Targets and therapies for pemphigoid and pemphigus

Peter Marinkovich,
Stanford University
Pemphigoid diseases: multiple antigens

- Desmogleins 1 and 3 (pemphigus)
- BPAG1/ BP230 (bullous pemphigoid)
- BP180/ cgn XVII (bullous/cicatritial pemphigoid)
- Cgn XVII exodomain (linear IgA pemphigoid)
- 1 M NaCl
- Laminin 332 (cicatritial pemphigoid)
- 105 kD, 200 kD antigens (anti-105, anti-200 pemphigoid)
- Type VII collagen (epidermolysis bullosa acquisita)
Bullous Pemphigoid
Cicatritial Pemphigoid
Fig 3 (a) Histopathology of bullous pemphigoid lesion shows subepidermal splitting and a dense inflammatory infiltrate of eosinophils and neutrophils in the upper dermis.

Mahaz Kayani, and Arif M Aslam BMJ 2017;357:bmj.j2169
Working towards an animal model of pemphigoid

Finding the right epitope

Liu and Diaz
Which immune cells are needed for pemphigoid?
Neutrophil elastase in pemphigoid

A \textit{In vitro} DEJ separation by NE

\begin{center}
\begin{tabular}{ccc}
\text{Treatment:} & NONE & NE & GB \\
\end{tabular}
\end{center}

B \textit{In vivo} DEJ separation by NE

\begin{center}
\begin{tabular}{c|cccc}
\text{Strain:} & WT & NE/- & GB/- & NE/- \\
\hline
\text{BP180} \text{(intact)} & & & & \\
\text{BP180} \text{(degraded)} & & & & \\
\hline
1 & - & - & 2.5m & - \\
2 & - & - & - & 2.5m \\
3 & - & - & - & - \\
4 & - & - & - & - \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c|ccc}
\text{mPMN:} & GB/- & NE/- & \\
\hline
\text{Blisters} & + & - & + \\
\end{tabular}
\end{center}
Mast cells and macrophages in pemphigoid

Liu and Diaz
Pemphigoid pathophysiology summary

Schmidt and Zillikens, Lancet, 2013
Current Pemphigoid Therapy

- Topicals – useful! (steroids, tacrolimus)
- Systemic steroids
- Steroid sparing agents
  - Cellcept
  - Cytoxan
  - Rituximab
- Adjuncts
  - Plasmapheresis
  - IV IgG
  - Tetracycline/Niacinamide/Curcumin
Rituximab Therapy

- Oncology dose: 375 mg/Meters\(^2\) weekly for 4 wks
- Rheumatology dose: 1000 mg two doses two weeks apart
- Pre-labs: Hepatitis panel, TB testing, CBC, screen for chronic infections
- Infusions: premeds: solumedrol, benadryl, acetaminophen
- Infusion reactions: urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events.
- For infusion reactions: Stop infusion, monitor vital signs
- For mild reactions, once patient stable restart at 50% infusion rate
- For severe reactions, give glucocorticoids, epinephrine, bronchodilators, oxygen as needed
IV IgG Therapy

• Loading Dose: 2g/kg given over three days
• Maintenance: 0.4 to 2 g/kg every three to four weeks
• Pre-labs Serum IgA, consider hepatitis panel
• Administration: Slow initial infusion rate
  • increasing gradually as tolerated
• Premeds: benadryl, tylenol, ondansetron or anti-nausea meds, solumedrol
Omalizumab in Bullous Pemphigoid

Yu et al, JAAD, 2014
Evaluation of Safety, Efficacy and Pharmacodynamic Effect of Bertilimumab in Patients With Bullous Pemphigoid

| Bertilimumab: Anti Eotaxin-1 mAb | Prevents Eotaxin-1-induced chemotaxis of eosinophils and neutralizes Eotaxin-1 in the circulation, preventing eosinophil migration |

- open-label treatment period lasting 4 weeks consisting of IV infusion of bertilimumab on Days 0, 14, 28 with follow-up of 13 weeks
- Patients will receive concomitant oral steroids
- Eligibility: moderate to severe BP age 60 and older
- Contact: Celia Zinger: celia.zinger@immunepharma.com
Eosinophils are Predominant in the BP Inflammatory Process

Bertilimumab Neutralizes Eotaxin-1, a Key Regulator of Eosinophils

Circulating autoantibodies bind to antigen BP 180 in the skin

- Circulating autoantibodies
- Antigen BP 180

A high density of autoantibodies induce complement binding and production of cytokines and chemokines in mast cells, including eotaxin-1

- Autoantibodies
- Complement binding
- Cytokines and chemokines
- Mast cells
- Eotaxin-1

Eotaxin-1 binds to CCR3, the main chemokine receptor expressed on eosinophils, to induce eosinophil migration

- Eotaxin-1
- CCR3

Immigration of eosinophils into the skin leads to secretion of large amounts of eosinophil-derived proteases

- Eosinophils
- Skin
- Secretion
- Proteases
Ixekizumab in the Treatment of Bullous Pemphigoid

- Interleukin (IL)-17 identified as driver of inflammation in Bullous Pemphigoid (BP)

- single center, exploratory, open-label study of 12 patients with BP.

- Study Start Date: August 15, 2017
  Scottsdale AZ, Mayo Clinic

- Contact Narcelle Jean-Louis
  480-301-4714

IL-17 inhibitors:
(Targets and inhibits the action of cytokine IL17, a messenger involved in the pro-inflammatory pathway)

Taltz® (ixekizumab) – Eli Lilly and Company

Recommended dose is a starting dose of 160mg, followed by a dose of 80 mg every 2 weeks for 3 months and then every 4 weeks for maintenance.

Given by self-injection

Zebrowska et al, Mediators Inflammation, 2017
Current Pemphigus Therapy

• Topicals – only mildly effective
• Steroid sparing agents
  • Cellcept – does not cause hepatitis like Imuran
  • Cytoxan
  • Rituximab – assuming greater importance
• Steroids
• Dapsone – only mild cases
• Adjuncts
  • Plasmapheresis
  • IV IgG
Autoantibodies in pemphigus: how do they work?

Kasperkiewicz et al, Nature Reviews: Disease Primers 2017
Targeted therapies in pemphigus

Kasperkiewicz et al, Nature Reviews: Disease Primers 2017
Targeted therapy for pemphigus

• An Open-Label, Phase 2, Pilot Study Investigating the Safety, Clinical Activity, Pharmacokinetics, and Pharmacodynamics of Oral Treatment with the BTK Inhibitor PRN1008 in Patients With Pemphigus Vulgaris
PRN1008 differentiation is driven by its unique features: superior safety, high efficacy

Highly selective with durable binding to BTK

Extended inhibition of BTK after single oral dose through covalent binding with short half-life

Reversibility of binding to avoid potential safety risks

<table>
<thead>
<tr>
<th>BTK IC₅₀ (nM)</th>
<th>% Occupancy (24h)</th>
</tr>
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<tbody>
<tr>
<td>BTK</td>
<td>BLK</td>
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<td>1.3</td>
<td>85</td>
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PRN1008 shows profound therapeutic effect with fast onset and disease reversal in animal model

**Ankle Diameter Over Time – Day 10 Enrollment**

Oral dosing in rat collagen induced arthritis (CIA) therapeutic model
- Rapid onset of action
- Disease reversal
- Joint and bone protection
PRN1008 reverses disease in therapeutic rat CIA model as shown in micro CT scans
A Safety Study of SYNT001 in Subjects With Pemphigus

• A Phase 1b, Multicenter, Open-Label, Safety, Tolerability, and Activity Study of SYNT001 in Subjects With Chronic Pemphigus (Vulgaris or Foliaceus)

• Contact: Syntimmune 617-913-1681 SYNT001Clinical@syntimmune.com
The (Not So) Neonatal Fc Receptor Is Widely Expressed in Adult Life

• Expression in numerous cell types
  • Parenchymal: hepatocytes, polarized epithelial cells, endothelial cells\(^1\)
  • Hematopoietic: macrophages, dendritic cells, neutrophils, B cells\(^1,2,3\)

• Expression in a wide range of tissues
  • Lung, intestines, kidney, GU tract, brain, liver\(^1\)

• Developmentally regulated\(^1\)
  • High levels neonatal rodent intestinal epithelium
  • Placenta of human

1. Roopenian DC, Nat Rev Immunol. 2007
FcRn protects IgG from breakdown

- FcRn binds IgG and protects it from degradation by trafficking away from the lysosome in antigen presenting cells and endothelial cells and responsible for the long serum IgG half-life

- Reason for the prolonged t½ IgG (21 days in humans)

- Avoidance of immunogenicity

Thanks from blistering disease clinic