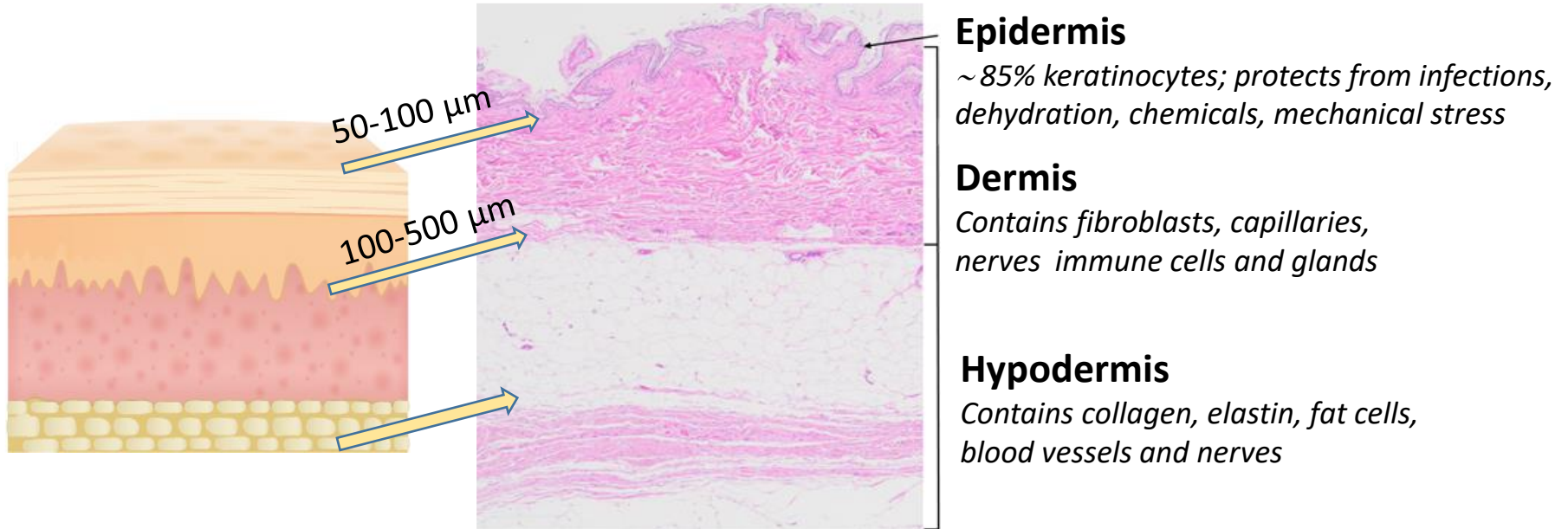


# Alpha1-Antitrypsin Deficiency and Panniculitis

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# Skin

For the average adult human, the skin has a surface area of between **1.5-2.0 m<sup>2</sup>**



- ❖ **Hypodermis** is the innermost layer of skin, largely composed of **adipose tissue (fat cells)**, **fibroblasts**, and **macrophages**.
- ❖ **Hypodermis** varies in thickness according to age, gender, and general health of individual
- ❖ **Hypodermis** influences the **skin temperature** and the speed of heat transfer from the muscle to the skin surface, and can have a dramatic effect on the appearance of the skin and the way aging impacts the skin, specifically in the area of the face and neck.

# Panniculitis

A group of inflammatory disorders in which the primary site of inflammation is in the *panniculus adiposis- a layer of fat of the subcutaneous tissue of the skin, known as Hypodermis*

**Present as tiny painful bumps or nodules protruding the skin surface**

*Inflammatory nodules and plaques are not exclusive to panniculitis, e.g. benign and malignant tumors can manifest as subcutaneous nodules*



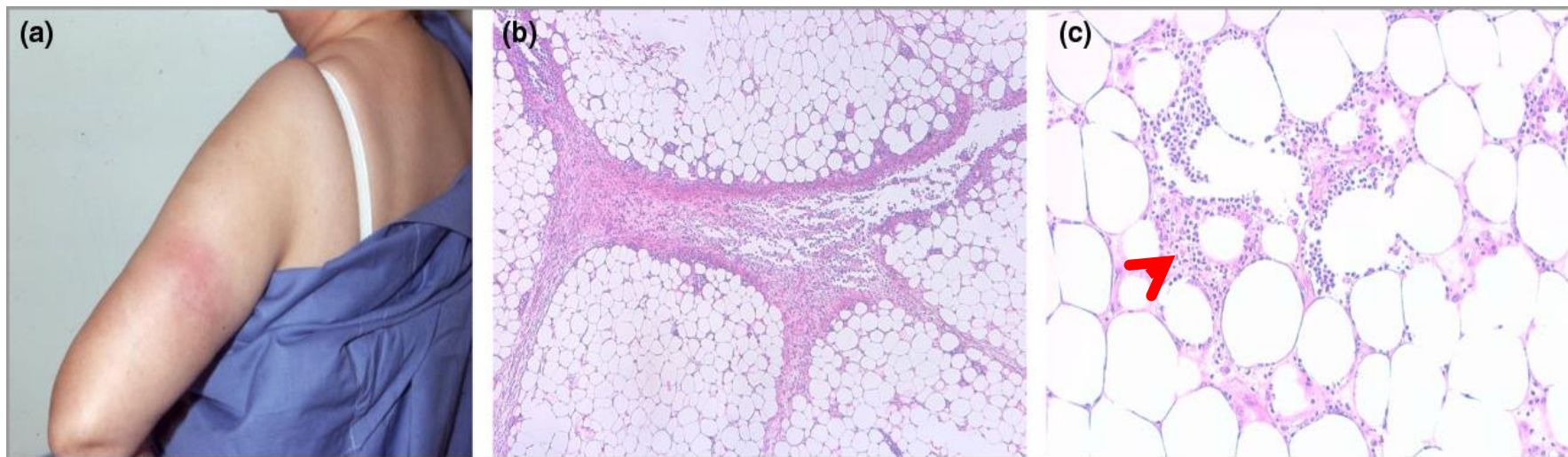
# Panniculitis

## Causes

- *Infection (due to bacteria, viruses, fungi or parasites)*
- *Trauma*
- *Chronic diseases (diabetes, rheumatoid arthritis)*
- *Pharmacotherapies (high doses of antibiotics, corticosteroids)*
- *Malignancy*
- *Enzymatic destruction (**alpha1-antitrypsin deficiency**)*
- *Depositions (renal failure "calciphylaxis" or gout "uric acid crystals")*
- *Others?*

# $\alpha$ 1-Antitrypsin Deficiency (AATD)-related panniculitis

- ❖ Panniculitis due to AATD was first described in **1972**
- ❖ A skin biopsy displaying excessive fat necrosis and neutrophil infiltration

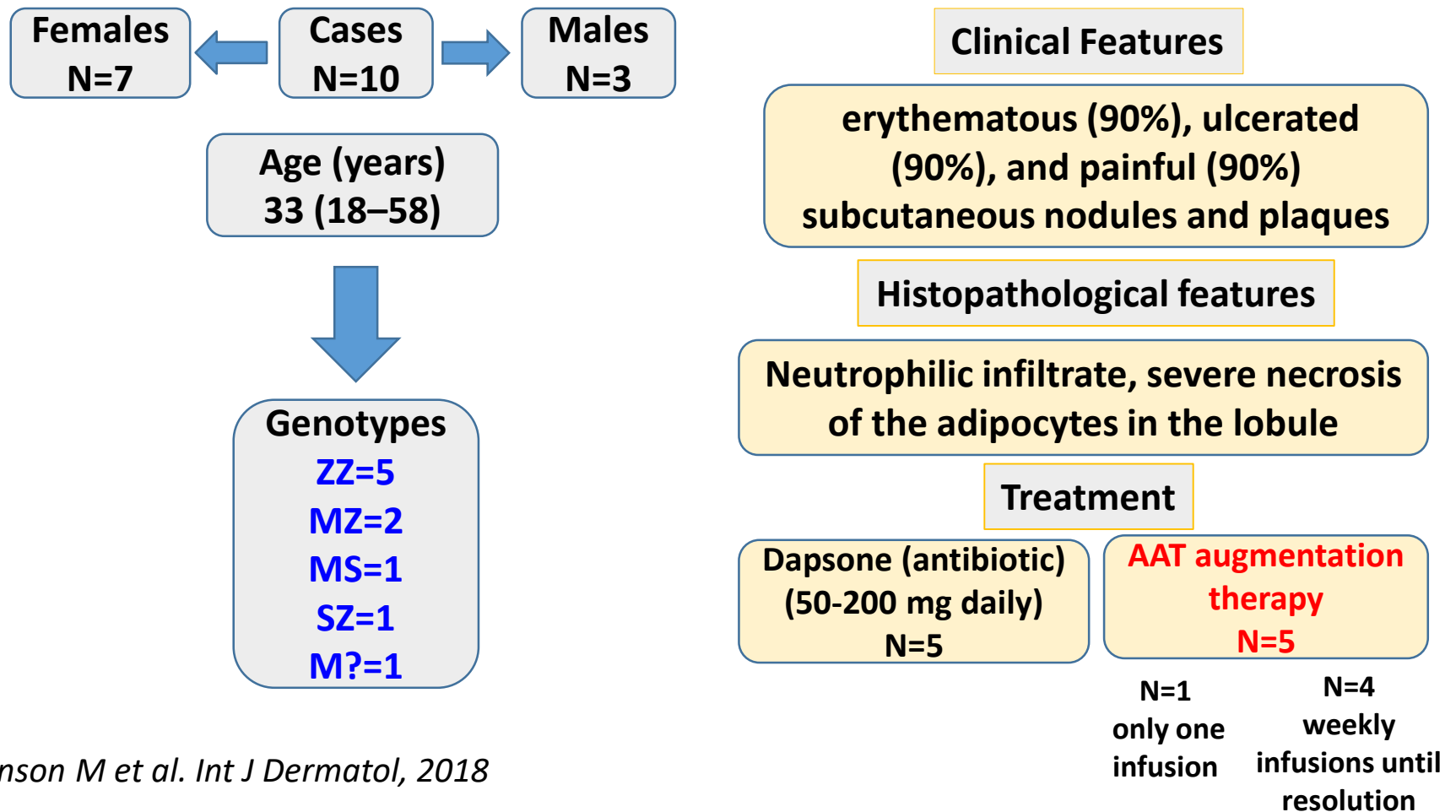


(a) 47-years female with AATD-related panniculitis; (b) neutrophils infiltrating between the collagen bundles; (c) typical lobular neutrophilic involvement

Warter J, et al. [Weber–Christian syndrome associated with an alpha-1 antitrypsin deficiency. Familial investigation]. *Ann Med Interne (Paris)* 1972

# AATD panniculitis: clinical and pathologic characteristics of 10 patients

*A retrospective review of 10 cases of AATD panniculitis at Mayo Clinic, Rochester, MN, from 1989 to 2016*



# AATD-related panniculitis

**Necrotizing panniculitis characterized by inflammatory lesions of the skin and subcutaneous tissue.**

**Distinguishing features- preference of lesions to the lower trunk and thighs, and release of more oily yellow discharge than seen in other forms of panniculitis.**

**Characteristic histology- *lobular fat necrosis of the lower reticular dermis and abundant neutrophil influx.***

**Reported in a variety of AAT genotypes: PiZZ (70%), PiMZ, PiSS, PiMS.**

**The mean age of onset is 40 years old.**

**Fewer than 100 cases are described to date.**

# A 13-year-old girl with PiZZ AAT who developed panniculitis

Girl at 5-weeks of age developed jaundice and PiZZ AATD was diagnosed (AAT level 0.29 g/L). She was healthy until the current illness.



At age of 13-year she developed deep, oozing and painless ulcerations. **The lesion arose after she injured her right foot on a bicycle pedal.** Ulcers developed on her legs that progressively involved her arms and trunk.



Prednisone therapy failed to control the progression of the disease. Skin ulcers healed within 6 weeks with **Dapsone therapy** 25 mg twice a day.

**PiZZ panniculitis was triggered by trauma?**



# AATD-related panniculitis: two cases with diverse clinical courses

## Case 1

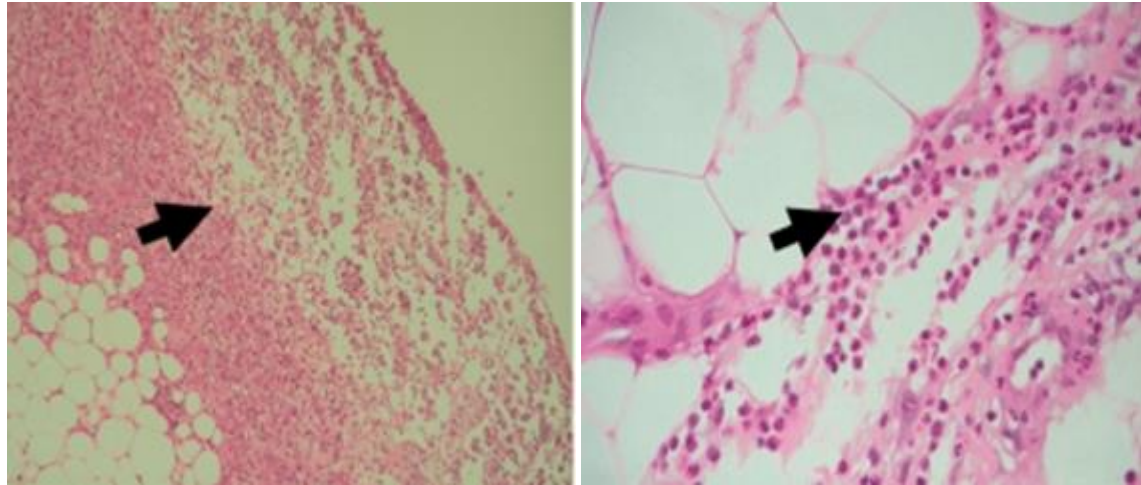
- ❖ 38 - year - old woman with an 8-month history of recurrent painful nodules on her legs.
- ❖ Physical and histological examination revealed a neutrophilic panniculitis. She failed to respond to nonsteroidal anti-inflammatory drugs and a prolonged course of oral corticosteroids (0.5 mg/kg).
- ❖ Investigations revealed a **PiZZ AATD (AAT level 0.17 g/L)** with no evidence of pulmonary emphysema or hepatic cirrhosis.
- ❖ She was treated with **colchicine 500 µg twice daily**, resulting in resolution of the panniculitis.
- ❖ Colchicine is a medication used to treat gout and Behçet's disease, decreasing swelling and lessening the build up of uric acid crystals.

# AATD-related panniculitis: two cases with diverse clinical courses

## Case 2

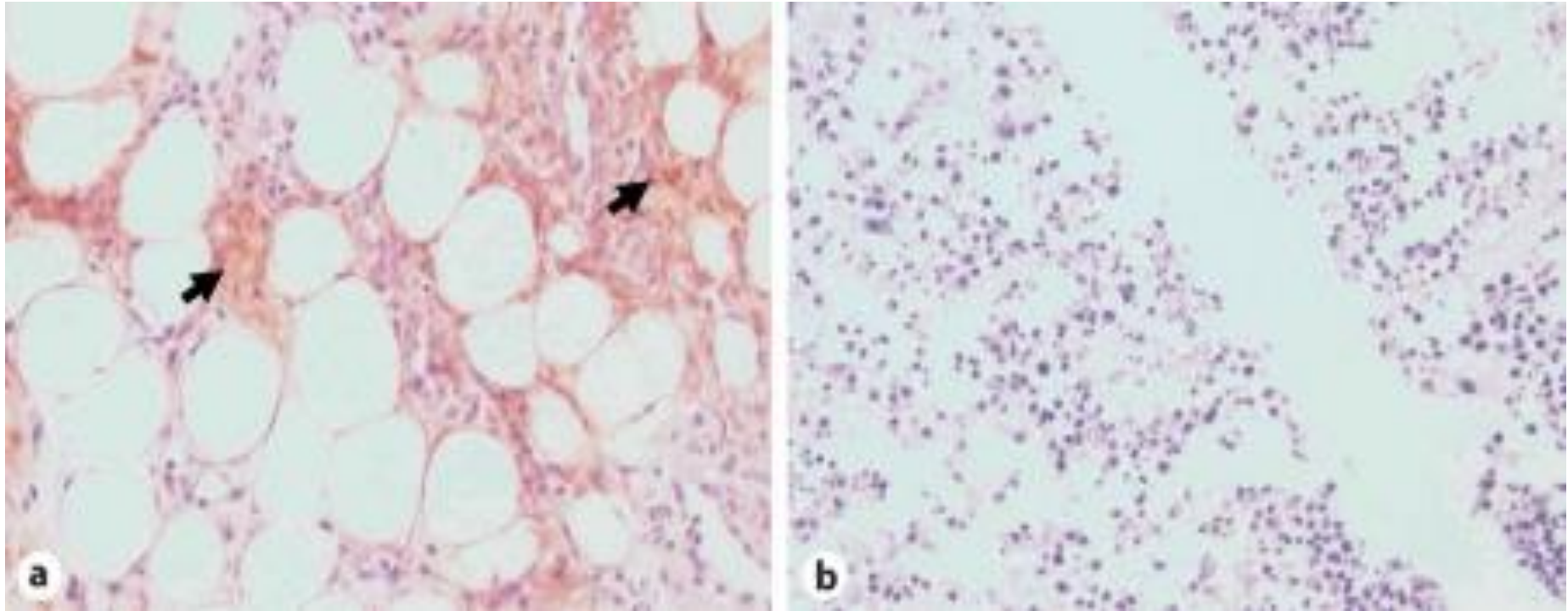
- ❖ 24-year-old woman with AATD (**PiZZ, AAT levels 0.25 g/L**) without hepatic or pulmonary disease and not taking any regular medications.
- ❖ She responded to therapy with Dapsone and remained well until the reported presentation. *Three weeks prior to her presentation, she had a minor injury to her leg.*
- ❖ Ulcerated plaques developed on the arms, abdomen, back, buttocks and thighs. The panniculitis failed to respond to standard treatments.
- ❖ Weekly intravenous infusions of **60 mg/kg (Prolastin©)** resulted in improvement.
- ❖ One month later, the patient experienced a severe unprovoked panniculitis, which resolved with dose escalation of the **AAT infusions to 120 mg/kg**.
- ❖ The disease became controlled when the patient received weekly AAT infusions to achieve serum AAT levels above 1 g/L.

# 31-year-old woman with PiZZ-associated panniculitis: Effects of AAT therapy



Acute lobular and septal panniculitis in skin biopsy. The arrows indicate inflammatory infiltrate and focal lobular fat cell degeneration.

# Staining of subcutaneous fatty tissue with antibody specific to polymeric form of Z-AAT



Immunostaining of skin biopsy from the reported PiZZ AAT patient (a) and from a control PiMM AAT individual (b). Original magnification  $\times 400$ .

# Augmentation therapy (90 mg/kg weekly) was highly effective

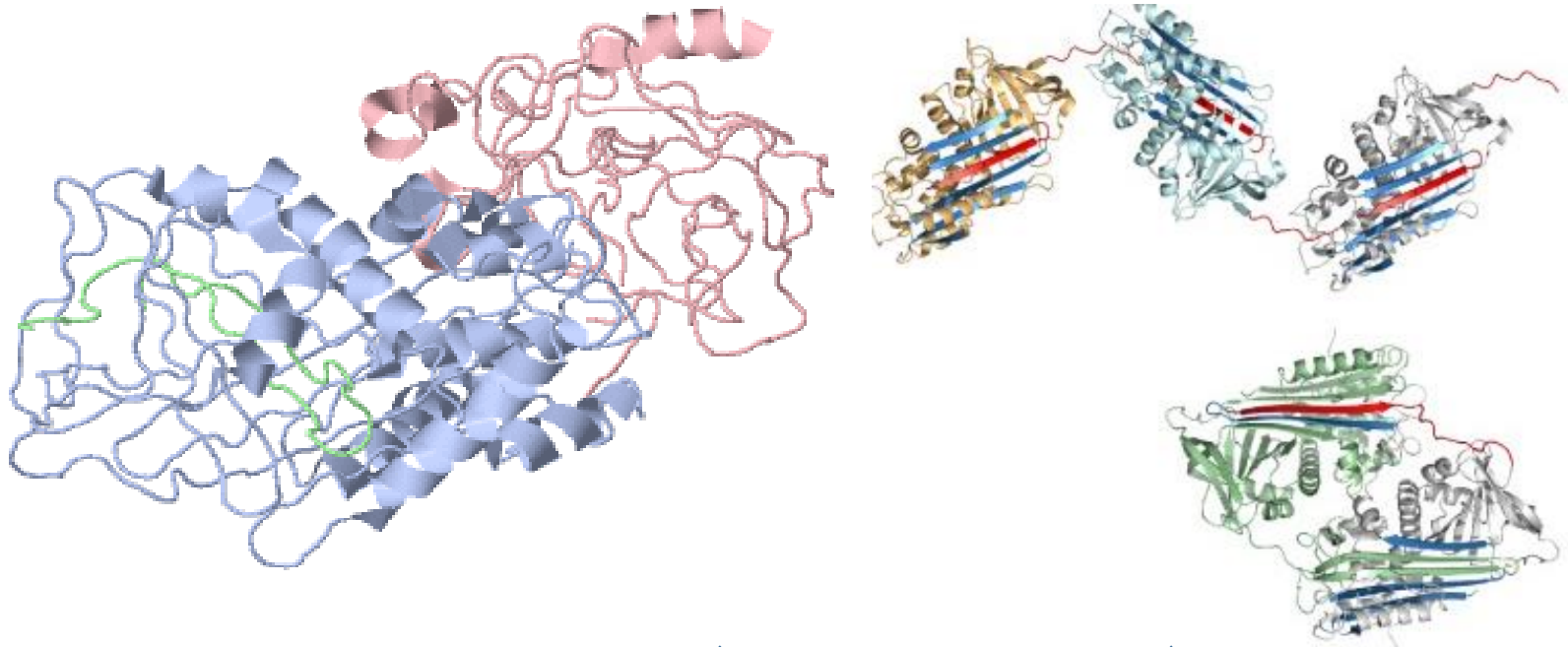


# AAT therapy for AATD panniculitis

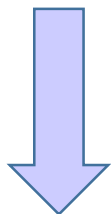
Year	Selected contributions
1987	Smith et al, in Rochester, Minnesota (USA), treat with success two Pi*ZZ patients with severe panniculitis with intravenous infusions of A1AT.
1996	Furey et al (Chicago, USA) successfully treat a Pi*ZZ patient with severe panniculitis with <i>Prolastin</i> ®.
1997	O'Riordan et al (Chicago, USA) successfully treat a Pi*ZZ case with severe panniculitis with <i>Prolastin</i> ®.
2002	Chowdhury et al (Cardiff, UK) successfully treat a Pi*ZZ patient with severe panniculitis with <i>Prolastin</i> ®.
2003	Kjus et al (Oslo, Norway) successfully treat a Pi*ZZ patient with severe panniculitis with <i>Prolastin</i> ®.
2009	Gross et al (Frankfurt, Germany) report the favorable outcome of treatment with <i>Prolastin</i> ® in a Pi*ZZ patient with panniculitis.
2011	Al-Niaimi et al (York, UK) successfully treat a Pi*ZZ patient with severe panniculitis with <i>Prolastin</i> ®.
2012	Olson et al (Seattle, USA) successfully treat a Pi*ZZ patient with severe panniculitis with <i>Prolastin</i> ®.
2014	Elsensohn et al (Salt Lake City, USA) successfully treat a Pi*ZZ patient with severe panniculitis with <i>Prolastin</i> ®.
2015	Cathomas et al (Bern, Switzerland) successfully treat with A1AT a Pi*ZZ patient with severe wound healing disturbance caused by a neutrophil panniculitis.
2015	Rasool et al (Leicester, UK) successfully treat a Pi*ZZ patient with severe panniculitis with <i>Prolastin</i> ®.

# The pathogenesis of AATD panniculitis remains poorly understood

*Factors causing acute inflammation in the fat layer of the skin, neutrophil infiltration, macrophage activation, increased protease activity and Z-AAT polymer accumulation-may provoke this condition in AATD*



**AAT  
native**



**Elastase**



**AAT  
polymers**



# Conclusions

- ❑ **AATD panniculitis is a predominantly neutrophilic in which the affected fat lobules are necrotic and replaced with an intense neutrophilic infiltrate.**
- ❑ **Therapy with AAT is very effective for patients with panniculitis**



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# Thanks a lot to all collaborators!



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