University of Iowa
Stead Family
Children's Hospital

C3 Glomerulopathy

Current Care

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Disclosures

University of Iowa Stead Family Children's Hospital

The following includes a list of current (within the last 24 months) affiliations:

Affiliation / Financial Interest	Organization
Associate Director	Molecular Otolaryngology and Renal Research Laboratory
NIH	1R01DK110023-01A1
Site Investigator	ChemoCentryx
Site Investigator	Achillion Pharmaceuticals
Site Investigator	Alexion Pharmaceuticals
Site Investigator, Research Funding	Novartis
Site Investigator	Retrophin
Advisory Board	BioCryst

My conflicts are managed by a University of Iowa mandatory conflict plan.
Both prior and current relationships are on record at the University of Iowa's Conflict in Research Office:
https://coi.research.uiowa.edu/

Objectives

- Review current evaluation and therapy of C3 Glomerulopathy
- Review treatment guidelines for C3 Glomerulopathy
- Efficacy of current treatment approaches to C3 Glomerulopathy

Current Therapeutic Approach

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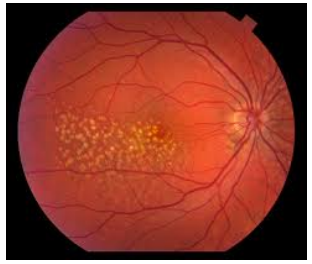
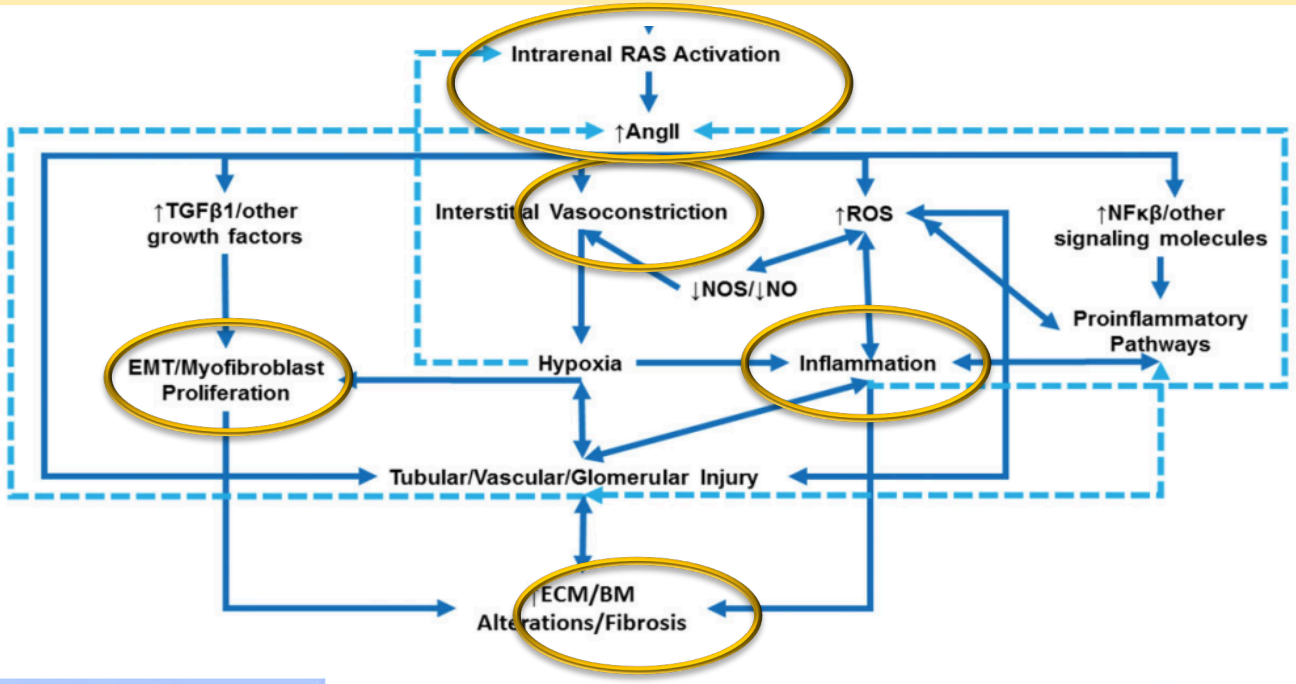
1. Supportive
   a. Blood Pressure Control
      i. Direct pressure related damage to renal blood vessels
      ii. Blockade of renin effects
   b. Urine protein control
   c. Base-line exam
      a. Eye Exam (10% will have Drusen)





2. Diagnostic Workup

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

Functional assays	CH50, AP50, FH function
Quantification of complement components and regulators	C3, C4, FI, FH, FB, Properdin
Measurement of complement activation	C3d, Bb, sMAC
Autoantibodies	Anti-FH, anti-FB, nephritic factors (C3, C4, C5)
Genetic testing	C3, CFH, CFI, CFB, CFHR-5 MLPA
Plasma cell disorders‡	Serum free light chains, serum and urine electrophoresis, and immunofixation†
Immunofluorescence studies on kidney biopsy specimen	IgA, IgG, IgM, C1q, C3, fibrinogen, kappa, lambda, C4d (usually bright C3 negative or minimal Ig, negative C4d)

Expert-Based – Kidney Disease Improving Global Outcomes

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Treatment of C3 Glomerulopathy

All Patients

- Optim… …trol
- Opt… …ormal growth in child… …t in adults
- Lipid co…

Manage other disease related features

Moderately Active Disease

Urine protein over 500 mg/24 h despite support
or
Moderate inflammation on renal biopsy
or
Recent increase in serum creatinine suggesting r

Prednisone
Mycophenolate m…

Balancing steroid effect with side-effect

Severe Disease

Urine protein over 2000 mg/24 h despite immunosuppression and supportive therapy
or
Severe inflammation represented by marked endo- or extracapillary proliferation with or without crescent formation despite immunosuppression and supportive therapy
or
Increased serum creatinine suggesting risk for progressive disease at onset despite immunosuppression and supportive therapy

KDIGO CLINICAL PRACTICE GUIDELINE ON GLOMERULAR DISEASES

Methylprednisolone pulse dosing as well as other anti-cellular immune suppressants have had limited success in rapidly progressive disease

- Data are insufficient to recommend eculizumab as a first-line agent for the treatment of rapidly progressive disease

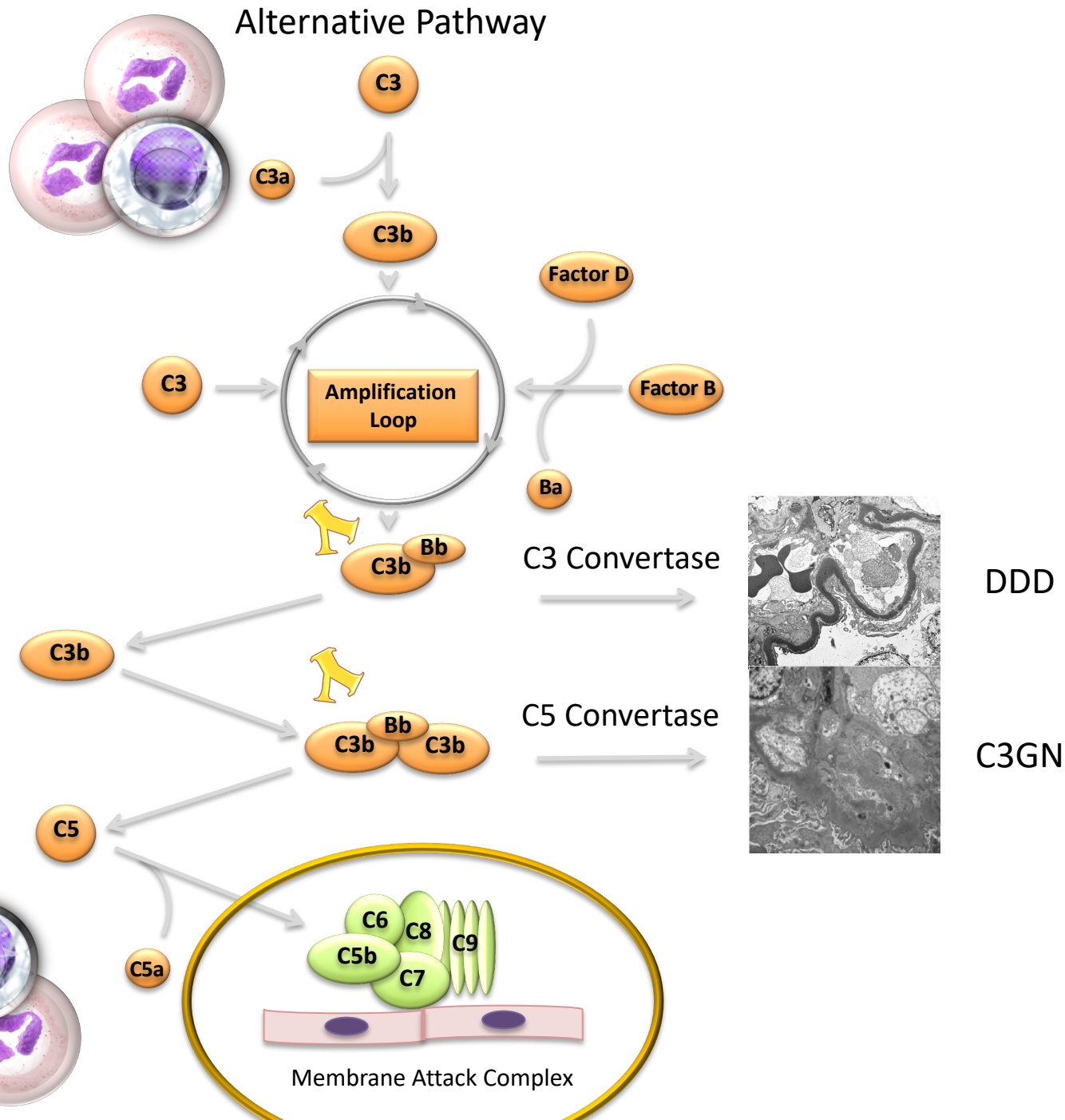
Kidney International (2017) 91, 539–551

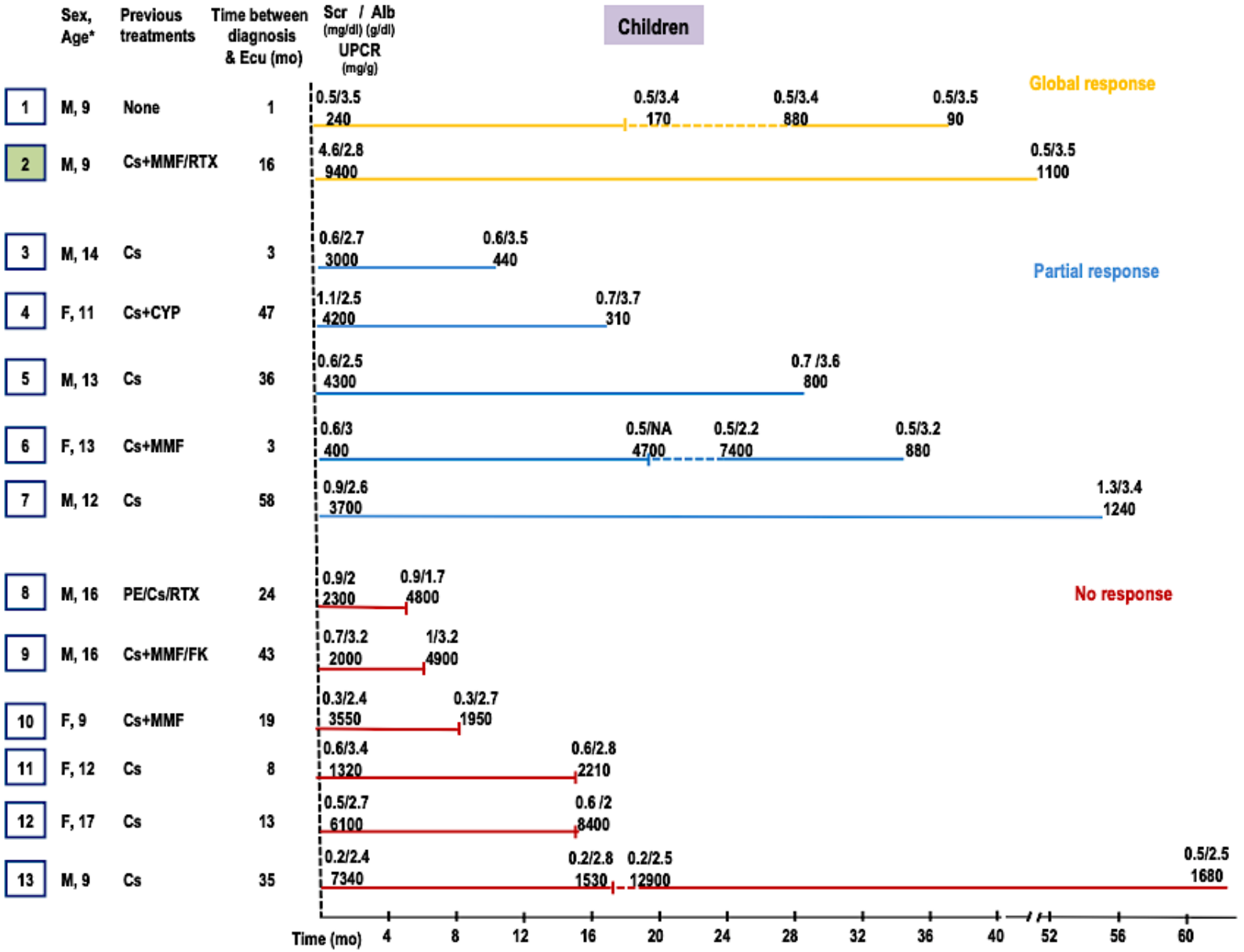
Current Therapeutic Approach

1. Mycophenolate mofetil and prednisone
   a. Cell-Mediated Immune Suppression

	Spanish
Number	60
Age	13-57 yo
Response	19/22 (86%)
	ESRD 0%

2. Terminal Complement Pathway (TP) Blockade
   1. Anti-inflammation – Anti-anaphylotoxin
   2. Neutralizing effect of TP





- 26 Patients
- Median duration 14 months of eculizumab
  - 6 (23%) with global response
  - 6 (23%) with partial response
  - 14 (23%) no response

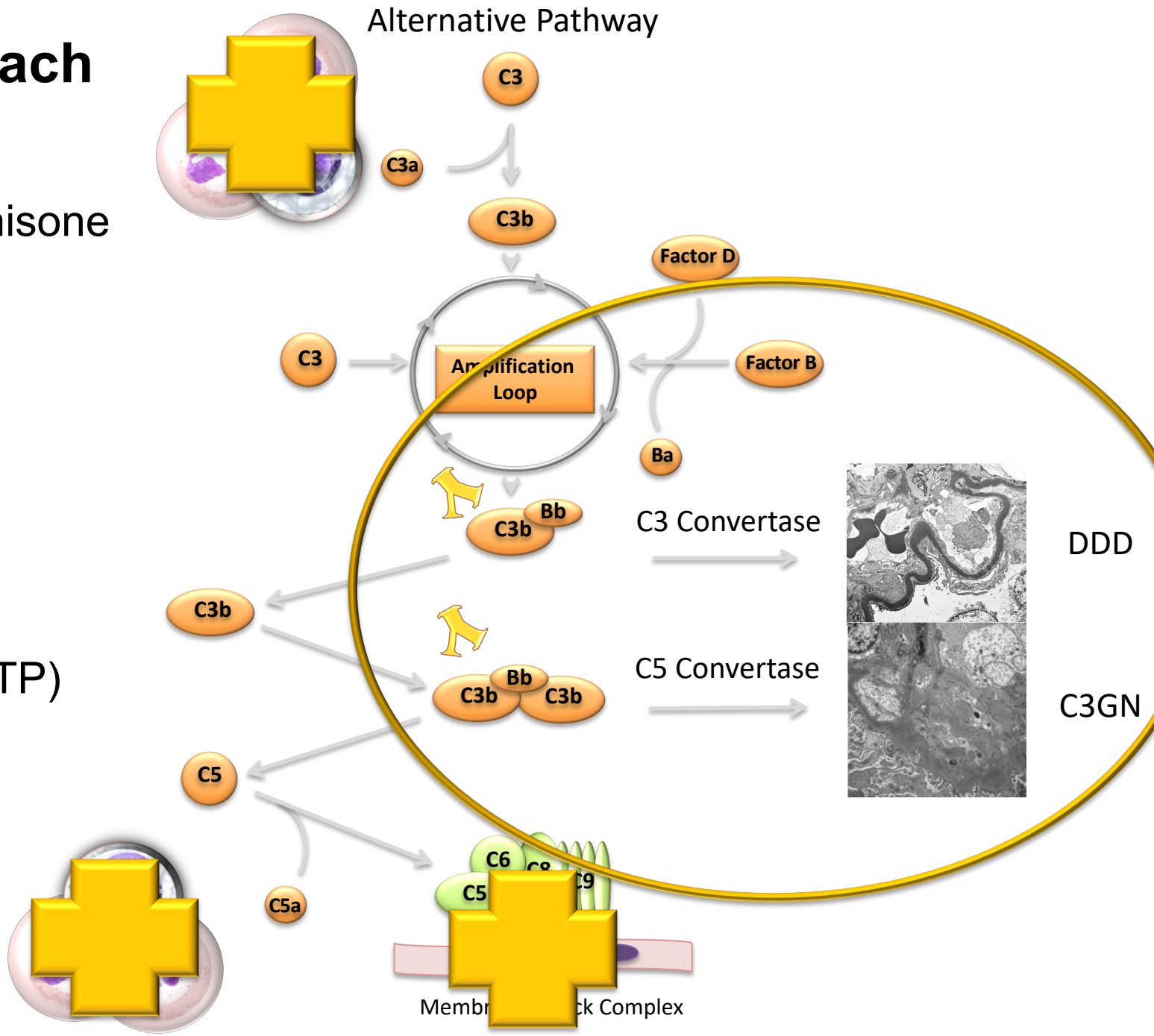
- Uncontrolled

Am J Kidney Dis. 2018 Jul;72(1):84-92

Current Therapeutic Approach

1. Mycophenolate mofetil and prednisone

2. Terminal Complement Pathway (TP) Blockade



Moving Forward

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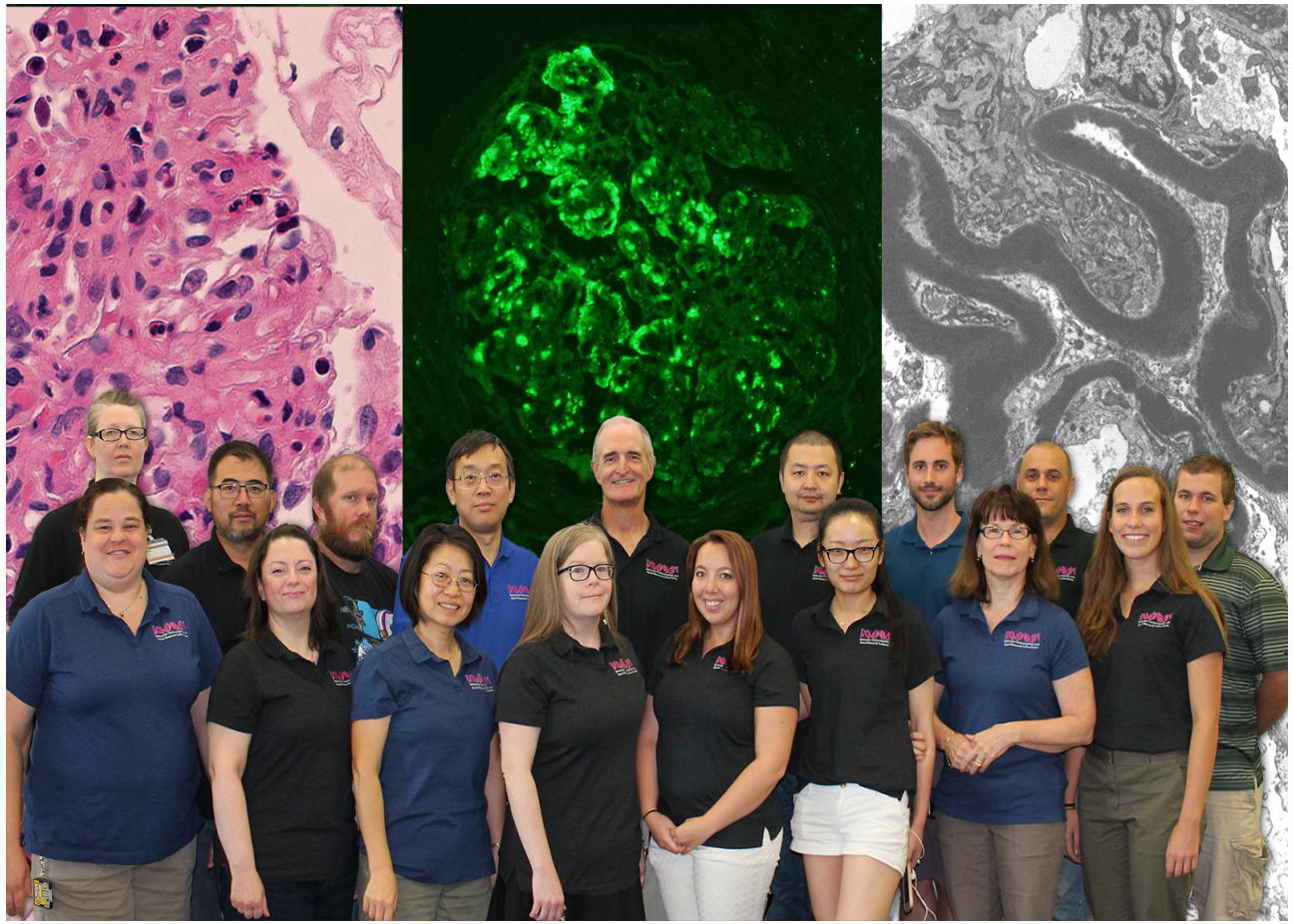
- Clear understanding of underlying drivers of disease in a given patient
  - i.e. understanding the role of the terminal complement pathway in disease
- Better understanding of role of "inflammation" in C3 Glomerulopathy manifestations
  - "Secondary" effects of complement dysregulation
- Controlled trials
  - Patient enrollment
    - Patient Tolerance - Safety
  - Positive Outcomes

Thank You

Good Health to All of You!

Division of Pediatric Nephrology

Molecular Otolaryngology and Renal Research Laboratory



I'm very thankful to have Two "Work" Families