# Autoimmune dermatoses in cats and dogs: *the pemphigus and pemphigoid complex*

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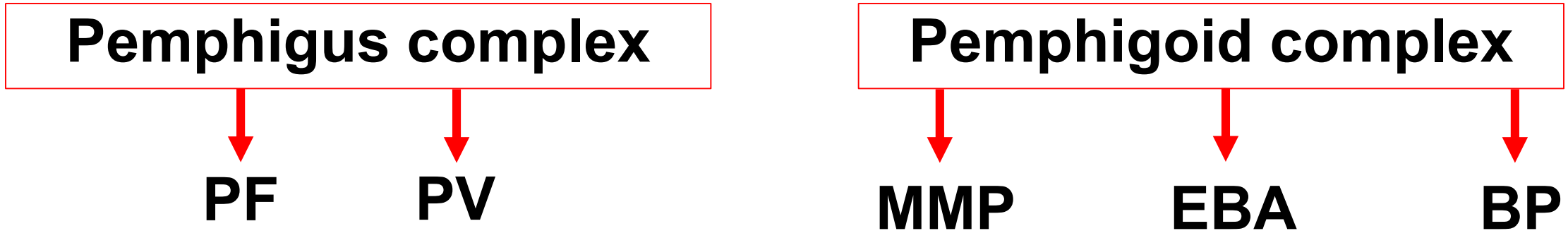
NAVDF RESIDENT EDUCATION FORUM
8TH MAY, 2023

Virginia-Maryland College of Veterinary Medicine

VIRGINIA TECH

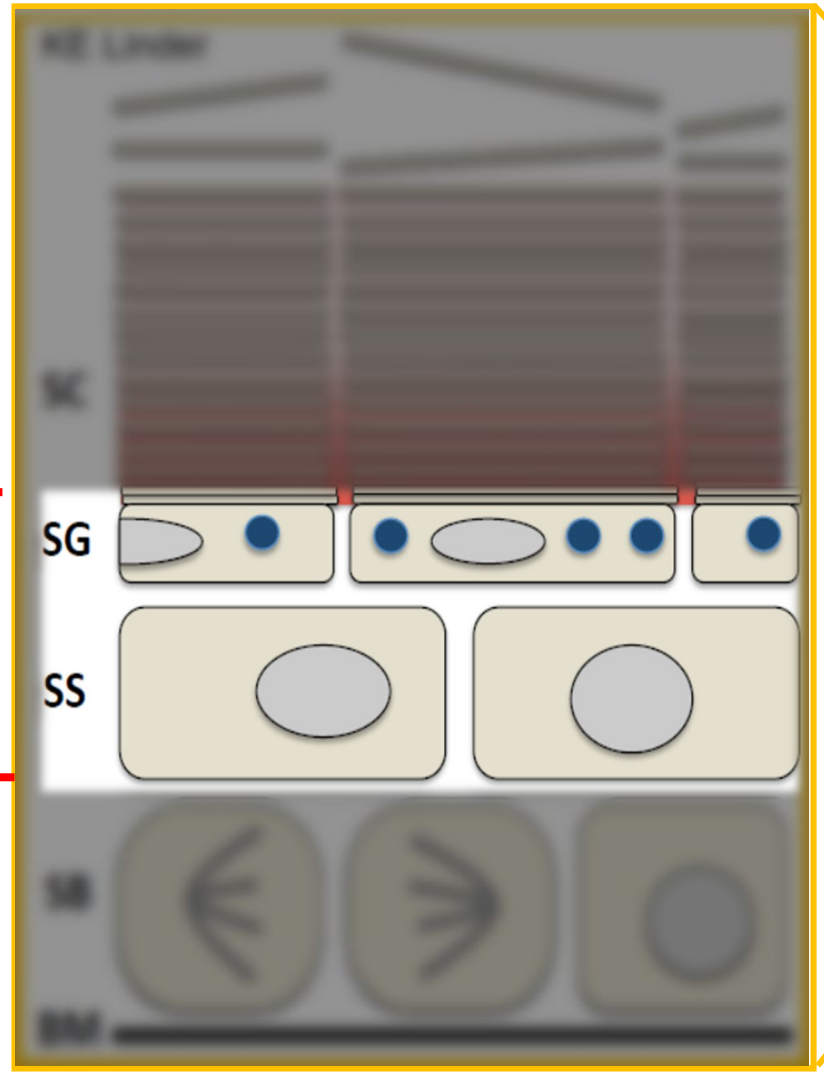
# Outline

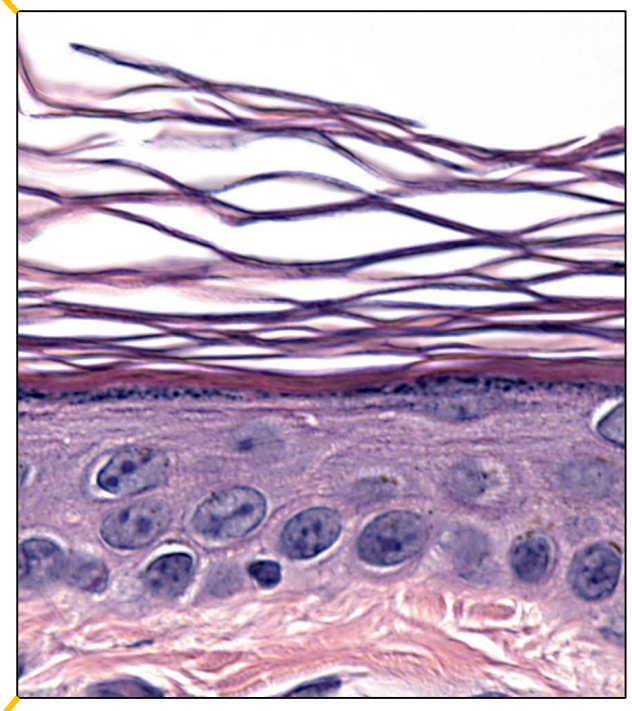



- Etiology: autoantigen(s)
- Pathogenesis: mechanisms of acantholysis and blister formation
- Clinicohistological features: highlights only
- Treatment and outcome: outline

# Pemphigus complex
## *Localization of lesions*

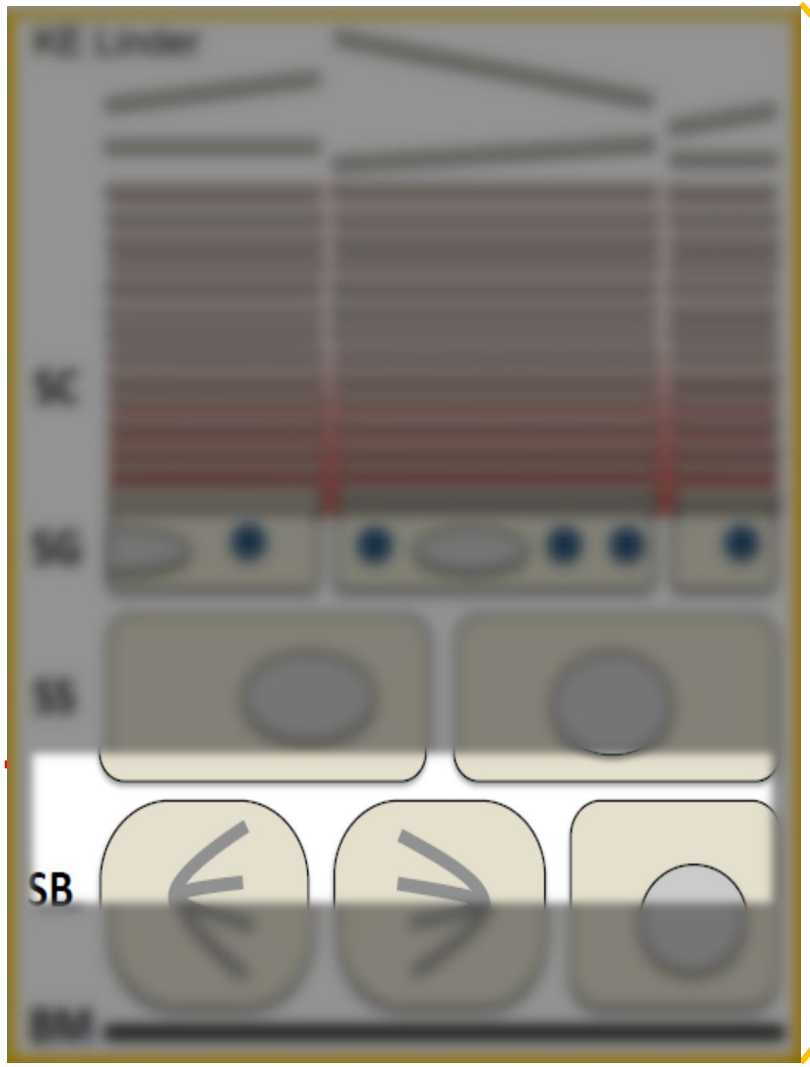
Pemphigus foliaceus

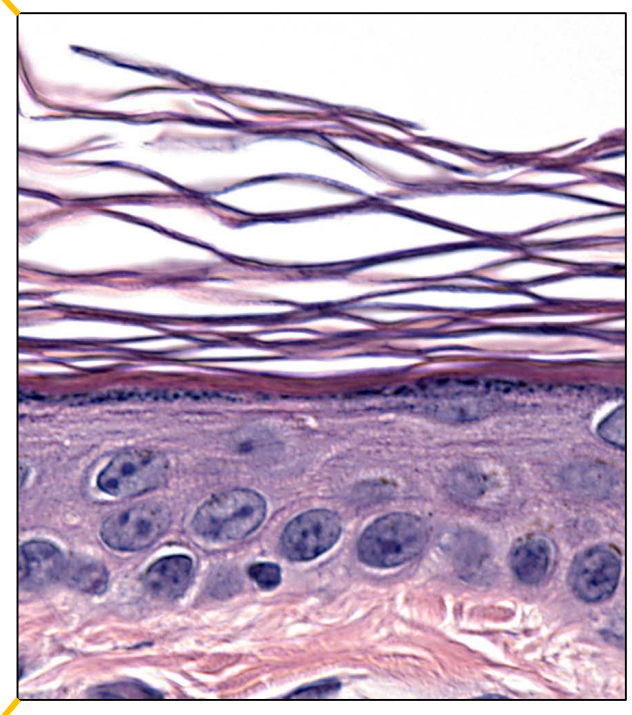


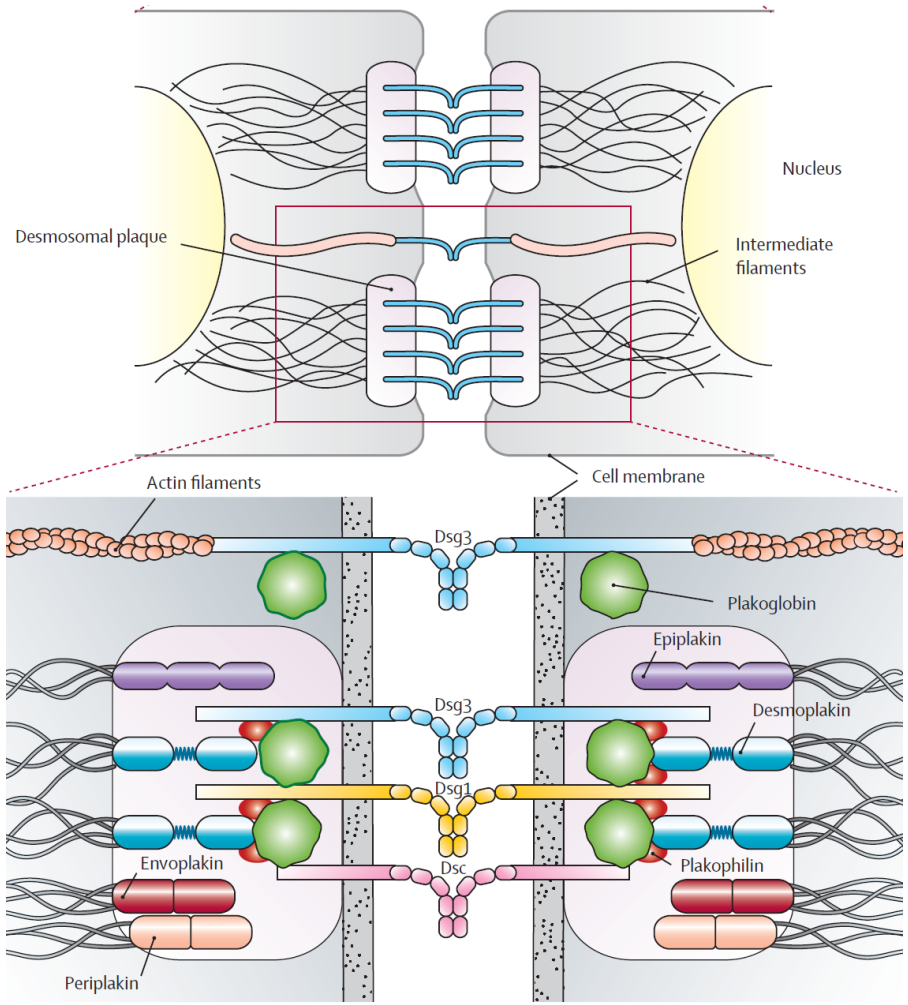
# Pemphigus complex
## *Localization of lesions*

Pemphigus vulgaris



# Pemphigus foliaceus




(Modified from Schmidt, Lancet 2019)

Major autoantigen:

- Humans: DSG-1
- Dogs: DSC-1
- Cats:
  - ➢molecular target is unknown yet
  - ➢anti-keratinocyte IgG was detected in 23 of 30 cats with PF (Levy *et al*, Vet Dermatol 2020)

# Pemphigus foliaceus
## *Etiopathogenesis*

- **Spontaneous**
- UV light – induction of flare (Olivry, *Vet Dermatol* 2006)

# Pemphigus foliaceus
## *Drug-triggered/associated*

## Dogs

- Trimethoprim-sulfamethoxazole**?** (White, *Vet Dermatol* 2002, Noli, *Vet Q* 1995)
- Topical ketoconazole**?** (Sung, *Can Vet* J 2017)
- Insecticide-triggered**?**:
  - Topical: Promeris®, Certifect®, Vectra3D®
  - Oral: Nexgard®

# Pemphigus foliaceus
## *Drug-triggered/associated*

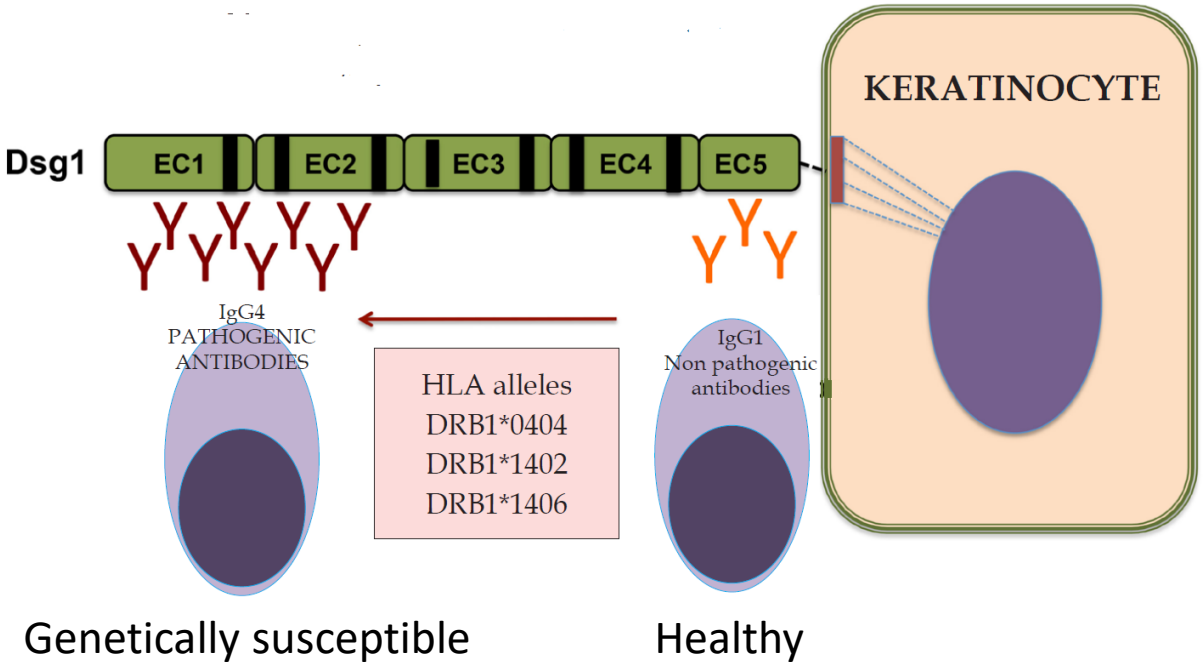
### Cats

- Econazole/neomycin/triamcinolone/amoxicillin (Affolter, *Vet Dermatol* 1992)
- Itraconazole/lime sulfur (Preziosi, *Vet Dermatol* 2003)
- **Cimetidine (McEwan, *JSAP* 1987)**
- **Doxycycline (Prelaud, *Point Vet* 1991)**

# ENDEMIC Pemphigus foliaceus
## *Etiopathogenesis*

*Fogo selvagem* (Brazil)

- sand fly salivary antigen **LJM11**




Endemic PF in south Tunisia

- younger women living in poor localities
- high temperature, intense UV radiation, contact with ruminants, bacterial infections, and genetic susceptibility (Masmoudi, *J Leukoc Biol* 2019)

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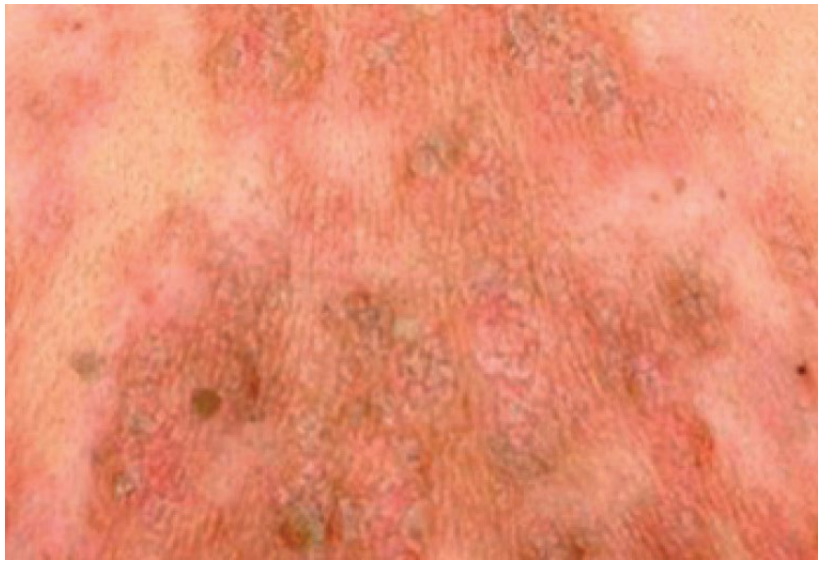
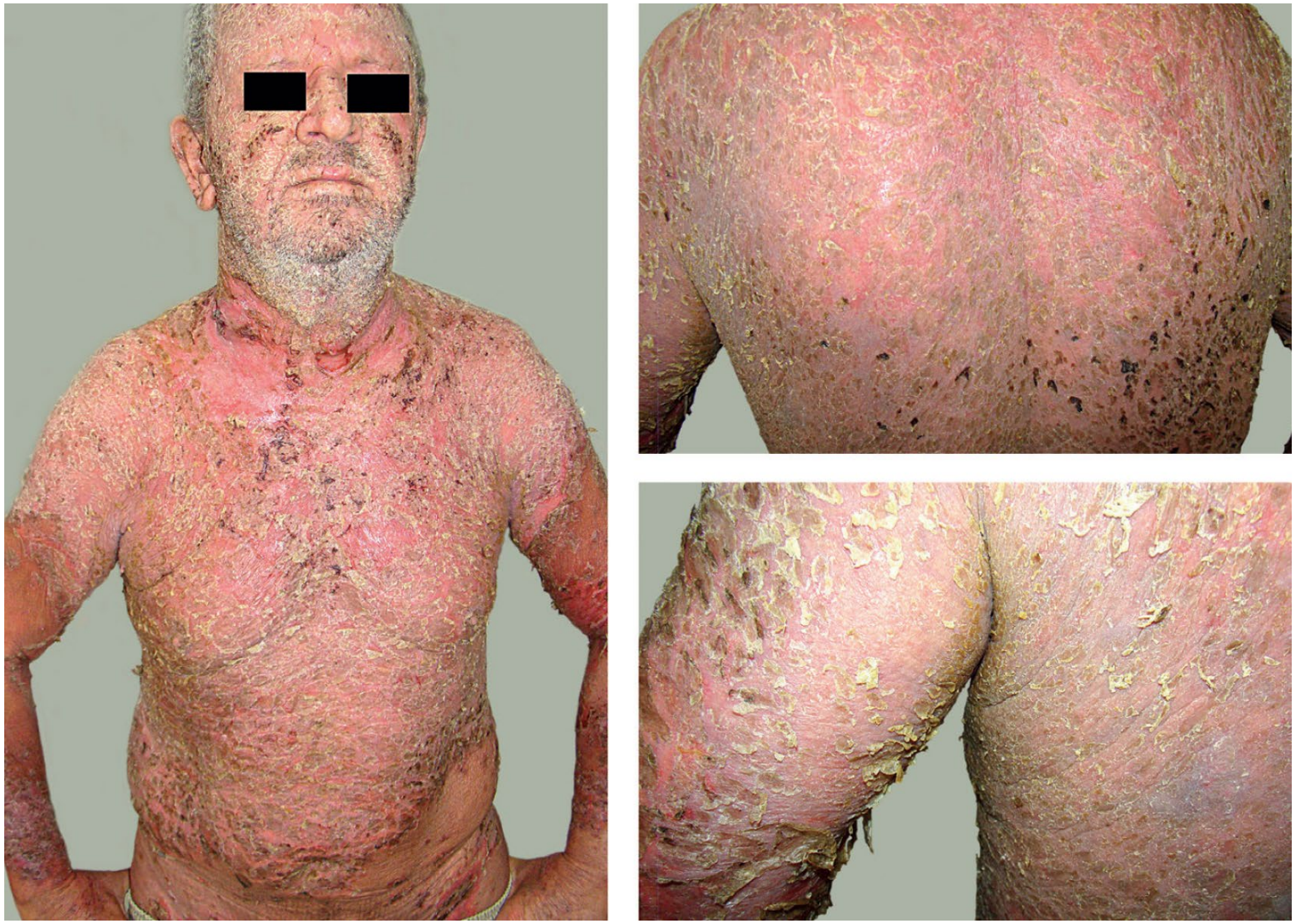
# Human pemphigus foliaceus
## *Clinical features*



Erythema, erosion and scaling

(Modified from Schmidt, Lancet 2019)

# Fogo selvagem



(Modified from Hans-Filho, An Bras Dermatol 2018)

# Canine pemphigus foliaceus
## *Clinical features*

- Facial-dominant

# Canine pemphigus foliaceus
## *Clinical features*

- Facial-dominant
- Generalized

# Canine pemphigus foliaceus
## *Clinical features*

- Facial-dominant
- Generalized
- Foot pad-exclusive

# Canine pemphigus foliaceus
## *Clinical features*

- Facial-dominant
- Generalized
- Foot pad-exclusive
- **Trunk-dominant**

ORIGINAL ARTICLE

Veterinary Dermatology

# Trunk-dominant and classic facial pemphigus foliaceus in dogs – comparison of anti-desmocollin-1 and anti-desmoglein-1 autoantibodies and clinical presentations

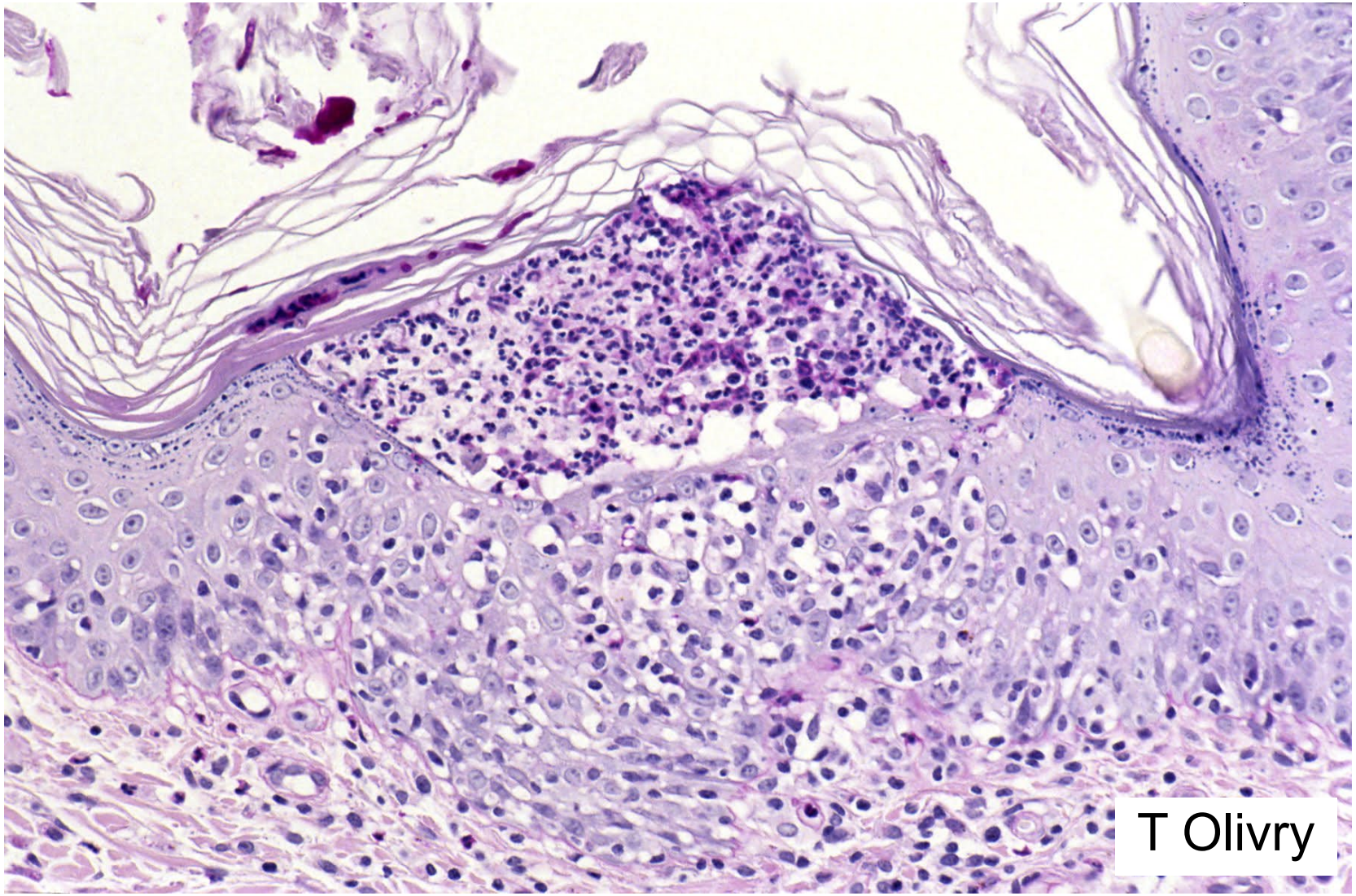
Petra Bizikova[1] | Keith E. Linder[2] | Lisa B. Mamo[1]

2022

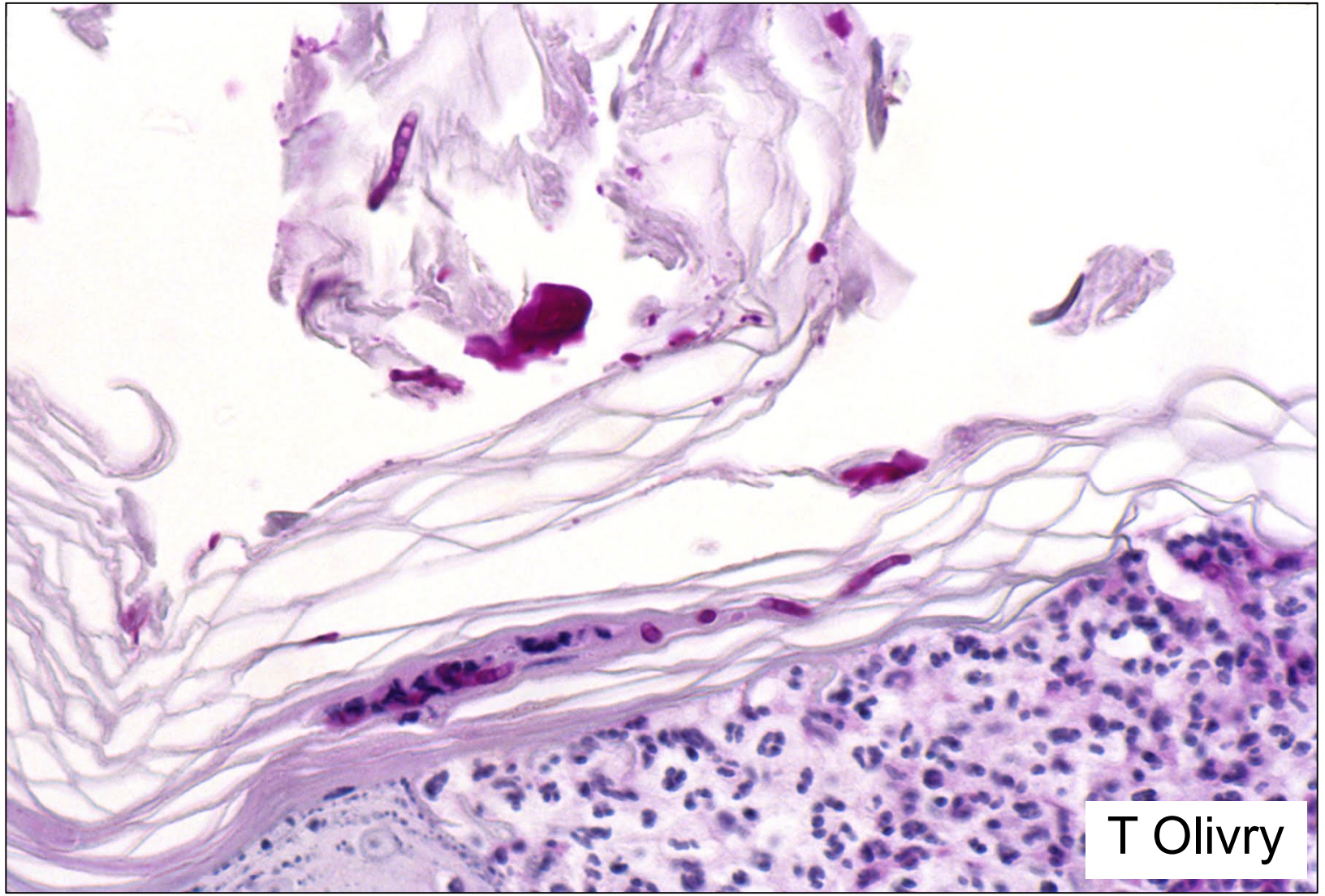
- Major autoantigen: DSC1 in trunk- and facial-dominant
- Ability to detect anti-DSC1 IgG lower in trunk-dominant (100% vs 58%)
- Negative detection of anti-DSC1 IgG **cannot** exclude PF
- Differentiation between pustular dermatophytosis and pyoderma (centrifugal expansion vs multiple foot pads, respectively)

# Pustular dermatophytosis
## *Clinical features*

# Histopathology



# Pustular dermatophytosis: *Histopathology*



# Feline pemphigus foliaceus
## *Clinical features*

*Compared to canine:*

- **Claw folds-exclusive** (14/122 cats, or 11%) (Bizikova *BMC Vet Res* 2019)

# Feline pemphigus foliaceus
## *Clinical features*

*Compared to canine:*

- Claw folds-exclusive (11%)
- **Areolar/periareolar region** (17/172 cats or 10%) (Bizikova, *BMC Vet Res* 2019)

# Canine pemphigus foliaceus
## *Treatment and outcome*

- Conventional vs pulse therapy of oral glucocorticoid (GC)

Veterinary Dermatology

*Vet Dermatol* 2015; **26**: 354–e77 DOI: 10.1111/vde.12241

# Oral glucocorticoid pulse therapy for induction of treatment of canine pemphigus foliaceus – a comparative study

**Petra Bizikova*† and Thierry Olivry*†**

**Pulse therapy group:**

- higher proportion of dogs achieving CR in the first 3 months
- a lower average of maximal oral GC
- minimal adverse effect when compared to 20 dogs that received the conventional dose

# Canine pemphigus foliaceus
## *Treatment and outcome*

- Conventional vs pulse therapy of oral GC
- Immunosuppressant: Azathioprine (AZA), cyclosporine (CsA), mycophenolate mofetil (MMF)
- Adjunct immunomodulatory drugs:
  - Tetracycline-niacinamide (White, *JAVMA* 1992: **1/8** dogs improved and Mueller, *JAAHA* 2006: **1/8** dogs benefited)
  - Polysulfated glycosaminoglycans (Simpson, *JAAHA* 2019):
- IVIG (Rahilly et al, *JVIM*, 2006) – 11 doses in total
- Bruton's tyrosine kinase inhibitor (BTKi)??

# Feline pemphigus foliaceus
## *Treatment and outcome*

| | Jordan, Vet Dermatol 2019 | Bizikova, BMC Vet Res 2019 |
|---|---|---|
| Oral glucocorticoid (GC) pulse vs conventional therapy | N/A | No apparent benefit |
| Most common drug used when clinical remission (CR) achieved | GC monotherapy (70%) | GC monotherapy (52%) |
| Complete remission with cyclosporine monotherapy | 0 | 2% |
| GC + cyclosporine: time-to-CR | N/A | 37 days (median) (n=140) |
| GC + chlorambucil: time-to-CR | N/A | 32 days (median) (n=140) |

Veterinary Dermatology

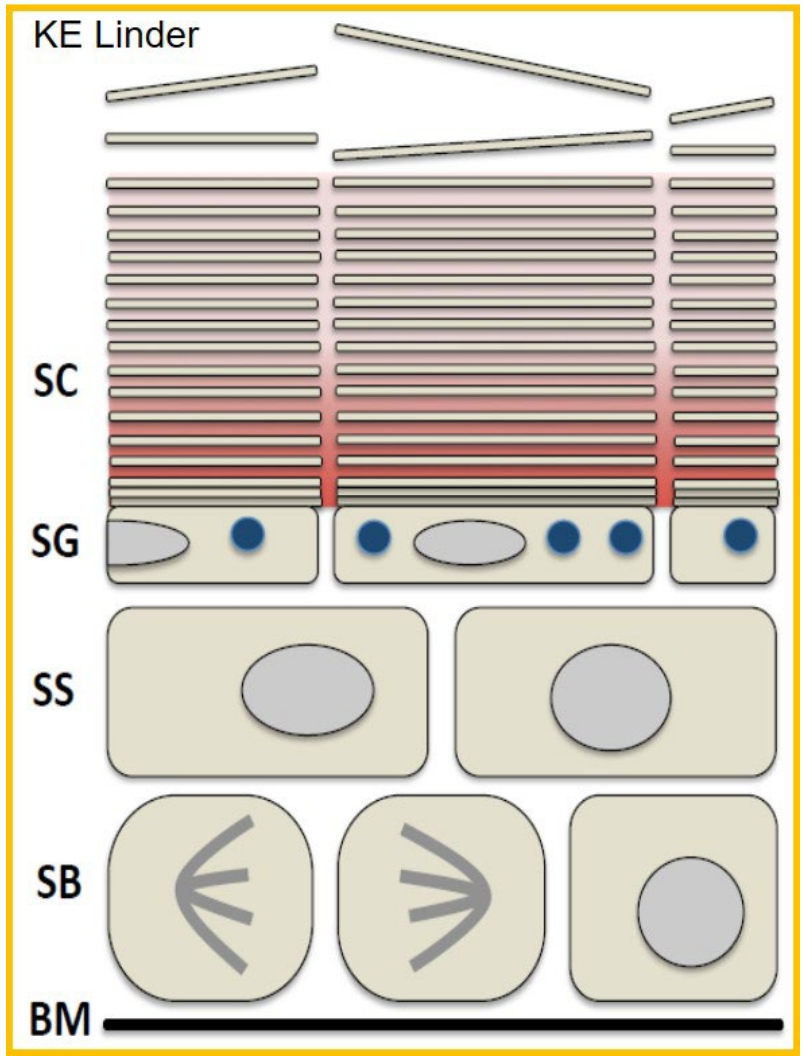
*Vet Dermatol* 2021; **32**: 299–301 DOI: 10.1111/vde.12949

# Beneficial effect of oclacitinib in a case of feline pemphigus foliaceus

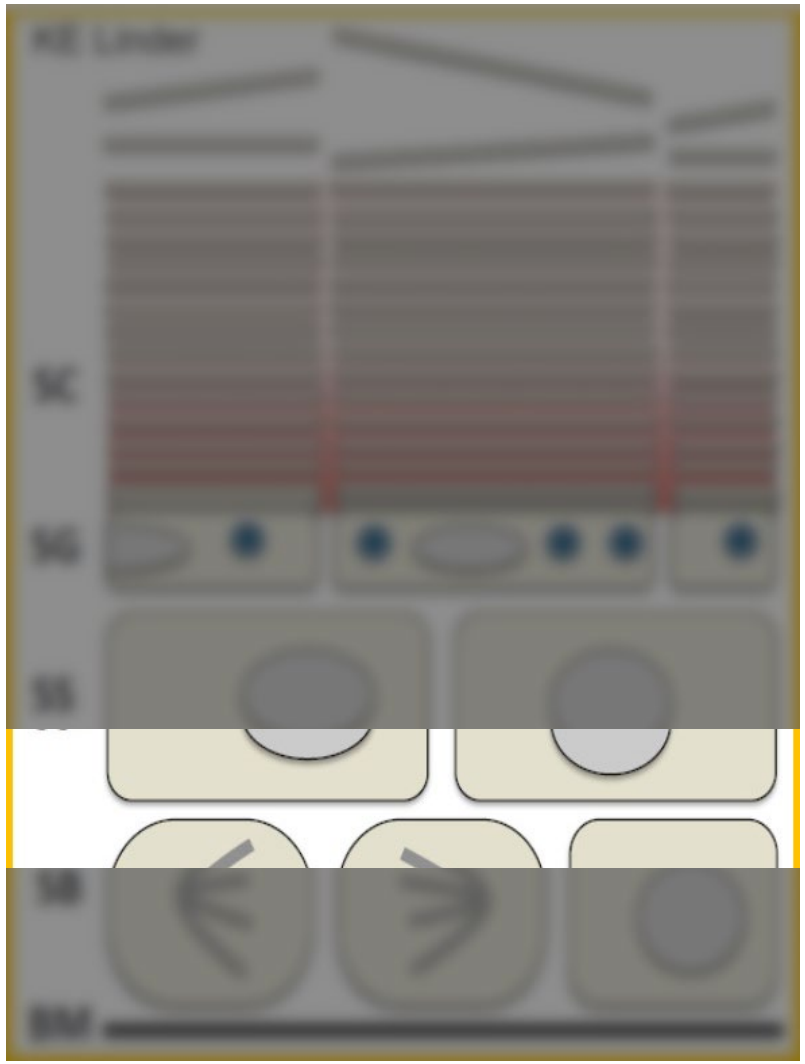
**Isaac Carrasco*, Marta Martínez* and Gloria Albinyana†**

- Oclacitinib 1mg/kg twice daily (BID)
- After 7 days: >50% decreased in pruritus and skin lesions
- Improvement maintained for up to 6 weeks on 0.5mg/kg BID

# Pemphigus vulgaris



# Pemphigus vulgaris

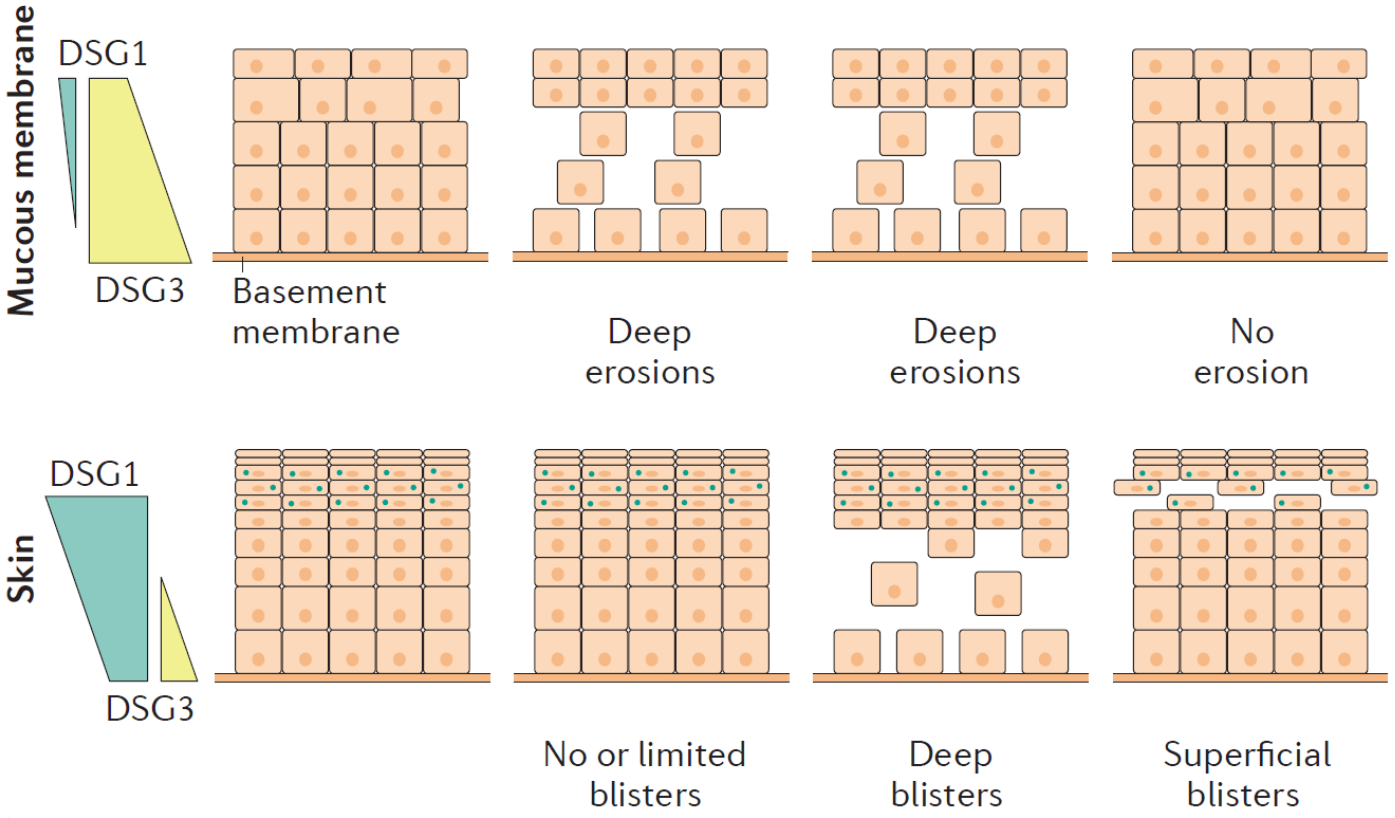


Major autoantigen:

- Humans: DSG-3 +/- DSG-1
- Dogs: DSG-3 (Olivry, *Exp Dermatol* 2003)
- Cats: unknown

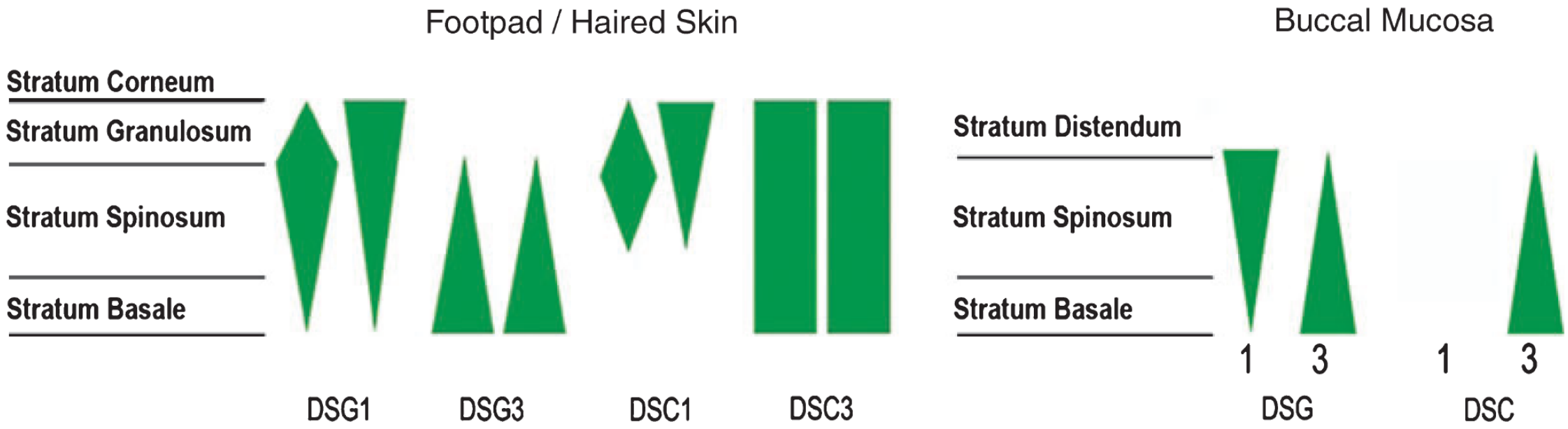
# Distribution and expression of DSG1 and DSG3: human skin vs mucous membrane

| | Healthy | Pemphigus vulgaris | | Pemphigus foliaceus |
|---|---|---|---|---|
| | | Mucosal-dominant type | Mucocutaneous type | |
| Anti-DSG1 IgG | No | No | Yes | Yes |
| Anti-DSG3 IgG | No | Yes | Yes | No |




(Modified from Kasperkiewicz et al, Nat Rev 2017)

# Distribution and expression of DSG1 and DSG3: **canine** footpad vs skin vs buccal mucosa




(Modified from Bizikova et al, Vet Dermatol 2010)

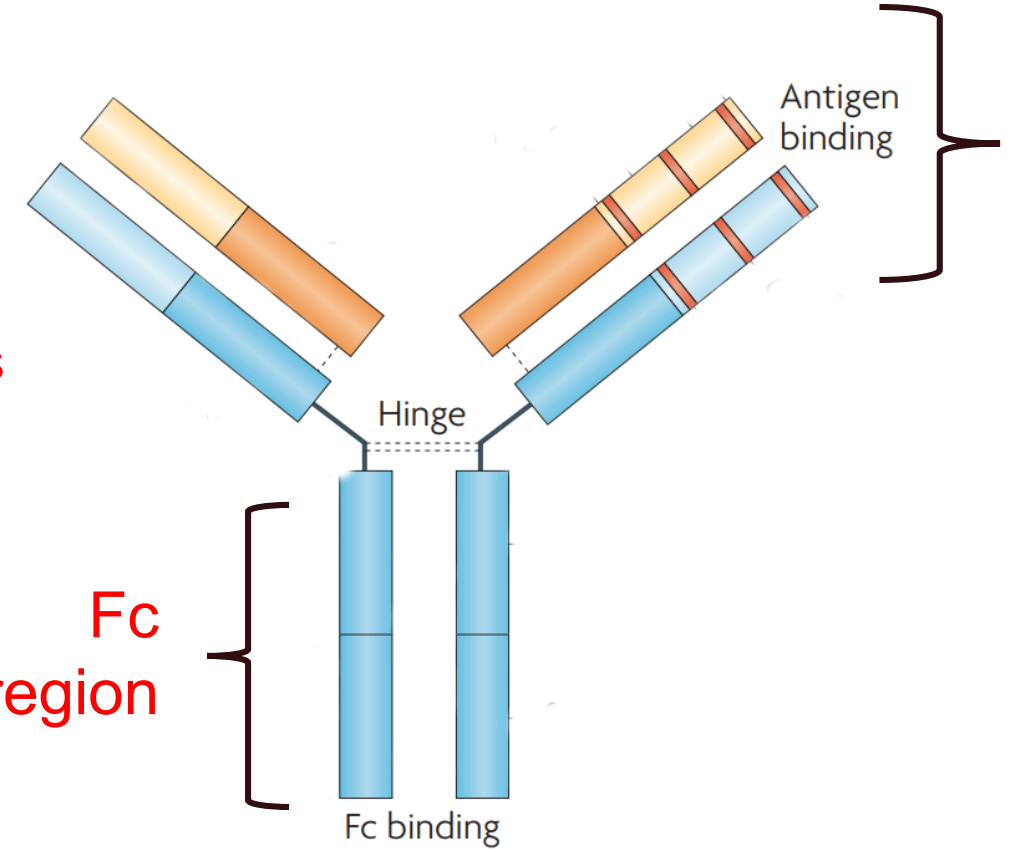
# Antibodies and mechanism of acantholysis

**Binds to:**

- Fcγ receptors on immune cells
- Neonatal Fcγ receptors (FcRn)
- C1q component of complement system

**Biological activity:**

- Antibody-dependent cell cytotoxicity (ADCC)
- Complement-dependent cytotoxicity (CDC)
- Antibody-dependent cell-mediated phagocytosis




**Binds to:**

- Antigen (autoantigen)
- Toxins
- Pathogens

**Biological activity:**

- Triggers desired/undesired biological effect

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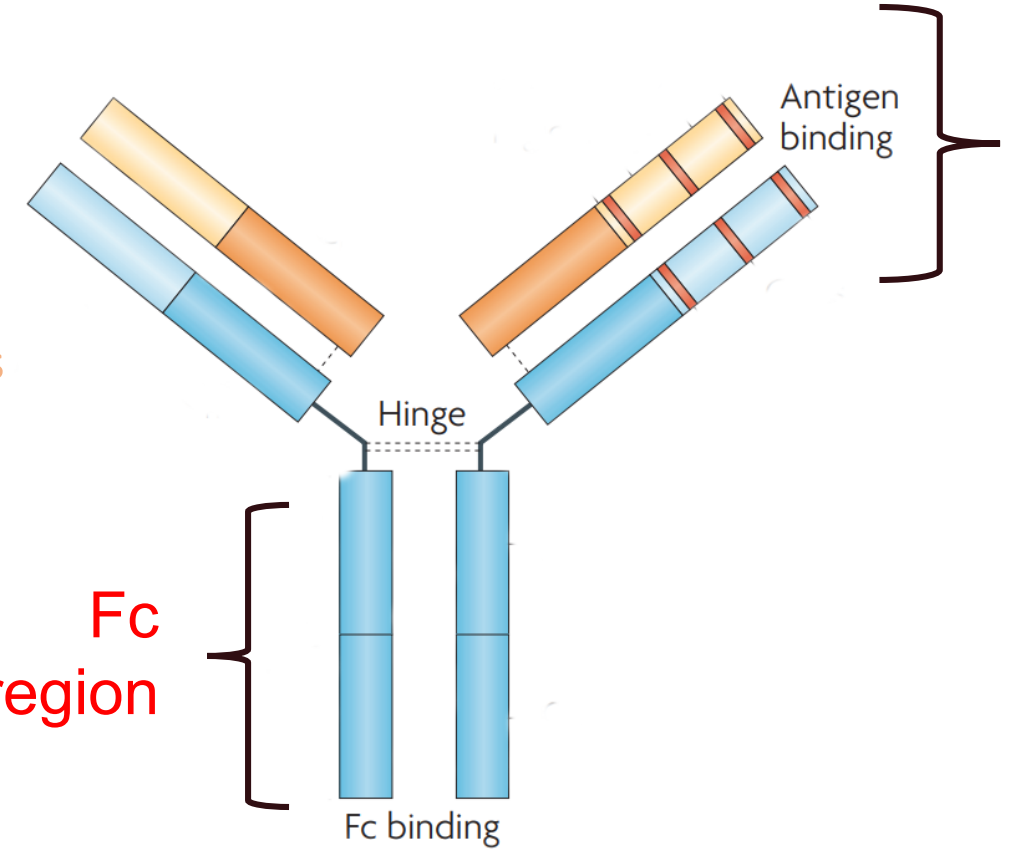


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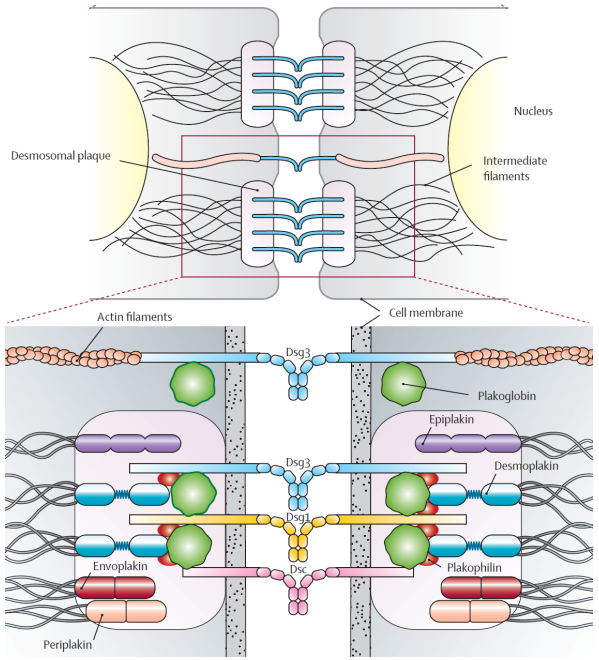
# *Mechanism of acantholysis in human PV*

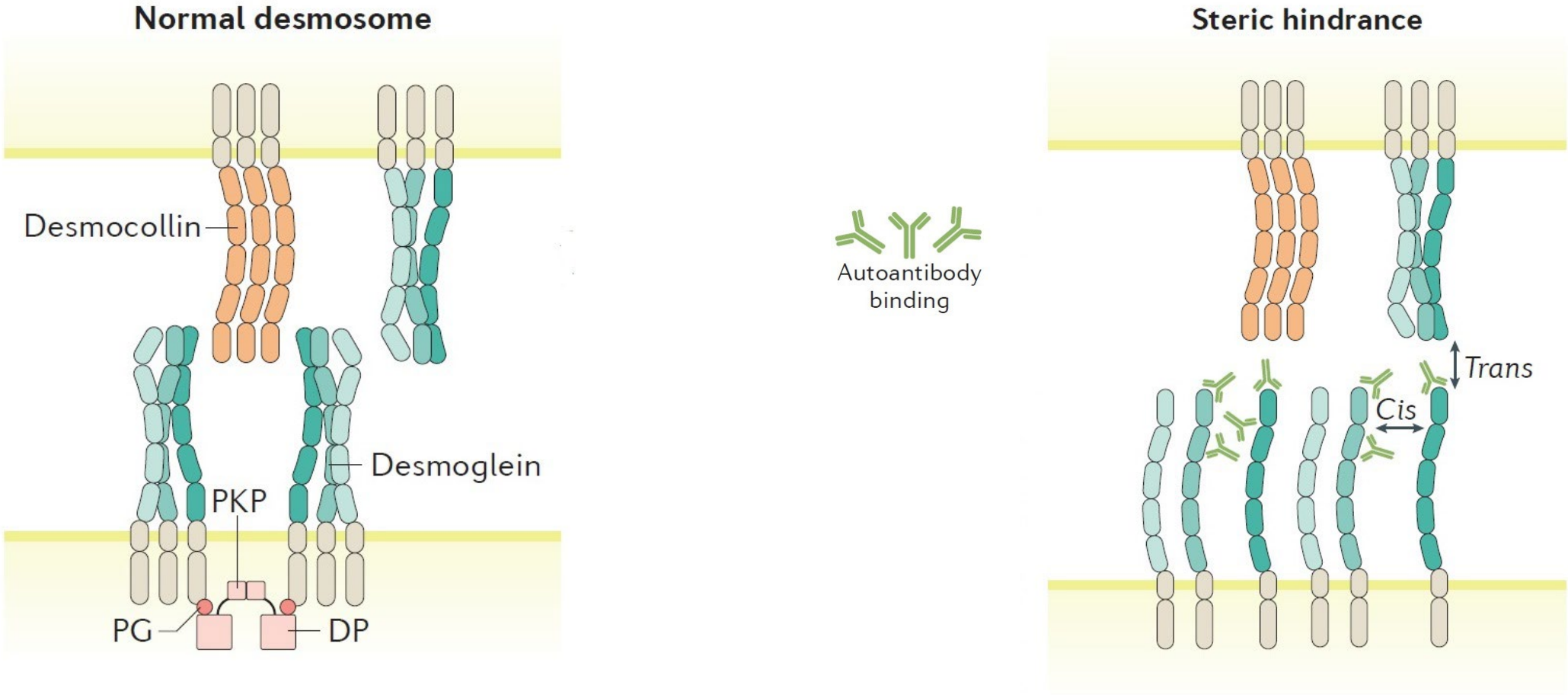
Steric hindrance

Desmoglein internalization and depletion

Signaling pathway interfering with cell adhesion

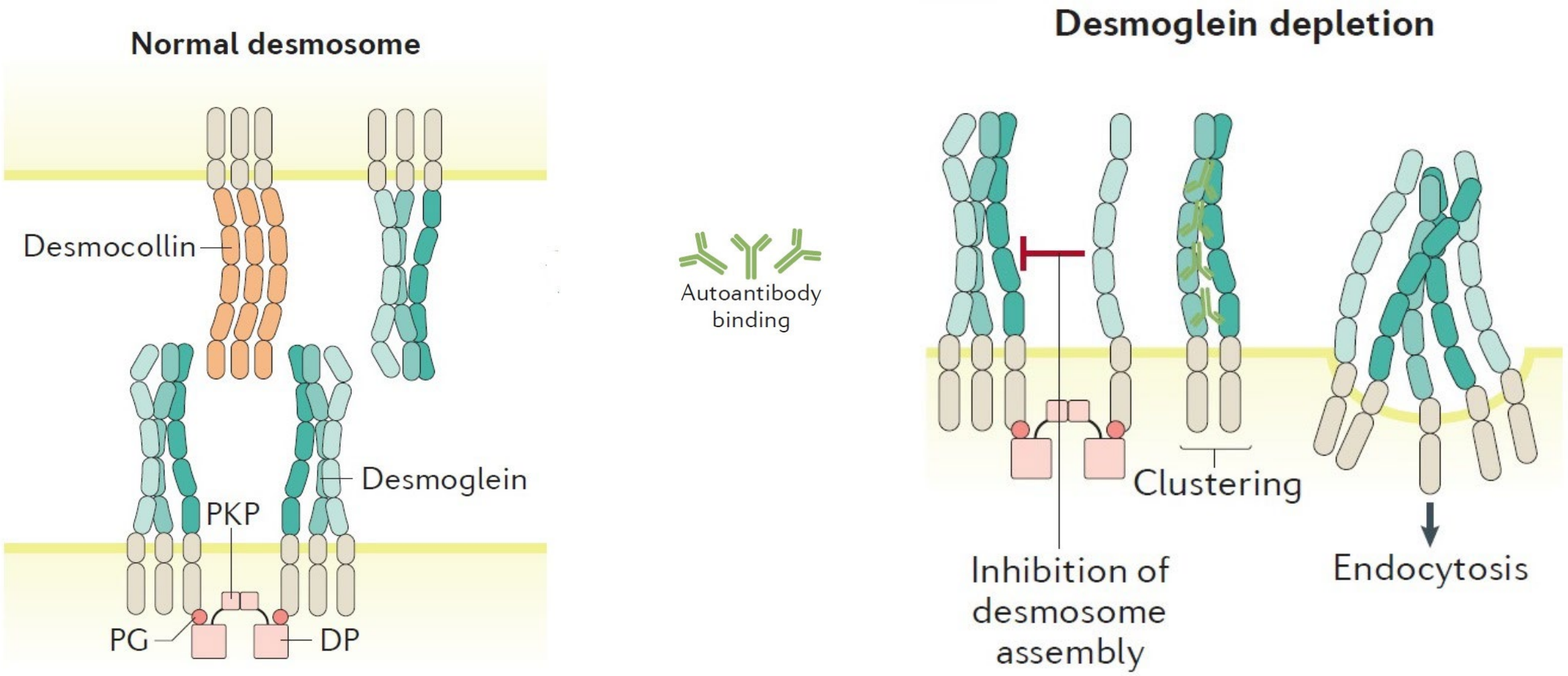


# *Mechanism of acantholysis in human PV*
## *Steric hindrance*




(Modified from Kasperkiewicz et al, Nat Rev 2017)

# Mechanism of acantholysis in human PV
## Desmoglein depletion

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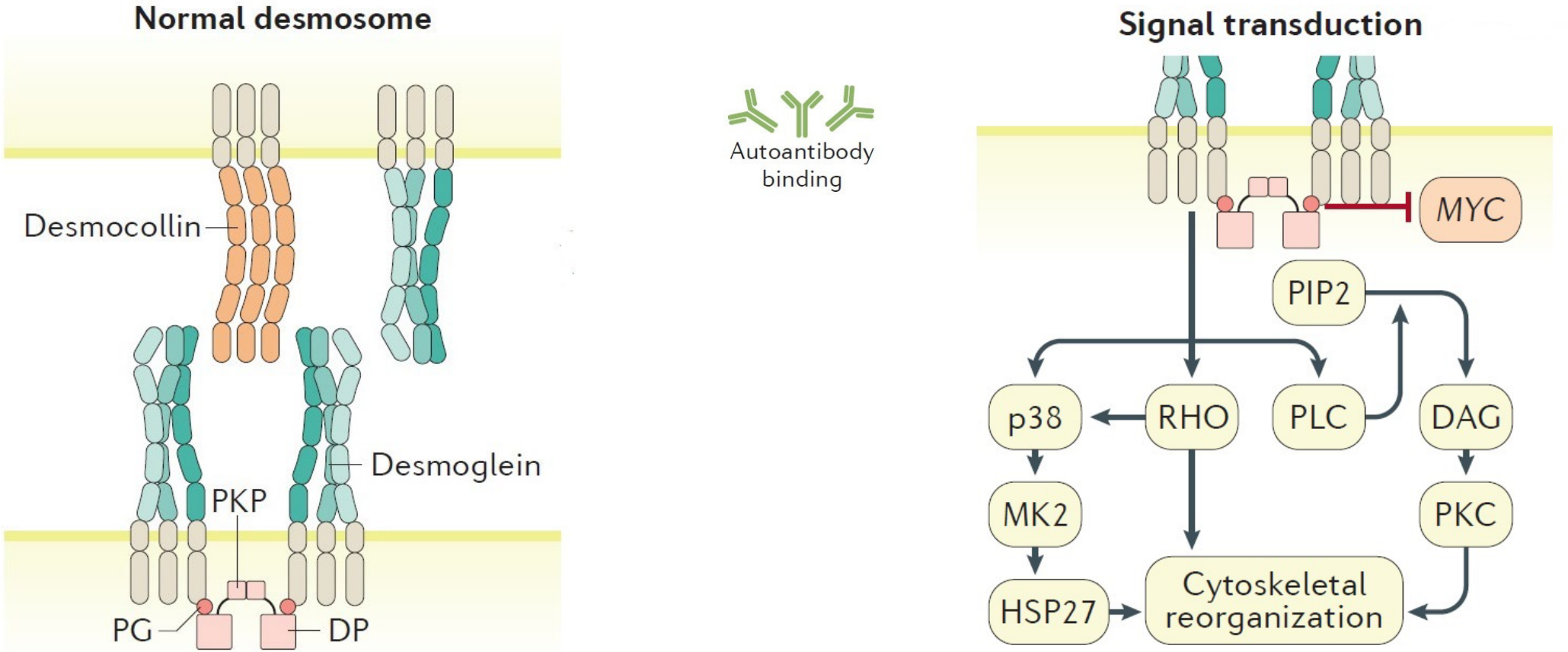
# Mechanism of acantholysis in human PV
## Signal transduction

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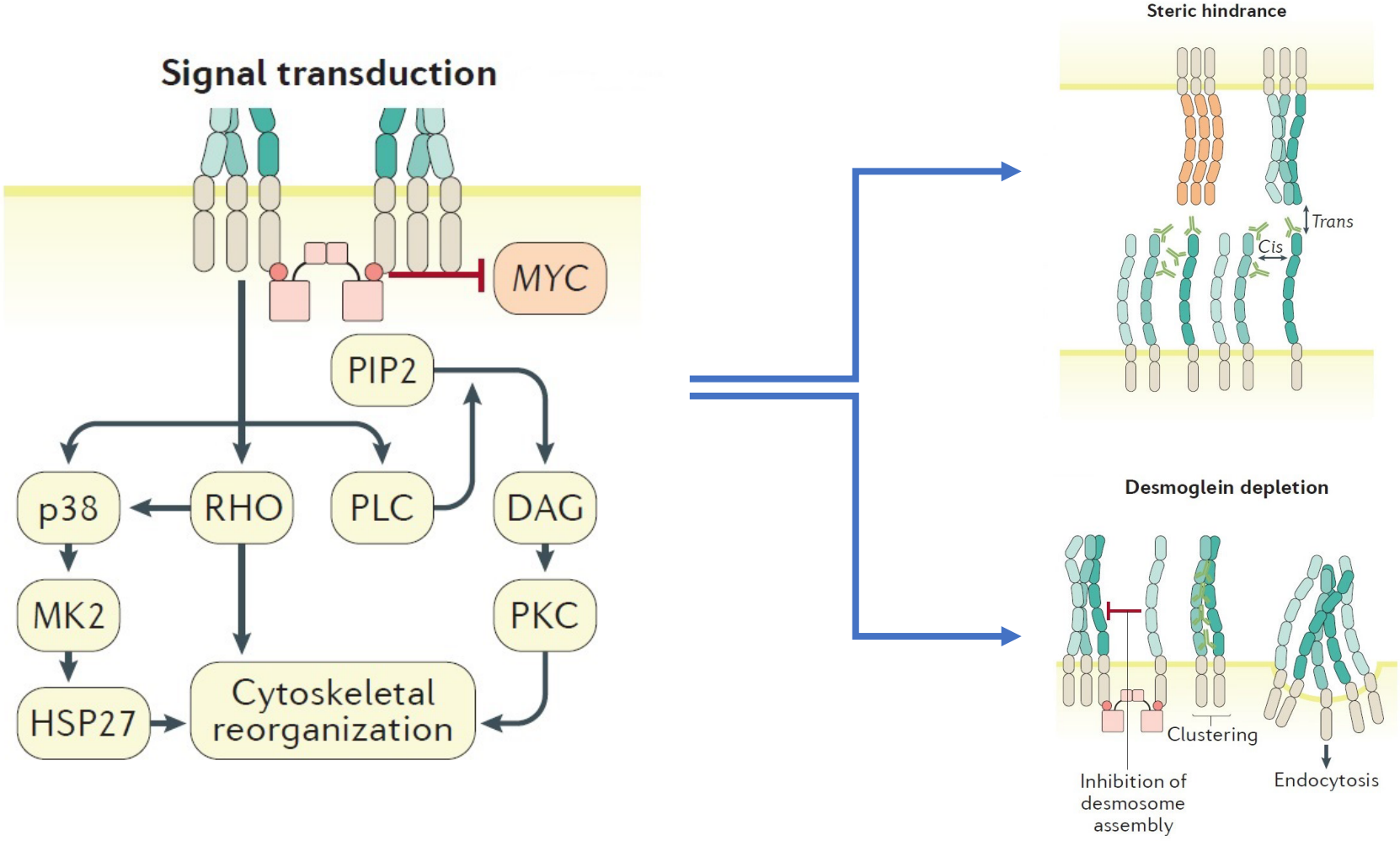
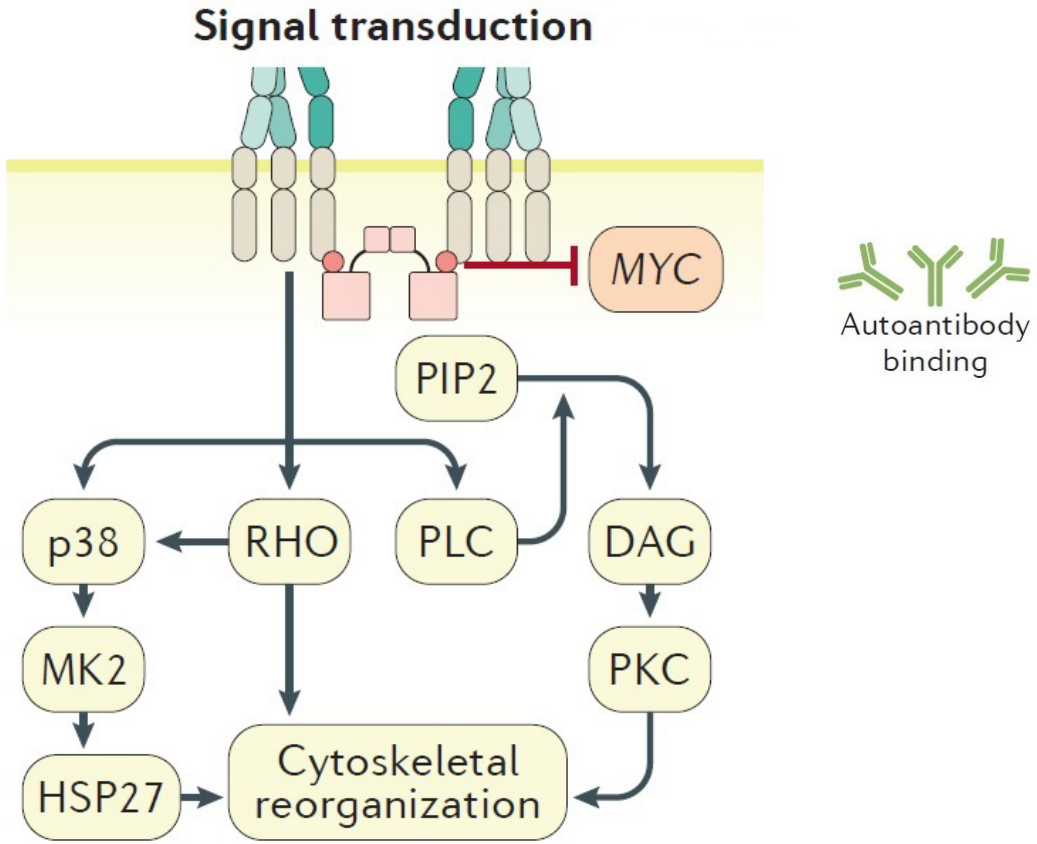
# Mechanism of acantholysis in human PV
## Signal transduction




(Modified from Kasperkiewicz et al, Nat Rev 2017)

# C-Myc in canine PV
## *Signal transduction*







- C-Myc: proto-oncogene that induces proliferation, transformation and apoptosis
- c-Myc is overexpressed in dogs with PV (Williamson et al, *Vet Dermatol* 2007)
- Overexpression of c-Myc interferes with signaling cascade involved in DSG-3 expression

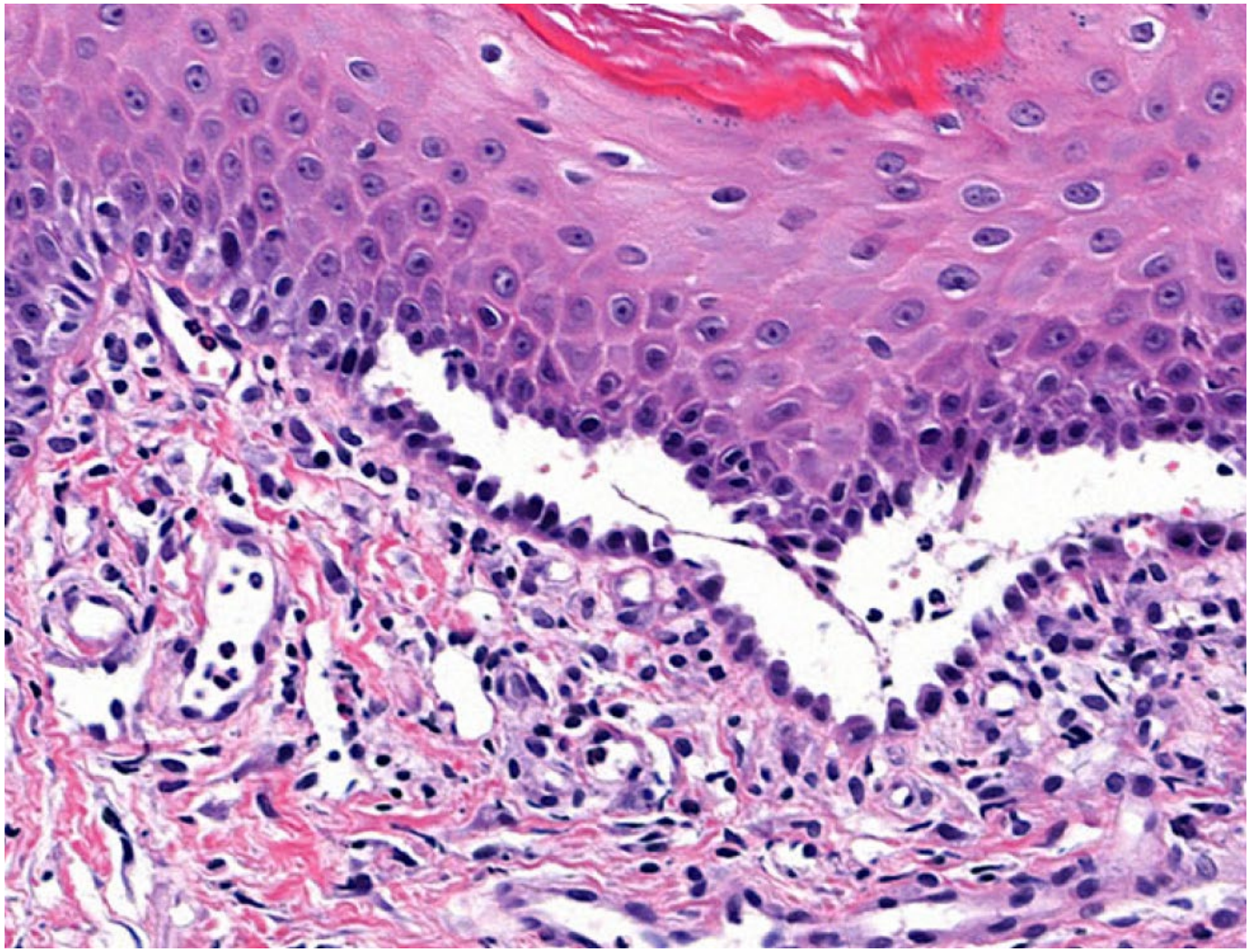
(Modified from Kasperkiewicz et al, Nat Rev 2017)

# *Canine pemphigus vulgaris*
## *Clinical features*

- **Nails-exclusive** involvement (sloughing) reported in 2 dogs (Scott, *JAAHA* 1982 and Carlotti, *PMCAC* 2000)
- **Foot pad-only involvement** reported in 1 dog (Carlotti, *PMCAC* 2000)

(Modified from Tham et al, *BMC Vet Res* 2020)

# Canine and feline PV: Histopathology

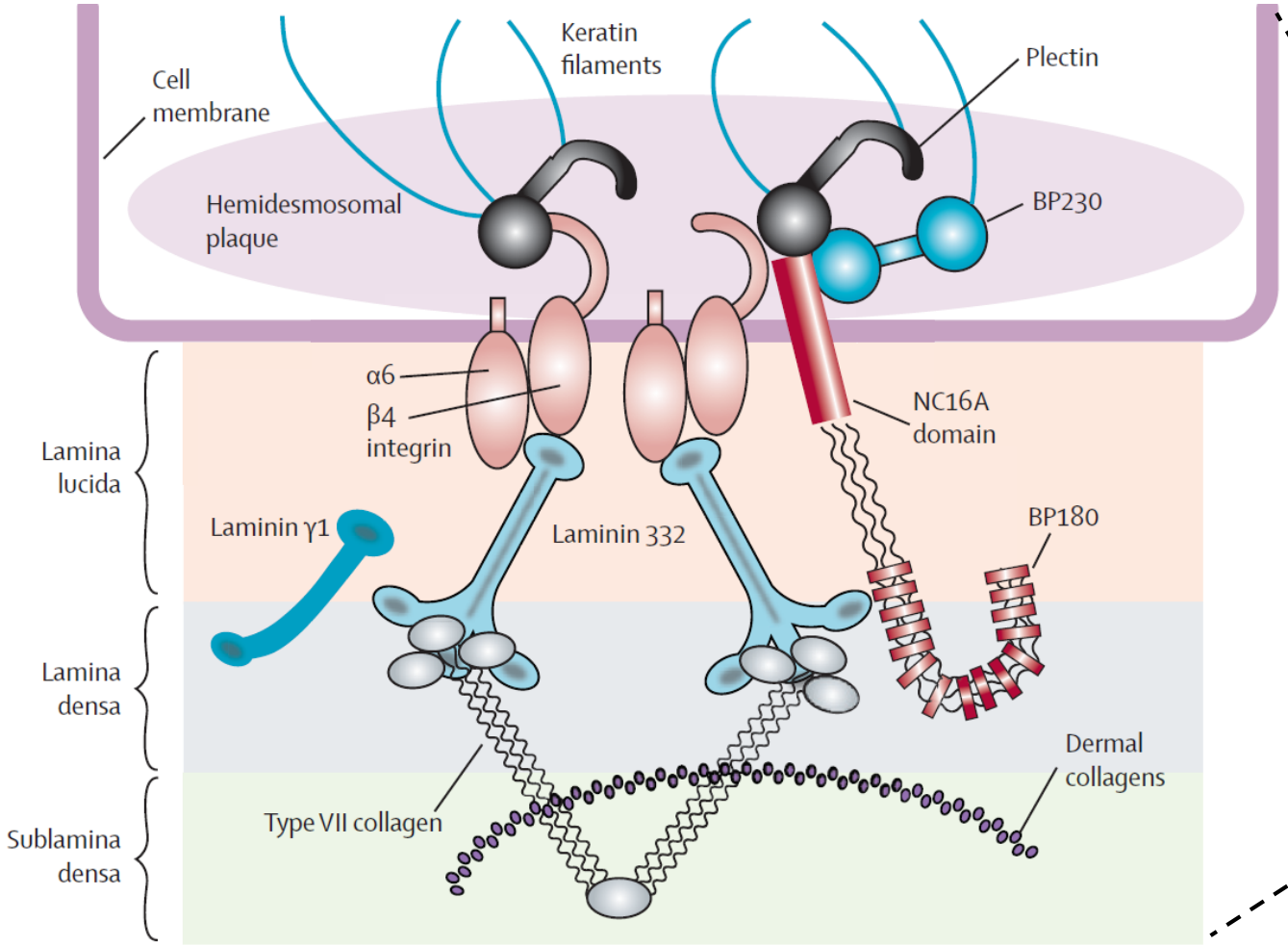


(Modified from Tham et al, BMC Vet Res 2020)

# *Canine pemphigus vulgaris*
## *Treatment and outcome*

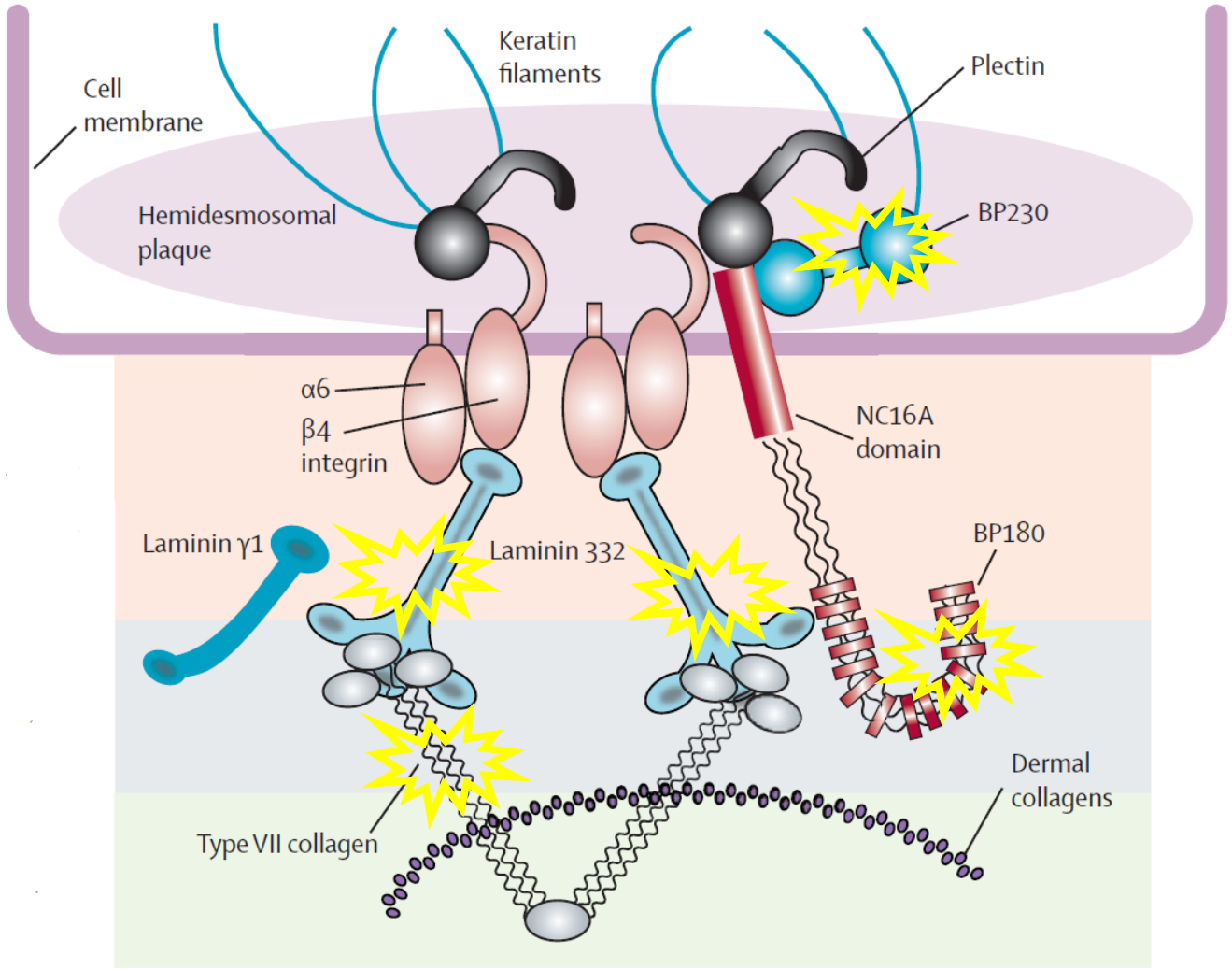
- Drugs reported to be effective: GC, AZA, CsA, heparin, doxycycline, and oclacitinib
- GC + AZA: most common combination therapy at complete remission (Tham, *BMC Vet Res*, 2020)
- Oclacitinib (0.5mg/kg BID): complete remission (CR) in 6 weeks (Martinez, *Vet Dermatol* 2022)

# The pemphigoid complex
## *Localization of lesions*




(Modified from Schmidt, Lancet 2013)

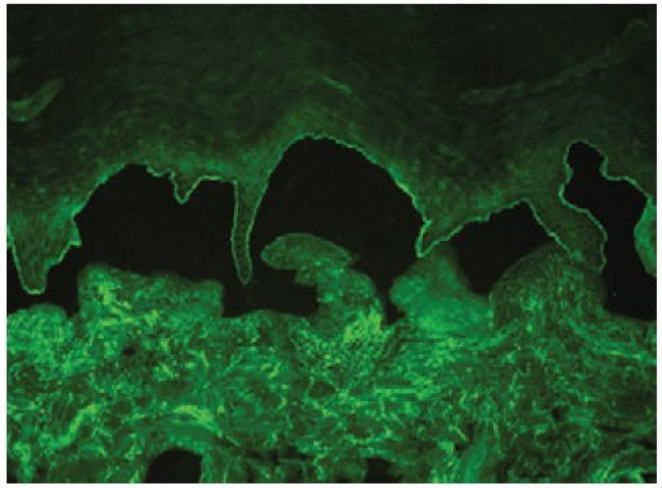
# The pemphigoid complex

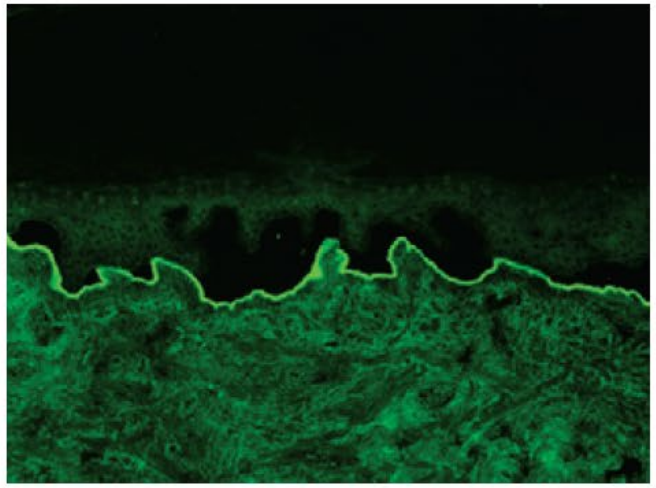



(Modified from Schmidt, Lancet 2013)

# Human pemphigoid complex:
## Target antigens

| | | | |
|---|---|---|---|
| **Bullous pemphigoid** | | | **Mucous membrane pemphigoid** |
| **Mucous membrane pemphigoid** | | | Laminin 332 |
| **Pemphigoid gestationis** | | | **Anti-p200 pemphigoid** |
| **Linear IgA disease** | | | Laminin γ1 |
| **Lichen ruber pemphigoides** | | | **Epidermolysis bullosa acquisita** |
| BP180 | α6β4 integrin | | Type VII collagen |
| BP230 | | | |





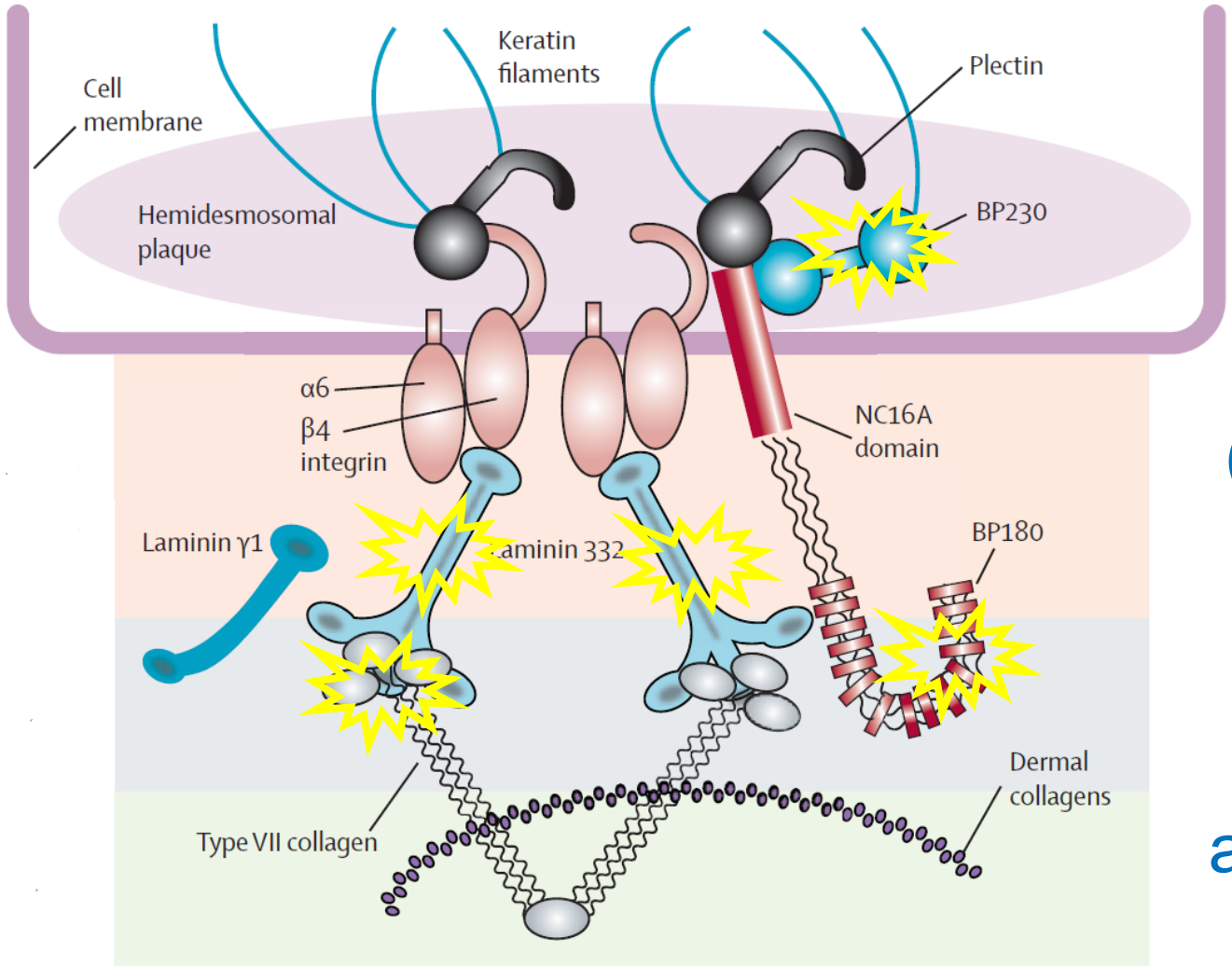
(Modified from Schmidt, Lancet 2013)

# Canine autoimmune subepidermal blistering dermatoses (AISBD)

| Disease name (alphabetically)<br>Disease abbreviation | Bullous pemphigoid<br>BP | Epidermolysis bullosa acquisita<br>EBA | Junctional epidermolysis bullosa acquisita<br>JEBA | Linear IgA disease<br>LAD | Mixed autoimmune subepidermal blistering dermatosis<br>MAISBD | Mucous membrane pemphigoid<br>MMP | Pemphigoid of gestation<br>PG | Type I bullous systemic lupus erythematosus<br>BSLE-I |
|---|---|---|---|---|---|---|---|---|
| Percentage of dogs with AISBD ($n$ = 77) | 10 | 26 | 6 | 3 | 4 | 48 | 1 | 1 |
| Rank among canine AISBDs | 3 | 2 | 4 | 6 | 5 | 1 | 7 | 7 |
| Percentage of humans with AISBD ($n$ = 100) | 69 | 2 | n.d. | 5 | n.d. | 12 | 4 | 2 |
| Rank among human AISBDs | 1 | 5 | n.d. | 3 | n.d. | 2 | 4 | 5 |
| Major antigen | COL17 | COL7 | n.d. | n.d. | n.d. | COL17 | n.d. | n.d. |
| Minor antigens | BPAG1e | n.d. | L332 | COL17 (secreted) | COL7 and L332 | L332, BPAG1e | Presumed COL17 | COL7 and nuclear antigens |

(Olivry, Vet Dermatol 2014)

# The canine pemphigoid complex




(Modified from Schmidt, Lancet 2013)

BP

(**BP180**, BP230)

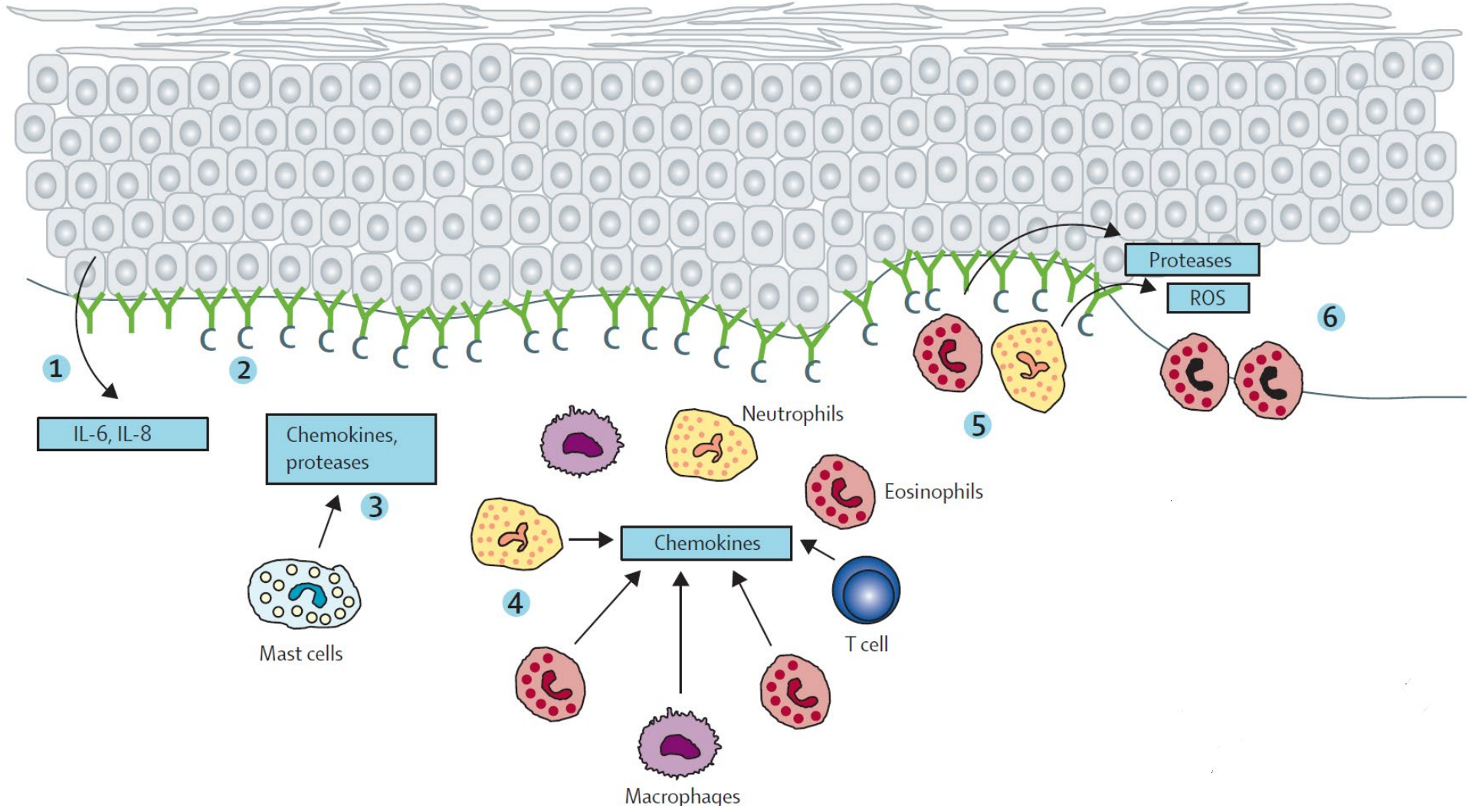
MMP

(BP180, BP230 and Laminin 332)

EBA

(Type **VII** collagen)

# Pathogenesis of blister formation in AISBD

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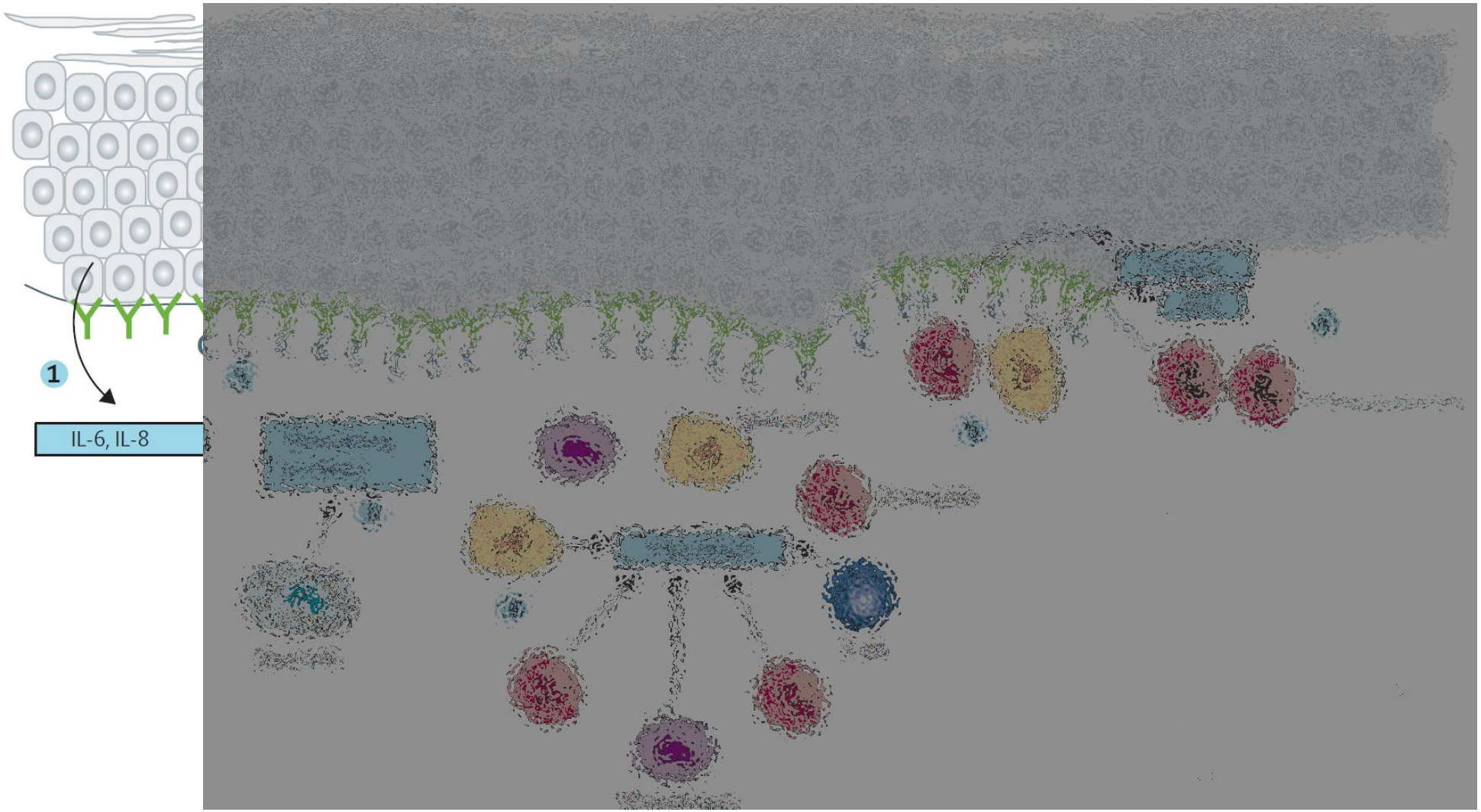
# Pathogenesis of blister formation in AISBD

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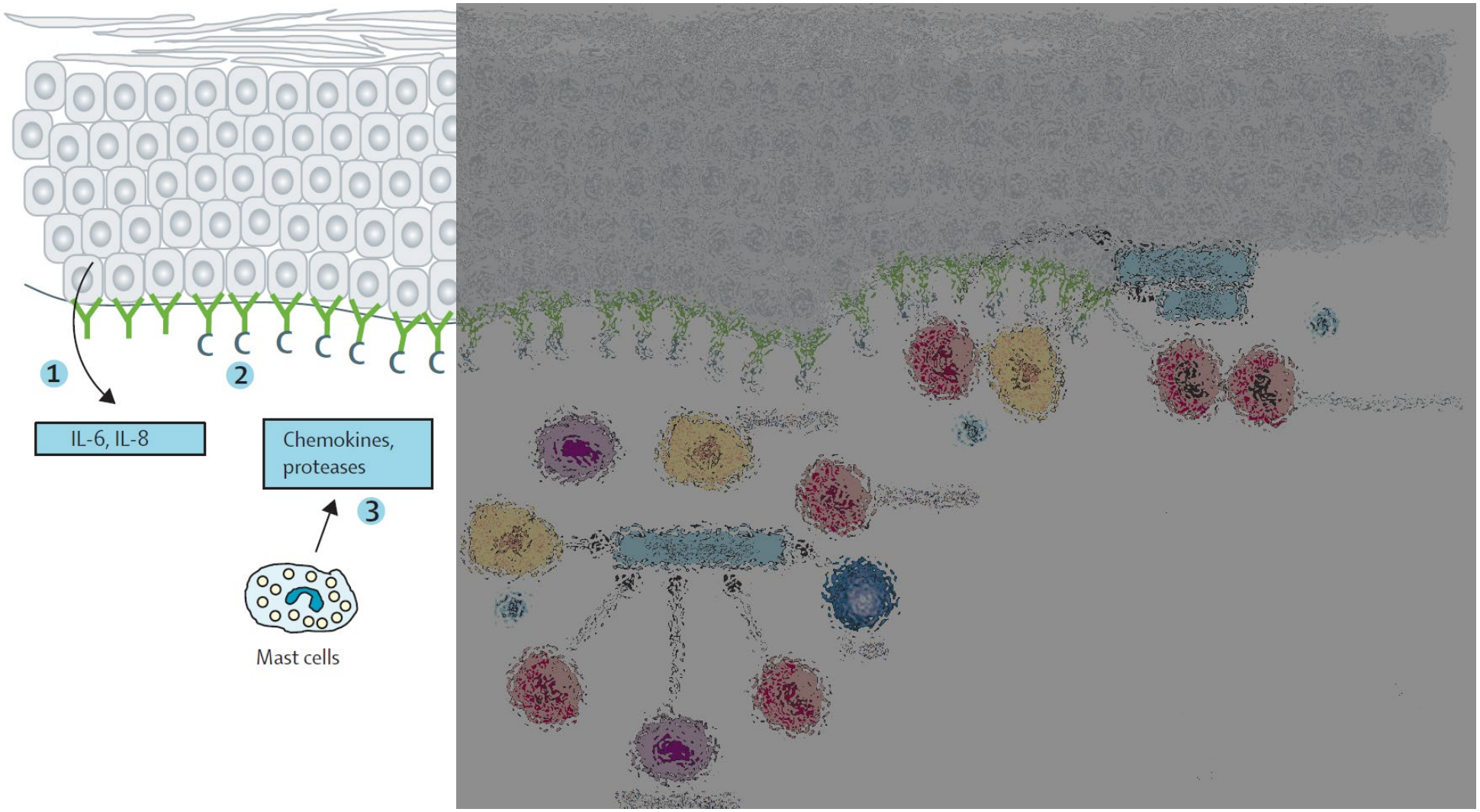
# Pathogenesis of blister formation in AISBD




(Modified from Schmidt, Lancet 2013)

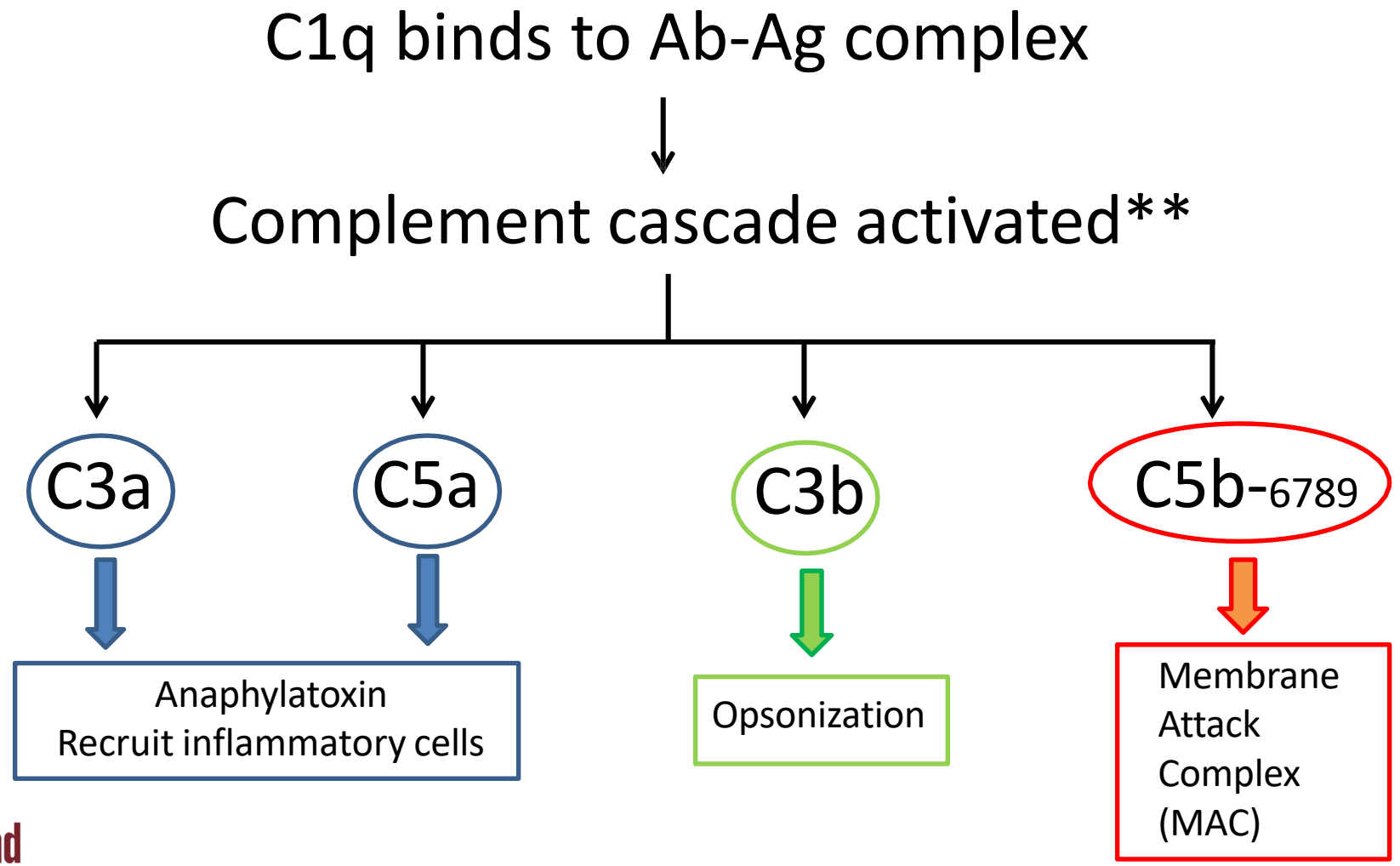
# Complement Activation Pathways

1. Classical Pathway (CP)
   - initiated by antigen-antibody complexes

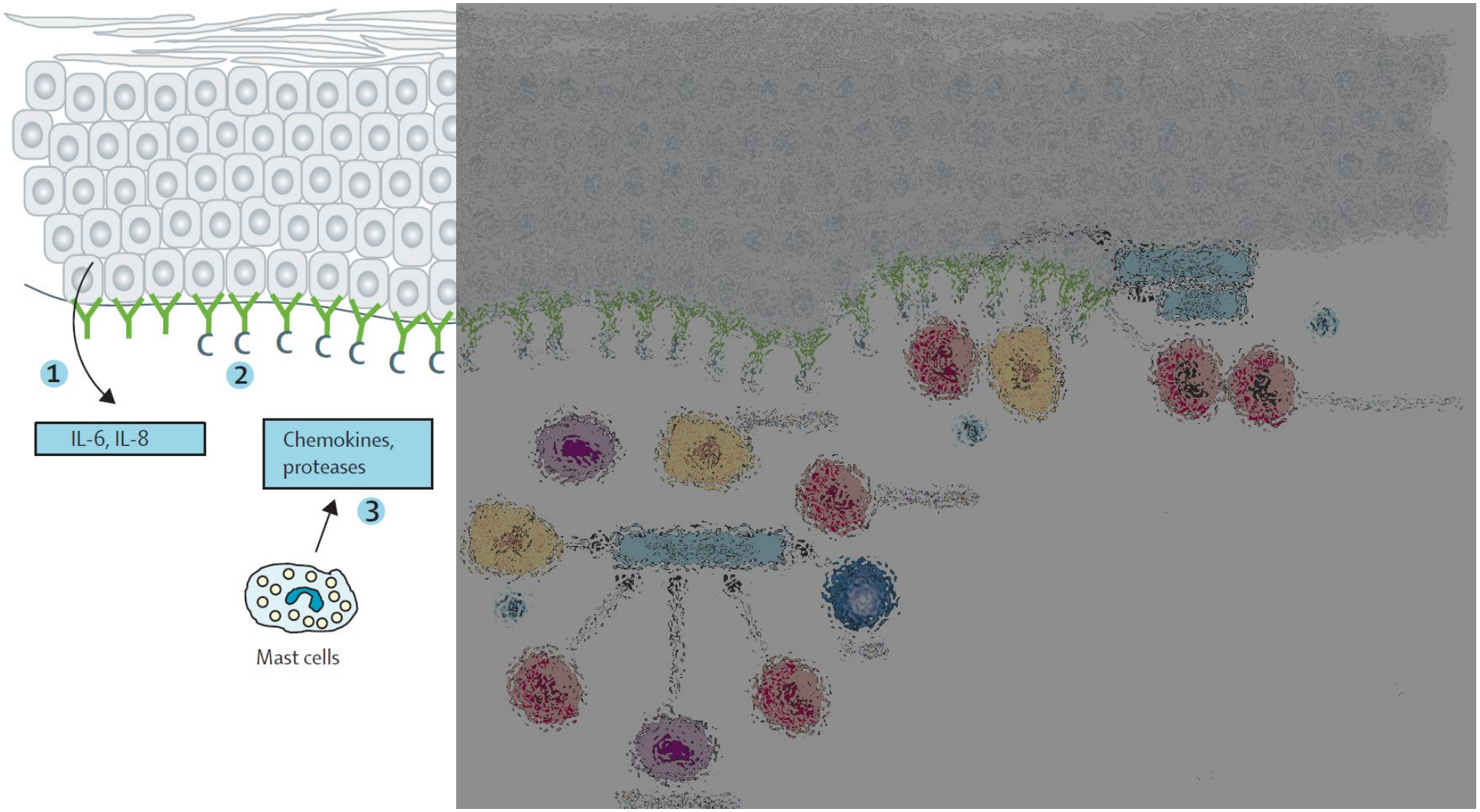
2. Lectin Pathway (LP)
   - binding to mannose residues on cell or pathogen surfaces

3. Alternative Pathway (AP)
   - Activated by spontaneous hydrolysis of C3 or via the classical or lectin pathway

# Complement activation: **Classical pathway**

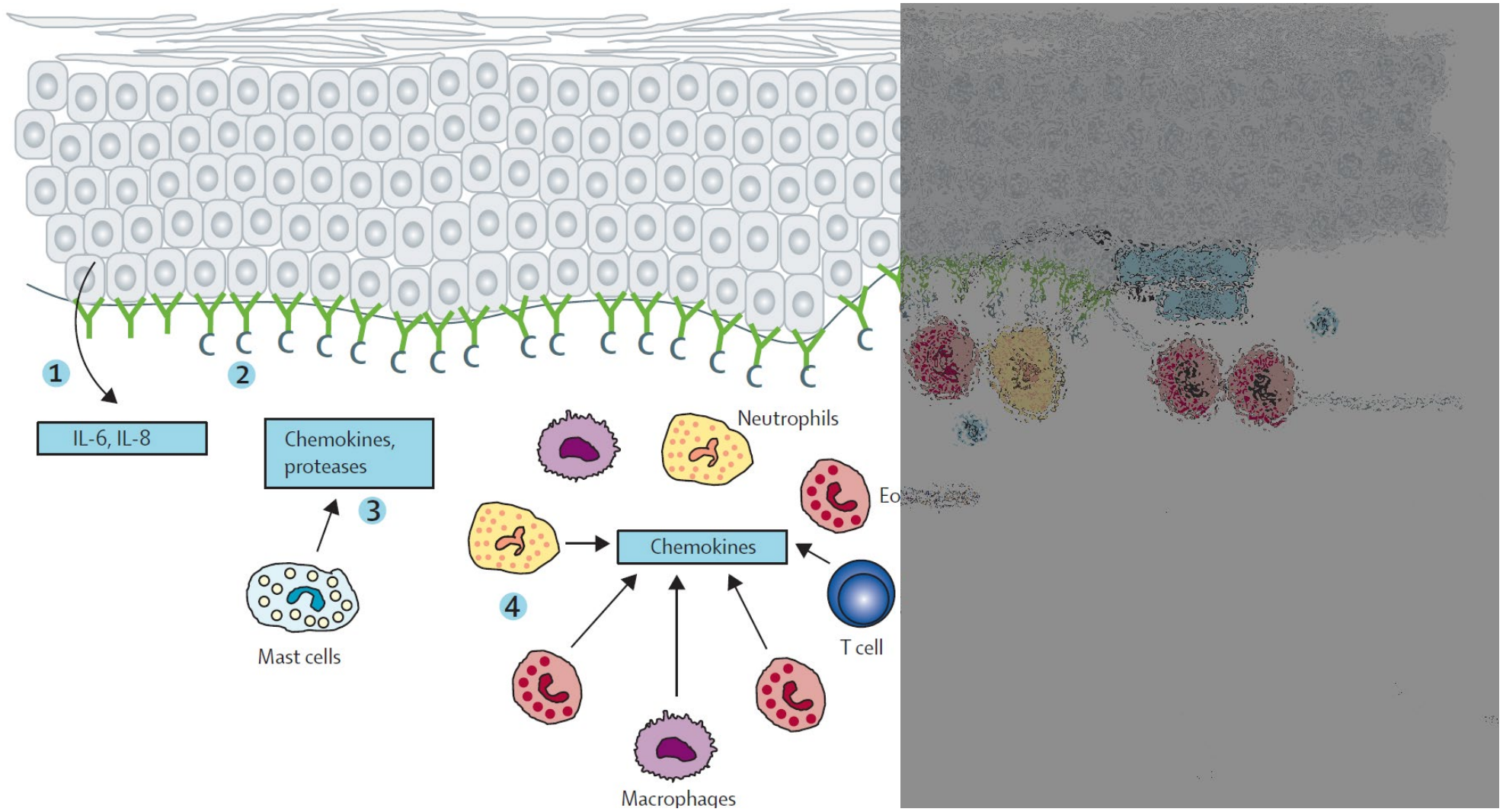


# Pathogenesis of blister formation in AISBD



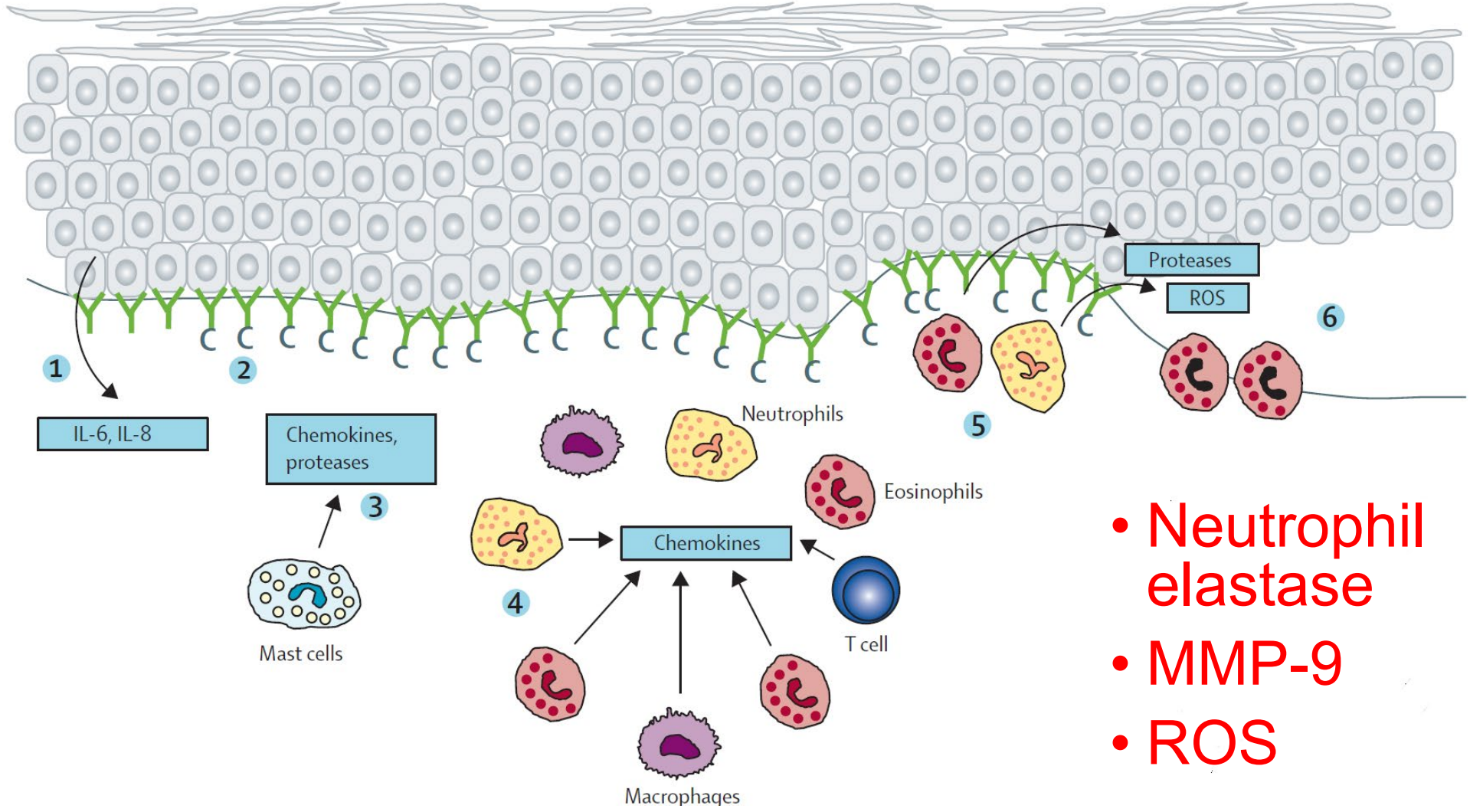

(Modified from Schmidt, Lancet 2013)

# Pathogenesis of blister formation in AISBD




(Modified from Schmidt, Lancet 2013)

# Pathogenesis of blister formation in AISBD




- Neutrophil elastase
- MMP-9
- ROS

(Modified from Schmidt, Lancet 2013)

# Canine AISBD: clinical features

Skin and/or mucosal lesions:

- Vesicles/bullae
- Ulceration
- Crust
- Depigmentation/scarring

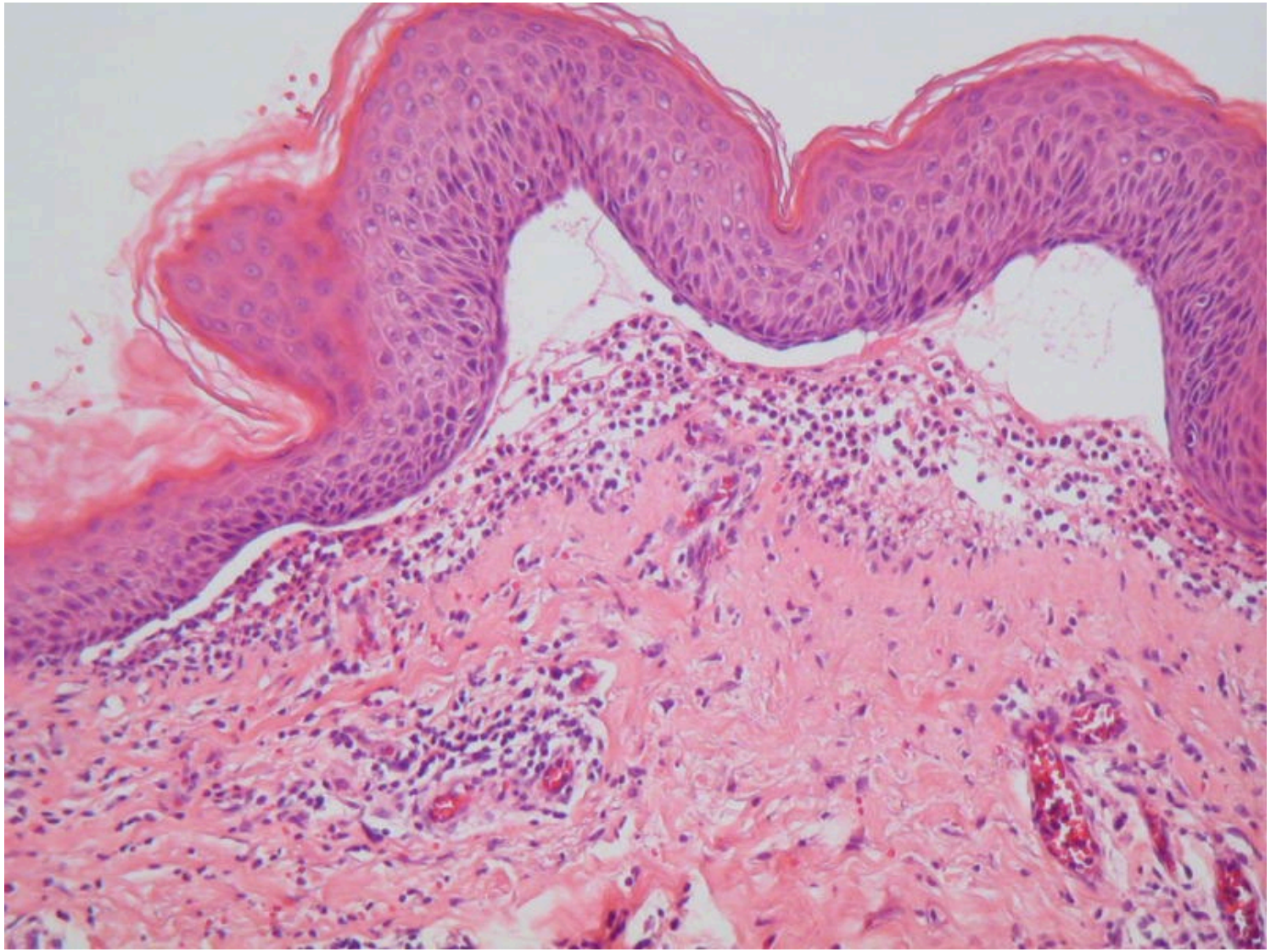
# Canine AISBD: diagnostic approach

Vesicles/bullae and/or ulcerations

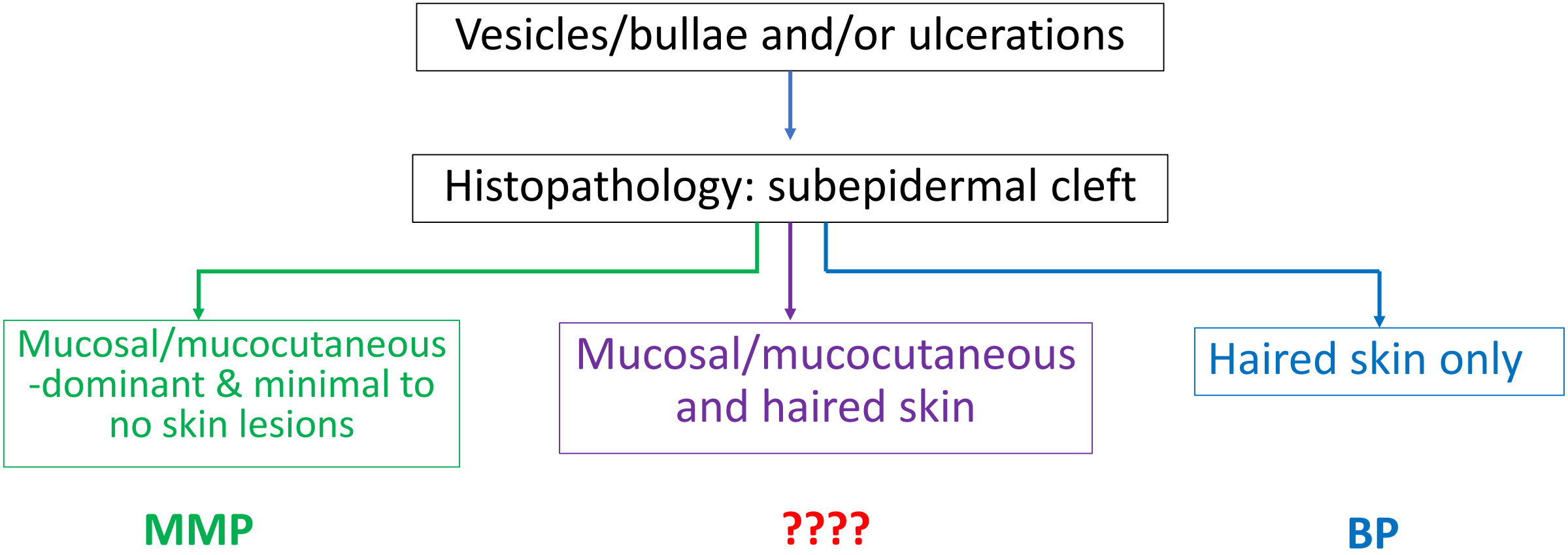
↓

Histopathology: subepidermal cleft

# Canine AISBD: histopathology



# Canine AISBD: clinical features



# Canine epidermolysis bullosa acquisita (EBA)

- Resembles the inflammatory variant (as appose to mechanobullous variant)
- Some features that MAY be helpful in distinguishing **EBA** from MMP or BP:
  1. Young dogs (median age of onset: 1-2 years old)
  2. Great Dane is the most common breed
  3. More severe systemic signs (fever, lymphadenopathy, lethargy and anorexia)

# **Canine AISBD:** treatment and outcome

- Chronic relapsing course
- MMP:
  - Tetracycline antibiotics + niacinamide
  - Oral GC + AZA/CsA/dapsone
- EBA:
  - Oral GC +/- AZA or colchicine
- Other non-specified AISBD
  - Oclacitinib (Aymeric, *Vet Dermatol* 2017)
  - Oral GC + MMF (Ginel, *J S African Vet Assoc*, 2010)

# Autoimmune dermatoses in cats and dogs: *the pemphigus and pemphigoid complex*

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8TH MAY, 2023

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