



# Closing Remarks

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## Award

Basic science

Diagnosis

Disease

- severity
- manifestation
- HRQoL

Trials

- pre-clinical
- clinical

Therapies

- adverse events

- women

Cohorts,

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- Congratulation to Konrad Bork for his work which was awarded “For HAE Patients”
  - In the past and even more in the future the optimal care to patients affected by this orphan disease needs *collaboration* by experts
  - Animals could do better!
  - A further opportunity not to miss for being successful in finding the roots of C1-INH deficiency: reading the ancient Chinese literature



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- The endothelial cell (EC) – function & dysfunction
  - Many ways to open and close junctions between ECs
  - BK alone not sufficient → cellular misbalances needed as well: thrombin, hypoxia, LPS, etc.
- The many ways of generation and control of bradykinin
  - APP and CPN
  - Effect of therapies on these kininases and not only on C1-INH synthesis
- *We others have to take an effort in following tightly the new developments which are directing into the future (personal opinion)*



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- Secretion of C1-INH: sugar structures having a main role
- There is still room for detection of new C1-INH mutants: substitution of two consecutive nucleotides resulting in a stop codon; no particular disease manifestation
- 2<sup>nd</sup> case of homozygous (!) deficiency in an exon of the C1-INH gene (+1 intron)



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- Laboratory assessment only in hands of experienced laboratories!
- Importance of diagnosis at early age in life
- Age-dependent normal values for antigenic and functional C1-INH are available now



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## *Round Table – Consensus*

- Problems around contraception, conception pregnancy, labour and post partum
- Home/self administration
- *We are awaiting the publications*

## *HAE with normal C1-INH function*

- Update
- One additional family from Spain with homozygous FXII mutation

## *Acquired C1-INH deficiency*

- C1q not in all cases < 50% of norm
- Challenge for therapy



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## *Items discussed being involved in diseases severity*

- Challenged by discussants
  - Base line levels of C1-INH activity
  - C1rC1sC1-INH complexes
  - C4 levels at remission significantly lower in patients with severe disease (C1-INH function)
- The new view: levels of kininases
  - Decreased by 10.7% for each increase of
  - Aminopeptidase P (APP) activity  $\uparrow$  by  $1 \text{ nmol}\cdot\text{min}^{-1}\cdot\text{ml}^{-1} \rightarrow \text{risk } 10.7\% \downarrow$
  - Carboxypeptidase N (CPN)  $\uparrow$  by  $1 \text{ nmol}\cdot\text{min}^{-1}\cdot\text{ml}^{-1} \rightarrow \text{risk } 4.5\% \downarrow$
  - Some of the plasma metalloproteases “disease modifying”?



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## *Prodromi*

- Heralding signs and symptoms of HAE attacks are frequent
- Rise awareness for recognition!
- Time elapsing to manifestation: not predictable
- Proposal for elaboration of a consensus protocol

## *Associated diseases*

- Thyroid alterations (20-25% of patients)
  - An additional type of autoimmune manifestation in association with HAE
- Recurrent pancreatitis repetitively responsive to C1-INH treatment (BK mediator of pancreatitis?)



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- Developmental work – PREHAET/Spain
  - Cultural adaptation
  - Preliminary clinical form of 26 questions.
- Development & validation of a disease-specific questionnaire for children and adults with HAE (HAE-QoL) and their parents – Germany/Italy – Focus Group type of study
  - Impact on every day life of adults in almost all aspects
  - Differences in recognition of disease burden by adults and children
  - Symptoms and treatment options have a different impact on patients' quality of life
- US - HRQoL and economic burden of US patients
  - Annual direct and indirect costs US \$ 44,597 (\$11,587 for mild attacks to \$104,857 for severe attacks)



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- Plasma-derived C1-INH via the subcutaneous route of application
  - Interesting concept: circumventing the i.v. application route while profiting from the long-term experience with replacement therapy of HAE patients
  - Animal model - safe in swine
  - Questions arising for future use in humans
    - Feasible for **acute attacks?** - what is the time point of application at which kinetics of adsorption still can compensate consumption
    - Might have advantage for **maintenance therapy** – less rapid decline in plasma levels compared to i.v. application
    - Which patients will be eligible?



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## *Studies with the aim to get marketing authorisation*

- Authorization status
  - One product got marketing authorisation for treatment of acute attacks in US and EU the other in EU only
  - Four products still are struggling to get on the international stage
- Plasma-derived C1-INH concentrate
  - Two studies; i.v. application
  - Otherwise long-standing experience in EU countries
  - Excellent safety profile; AE in patients at particular risk
- Selective competitive antagonist at the bradykinin type 2 receptor
  - S.c. route of application! Not for self-administration
  - No AE
  - Limitations in dose per time unit
  - Probably best clinical experience in France (Grenoble)



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- Long-term use of Danazol with increase in yearly frequency of attacks; dose dependency
- Plasma derived C1-INH – Grenoble (Poster)
  - Supposedly anti-C1-INH mediated loss of effect
  - Study considered being incomplete: functional studies definitively missing! (lot to learn form coagulation factor inhibitor studies)
- pdC1-INH – Frankfurt
  - Allergic patient: 4 reactions; 2 different batches
  - Anti-pdC1-INH not detectable
  - No skin tests performed
  - *In vitro*: basophils are concentration-dependently activated by pdC1-INH
  - Increase spontaneous activation of patient's basophils
- Selective BK2R antagonist
  - AE at the injection site only
  - Recurrence of oedema within relative short time after treatment may occur in a significant number of treated patients



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## *Pregnancy*

- Reports from Hungary, UK, Germany, Poland
  - Change in frequency of attacks; heterogeneous picture
- Care best provided by a well trained, interested *team*
- In general no major problems
- Consensus meeting: we are waiting for a report



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- Cohort studies: always providing some deeper or more precise insights
- France: 210 type I HAE patients
- The Swiss struggle hard to get back on stage – and were able bringing up that HAE and allergy can coexist and concomitant therapy is feasible
- Belgium
- Brazil
- China
- Ukraine



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- The success of the French system and in particular of the group in Grenoble = A National Angioedema Center in France
- Ensuring sustainability is a challenge for the future



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*The great job of patient organisations has to be mentioned and acknowledged*

- German patient organisation: 600 patients interviewed
- Denmark
- South Africa
- Sweden
  
- US home therapy survey

# Thanks

- Inspired by Konrad Bork's searches in the far past own search started to detect the origin of HAE
- PubMed, Google & Wikipedia etc.
- Found: picture of two Egyptian Goddesses of HAE treatment

# Thanks



to the Egyptian Goddesses for having  
organised this excellent workshop



from: Papyrus HAEensis

# Thanks

- To the ‘angyalkák’ (the ‘angels’) / Goddesses
- To George Füst “ the father” of these meetings
- To the ‘backstage’ (collaborators) of the ‘angels’
- To the presenters
- To the representatives of patient organisations
- To the delegates
- To the sponsoring companies



We meet again  
in two years  
in Budapest?

Have a safe trip home