



# From blisters to blisters

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**PhD Tudományos Napok**

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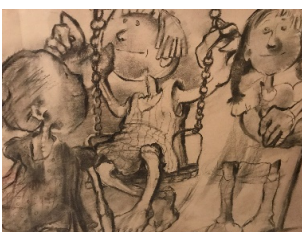
**Quiz**



## Dermatology at the Heim Pál Hospital for Children- the clinical experience

### Bicycling – art and blisters

- Pediatric dermatology with Eva Török
  - 1976-1988 (1993)
- How many patients in 6 hours?
- How to diagnose autoimmune blistering diseases?
  - scholarship to Poland



Monika  
Hajósy



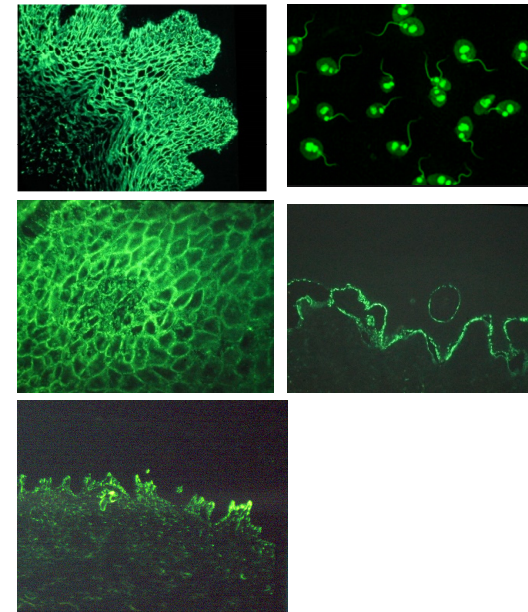
Miklos  
Merksz



## Fluorescence, Revolution –Lech Walesa- and the play *Ojciec naszego brata* by Karol Woytyla



- Warsaw, Stefania Jablonska, Dermatology Clinic
  - the sacral place of blisters
- Secret studies on blistering diseases
  - autoradiography
- A perfect IF method and the smuggled *Critidia luciliae*
- A forgotten language and life long connections



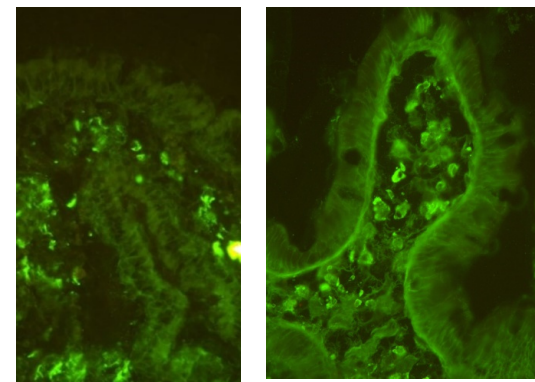


## Kosher shlauphter and cercof monkeys for blistering kids True for skin, true for jejunum?

- Diagnosis of childhood blistering diseases at the Heim Pál Hospital
  - Introduction of IF – direct, indirect IF; ENA, dsDNA (*Critidia luciliae*)
  - Dermatitis herpetiformis: known association with celiac disease
  - Description of tubular-linear IgA in DH in the small bowel
    - Kárpáti S, Török E, Kósnai I. J Invest Dermatol. 1986 Dec;87(6):703-6.
  - Circulating IgA binding to the jejunum
    - Kárpáti S, Török E, Kósnai I.. J Invest Dermatol. 1986 Dec;87(6):703-6).
- Introduction of EMA in Hungary- the first specific diagnostics for CD
  - Student : dr. Ilma Korponay Szabó

### PhD degree

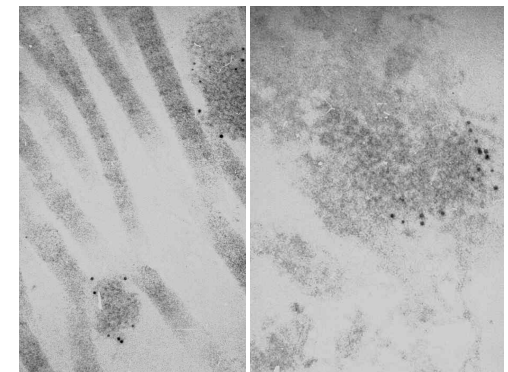
- Where is the binding site of EMA? Jejunal antibodies?
- Humboldt fellowship to Munich





## Munich – LMU, gold hunting in German blisters Race with Keyo, Japan

- Otto Braun Falco, Thomas Krieg
  - **New** studies: EM
  - **Immunoelectronmicroscopy- immunogold labelling**
    - Identification of IgA or IgG antibody binding sites in the skin
      - Dermatitis herpetiformis (DH) with underlying celiac disease, linear IgA disease, pemphigoid gestationis, EBA,
      - EMA, jejunal staining, cell culture
- Kárpáti et al JID, JAAD, BrJ Derm, Gut
- **Description of the pathological autoantibody of celiac disease by indirect IF: true for DH, true for celiac disease**
    - Kárpáti S., Lancet. 1990 Dec 1;336(8727):1335-8.
    - Targeted : TG2: Korponay-Szabó IR, Halttunen T, Szalai Z, Laurila K, Király R, Kovács JB, Fésüs L, Mäki M. Gut. 2004 May;53(5):641-8.
  - Introduction into the international world
  - Life-long connections
  - Invited to NIH, US - Fogarty scholarship



DH  
bodies



NIH- Bethesda, Dermatology Branch - American blisters  
Home made Jesus Christus superstar and the lost mouse

Steve Katz, John Stanley and Masayuki Amagai

- **Back to the school:** molecular biology, PCR, cloning, production of fusion proteins and epitope specific antibodies
- Pemphigus research - **ultrastructural localization of PV antigen**
- Kárpáti S, Amagai M, Prussick R, Cehrs K, Stanley JR. J Cell Biol. 1993 Jul;122(2):409-15.
- **Extracellular domains of Dsg3 are pathogenic;**
  - J Clin Invest,
  - Dermatol,
  - J Invest Dermatol
- **Baseball, judo, master swimming at the YMCA**
- **US: Farewell by street jess balet – Lamamba**
- 



## Main targeted desmosomal molecules: desmoglein (dsg) 1 and 3

### Autoantibodies from autoreactive B cells: Association with pathogens

#### Rotavirus

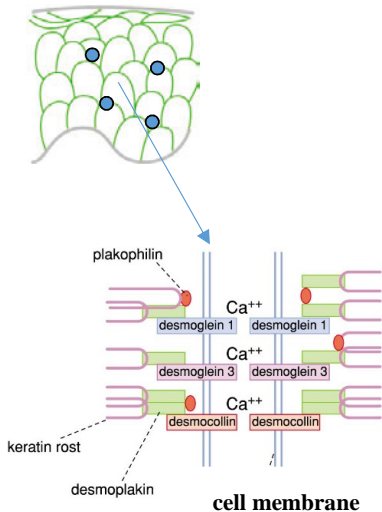
- Dsg3-reactive B cells may utilize VH1–46 antibody heavy chain genes in PV and PNP (2012, J. Invest. Dermatol. 132:1141)
- VH1–46 gene usage by B cells reactive to rotavirus capsid protein
- Cross-reactive mAbs to both Dsg3 and VP6 prevent rotavirus replication and disrupting keratinocyte adhesion (2016, J. Immunol. 189:1535)

#### Sandfly

In endemic PF: anti-Dsg1 mAbs crossreact with the sandfly antigen LJM11 -molecular mimicry between LJM11 and Dsg1 induce endemic PF? (2008, J. Immunol. 189:1535).

#### Exfoliatin toxin producing Staph aureus

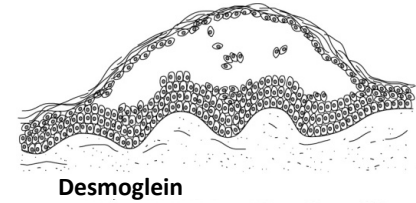
Few patients with SSSS (staphylococcal-scalded skin syndrome) may have transient anti-Dsg1 IgG antibodies (2006, J. Invest. Dermatol. 126:2139)



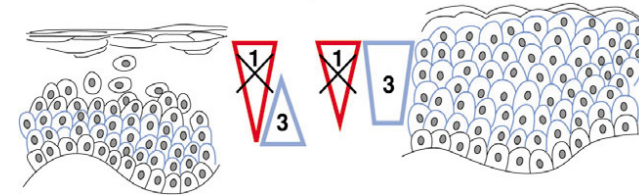


No mucose membrane symptoms in pemphigus foliaceus, but present in PV

Drug induced and paraneoplastic forms

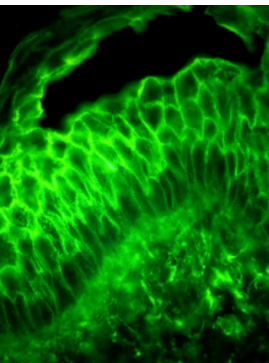


Desmoglein



Compensation theory

Masayuki Amagai and John Stanley



**Role of autoreactive CD4 + T cells :** T cell dependent humoral autoimmune reactions to Dgs

Strong association of PV with MHC class II haplotypes : Specific Dsg3 peptides can be presented

DRB1\*04:02 in Jewish populations (1990, Proc. Natl Acad. Sci. USA 87:7658),

DQB1\*05:03 in non-Jewish Caucasian populations (1991, Proc. Natl Acad. Sci. USA 88:5056.)

DRB1\*14 and DQB1\*05:03 in Japanese populations (1997 J. Invest. Dermatol. 109:615)

IgG4 subclass among anti-Dsg3 antibodies - switch (1993. Clin. Exp. Dermatol. 18:226).

Somatic hypermutations in complementarity-determining regions (CDRs) of anti-Dsg3 antibodies (2010, J. Clin. Invest. 120:4111)





## Hungary: Definition of overeducation Joining the Semmelweis University, back to Hungarian blisters

### Prof. Attila Horvath

- Overtaking the autoimmun bullosis diagnostic and clinics and the pediatric dermatology
- **Novel autoantigens in collaboration with Japan- in paraneoplastic pemphigus, IgA pemphigus**
- [Exacerbation of paraneoplastic pemphigus by cyclophosphamide treatment: detection of novel autoantigens and bronchial autoantibodies.](#) Preisz K, Horváth A, Sárdy M, Somlai B, Hársing J, Amagai M, Hashimoto T, Nagata Y, Fekete S, Kárpáti S. Br J Dermatol. 2004 May;150(5):1018-24.
- [Identification of desmoglein 1 as autoantigen in a patient with intraepidermal neutrophilic IgA dermatosis type of IgA pemphigus.](#) Kárpáti S, Amagai M, Liu WL, Dmochowski M, Hashimoto T, Horváth A. Exp Dermatol. 2000 Jun;9(3):224-8.

### DSC degree

- Foundation of Dermatological Program at the Semmelweis Doctoral School
- New: Problemes of severe inherited skin diseases

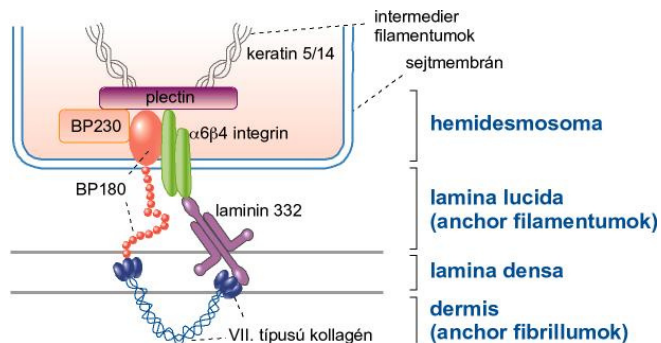


# To start studies on a different blisterformation

Pathology of the same molecules in inherited and autoimmune blistering

## Back to the school

- New: Inherited blistering – epidermolysis bullosa—
- Introduction of diagnostic and prenatal diagnostic genetic testing for severe inherited skin diseases in Hungary
- Genes along the cutaneous BM and in other locations





## Skateboard, roller skates and fishing rod in a lab

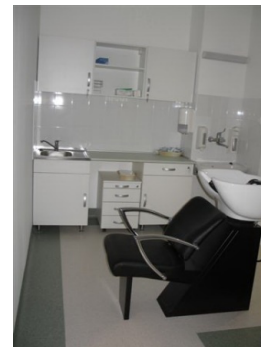
PhD students with collaborative research subjects:

- inherited blistering diseases
  - collaboration with New York, Columbia University, Peter Cserhalmi-Friedman
    - Exp Dermatol. 1997 Apr;6(2):70-4.
    - Exp Dermatol. 1999 Apr;8(2):143-5.
    - Arch Dermatol Res. 1997 Oct;289(11):640-5.
- severe inherited cornification defects
  - collaboration with Münster University, Marta Medvecz
    - Br J Dermatol. 2005 May;152(5):879-86.
    - Clin Exp Dermatol. 2003 Mar;28(2):163-6.
- transglutaminases in dermatitis herpetiformis
  - collaboration with Cologne- Mats Paulsson, Miklos Sárdy- the current chair of the Clinic
- [Epidermal transglutaminase \(TGase 3\) is the autoantigen of dermatitis herpetiformis.](#) Sárdy M, Kárpáti S, Merkl B, Paulsson M, Smyth N. J Exp Med. 2002 Mar 18;195(6):747-57.
- [Recombinant human tissue transglutaminase ELISA for the diagnosis of gluten-sensitive enteropathy.](#) Sárdy M, Odenthal U, Kárpáti S, Paulsson M, Smyth N. Clin Chem. 1999 Dec;45(12):2142-9.
- **Patent for TG3 ELISA**



Hungarian Rhapsody: Loss of ~ 50 salaries when closing the National STD Center at the Clinic. Who will take care of STD patients?

- Chair : Dept. Dermatology, Venerology and Dermatoooncology, or ? ~~Venereology~~
- Establishing the Nekam Foundation
- Novel STD lab- novel STD Center, Allergology Lab, Laser Center- Cosmetology
- Norway grant for education
  - Jorgen Ronnevig- friendship in the executive by EADV (treasurer)
  - Siri Elen Stettner , Ambassador of Norway
- Restoration of 60% of the Clinic - introduction of novel molecular and metabolic toxicology education at the Peter Pazmany University, Bioinformatics
- Novel genetic laboratory for inherited skin diseases and stem cell research 2015, Dr Mayer, dr Németh
- European Rare Disease Center for inherited skin diseases- 2012



# Cycling from Helsinki to Kyoto, and international tram travel in Budapest

- ESDR- European Society for Dermatology Research
  - Annual Meeting at the Semmelweis University 2009
    - Memory tram travel in Budapest with international friends

Member of the German Academy of Sciences



# Transglutaminase enzymes (TG)

## TG enzymes in blistering and non blistering inherited diseases:

- Autoimmune blistering: dermatitis herpetiformis: TG2 (bowel pathology), TG3 (skin pathology) , ev. TG6 (brain pathology)
- Inherited blisterformation: TG5- acral peeling skin syndrome
- Barrier defects:
  - TG3 KO mice - possible role in contact dermatitis?
  - TG1 mutations in severe ichthyosis
- [Epidermal transglutaminase \(TGase 3\) is the autoantigen of dermatitis herpetiformis.](#)  
Sárdy M, Kárpáti S, Merkl B, Paulsson M, Smyth N. J Exp Med. 2002 Mar 18;195(6):747-57.
- [Transglutaminases in autoimmune and inherited skin diseases: The phenomena of epitope spreading and functional compensation.](#)Kárpáti S et al. Exp Dermatol. (2018)
- [Circulating Transglutaminase 3-Immunoglobulin A Immune Complexes in Dermatitis Herpetiformis.](#) Görög A et al. J Invest Dermatol. (2016)
- [Reduced inflammatory threshold indicates skin barrier defect in transglutaminase 3 knockout mice.](#)Bognar P et al. J Invest Dermatol. (2014)



## Stem cell research

**Back to the school desk:** Stem cell research as a far hope for the treatment of inherited blistering skin diseases and tumors

- Collaboration with NIH- US, Eva Mezey
    - Krisztián Németh, Balázs Mayer, the 1.5 man story
  - [Detection of hair follicle-associated Merkel cell polyomavirus in an immunocompromised host with follicular spicules and alopecia.](#) Nemeth K, Gorog A, Mezey E, Pinter D, Kuroli E, Harsing J, Kovacs L, Fischer M, Rady P, Sillo P, Tyring S, **Karpati S.** Br J Dermatol. 2016
  - [Characterization and function of histamine receptors in human bone marrow stromal cells.](#) Nemeth K, Wilson T, Rada B, Parmelee A, Mayer B, Buzas E, Falus A, Key S, Masszi T, Karpati S, Mezey E. Stem Cells. 2012 Feb;30(2):222-31. doi: 10.1002/stem.771.
  - [Analyses of donor-derived keratinocytes in hairy and nonhairy skin biopsies of female patients following allogeneic male bone marrow transplantation.](#) Nemeth K, Key S, Bottlik G, Masszi T, Mezey E, Karpati S. Stem Cells Dev. 2012 Jan;21(1):152-7
  - [Bone marrow stromal cells use TGF-beta to suppress allergic responses in a mouse model of ragweed-induced asthma.](#) Nemeth K, Keane-Myers A, Brown JM, Metcalfe DD, Gorham JD, Bundoc VG, Hodges MG, Jelinek I, Madala S, Karpati S, Mezey E. Proc Natl Acad Sci U S A. 2010 Mar 23;107(12):5652-7. doi: 10.1073/pnas.0910720107. Epub 2010 Mar 15. Erratum in: Proc Natl Acad Sci U S A. 2010 Apr 27;107(17):8041
- 
- Novel education at the Pazmany Péter University: Stem cell research
    - Balázs Mayer

# Melanoma – one or 10 or how many tumor clones? and a hope for survive

- **Back to school desk:** immunecheckpoint inhibitors in melanoma
- PhDs :
  - description of GPER in melanoma
  - [Expression of G protein-coupled oestrogen receptor in melanoma and in pregnancy-associated melanoma](#). Fábíán M, Rencz F, Krenács T, Brodszky V, Hársing J, Németh K, Balogh P, Kárpáti S. J Eur Acad Dermatol Venereol. 2017 Sep;31(9):1453-1461. doi: 10.1111/jdv.14304. Epub 2017 Jun 20.
  - [Clinicopathological Characteristics of Pregnancy Associated Melanoma](#). Fábíán M, Tóth V, Somlai B, Hársing J, Kuroli E, Rencz F, Kuzmanovszki D, Szakonyi J, Tóth B, Kárpáti S. Pathol Oncol Res. 2015 Sep;21(4):1265-71. doi: 10.1007/s12253-015-9961-4. Epub 2015 Jul 1
  - germline mutations in multiplex tumors associated with melanoma
  - [Genotype analysis in Hungarian patients with multiple primary melanoma](#). Hatvani Z, Brodszky V, Mazán M, Pintér D, Hársing J, Tóth V, Somlai B, Kárpáti S. Exp Dermatol. 2014 May;23(5):361-4. doi: 10.1111/exd.12382.
  - epidemiology of melanoma
  - [Risk of subsequent primary tumor development in melanoma patients](#). Tóth V, Hatvani Z, Somlai B, Hársing J, László JF, Kárpáti S. Pathol Oncol Res. 2013 Oct;19(4):805-10.





**Future:** Proteomics, transcriptomics, genomics,  
Big data analysis and clinical course, broad international  
collaboration

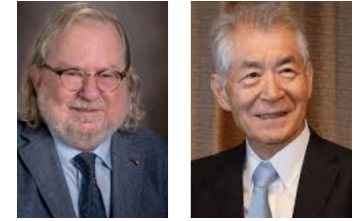
Melanoma- joining the Swedish Cancer Moon Shot project  
Lund University, Marko- Varga György

- Collaboration with the Lund and Pázmány Péter University
- We have several questions to answer
- Who will analyze the data?
- [Clinical protein science in translational medicine targeting malignant melanoma](#). Gil J, Betancourt LH, Pla I, Sanchez A, Appelqvist R, Miliotis T, Kuras M, Oskolas H, Kim Y, Horvath Z, Eriksson J, Berge E, Burestedt E, Jönsson G, Baldetorp B, Ingvar C, Olsson H, Lundgren L, Horvatovich P, Murillo JR, Sugihara Y, Welinder C, Wieslander E, Lee B, Lindberg H, Pawłowski K, Kwon HJ, Doma V, Timar J, Karpati S, Szasz AM, Németh IB, Nishimura T, Corthals G, Rezeli M, Knudsen B, Malm J, Marko-Varga G. Cell Biol Toxicol. 2019 Mar 21. doi: 10.1007/s10565-019-09468-6 Epub ahead of print

## Summary

- Learn in the best centers from the best people
- Consider your everyday activity as your hobby
- Have an established family background and/or good friends
- Never give up research and learning
- Make good international connections
- Choose dermatology

# What a year for dermatology



2018: Nobel Prize for science related to skin diseases

- **Nobel Prize in Physiology or Medicine** James P. Allison (CTLA4) and Tasuku Honjo (PD1) for their discovery of cancer therapy by inhibition of negative immune regulation (melanoma)
- **Nobel Prize in Chemistry** George Smith of the University of Missouri, and Sir Gregory Winter from the MRC Laboratory of Molecular Biology, in Cambridge, UK, for their work on phage display of peptides and antibodies  
Psoriasis –adalimumab (Humira)



*Sir Gregory Winter*



*George Smith*

## Quiz: What is wrong ?

1. Dermatitis herpetiformis: TG2, TG3
2. Celiac diseases: TG2, TG6
3. **Gluten ataxia: TG2, TG5**
4. Acral peeling skin syndrome: TG5
5. None of them

# Quiz

What can induce pemphigus

1. Drugs
2. Sandfly
3. Rotavirus
4. Tumors
5. All of them

# Quiz

Critidia luciliae is used to detect antibodies to

- dsDNA
- sDNA
- TG5
- Desmoglein 3
- PD1