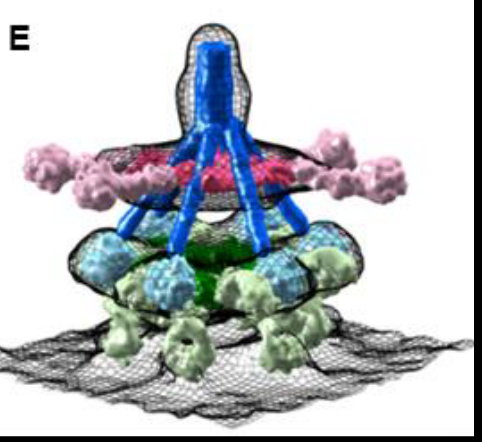
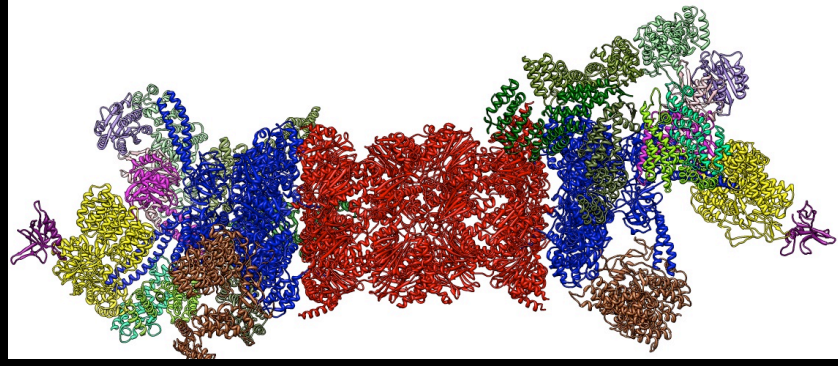
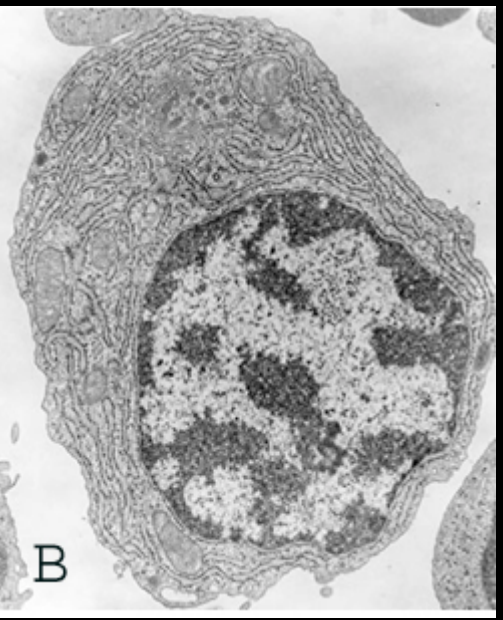
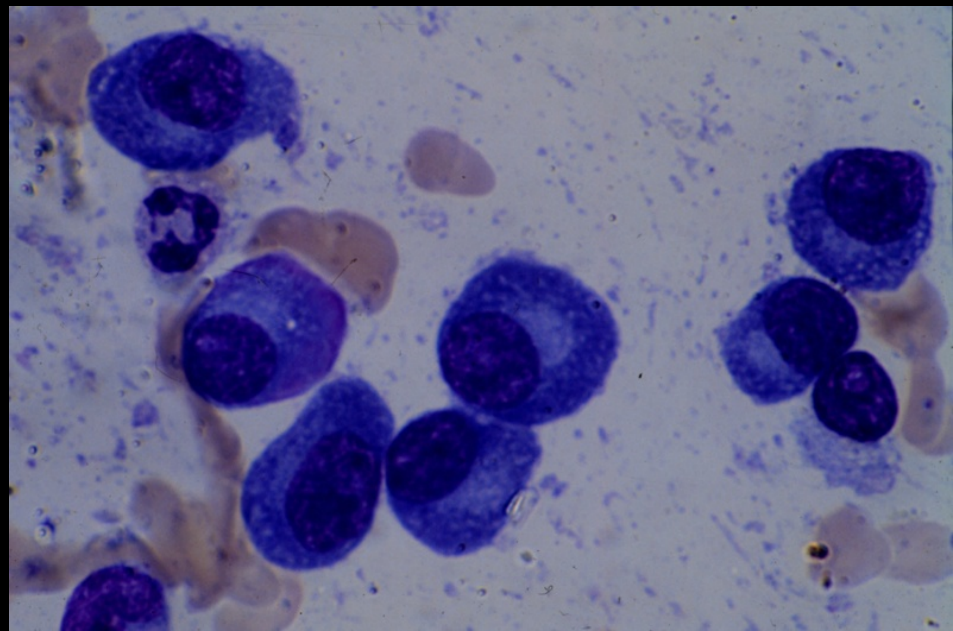




AMR Therapies:
Update 2010- Present





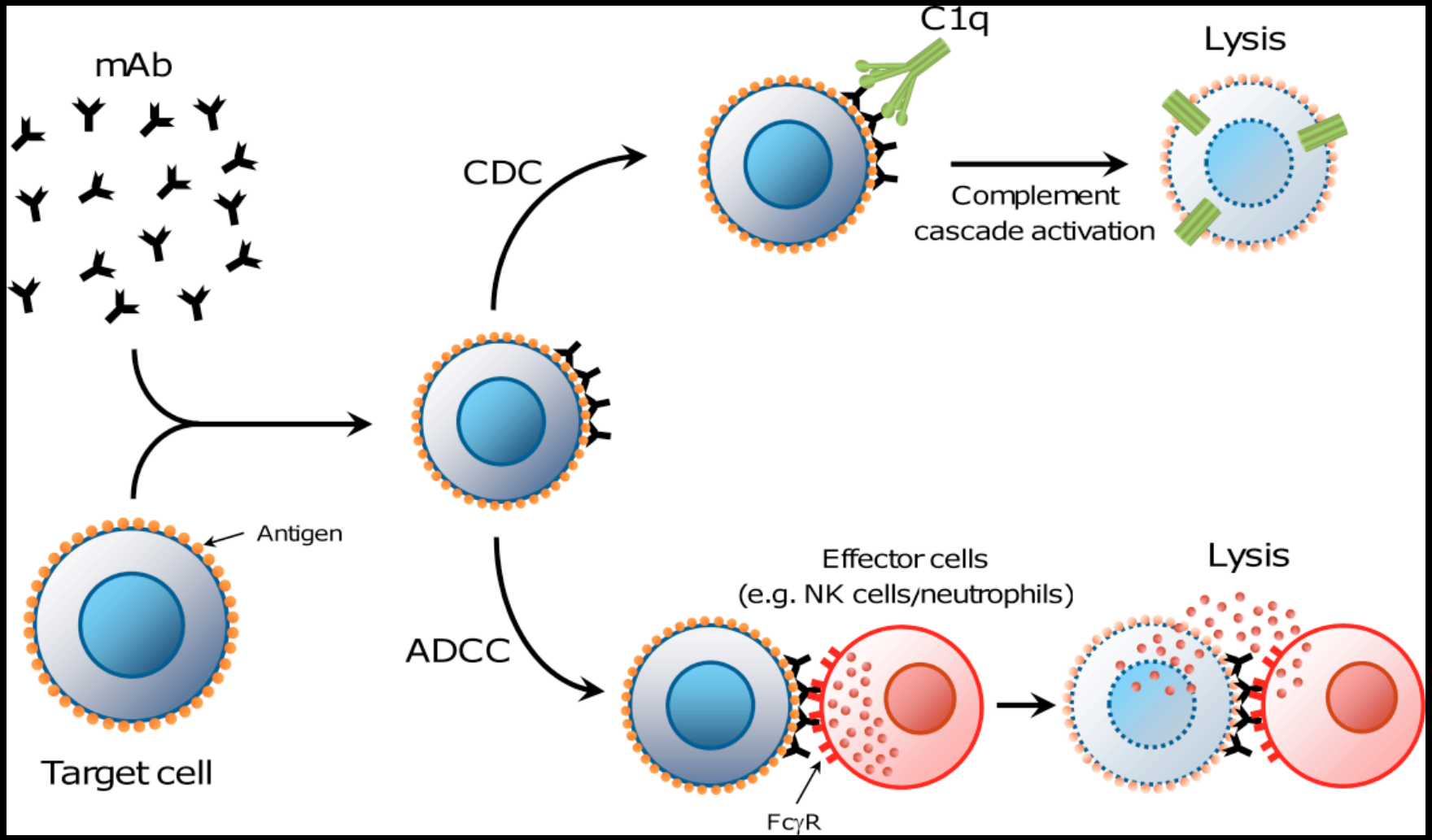
Conflicts of Interest

- Grants
  - Amgen
  - Bristol Myers Squibb
  - Genentech
  - Glaxo Smith Kline
  - Novartis
  - Sanofi

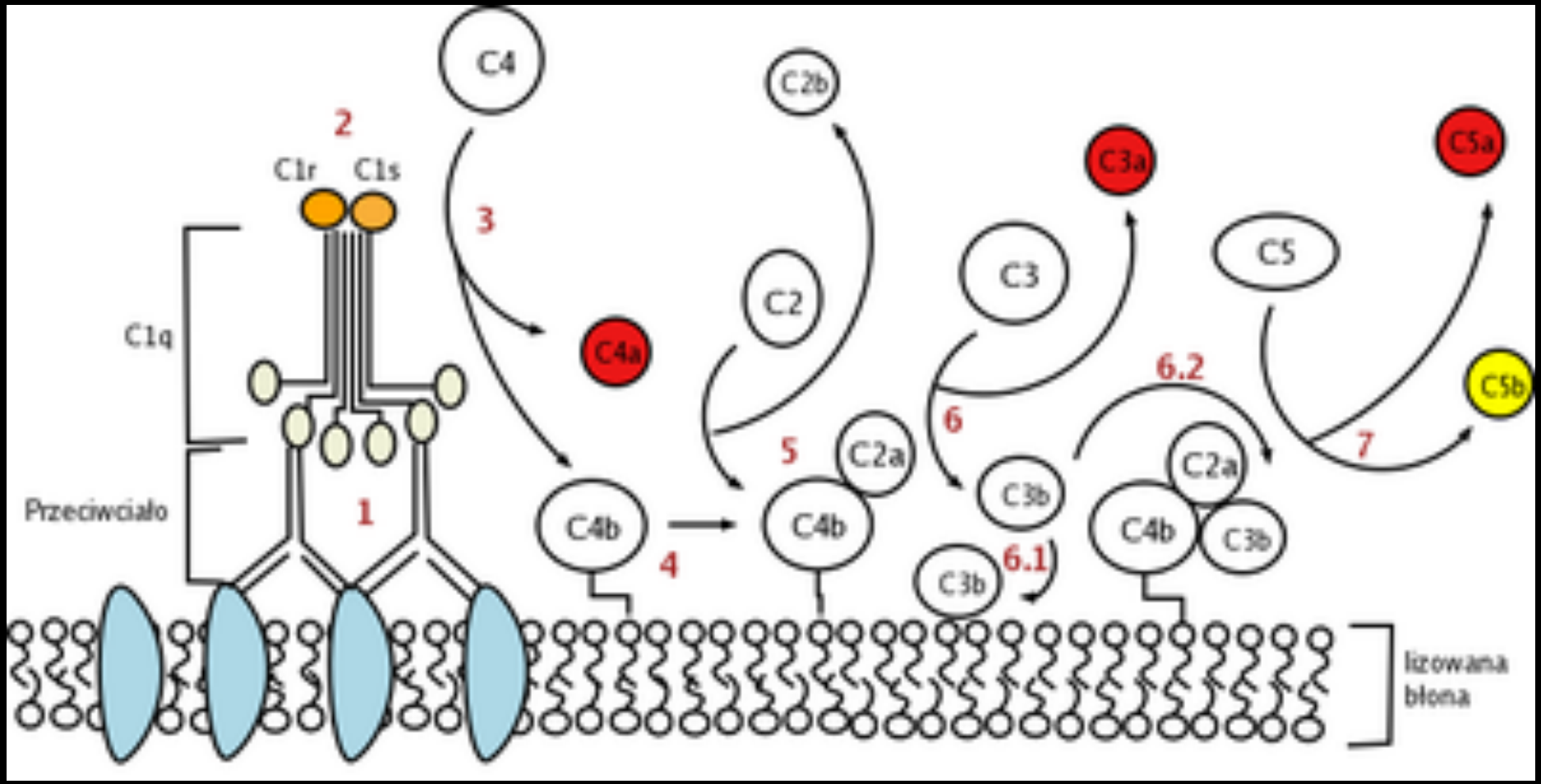
AMR Therapies

- Extracellular protein targets
  - Complement inhibitors
    - Distal
    - Proximal
  - Immunoglobulin
    - Enzymatic cleavage
    - Physical removal
- Plasma Cells
  - Proteasome inhibitors
    - Reversible
    - Irreversible

Anti-HLA Antibody Function: Transplant Injury



Proximal v Distal Complement Inhibition



Distal Complement Inhibition

- Eculizumab (*Soliris*) Alexion
  - Binds C5 and inhibits conversion to C5a
  - Prevents MAC generation

  - Approved 2007 for PNH
  - Approved 2011 of aHUS

  - “Most expensive drug” yearly cost $400k/yr

Distal Complement Inhibition

- Eculizumab (*Soliris*) Alexion

American Journal of Transplantation 2011; 11: 2405–2413
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2011.03757.x

Terminal Complement Inhibition Decreases Antibody-Mediated Rejection in Sensitized Renal Transplant Recipients

M. D. Stegall[a,*], T. Diwan[a], S. Raghavaiah[a], L. D. Cornell[b], J. Burns[a,c], P. G. Dean[a], F. G. Cosio[d], M. J. Gandhi[b], W. Kremers[e] and J. M. Gloor[d]

[a] William J. von Liebig Transplant Center, Division of Transplantation Surgery, Mayo Clinic, Rochester, MN

Key words: Alloantibodies, anti-HLA antibodies, antibody-mediated rejection, complement, chronic rejection, kidney transplantation, sensitized recipients

Abbreviations: AMR, antibody-mediated rejection; BFXM, B-cell flow cytometric crossmatch; DSA, donor-specific alloantibody; HLA, human leukocyte antigens; PE, plasma exchange.

Single arm study
Historical controls
Reduction of AMR in high risk pts

AMR occurred in 8% of pts
Despite terminal C inhibition

Outcomes beyond 1 year showed TG still occurs

TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Antibody-mediated rejection despite inhibition of terminal complement

Andrew Bentall,[1,2] Dolly B. Tyan,[3] Flavia Sequeira,[3] Matthew J. Everly,[4] Manish J. Gandhi,[5] Lynn D. Cornell,[6] Han Li,[1] Nicole A. Henderson,[5] Suresh Raghavaiah,[1] Jeffrey L. Winters,[5] Patrick G. Dean[1] and Mark D. Stegall[1]

1 Division of Transplantation Surgery, William J. von Liebig Transplant Center, Mayo Clinic, Rochester, MN, USA
2 Renal Institute of Birmingham, Queen Elizabeth Hospital, Birmingham, UK
3 Histocompatibility, Immunogenetics & Disease Profiling Laboratory, Department of Pathology, Stanford University School of Medicine, Palo Alto, CA, USA
4 Terasaki Foundation, Los Angeles, CA, USA
5 Division of Transfusion Medicine, William J. von Liebig Transplant Center, Mayo Clinic, Rochester, MN, USA
6 Division of Anatomic Pathology, William J. von Liebig Transplant Center, Mayo Clinic, Rochester, MN, USA

Distal Complement Inhibition

- Eculizumab (*Soliris*) Alexion
- Safety and Efficacy of Eculizumab to Prevent AMR in Living Donor Kidney Transplant Recipients Requiring Desensitization
  - NCT01399593
  - Randomized open label
  - Primary EP tx failure (AMR,GL, death, loss to F/U
  - 102 pts (39 sites)
  - Study terminated “did not achieve significance for primary endpoint”
  - Estimated rejection rate in study was lower than assumed in power calculation for study design
  - Lower risk patients were allowed in study at midpoint due to low enrollment
  - Primary completion date March 2015, final data not in clinicaltrials.gov

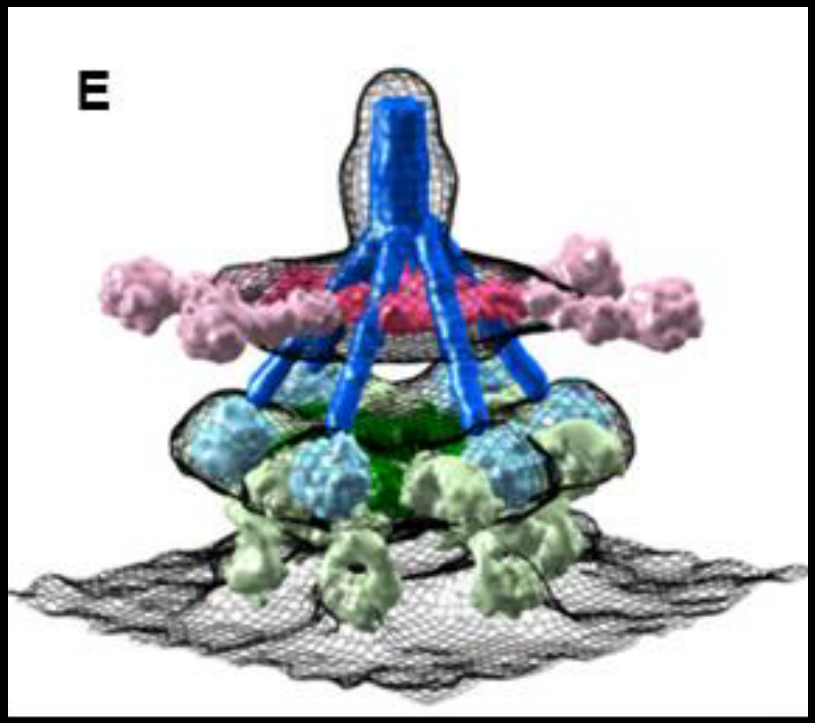
Distal Complement Inhibition

- Eculizumab (*Soliris*) Alexion
  - Safety and Efficacy of Eculizumab in the Prevention of AMR in Sensitized Recipients of a Kidney Transplant From a Deceased Donor
  - NCT01567085
  - Interventional, single limb open label
  - Posttransplant tx failure (AMR,GL, death, loss to F/U
  - 80 pts 15 sites
  - Last updated clinicaltrials.gov Oct 2016, estimated study completion June 2017

Distal Complement Inhibition

- Eculizumab (*Soliris*) Alexion
- Eculizumab Therapy for Chronic Antibody-Mediated Injury in Kidney Transplant Recipients: A Pilot Randomized Controlled Trial
- Kulkarni S, Pober J et al
- First published: AJT 16 September 2016

Proximal Complement Inhibition

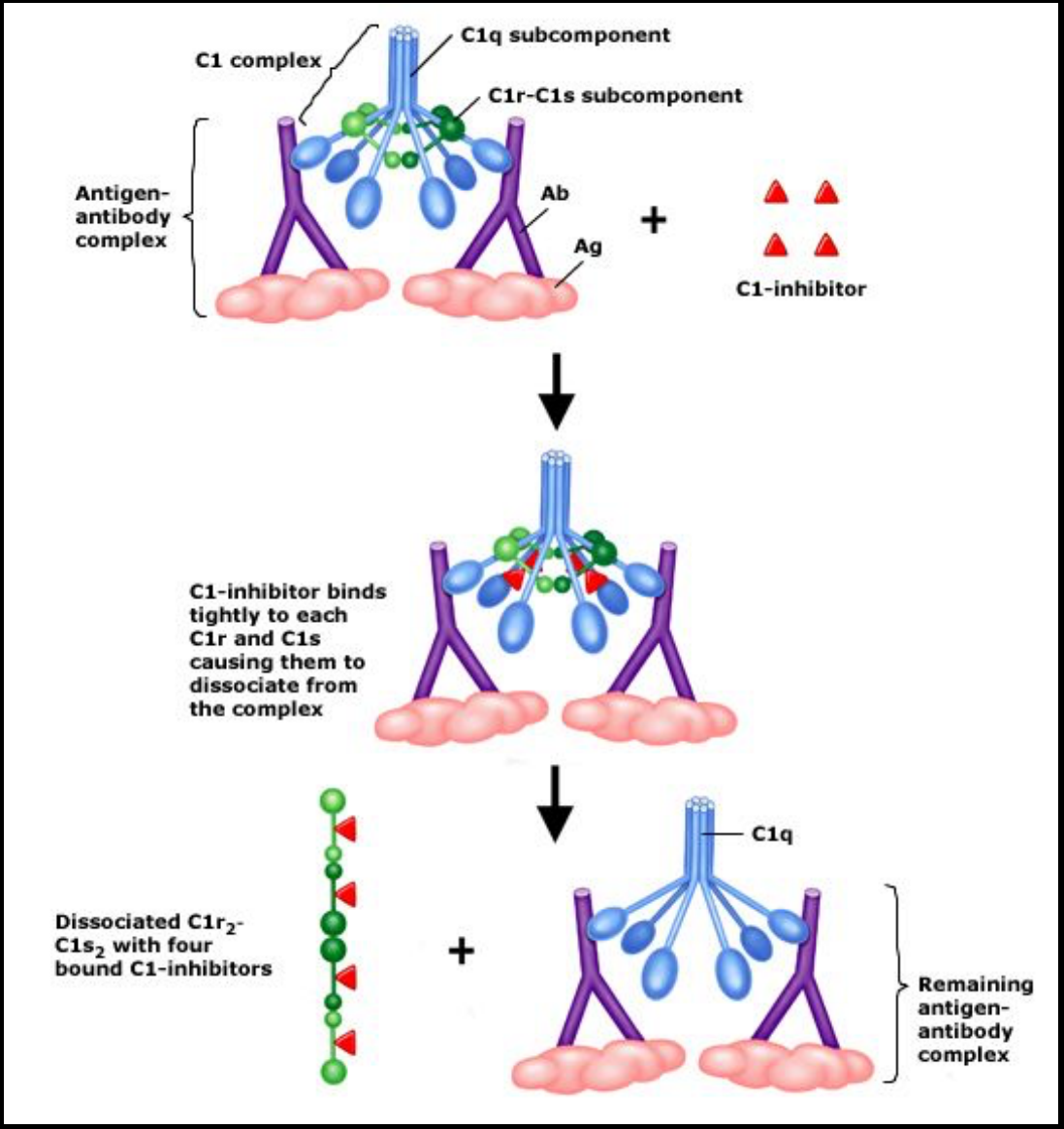


REPORTS

Complement Is Activated by IgG Hexamers Assembled at the Cell Surface

Christoph A. Diebolder,[1,2]* Frank J. Beurskens,[3]* Rob N. de Jong,[3] Roman I. Koning,[2] Kristin Strumane,[3] Margaret A. Lindorfer,[4] Marleen Voorhorst,[3] Deniz Ugurlar,[1] Sara Rosati,[5] Albert J. R. Heck,[5] Jan G. J. van de Winkel,[3,6] Ian A. Wilson,[7,8] Abraham J. Koster,[2] Ronald P. Taylor,[4] Erica Ollmann Saphire,[9] Dennis R. Burton,[8,9,10] Janine Schuurman,[3] Piet Gros,[1]† Paul W. H. I. Parren[3]†

C1 Inhibitor



Proximal Complement Inhibition

Berinert	CSL Behring	C1 esterase inhibitor	plasma derived
Cinryze	Shire (Viropharma)	C1 esterase inhibitor	plasma derived
Ruconest	Pharming	C1esterase inhibitor	recombinant

Proximal Complement Inhibition

A Phase I/II Placebo-Controlled Trial of C1-Inhibitor for Prevention of Antibody-Mediated Rejection in HLA Sensitized Patients

Ashley A. Vo,[1] Adriana Zeevi,[2] Jua Choi,[1] Kristen Cisneros,[1] Mieko Toyoda,[3] Joseph Kahwaji,[1] Alice Peng,[1] Rafael Villicana,[1] Dechu Puliyanda,[1] Nancy Reinsmoen,[4] Mark Haas,[5] and Stanley C. Jordan[1]

Background. Antibody-mediated rejection (AMR) is a severe form of rejection, mediated primarily by antibody-dependent complement (C) activation. C1 inhibitor (C1-INH, Berinert) inhibits the classical and lectin pathways of C activation. We performed a randomized, placebo-controlled study using C1-INH in highly sensitized renal transplant recipients for prevention of AMR. **Methods.** Twenty highly sensitized patients desensitized with IVIG + rituximab ± plasma exchange were enrolled and randomized 1:1 to receive plasma-derived human C1-INH (20 IU/kg/dose) versus placebo intraoperatively, then twice weekly for 7 doses. Renal function, adverse events (AEs)/serious AEs, C3, C4, and C1-INH levels were monitored and C1q+ HLA antibodies were also blindly assessed. **Results.** One patient in the C1-INH group versus 2 patients in the placebo group developed serious AEs, but none were re-

- CSL Behring
- Phase 1-2 randomized placebo controlled pilot study
- 20 patients

Proximal Complement Inhibition

American Journal of Transplantation 2016; 16: 3468–3478
Wiley Periodicals Inc.

doi: 10.1111/ajt.13871

Plasma-Derived C1 Esterase Inhibitor for Acute Antibody-Mediated Rejection Following Kidney Transplantation: Results of a Randomized Double-Blind Placebo-Controlled Pilot Study

R. A. Montgomery[1,*], B. J. Orandi[1], L. Racusen[2], A. M. Jackson[3], J. M. Garonzik-Wang[1], T. Shah[4], E. S. Woodle[5], C. Sommerer[6], D. Fitts[7], K. Rockich[7], P. Zhang[7] and M. E. Uknis[7]

patients achieved supraphysiological levels throughout. This new finding suggests that C1 INH replacement may be useful in the treatment of AMR.

Abbreviations: AMR, antibody-mediated rejection; AE, adverse event; C1 INH, C1 esterase inhibitor; C4d, fourth complement protein degradation pro-

- Shire/Viropharma
- Phase 2b randomized double blind placebo controlled pilot study
- 18 patients

Proximal Complement Inhibition

Brief Communication

doi: 10.1111/ajt.13663

C1 Inhibitor in Acute Antibody-Mediated Rejection Nonresponsive to Conventional Therapy in Kidney Transplant Recipients: A Pilot Study

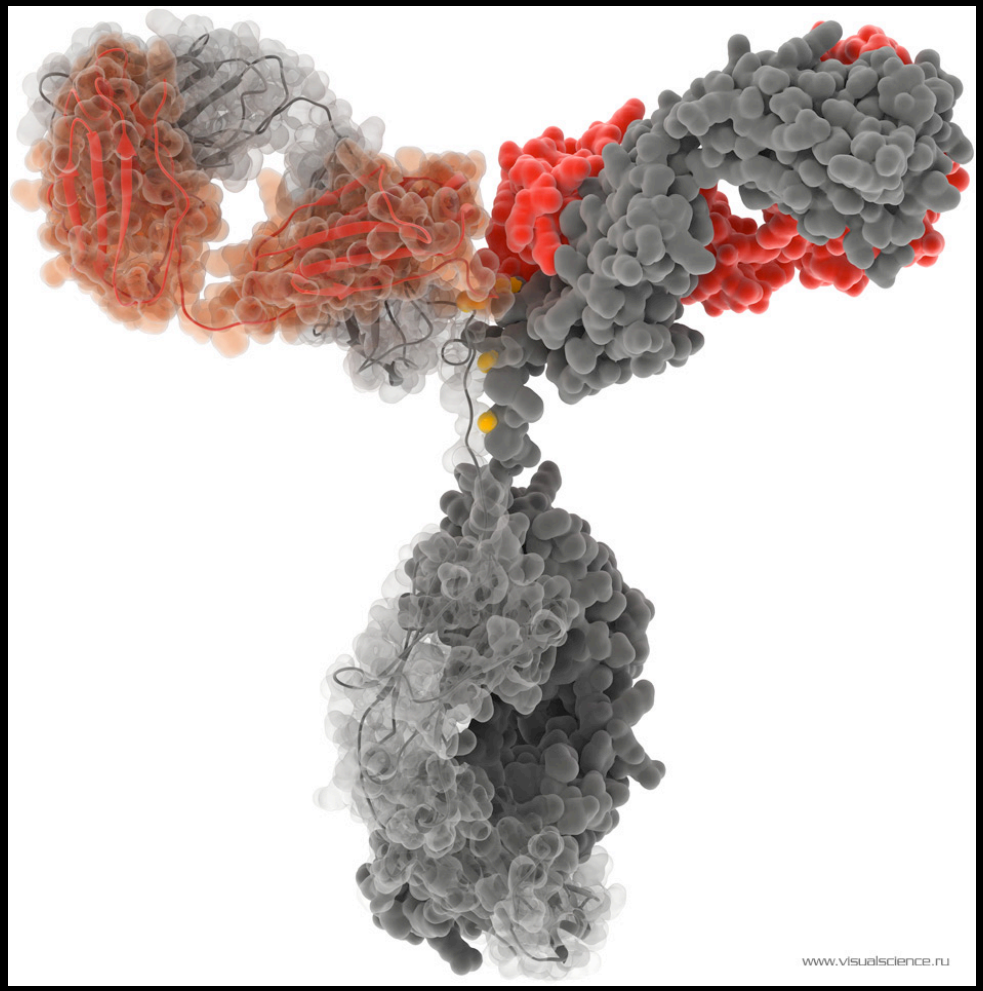
D. Viglietti[1,2,†], C. Gosset[1,†], A. Loupy[2,3], L. Deville[4], J. Verine[5], A. Zeevi[6], D. Glotz[1] and C. Lefaucheur[1,2,*]

[1]Department of Nephrology and Kidney Transplantation, Saint-Louis Hospital, Assistance Publique - Hôpitaux de Paris, Paris, France

Abbreviations: ABMR, antibody-mediated rejection; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate; INH, inhibitor; IVIG, intravenous immunoglobulin; MFI, mean fluorescence intensity; SOC, standard of care

- CSL Behring
- 6 patient pilot study

Immunoglobulin



IdeS

INFECTION AND IMMUNITY, Jan. 2006, p. 497–503 Vol. 74, No. 1
0019-9567/06/$08.00+0 doi:10.1128/IAI.74.1.497–503.2006

IdeS, a Highly Specific Immunoglobulin G (IgG)-Cleaving Enzyme from *Streptococcus pyogenes*, Is Inhibited by Specific IgG Antibodies Generated during Infection

Per Åkesson,[1]† Linnea Moritz,[2]† Mikael Truedsson,[3] Bertil Christensson,[1] and Ulrich von Pawel-Rammingen[2]*

Department of Clinical Science, Lund University, Lund, Sweden[1]; Department of Molecular Biology, Umeå University, Umeå, Sweden[2]; and Department of Community Medicine, Malmö University Hospital, Lund University, Malmö, Sweden[3]

Received 13 September 2005/Accepted 19 October 2005

- Bacterial enzyme- cysteine protease
- Specifically cleaves human IgG
- Cleaves IgG into F(ab)'2 and Fc fragments
- Humans commonly produce neutralizing activity during clinical streptococcal infection
- Anti-IdeS neutralizing antibodies commonly found in humans

OPEN ACCESS Freely available online

PLoS one

IdeS: A Bacterial Proteolytic Enzyme with Therapeutic Potential

Björn P. Johansson, Oonagh Shannon, Lars Björck*

Division of Infection Medicine, Department of Clinical Sciences, Biomedical Center (BMC), Lund University, Lund, Sweden

Abstract

Background: IdeS, a proteinase from *Streptococcus pyogenes*, cleaves immunoglobulin (Ig)G antibodies with a unique degree of specificity. Pathogenic IgG antibodies constitute an important clinical problem contributing to the pathogenesis of a number of autoimmune conditions and acute transplant rejection. To be able to effectively remove such antibodies is therefore an important clinical challenge.

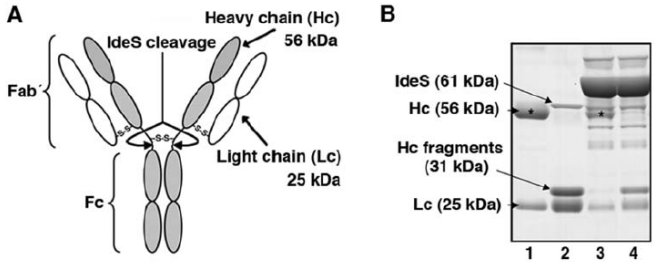


Figure 1. IdeS cleaves IgG in human blood. (**A**) Structure of IgG. The IdeS cleavage sites are indicated. (**B**) The following samples were separated by SDS-PAGE. Lane 1: Five μg of human polyclonal IgG in 10 μl PBS. Lane 2: Five μg of human polyclonal IgG and 1 μg of IdeS in 10 μl PBS (IgG and IdeS were preincubated for three hours at 37°C before SDS-PAGE). Lane 3: Ten μl of plasma from human blood diluted 1:50 in PBS Lane 4: One hundred μl of human blood was preincubated with 1 μg of IdeS for three hours at 37°C. The plasma from this sample (containing approximately 20 μg/ml) was diluted 1:50 in PBS, and 10 μl of this material was separated in lane 4. The asterisk indicates the IgG heavy chain.
doi:10.1371/journal.pone.0001692.g001

IdeS

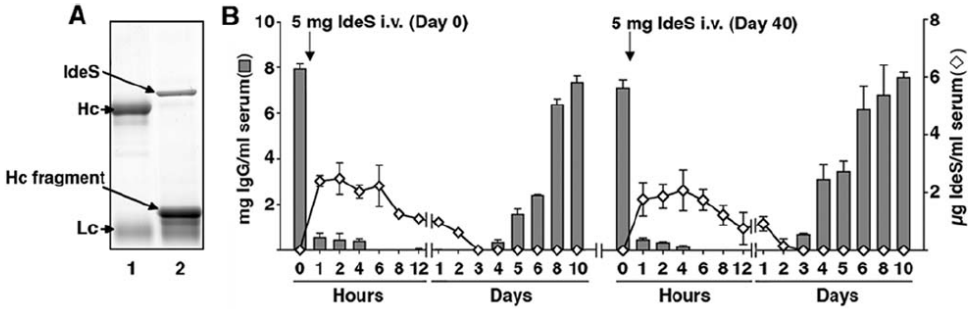
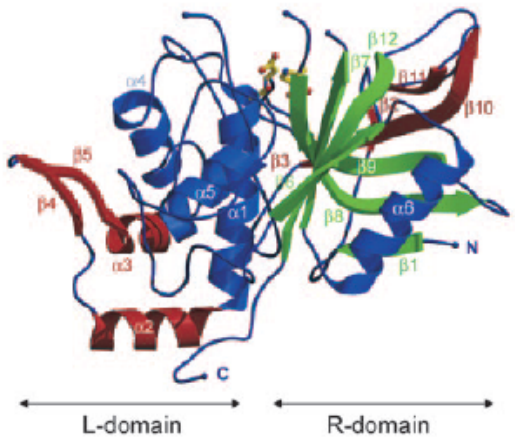


Figure 3. ***Invivo*** **cleavage and removal of IgG from the blood circulation of rabbits injected with IdeS.** (**A**) SDS-PAGE of rabbit polyclonal IgG (5 μg in 10 μl PBS) alone (lane 1), or preincubated with IdeS (5 μg IgG and 1 μg IdeS in 10 μl PBS) for three hours at 37°C (lane 2). Bands corresponding to IdeS (61 kDa), IgG heavy chains (Hc, 56 kDa), IdeS-generated Hc fragments (31 kDa) and IgG light chains (Lc, 25 kDa), are indicated. (**B**) Levels of IgG (grey bars) and IdeS (◇) in serum samples from a rabbit injected i.v. with IdeS (5 mg diluted in 2.5 ml PBS). IgG was determined by ELISA and IdeS by Western blotting and chemoluminescence in a Chemidoc XRS Imaging system. Samples were analyzed three times and mean values±SD are indicated.
doi:10.1371/journal.pone.0001692.g003



PNAS

Structure of the streptococcal endopeptidase IdeS, a cysteine proteinase with strict specificity for IgG

Katja Wenig*†, Lorenz Chatwell*, Ulrich von Pawel-Rammingen‡, Lars Björck§, Robert Huber*, and Peter Sondermann*¶

*Department of Structural Research, Max Planck Institute for Biochemistry, D-82152 Martinsried, Germany; ‡Department of Molecular Biology, Umeå University, SE-90187 Umeå, Sweden; and §Department of Cell and Molecular Biology, Biomedical Center, Lund University, B14, SE-221 84 Lund, Sweden

Contributed by Robert Huber, October 28, 2004

Pathogenic bacteria have developed complex and diverse virulence mechanisms that weaken or disable the host immune defense

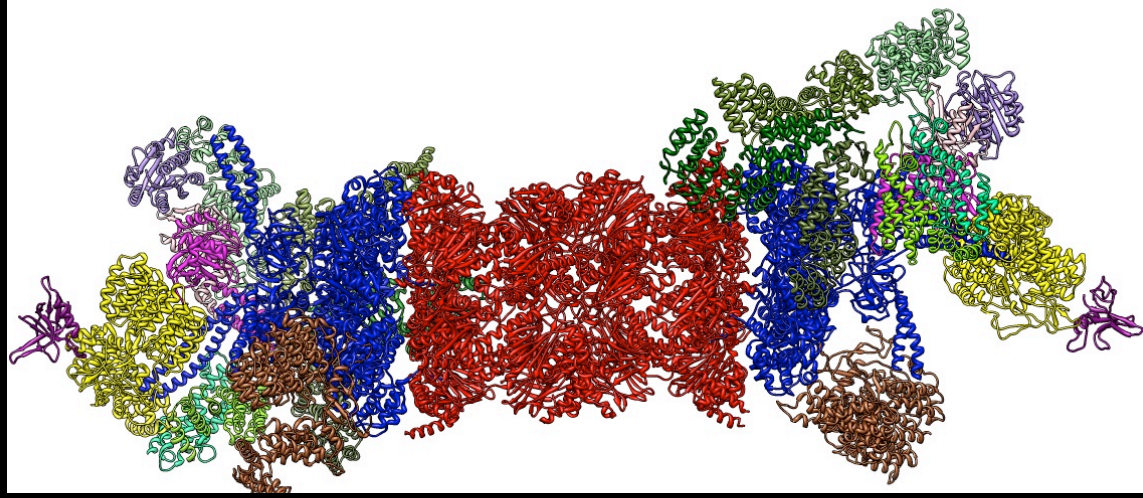
exotoxin B), IdeS contains an RGD motif (4, 14, 15), which is involved in the interaction of IdeS with vitronectin ($\alpha_V\beta_3$) and

IdeS Clinical Trials

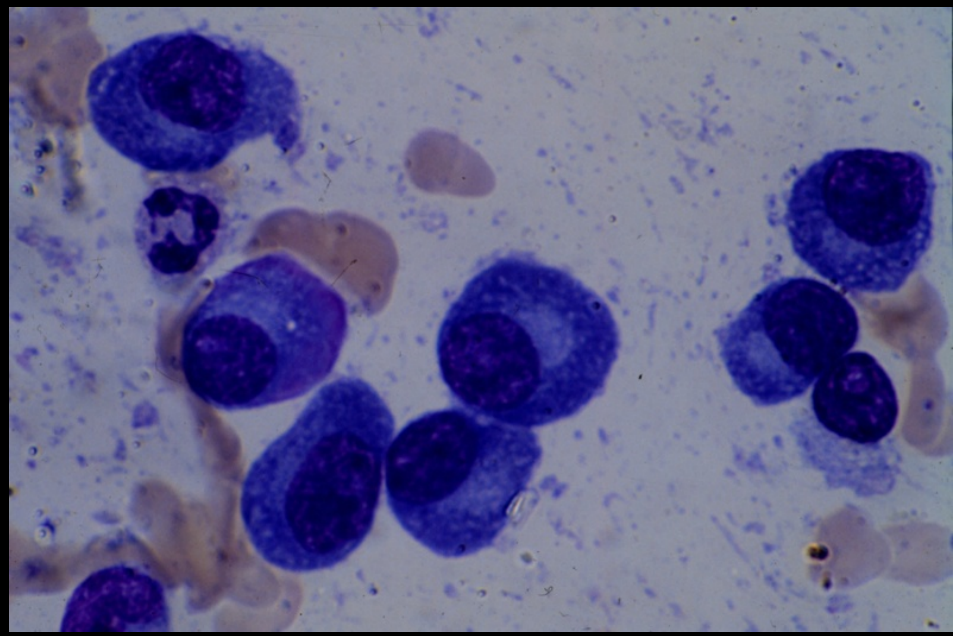
- *Phase 1-2 Trial to Evaluate Safety and Tolerability of IdeS (IgG endopeptidase) To Eliminate Donor-Specific HLA Antibodies and Prevent AMR in Highly HLA Sensitized Patients*
- Interventional single limb pilot
- 20 pts, single center
  - Jordan and Hansa Medical AB

Plasma Cell Targeting

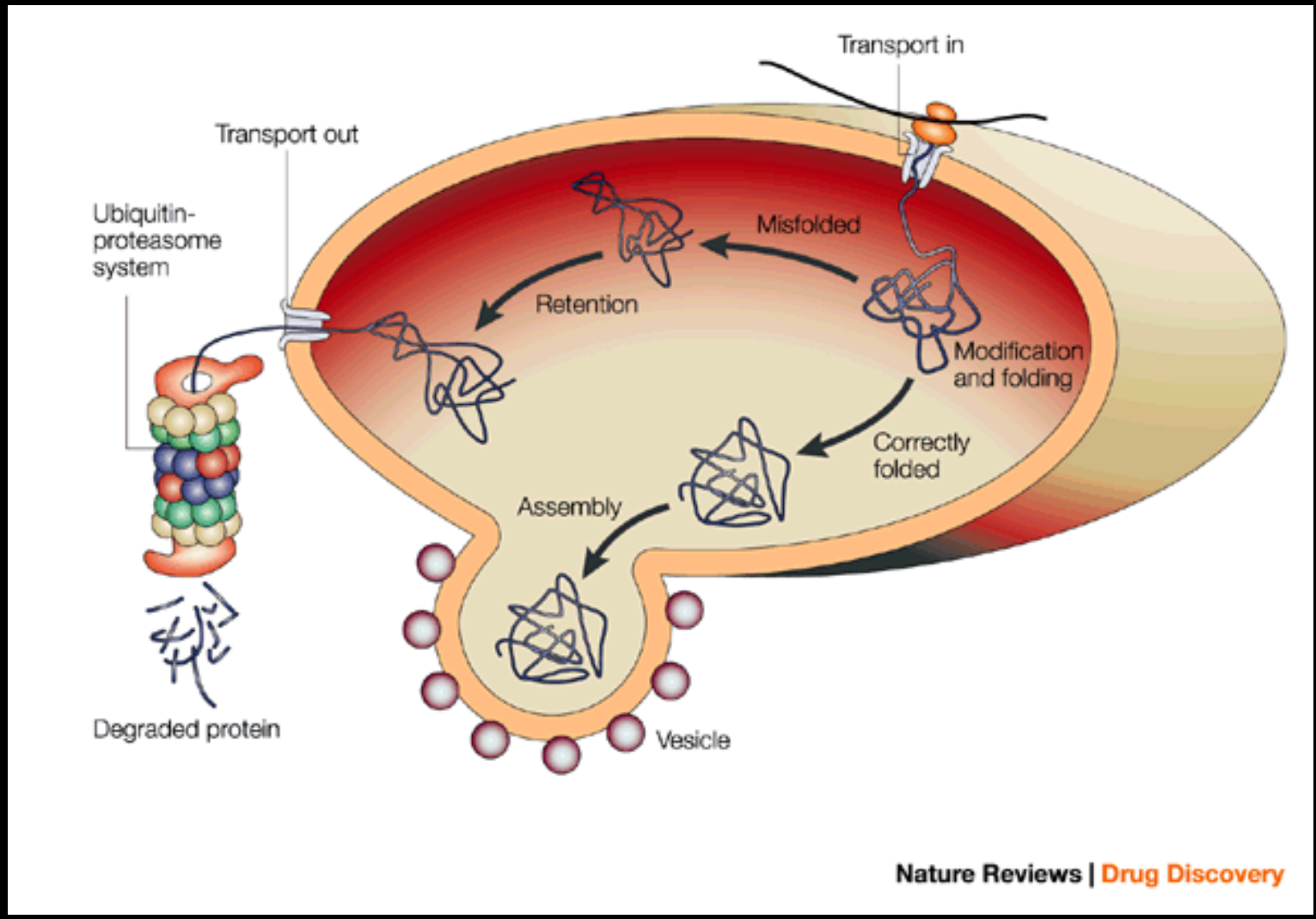
- Proteasome inhibitors
  - Distal
    - Inhibition of protease activity
      - Constitutive proteasome inhibitors
      - Immunoproteasome inhibitors
  - Proximal
    - Non-protease inhibitors
      - Ubiquitin binding inhibitors
      - Deubiquitinases (DUBs)
- ER Stress and autophagy modulation
  - Proximal UPR inhibitors
  - Autophagy inhibitors
- Plasma cell niche and survival factors
  - CXCR4 antagonists
  - BAFF antagonists
  - IL-6 antagonists
- Combinatorial approaches



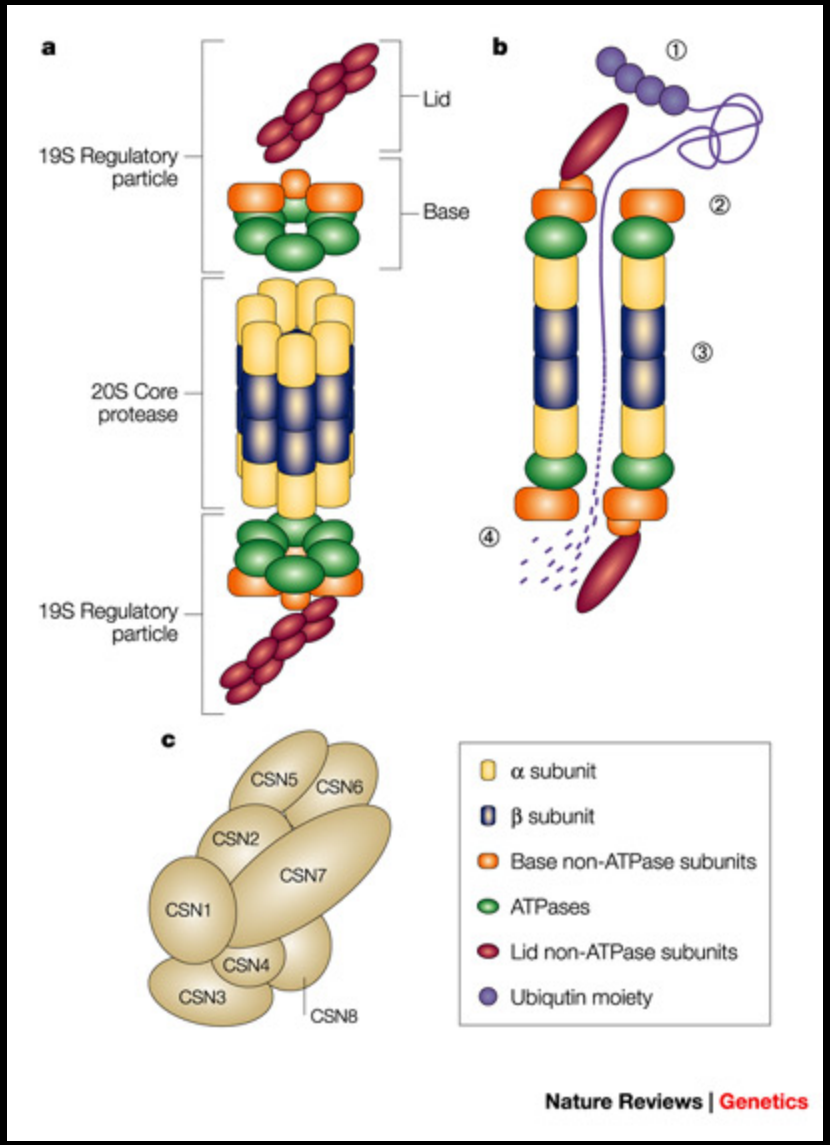
Proteasome Inhibition



ER Stress


Transport in
Transport out
Ubiquitin-proteasome system
Misfolded
Retention
Modification and folding
Correctly folded
Assembly
Degraded protein
Vesicle
Nature Reviews | Drug Discovery

Proteasome Structure



Proteolysis is conducted by three beta subunits, beta1, beta2, and beta5, of the 20S proteasome.

Enzymatic v nonenzymatic inhibitors

Bortezomib AMR Papers

Bortezomib Provides Effective Therapy for Antibody- and Cell-Mediated Acute Rejection

Matthew J. Everly,[1] Jason J. Everly,[1] Brian Susskind,[2] Paul Brailey,[2] Lois J. Arend,[3] Rita R. Alloway,[4] Prabir Roy-Chaudhury,[4] Amit Govil,[4] Gautham Mogilishetty,[4] Adele H. Rike,[1] Michael Cardi,[5] George Wadih,[5] Amit Tevar,[1] and E. Steve Woodle[1,6]

RAPID COMMUNICATION

Proteasome Inhibitor-Based Primary Therapy for Antibody-Mediated Renal Allograft Rejection

R. Carlin Walsh,[1] Jason J. Everly,[1] Paul Brailey,[2] Adele H. Rike,[1] Lois J. Arend,[3] Gautham Mogilishetty,[4] Amit Govil,[4] Prabir Roy-Chaudhury,[4] Rita R. Alloway,[4] and E. Steve Woodle[1,5]

Early and Late Acute Antibody-Mediated Rejection Differ Immunologically and in Response to Proteasome Inhibition

R. Carlin Walsh,[1] Paul Brailey,[2] Alin Girnita,[2] Rita R. Alloway,[3] Adele Rike Shields,[1] Garth E. Wall, Basma H. Sadaka, Michael Cardi,[4] Amit Tevar,[1] Amit Govil,[3] Gautham Mogilishetty,[3] Prabir Roy-Chaudhury,[3] and E. Steve Woodle[1,5]

Rapid Reduction in Donor-Specific Anti-Human Leukocyte Antigen Antibodies and Reversal of Antibody-Mediated Rejection With Bortezomib in Pediatric Heart Transplant Patients

William Robert Morrow,[1] Elizabeth A. Frazier,[1] William T. Mahle,[2] Terry O. Harville,[1] Sherry E. Pye,[1] Kenneth R. Knecht,[1,6] Emily L. Howard,[1] R. Neal Smith,[3] Robert L. Saylors,[1] Xiomara Garcia,[1] Robert D.B. Jaquiss,[4] and E. Steve Woodle[5]

CLINICAL AND TRANSLATIONAL RESEARCH

Prospective Evaluation of the Toxicity Profile of Proteasome Inhibitor–Based Therapy in Renal Transplant Candidates and Recipients

Nicole Schmidt,[1] Rita R. Alloway,[2] R. Carlin Walsh,[1] Basma Sadaka,[2] Adele R. Shields,[1] Alin L. Girnita,[3] Dennis J. Hanseman,[4,5] and E. Steve Woodle[1,6]

Proteasome inhibitor treatment of antibody-mediated allograft rejection

E. Steve Woodle[a], Rita R. Alloway[b] and Alin Girnita[c,a]

[a]Division of Transplantation, Department of Surgery, [b]Section of Transplantation, Division of Nephrology, Department of Internal Medicine and [c]Transplant Immunology Division, Hoxworth Blood Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

Correspondence to E. Steve Woodle, MD, Division of

Purpose of review

Bortezomib is a first-in-class proteasome inhibitor that was originally Food and Drug Administration approved for the treatment of multiple myeloma. In the past few years, off-label use in solid organ transplant recipients has demonstrated its ability to provide plasma cell-targeted therapy in humans. The purpose of this review is to provide an

Pediatr Transplantation 2011: 15: 548–556

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2011.01543.x

Proteasome inhibitor therapy for antibody-mediated rejection

Woodle ES, Walsh RC, Alloway RR, Girnita A, Brailey P. Proteasome inhibitor therapy for antibody-mediated rejection.

E. S. Woodle[1], R. C. Walsh[1], R. R. Alloway[2], A. Girnita[3] and P. Brailey[3]

New Proteosome Inhibitors

AGENT	TARGET	CLASS	PHARMA	AREA OF DEVELOPMENT	PHASE
Carfilzomib (PR-171)	NF-kB	2nd Generation Proteasome Inhibitor (IV)	Onyx	Relapsed/Refractory MM	Phase II
				Relapsed Solid Tumors	Phase Ib/II
				Carfilzomib + Lenalidomide + Dexamethasone in Relapsed MM	Phase Ib
				Relapsed MM	Phase II
MLN9708 ixazomib	NF-kB	2nd Generation Proteasome Inhibitor (IV)	Millennium	Relapsed/Refractory MM	Pre-Clinical

Carfilzomib and Lung Transplant Rejection

American Journal of Transplantation 2017; XX: 1–9
Wiley Periodicals Inc.

doi: 10.1111/ajt.14222

Brief Communication

Proteasome Inhibitor Carfilzomib-Based Therapy for Antibody-Mediated Rejection of the Pulmonary Allograft: Use and Short-Term Findings

C. R. Ensor[1,2,*], S. A. Yousem[3], M. Marrari[3], M. R. Morrell[2], M. Mangiola[3], J. M. Pilewski[2], J. D'Cunha[4], S. R. Wisniewski[5], R. Venkataramanan[3,6], A. Zeevi[3,†] and J. F. McDyer[2,†]

[1]School of Pharmacy, Department of Pharmacy and Therapeutics, University of Pittsburgh, Pittsburgh, PA

dysfunction or progression versus nonresponders (25% vs. 83%, p = 0.04). No deaths occurred within 120 days and 7 patients died post CFZ therapy of allograft failure. Larger prospective interventional studies are needed to further describe the benefit of CFZ-based therapy for pulmonary AMR.

Abbreviations: ACR, acute cellular rejection; AHG-CDC, anti-human globulin complement dependent

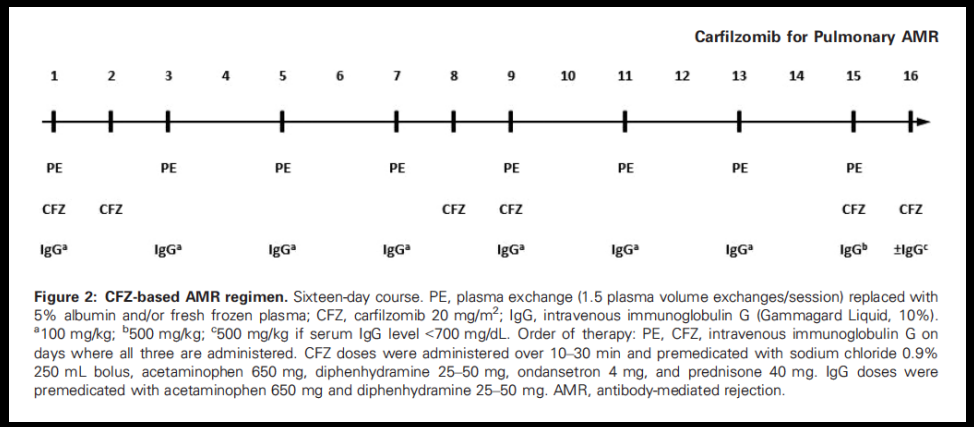


Figure 2: CFZ-based AMR regimen. Sixteen-day course. PE, plasma exchange (1.5 plasma volume exchanges/session) replaced with 5% albumin and/or fresh frozen plasma; CFZ, carfilzomib 20 mg/m^2; IgG, intravenous immunoglobulin G (Gammagard Liquid, 10%). [a]100 mg/kg; [b]500 mg/kg; [c]500 mg/kg if serum IgG level <700 mg/dL. Order of therapy: PE, CFZ, intravenous immunoglobulin G on days where all three are administered. CFZ doses were administered over 10–30 min and premedicated with sodium chloride 0.9% 250 mL bolus, acetaminophen 650 mg, diphenhydramine 25–50 mg, ondansetron 4 mg, and prednisone 40 mg. IgG doses were premedicated with acetaminophen 650 mg and diphenhydramine 25–50 mg. AMR, antibody-mediated rejection.

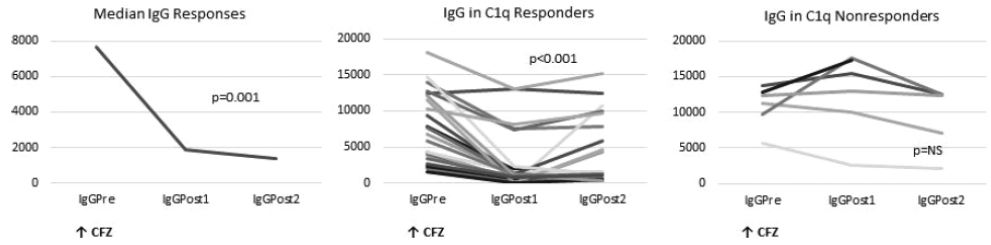
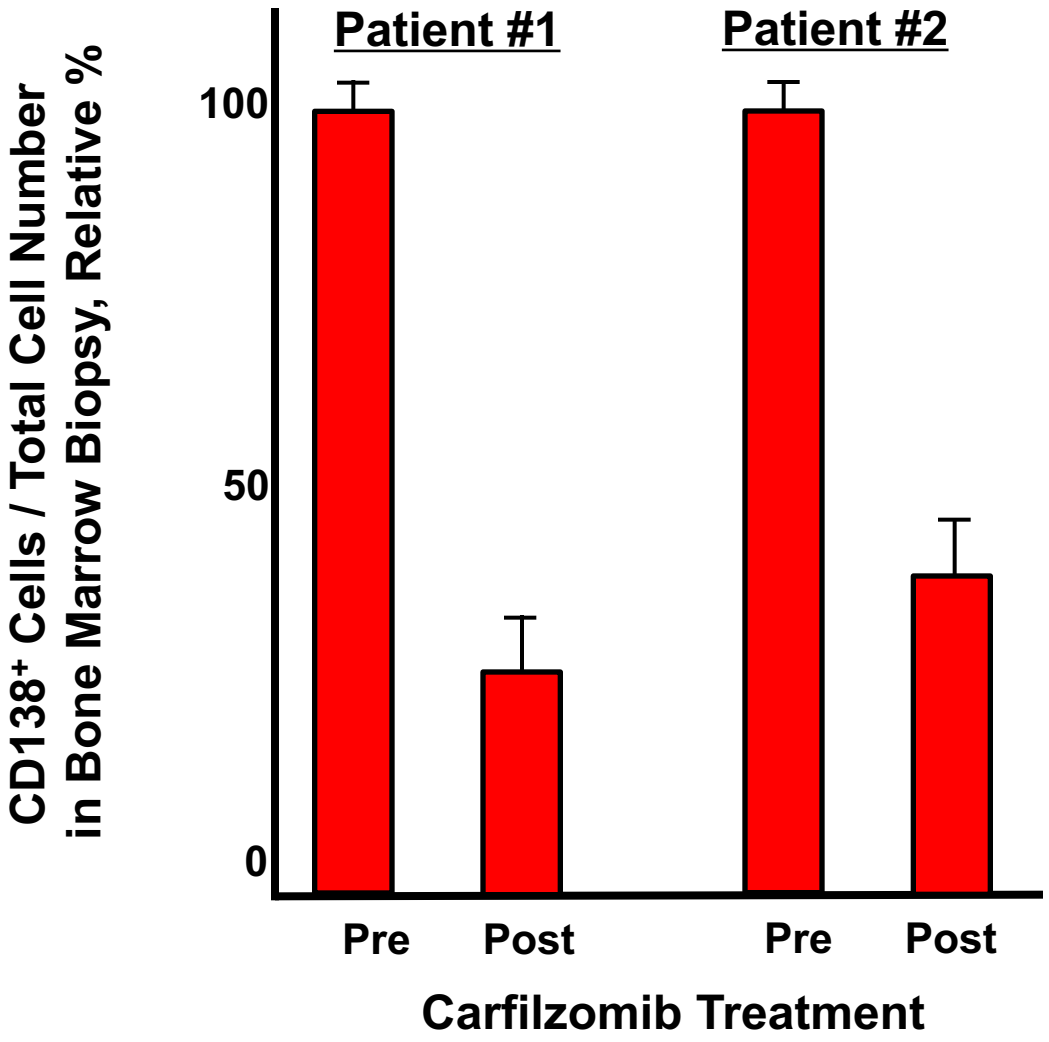


Figure 4: Single-antigen bead neat IgG MFI responses. IgGPre, neat IgG MFI at AMR (day 0); IgGPost1, neat IgG MFI at day 16; IgGPost2, neat IgG MFI at day 42. All (left), C1q responders (center), C1q nonresponders (right). AMR, antibody-mediated rejection; C1q, complement-1q; IgG, immunoglobulin G; MFI, mean fluorescence intensity; NS, not significant; Pre, value prior to AMR; Post, value after CFZ therapy.

U of Cincinnati Carfilzomib Trial

- FDA IND and UC IRB approval
- Enrollment initiation Nov 2014
- Desensitization trial
- Proof of concept
- Iterative design
- Adaptive enrollment based on precision estimates of treatment effect
- Biologic assessment of resistant BMNR LLPCs

Carfilzomib Monotherapy BMPC Depletion



BRIEF COMMUNICATION www.jasn.org

Humoral Compensation after Bortezomib Treatment of Allosensitized Recipients

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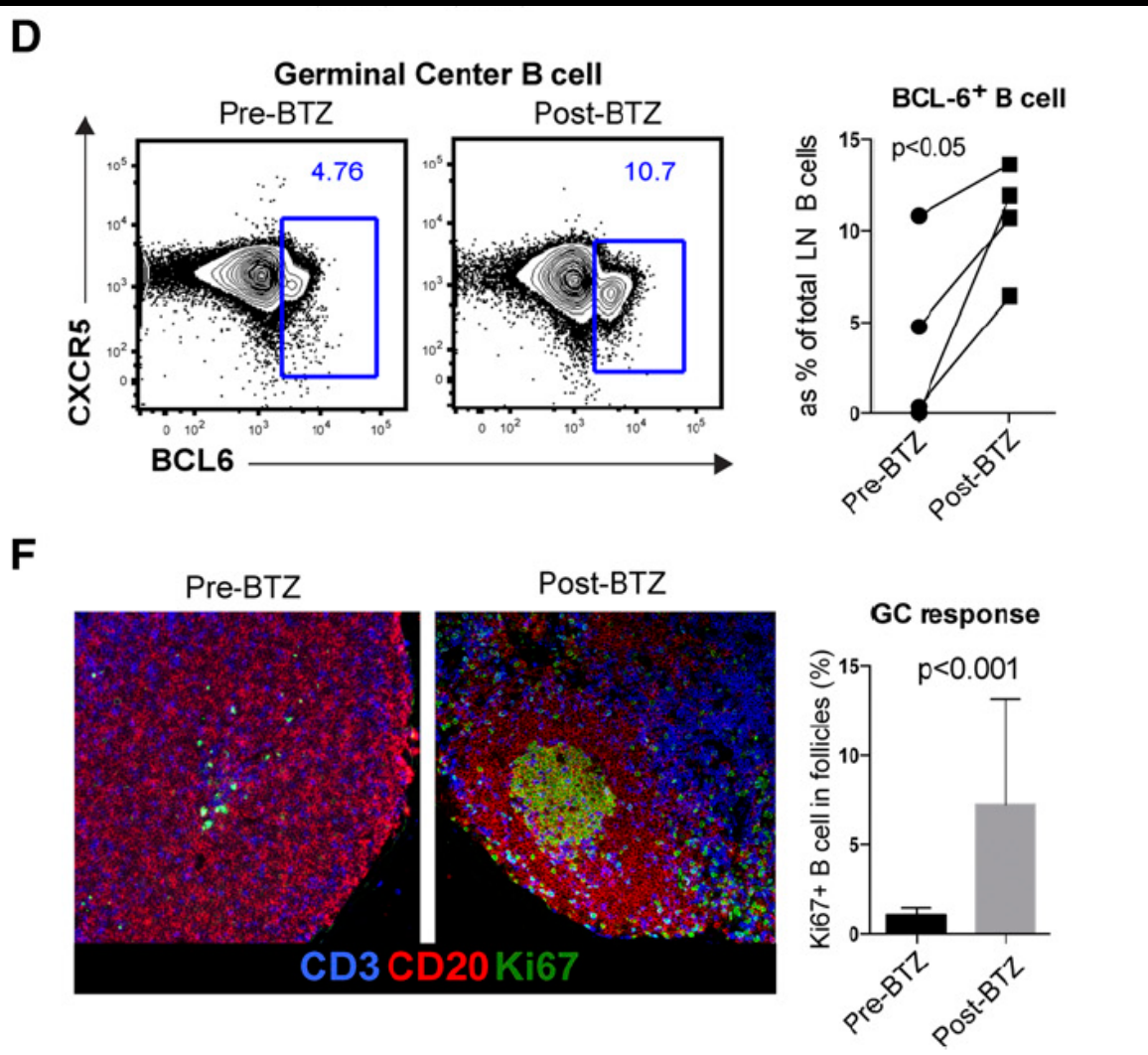
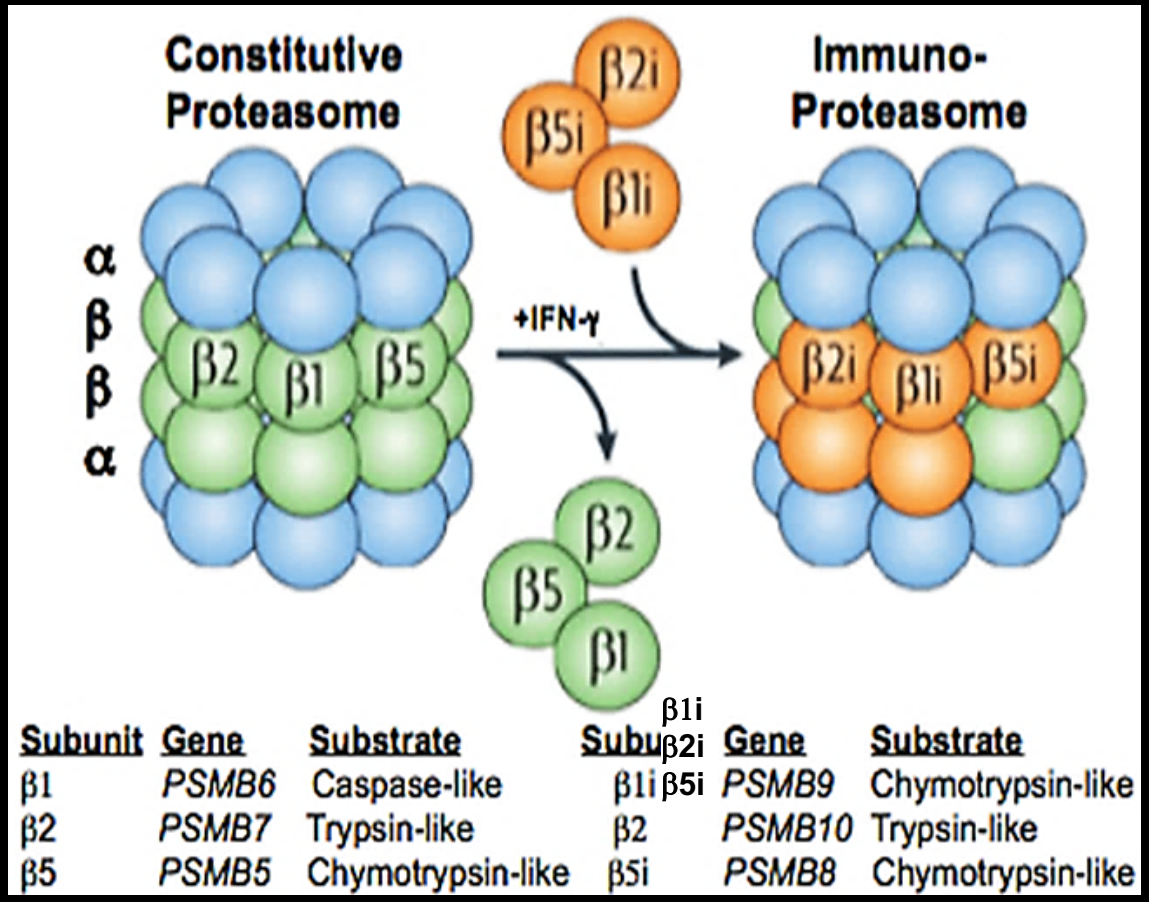
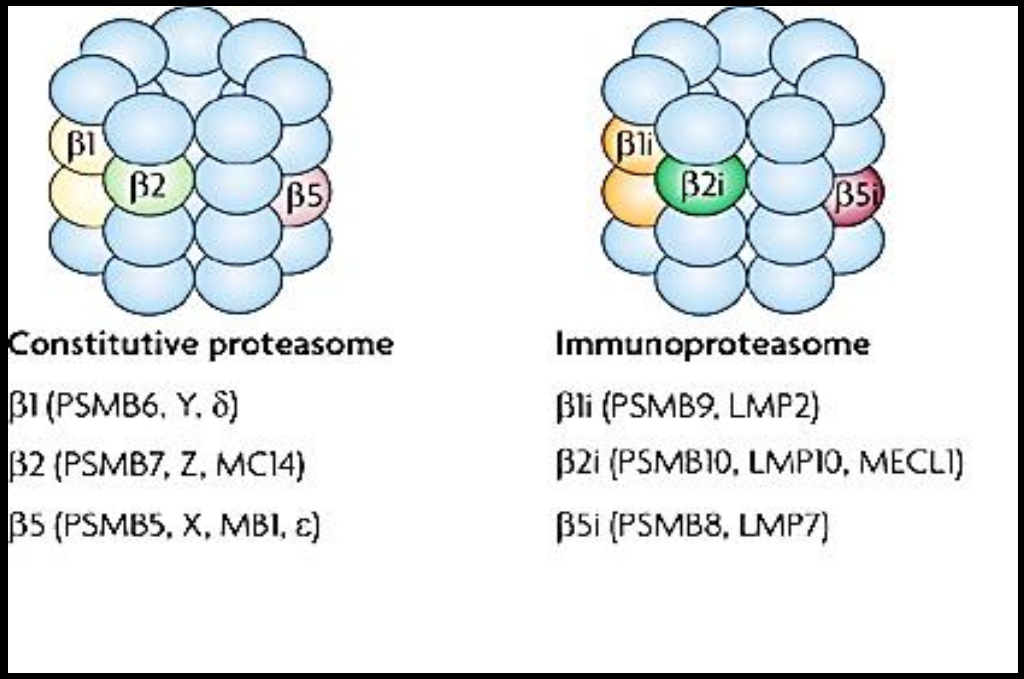


Constitutive Proteasome Conversion to Immunoproteasome

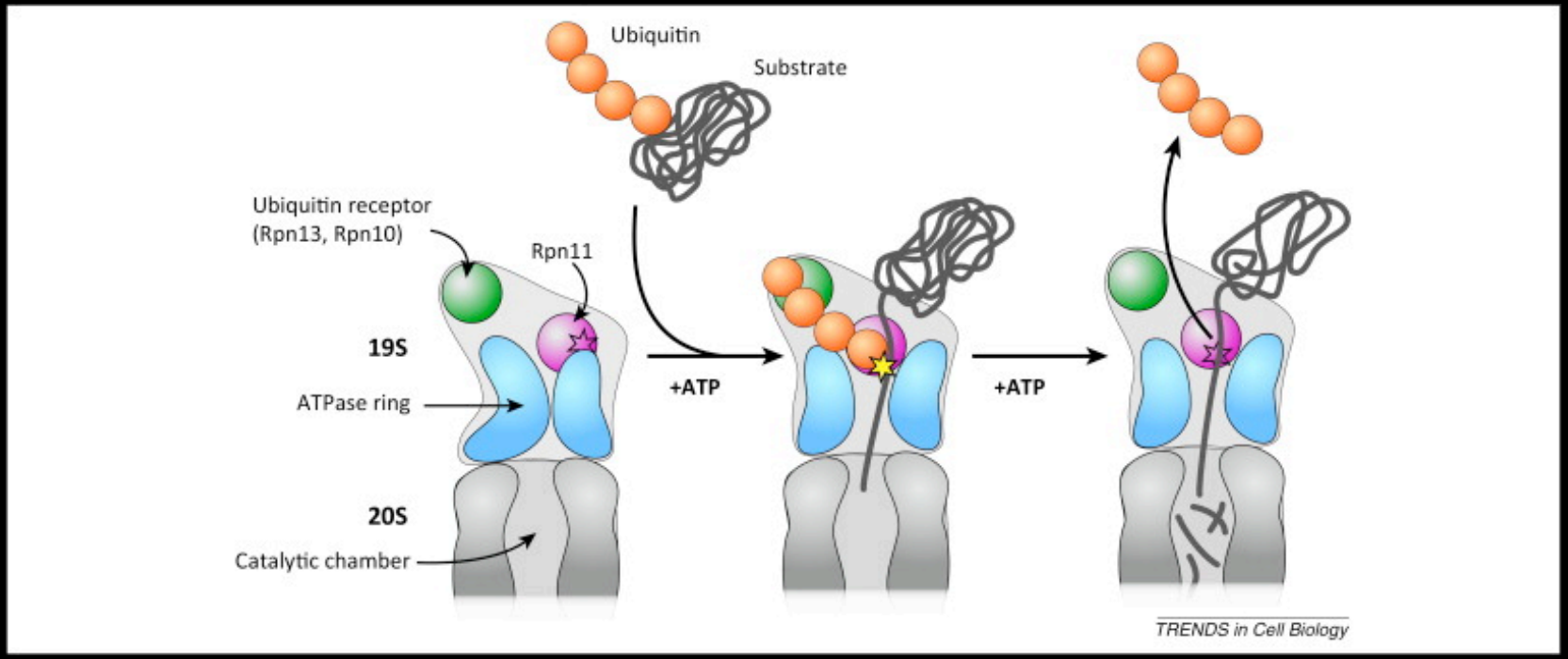


Subunit	Gene	Substrate	Subunit	Gene	Substrate
β1	*PSMB6*	Caspase-like	β1i	*PSMB9*	Chymotrypsin-like
β2	*PSMB7*	Trypsin-like	β2	*PSMB10*	Trypsin-like
β5	*PSMB5*	Chymotrypsin-like	β5i	*PSMB8*	Chymotrypsin-like

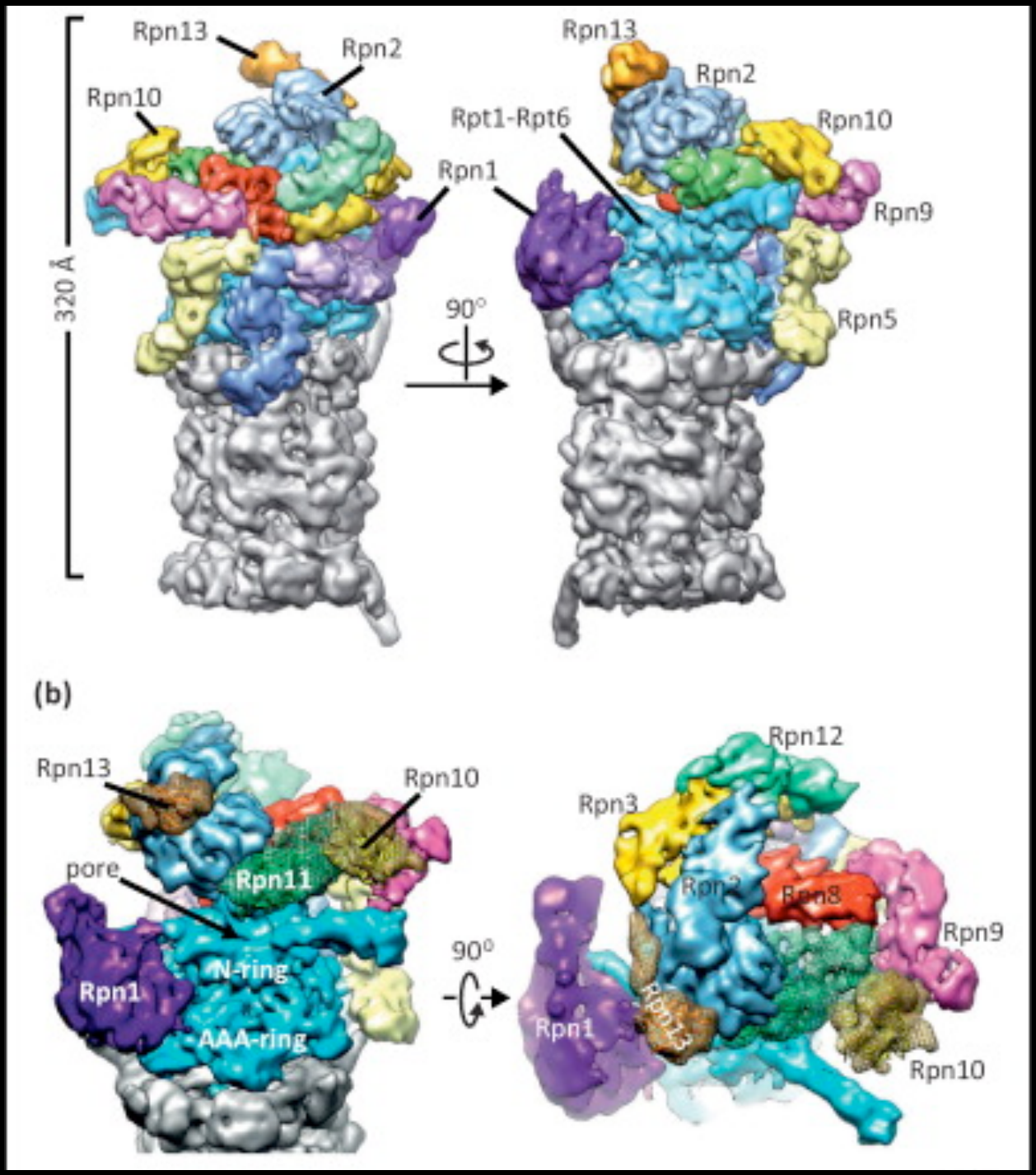
Immunoproteasome



Proteasome Degradation: Events Proximal To Protein Degradation



- Ubiquitin recognition and binding
- Protein unfolding and chamber entry
- Deubiquitination



19S regulatory cap consists of:

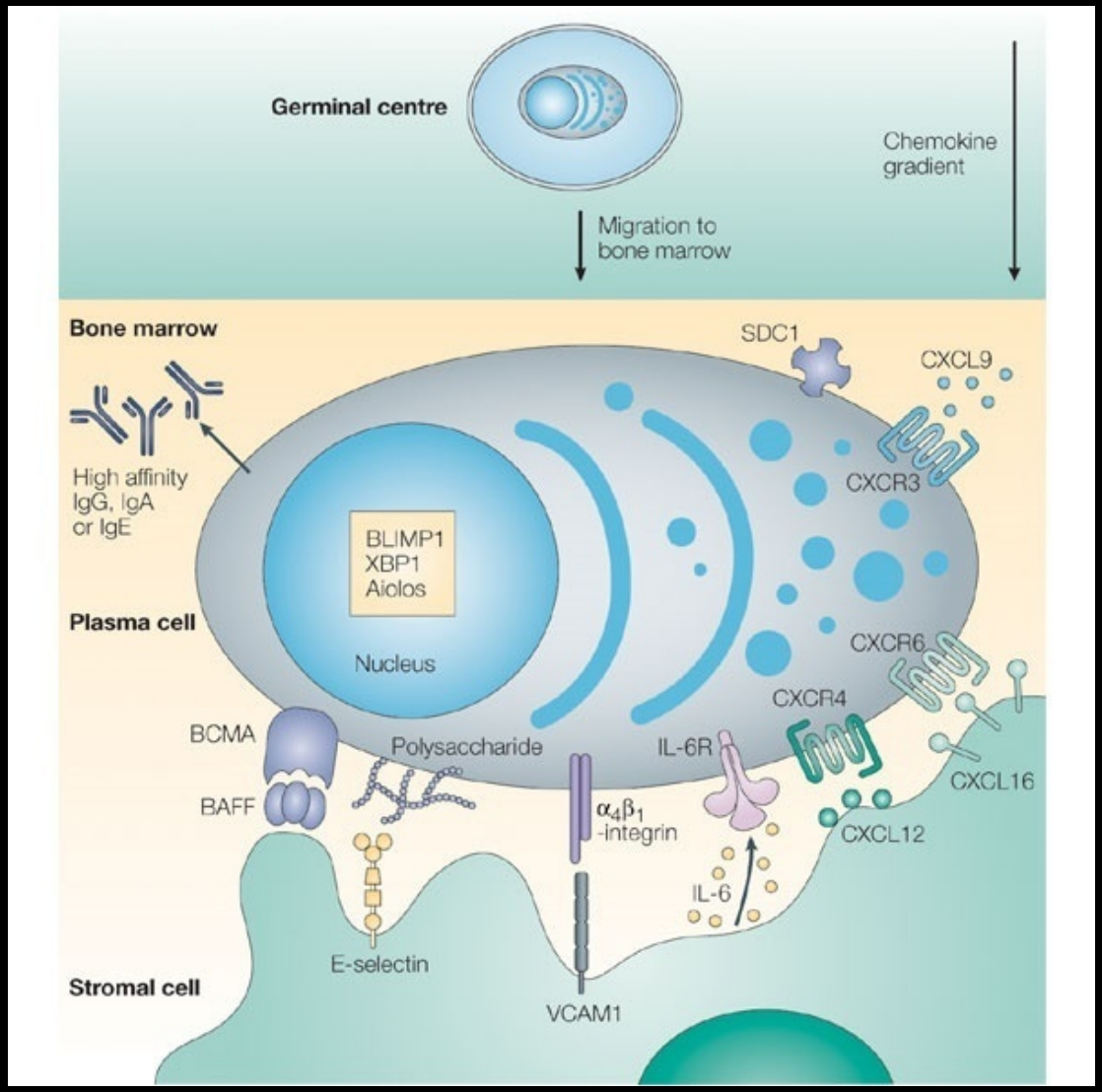
6 ATPases
3 DUBs
2 Ub receptors

Plasma Cell Niches

- PC niches exist in bone marrow, spleen and LN
- Bone marrow niche is the most characterized
- Consists of multiple cell types
  - Bone marrow stromal cells, osteoclasts, macrophages, eosinophils
  - Multiple cytokine, chemokines and cell surface protein sinteractions are thought to be important in promoting long term PC survival

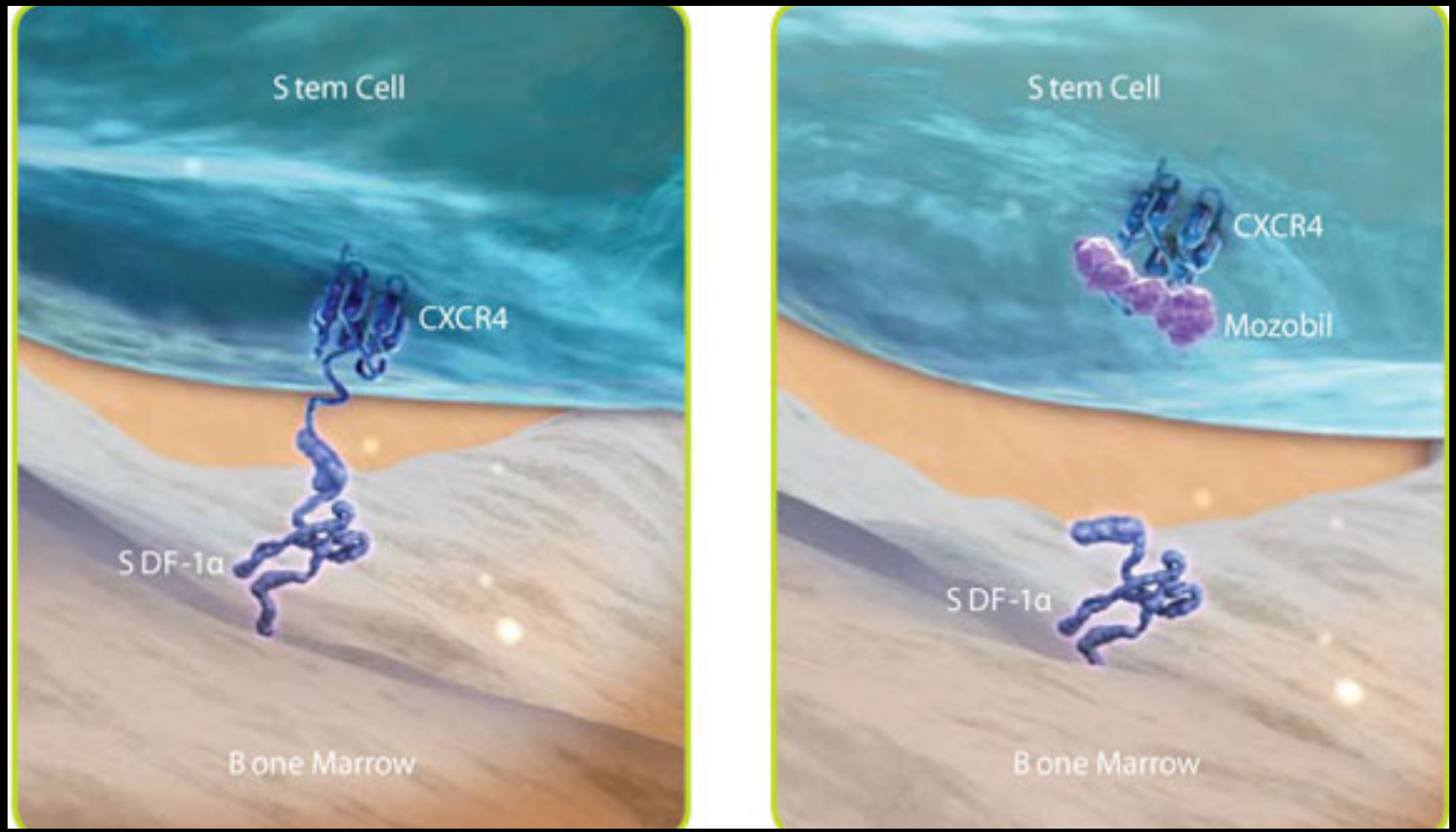
- Spleen and LN niches are less well characterized

BMNR LLPC Niche: Druggable Targets



CXCR4:CXCL12 Blockade

- Plerixafor (*Mozobil*, Sanofi)



IL-6 Blockade

- *Tocilizumab (Actemra,* Genentech*)* IL6R
- *Siltuximab (Sylvant,* Janssen*)* IL6

BAFF Inhibition

- Belimumab (*Actemra*, Glaxo Smith Kline)
- Tabalumab (Lilly)

New Druggable Targets for AMR: Conclusions

- A significant number of innovative approaches have emerged over the past several years that
  - Ig degradation
  - Target early stages of classical complement cascade

New Druggable Targets for AMR: Conclusions

- Plasma cell targeted therapeutic approaches include
  - Newer proteasome inhibitors
    - Irreversible inhibitors
  - Selective IP inhibitors
  - Proximal proteasome inhibitors
  - Plasma cell niche components

New Druggable Targets for AMR: Combinatorial Regimens

- Antihumoral therapeutic regimens, similar to those that target T cell responses are likely to be combinatorial regimens

- Requisite properties for AMR regimens
  - Mechanism for dealing with preexisting Ab
  - Mechanisms for dealing with preexisting cell populations
  - Mechanisms for dealing with newly produced cellular populations

- *Combinatorial regimens provide the opportunity to achieve synergy*