related adverse events such as nephrotoxicity increase with time post transplant

Source: Vincenti, 2007.
Note: NODAT = New Onset Diabetes Mellitus After Transplantation.

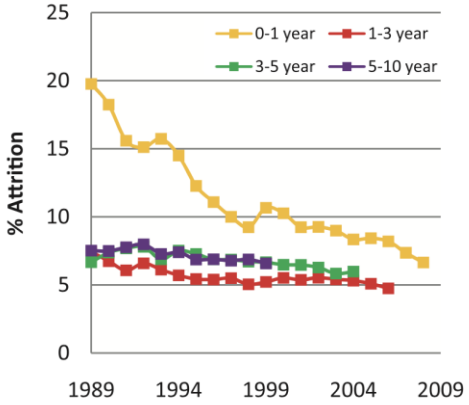
CNI Nephrotoxicity Over Time is a Leading Cause of Long-Term Transplant Graft Failure



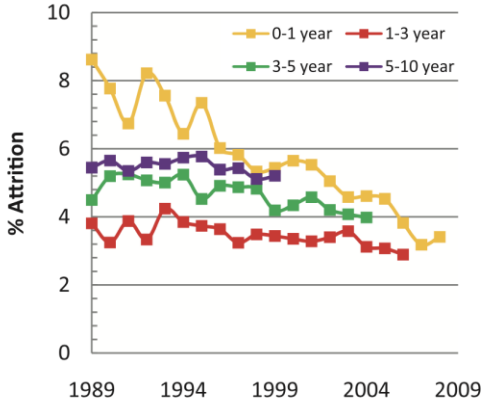
Source: Nankivell 2003; ATC 2018.

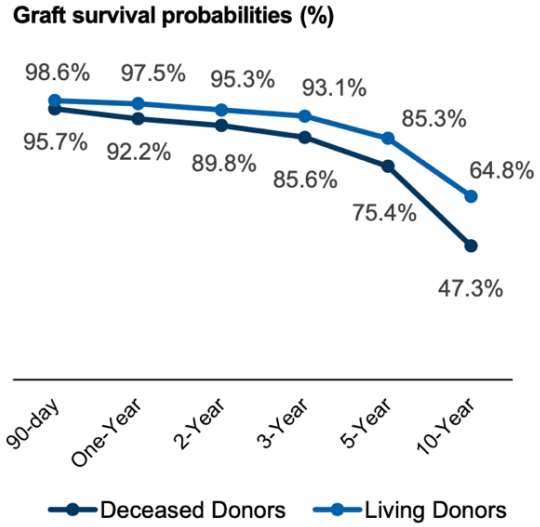
Long-Term Graft Failure Rates Have Not Substantially Improved in Decades With U.S. Average Graft Survival Remaining ~10 Years

Deceased Donor



Living Donor





Increasing the lifespan of transplanted kidneys would help alleviate both the shortage of organs for transplantation and the wait time for an available organ by decreasing the number of yearly re-transplants

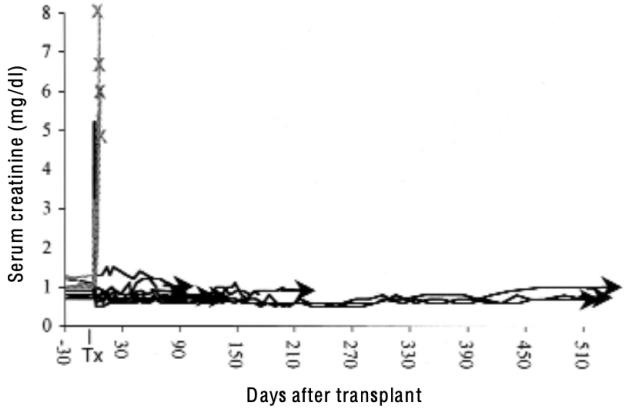
Source: Lamb 2011; ATC 2018; USRDS 2018

Clinical Development Experience with Costimulatory Blockade

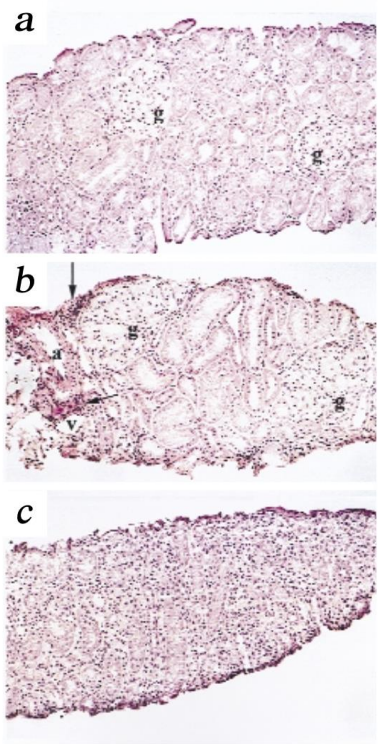
- Belatacept experience demonstrate the potential of a novel costimulatory blocker, but
  - Belatacept has suffered from safety concerns (e.g., first year kidney rejection data vs. SoC, PTLD risk, and Black Box in liver transplantation) as well as reported supply shortages
- Clinical development currently requires concomitant immunosuppressive regimens
  - A steroid taper maybe required as part of costimulatory blockade
  - Antiproliferative agents may ultimately not be needed as a component of long-term maintenance therapy
- Induction therapy with robust T cell depletion is necessary to prevent graft rejection with costimulatory blockade
  - Kidney transplantation costimulatory blockage experience has demonstrated better results with T lymphocyte-depleting rabbit-derived antithymocyte globulin (rATG) induction therapy than with an IL-2 receptor antagonist (IL2RA)
  - Choice of induction therapy may be less relevant with CNIs than with costimulatory blockers

Long Term Renal Transplant Function and Survival in Nonhuman Primates with Anti-CD40L Treatment

Monotherapy anti-CD40L treatment (5c8) prevents graft rejection and maintains graft function (as measured by serum creatinine) in nonhuman primates for over 500 days

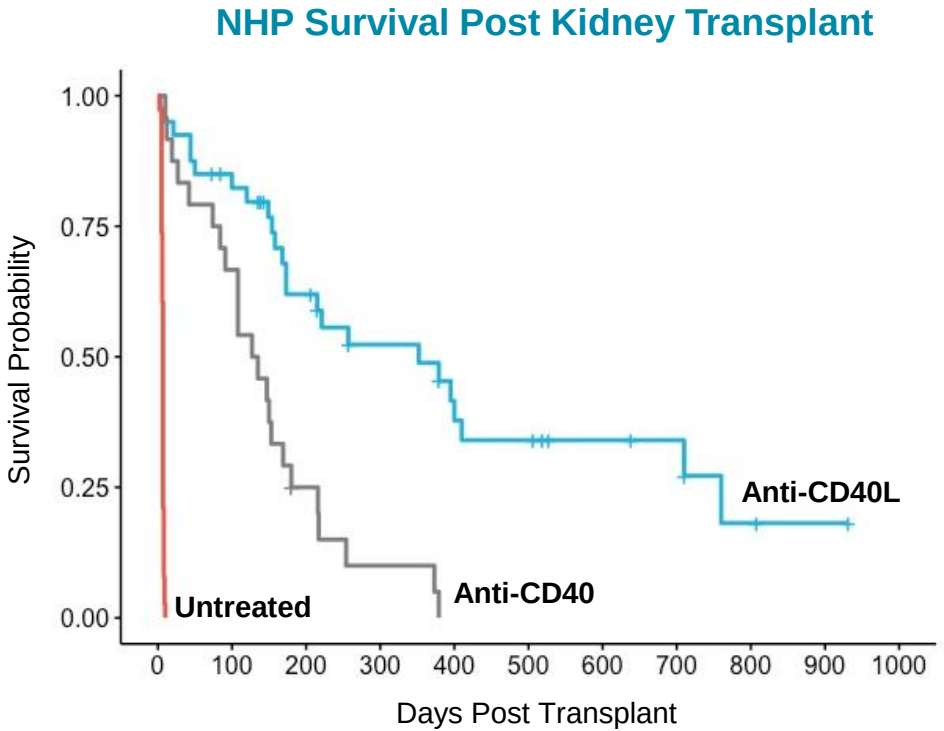


- Transplanted grafts display normal glomerular and tubular architecture at 400 days but have mononuclear infiltrates starting at 28 days (Panel a)
- Grafts have normal vascular architecture with no intimal hyperplasia or thickening and mild perivascular infiltrate (Panel b) as opposed to untreated, rejecting grafts (Panel c)



Source: Kirk 1999.

Inhibition of CD40L Improved Survival vs. CD40 Inhibition in Non-Human Primate (NHP) Kidney Transplantation Monotherapy Studies



In aggregated data from published studies, **NHPs receiving anti-CD40L** (e.g., 5c8, AI794, IDEC-131) immunomodulation monotherapy post kidney transplantation **had longer average survival** than both those receiving anti-CD40 monotherapy (e.g., 4D11, cH5D12, Chi220, ASKP1240) and untreated controls

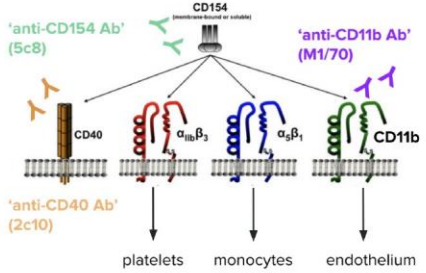
Source: Perrin 2022.
Note: **Meta-analysis not based on head-to-head studies.** Differences between any individual programs may vary.

Eledon Pharmaceuticals

Recent NHP Study Demonstrated Advantage of Blocking CD40L vs. CD40R in Xenotransplantation

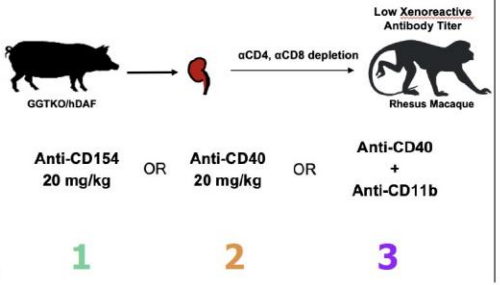
Combined CD11b/CD40 Blockade is Superior to CD40 Blockade Alone in Prolonging Survival in Pig-to-Nonhuman Primate Renal Xenotransplantation

How does combination CD11b/CD40 blockade affect graft survival in a pig-to-NHP model of renal xenotransplantation?

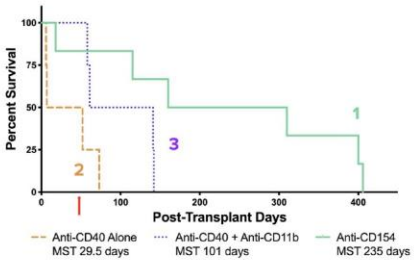


Pig-to-NHP renal xenotransplantation performed to one of three groups:

(1) anti-CD154; (2) anti-CD40 alone; (3) anti-CD40 plus anti-CD11b



- Treatment with anti-CD11b mitigates early xenograft rejection seen with anti-CD40 therapy
- CD11b acts as an additional ligand of CD154 through which rejection signals can bypass CD40 blockade



Emory University, University of Minnesota;
Faber, Lovasik, Matar, Breeden, Kim, Adams

Abstract number 2

Source: Adams @ ACT 2021.

Summary

- Since the beginning of their use in the 1980s, CNIs have revolutionized transplantation maintenance therapy but despite excellent short-term results with current immunosuppressants, there remains an unmet medical need for new regimens to both lower side-effect burden and improve medium and long-term graft survival
  - CNI toxicity may play a role in shortening long-term graft survival
  - Improving graft survival would help alleviate re-transplants and thus the ongoing organ shortage
- Co-stimulatory blockers have demonstrated efficacy in the prevention of allograft rejection in both humans and animal models
  - Approval of belatacept in 2011 demonstrated the potential of a biological non-nephrotoxic maintenance immunosuppression by blocking co-stimulatory signals, but adoption has been hampered by a black box warning, cases of PTLD, mixed early data, and limited availability
- Co-stimulatory blockers, particularly against CD40-CD40L (CD154), have been highly effective in animal transplant models
  - In animal models, anti-CD40L immunomodulation monotherapy post kidney transplantation led to longer average animal survival than with anti-CD40 immunomodulation monotherapy

Islet Cell Transplantation

Piotr Witkowski, MD, PhD

Associate Professor of Surgery
Director, Pancreatic and Islet Transplant Program
University of Chicago

Brittle Type 1 Diabetes: A Significant Unmet Need

- ~1.3M Americans live with Type 1 diabetes, ~70,000 (5%) estimated to have “BT1D, ” the Brittle form of Type 1 Diabetes
- Overall, people with Type 1 diabetes experience at least one episode of severe hypoglycemia per year
- BT1D patients have difficult-to-manage glucose levels with severe blood glucose fluctuations and multiple episodes of severe hypoglycemic unawareness despite optimized treatment

- Severe hypoglycemia can be fatal in addition to causing coma, seizures and brain damage
  - Accounts for up to 10% of deaths among young people with Type 1 diabetes
- Insulin-mediated hypoglycemic events account for ~100,000 U.S. emergency department visits per year
- Continuous glucose monitoring (CGM) helps but use decreases rapidly over time
- Comparison of impaired awareness of hyperglycemic events post islet cell transplant compared to a control group using CGM demonstrated less frequent events in the ICT group (12%) compared to the CGM group (33%)

Source: Brittle Diabetes Foundation; NIDDK; Pokrywczynska, 2017; Cartwright 2011; Geller,2014; Reno, 2019; Lin, 2019; Chase, 2010; Nakamura, 2020.

Islet Cell Transplantation: State of the Art

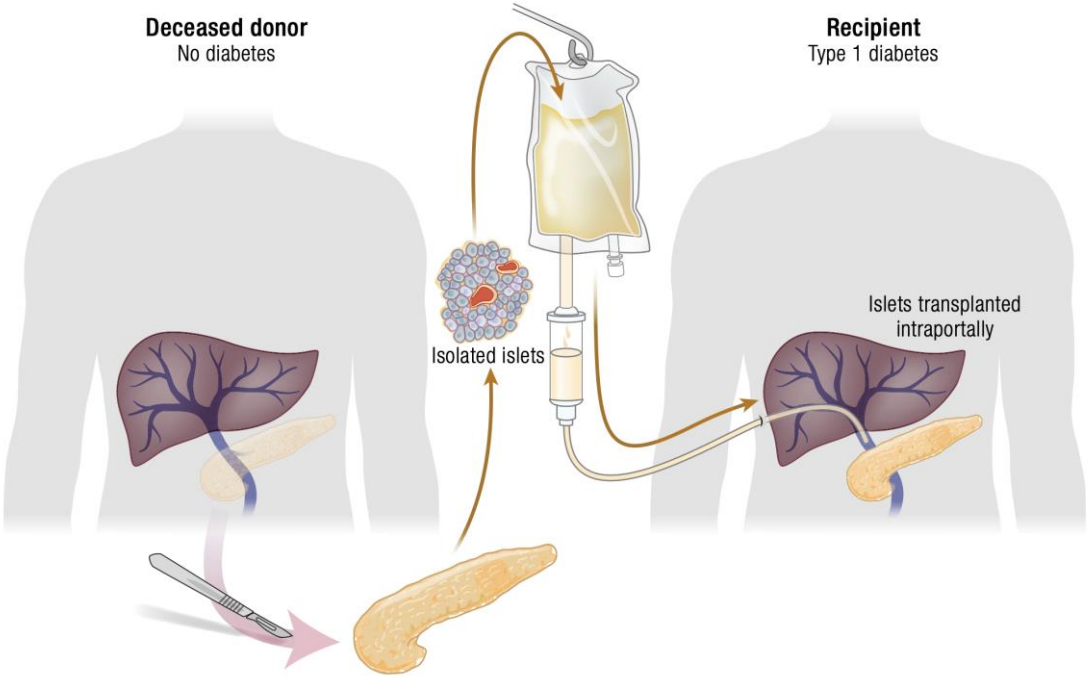
Current Status

- Offers hope for a functional cure for Type 1 diabetes
  - Some patients have been insulin free for years post transplant
- Current approach limited in part due to:
  - Cell quality and quantity
  - CNIs, the backbone therapy for prevention of rejection, are both nephrotoxic and toxic to islet cells
  - As a result, multiple donor pancreases and often transplant procedures are necessary for optimal outcomes
  - Regulatory constrains (BLA is not approved for cell production) and a related lack of reimbursement system in US

Future Vision

- Adopted and scalable functional cure for Type 1 diabetes
  - Single procedure for optimal outcome
- Standardized high quality cells
  - Potentially in abundance from a stem cell derived approach
- Replace CNIs in prevention of rejection with effective agent that is not toxic to the cells and promotes a more tolerogenic environment to reduce the long term need for immunosuppression
  - Opportunity for tegoprubart, the first therapeutic with an open US IND for Islet Cell Transplantation

Islet Cell Transplantation Procedure

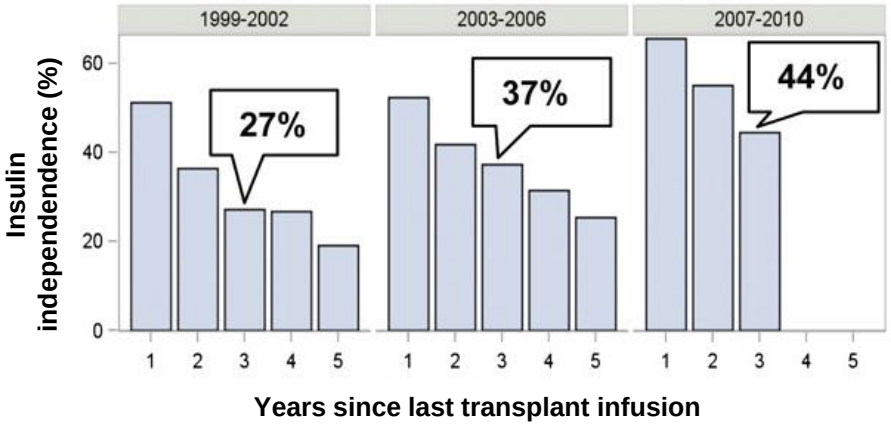


First successful human islet allotransplantation resulting in long-term reversal of diabetes was performed at the University of Pittsburgh in 1990

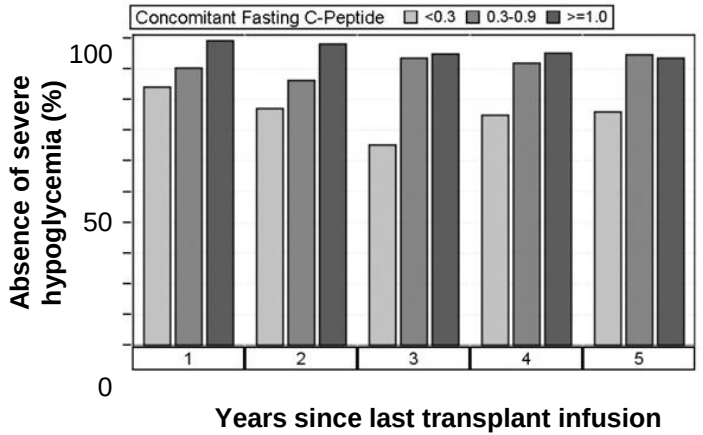
Source: Rickels, 2019.

Islet Cell Transplantation Success Has Improved Over Time in People with Type 1 Diabetes

Insulin Independence Post Transplant



No Severe Hypoglycemia Post Transplant



- 64% of patients required two to four, or more, transplant infusions
- Calcineurin inhibitors are necessary but associated with a wide array of side effects

Source: Barton, 2012.

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North American Experience with Islet Cell Transplantation

Islet Cell Transplantation (CIT-07)

American Diabetes Association. Diabetes Care

Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia

Islet Cell Transplantation Post Kidney Transplant (CIT-06)

American Journal of TRANSPLANTATION

AST American Society of Transplantation ASTS

Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes

Center	Approach	5-Year Insulin Independence	Year	Reference
Minnesota	Anti-CD3 + etanercept	70% (at Yr. 7)	2011	Hering *et al.*
Minnesota CITR	T cell depletion + anti-TNF	50%	2012	Bellin *et al.*
Edmonton	Alemtuzumab + Tac + MMF + anakinra + etanercept	60%	2012	Shapiro *et al.*
UCSF	ATG + efalizumab / belatacept + SRL or MMF	80% (at Yr. 4)	2012	Posselt *et al.*
UIC	Tac/SRL or MMF + exenatide + etanercept	60%	2012	Gangemi *et al.*
Lille, France	Tac/SRL	50%	2012	Vantyghem *et al.*
Geneva, GRACIL	ATG + Tac/SRL	50%	2012	Berney *et al.*
Univ. of Penn.	**ATG + SRL/Tac + etanercept (CIT07)**	**70%**	**2017**	**Rickels @ IPITA**
Univ. of Chicago	**ATG + Tac + MMF + Reparixin**	**50%**	**2021**	**Witkowski @ ADA**

Source: Witkowski.

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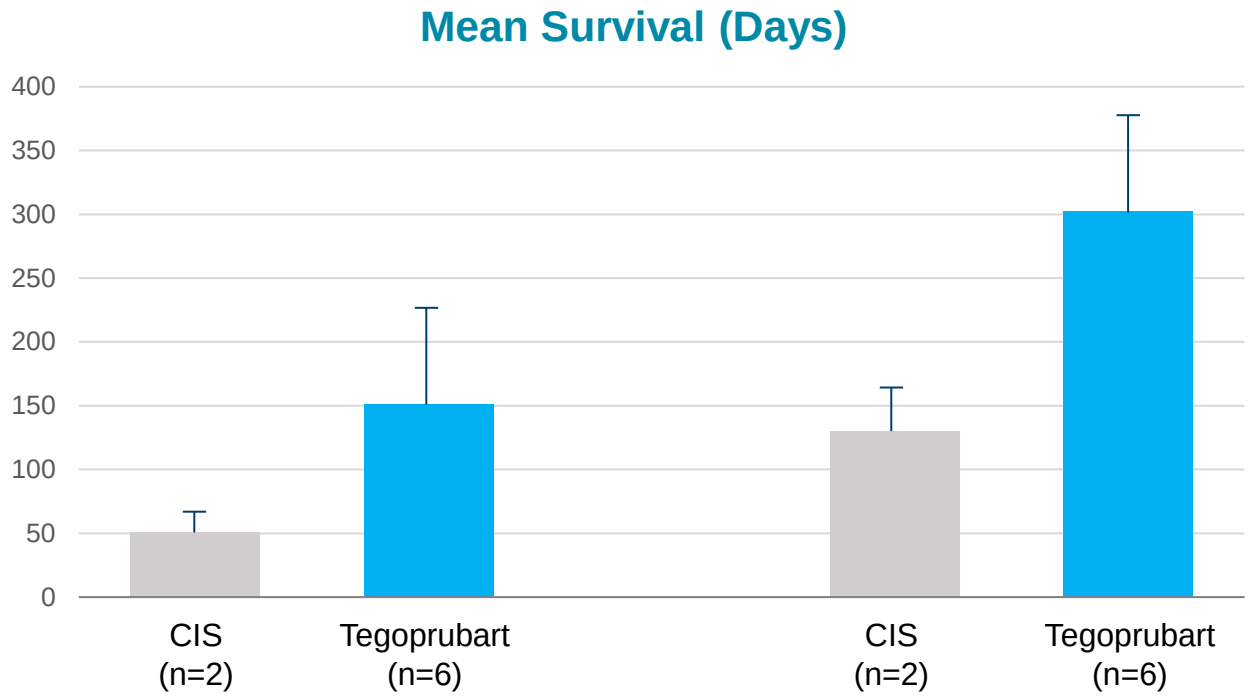
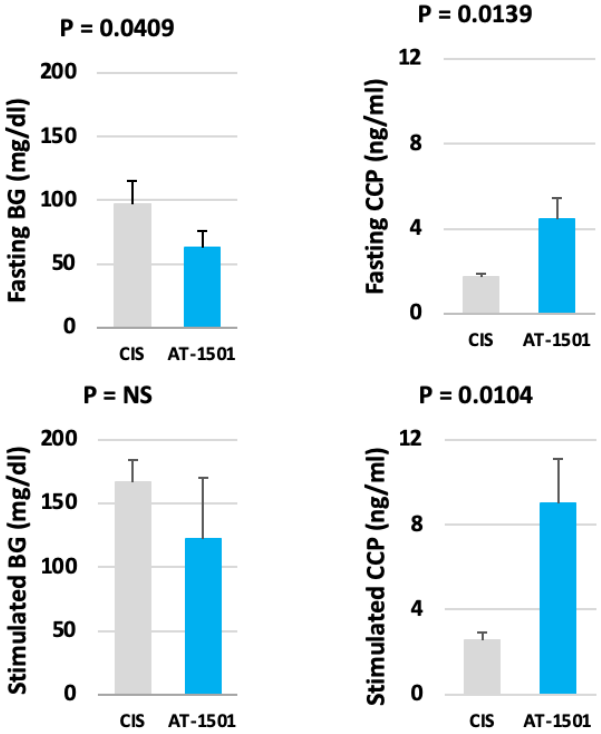
Tegoprubart Demonstrated Potential for Insulin Independence in a Non-Human Primate Proof of Principle Study

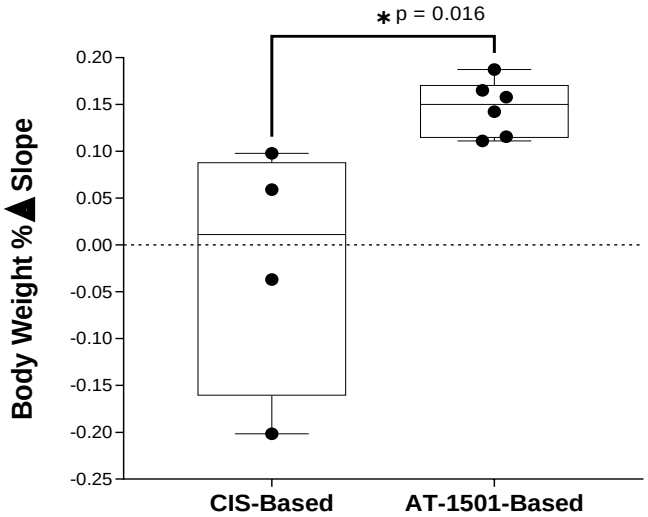


Note: CIS = CNI containing regimen.
Source: Kenyon @ IPITA 2021.

Tegoprubart was Associated With Better Metabolic Control as Well as Healthier Animals Overall as Demonstrated by Body Weight

Tegoprubart (AT-1501) vs. CNI Regimens (CIS) in NHP Islet Cell Transplantation Model





Source: Kenyon @ IPITA 2021.

Summary

- A significant unmet needs exists in the treatment of people with T1D, particularly for persons living with the Brittle form and experiencing severe hypoglycemia unawareness
- Significant progress has been made in the isolation of high quality donor derived islet cells
  - New technologies for beta pancreatic cell replacement are in development and provide hope for a new source of cells, but these still have limited clinical experience
- Islet cell transplantation has demonstrated the ability to improve HbA1c, decrease or eliminate the need for exogenous insulin, and improve the quality of life for people
- Current state of the art in islet cell transplant is hampered by the toxicities associated with immunosuppression and the need for multiple islet cell transplants to reduce HbA1c and maintain stable insulin production from transplanted islets
- Inhibition of CD40L in nonhuman primates suggests an opportunity to improve islet cell survival and function after islet cell transplant vs. current standard of care
- Tegoprubart has potential to advance islet cell transplant field by:
  - Improving islet cell graft survival
  - Reducing side effects associated with standard of care regimens including CNIs
  - Providing a potential backbone for tolerance induction (protocols eliminating need for long term immunosuppression) as well as for xeno transplantation

Tegoprubart Clinical Development Plan

Jeff Bornstein, MD

Chief Medical Officer

Tegoprubart: Pipeline Overview

Product Candidate	Indication	Development Stage				Anticipated Milestones
		Pre-clinical	Phase 1	Phase 2	Phase 3	
Tegoprubart (AT-1501)	**Amyotrophic Lateral Sclerosis (ALS)**					Phase 2 top-line data in 2Q2022
	Kidney Transplantation					Enroll first Phase 1b patient Interim data readout late 2022
	Islet Cell Transplantation for Type 1 Diabetes					Enroll first Phase 2 patient Interim data readout late 2022
	IgA Nephropathy					Enroll first Phase 2 patient Interim data readout late 2022

Note: Development plans and timelines may change, including based on US and global regulatory interactions.

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Phase 2 ALS Study Design

DESIGN

- 12-week, open label, multiple ascending dose level study
- Four dose cohorts of up to ~18 patients each
- Each subject serves as own control by comparing changes from baseline

PLANNED DATA GENERATION

- **Safety & tolerability**
- **Biomarkers of CD40L target engagement**
  - e.g., CXCL13
- **Pro-inflammatory chemokines and cytokines upregulated in ALS**
  - e.g., TNF-α, MCP1, IL-6, IL-1, En-raged
- **Exploratory endpoints**
  - e.g., ALS Functional Rating Scale, respiratory function, Neurofilament Light Chain

Note: Development plans may change, including based on US and global regulatory interactions.

Phase 1b Kidney Transplantation Study Design

DESIGN

- 52-week, open label, single dose level study
- 6 – 12 subjects undergoing kidney transplantation at multiple sites in Canada and the United Kingdom
- Kidney transplant using standard induction therapy plus maintenance therapy with tegoprubart as a replacement for CNIs (tacrolimus)

PLANNED DATA GENERATION

- **Safety & tolerability**
- **PK/PD**
- **Graft survival & function**
- **Biopsy proven acute rejection**
- **Immune cell infiltrate of graft biopsy**
- **Biomarker measures of kidney injury and rejection risk**

Note: Development plans may change, including based on US and global regulatory interactions.

Phase 2 Islet Cell Transplantation for T1D Study Design

DESIGN

- 52-week, open label, single dose level studies
- Initial group of up to 6 subjects with Type 1 Diabetes (T1D) at a Canadian and at an American site
- Islet cell transplant combined with induction therapy plus tegoprubart and mycophenolate mofetil (MMF) every third week by IV infusion

PLANNED DATA GENERATION

- **Safety & tolerability**
- **Graft function & insulin independence**
  - e.g., C-peptide, HbA1C
- **Number of hypoglycemic events**
- **Need for repeat islet cell transplant(s)**

Note: Development plans may change, including based on US and global regulatory interactions.

Phase 2 IgAN Study Design

DESIGN

- 96 week open-label, dose-ranging trial
- Primary endpoint at week 24
- Up to 42 subjects with IgAN in low dose and high dose cohorts
- Elevated proteinuria (>0.75g / 24 hours) despite optimized ACE / ARB therapy

PLANNED DATA GENERATION

- **Safety & Tolerability**
- **Change in protein / UPCR**
- **Change in eGFR**
- **Comparison of efficacy in low dose vs. high dose of tegoprubart**

Note: Development plans may change, including based on US and global regulatory interactions.

Q&A

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