

ESF Exploratory Workshop on  
**The Proteomics, Epigenetics, and  
Pharmacogenetics of Pendrin**

Leogang (Austria), 8-10<sup>th</sup> of April 2011

Convened by:  
**Markus Paulmichl, Karen Avraham  
and Christine Petit**

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**SCIENTIFIC REPORT**

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## **1. Executive summary**

The ESF Exploratory Workshop on "Proteomics, Epigenetics, and Pharmacogenetics of Pendrin (PEPP)" was held in Leogang, Austria over three days from the 8th to the 10th of April 2011. The total number of attendees was 22 from 10 countries. In addition to the official list of attendees, students from the organizing University had the opportunity to participate. Lectures were organized in the morning and late evening in order to allow the participants to network and discuss science in the afternoon. The atmosphere was vibrant and members of the meeting already are engaged in common projects. The journal "Cellular Physiology and Biochemistry" (IF 3.8) agreed to dedicate a special issue to the meeting. The organizer (Prof. Paulmichl) will act as guest editor and 22 papers (reviews and original articles) will be published in October 2011. The Sunday business meeting, which was dedicated to discuss a possible common grant-application to FP-7, was also very efficient. A representative from the Austrian FGG (coordinator for EU-projects) gave an overview on the different possibilities and the group paged for a common application.

## **2. Scientific Content of the meeting**

The scientific meeting was started on the evening of the 8th of April after transferring all the participants from Salzburg to Leogang. The opening remarks were given by the organizer (Prof. Paulmichl) and the responsible person for research in the county of Salzburg (HR Brandstetter). Prof. Syka, the official observer from the ESF, gave an overview of the ESF foundation. After this presentation, the meeting moved on to the scientific topics. Prof. Bob Diasio chaired the session on the promoter studies of Pendrin. Charity Nofziger, PhD characterized the Pendrin promoter and showed an in depth analysis on how the pendrin promoter is activated by the interleukins IL4 & IL13. The activation includes a signaling cascade leading to an activated STAT6 transcription factor and this transcription factor is activating the Pendrin promoter by binding on a nucleotide site, which was also characterized by Dr. Nofziger. The second talk was given by Adam Lee, PhD (Mayo, USA) who summarized the effect of methylation on Pendrin promoter efficacy. He also showed preliminary data on the methylation of the pendrin promoter. It became evident for the audience that epigenetic regulation (like methylation) could be an important part of Pendrin expression.

On the next day, the scientific meeting was started with a talk given by Philine Wangemann PhD (UNI-Kansas, USA). Dr. Wangemann showed in detail the different steps in murine inner ear development and their effect on hearing. Exciting new insights were given on the importance of

Pendrin on hearing development. This talk was tightly connected to the second talk given this day. Unfortunately Prof. Griffith (NIH-USA) was unable to join the meeting since the NIH budget was on strike and he was not allowed to leave the country. Prof. Wangemann gave his talk and exciting new unpublished data was shared with the audience. The data of Prof. Griffith clearly showed that functional Pendrin is only necessary during the time of inner ear development. After the development of hearing, an inhibition of the transporter was without any effect on hearing function. The second block of talks was focused on the function of Pendrin in the thyroid gland. Profs. Jacques Dumont (Belgium, Europe) as well as Peter Kopp (Chicago, USA) guided the audience through the iodide transport effectuated by Pendrin in the follicular cells of the thyroid gland. Although discussed in a controversial way in the past, the audience found consensus on the importance of Pendrin regarding iodide transport in the thyroid gland. Next, Prof. Seth Alpern (Harvard, USA) emphasized the role of the STAT domain on Pendrin function. Exciting new structural insights were presented on how the STAT domain modulates Pendrin function. Prof. Dominique Eladari (Paris-Europe) showed next that there is an exciting interplay between Pendrin and the thiazide-sensitive transporter in the kidney. The findings presented showed a clear way how a future Pendrin-blocker could be an exceptional new drug for fighting hypertension. In the fourth block of the same day, Prof. Kenji Izuhara (Saga, Japan) introduced the audience into a whole new functional dimension of Pendrin—namely the involvement of Pendrin in asthma bronchiale. From the talks of Dr. Nofziger and Prof. Izuhara, it became evident that a blocker for Pendrin could open a whole new paradigm in asthma bronchiale therapy. Doz. Silvia Dossena, PhD (PMU, Austria) then showed the functional implications of several Pendrin mutations characterized in the Caucasian population so far. From these data, Dr. Dossena could deduce a new algorithm for predicting Pendrin functionality solely using amino acid sequence information. This approach allows physicians to predict Pendrin function without doing functional tests. In the last block of the same day, Amiel Dror, PhD and Prof. Karen Avraham (both Tel Aviv, Israel) gave an overview on the recent findings of a new Pendrin mutation in mouse leading to symptoms similar to Pendrin mutations in human. The results are of particular interest, since the mouse model allows to studies regarding Pendrin in a model organism. In addition, Prof. Avraham showed preliminary results obtained with deep sequencing of the Pendrin gene in the Israeli population.

The last day of the meeting was used for discussion concerning a common grant we plan to submit to the FP7 program. Before the extensive discussion of the meeting, members Ylva Huber, PhD from the FFG (the contact point for FP projects in Austria) gave an in-detail overview on the different funding schemes issued by the EU. In this session we agreed that the organizer (Prof.

Paulmichl) will act as the coordinator and we will submit the first-step application by the deadline in October, 2011. The ESF meeting, as well as the special issue which will be published in September 2011 will help to demonstrate that the network is already in place.

### **3. Assessment of the results, contribution to the future direction of the field**

The explorative Workshop provided a foundation for significant extension of an existing collaboration, to a truly European Network focused on Pendred Syndrome. The workshop further prepared the ground for developing an application to the EC framework programme. Pendred Syndrome is the most common form of syndromic congenital hearing loss in which malfunction of the Pendrin protein occurs. The shared theme on which the aforementioned scientific collaborations are based is "Proteomics, Epigenetics and Pharmacogenetics of Pendrin" (PEPP).

The aim of the explorative Workshop was to extend, fortify and intensify the scientific exchange and connectivity between 20 research groups - 15 in Europe, one in Israel, one in Japan and 4 in the USA. The common theme on which the scientific collaborations are based is "Proteomics, Epigenetics, and Pharmacogenetics of Pendrin" (**PEPP**). "Proteomics" within this collaboration refers to how the pendrin protein alone or in conjunction with other proteins impacts the observed function; "epigenetics" refers to how inherited genetic information and genetic information not encoded in the DNA sequence translates to variations in the overall function of pendrin; and finally, "pharmacogenetics" explores how genetic differences in the pendrin gene could be translated into differences in the way that possible drugs affect pendrin function. Extension of the existing collaboration between the PEPP partner-laboratories into a true European dimension will add significant momentum to the knowledge-transfer between the different groups. The groups have individual funding for the respective research, and the Workshop promoted substantial broadening of the existing network and to set ground for a future common FP7-grant.

#### 4. Final Programme

### Friday 8 April 2011

- 12.00–15.00 **Welcoming Ceremony in the Institute of Pharmacology and Toxicology, PMU, Strubergasse 21, 5020 Salzburg, Austria**
- 15.00–16.30 Transfer to Der Krallerhof, Leogang
- 16.30–19.30 *Idea translation and Relax*
- 19.30–21.00 *Gala-Dinner*
- 21.00–22.00 **Opening**
- Markus Paulmichl**, PMU, Salzburg, Austria  
**Gerfried Brandstetter**, Amt der Salzburger Landesregierung, Salzburg, Austria
- Presentation of the European Science Foundation (ESF)**
- Josef Syka** (ESF Standing Committee for the European Medical Research Councils (EMRC))
- 22.00–23.00 **Chair: Bob Diasio**, Mayo Clinic, Rochester, USA
- Every talk will be 20 minutes and 10 minutes discussion**
- 22.00–22.30 Talk **Charity Nofziger**, PMU, Salzburg, Austria  
*“Functional characterization of the human pendrin promoter”*
- 22.30–23.00 Talk **Adam Lee**, Mayo Clinic, Rochester, USA  
*“Assessment of CpG Site-Specific Promoter Methylation using MALDI-TOF Mass Spectrometry”*
- 23.00- *“Spirits”*

### Saturday 9 April 2011

- 08.00-09.00 *Breakfast*
- 09.00-10.00 **Chair: Charity Nofziger**, PMU, Salzburg, Austria
- 9.00-9.30 Talk **Philine Wangemann**, Kansas State University, USA  
*“Pendrin expression in the murine inner ear is essential for the development of hearing”*
- 9.30-10.00 Talk **Andrew J. Griffith**, NIDCH/NIH, Rockville, USA  
*“An inducible-Slc26a4 mouse model of hearing loss associated with enlargement of the vestibular aqueduct”*
- 10.00-10.30 *Coffee Break*
- 10.30-11.30 **Chair: Silvia Dossena**, PMU, Salzburg, Austria
- 10.30-11.00 Talk **Jacques Dumont**, Université Libre de Bruxelles, Belgium  
*“Role of pendrin in thyroid cell physiology”*
- 11.00-11.30 Talk **Peter Kopp**, Northwestern University, Chicago, USA  
*“Pendrin and apical iodide transport in thyroid follicular cells”*
- 11.30-12.00 *Coffee Break*

12.00–13.00	<b>Chair: Florian Lang</b> , Eberhard-Karls-University Tübingen, Germany
12.00-12.30	Talk <b>Seth L. Alper</b> , Harvard Medical School, Boston, USA “STAS domain structure in SLC26-like bacterial SulP polypeptides: implications for SLC26 function”
12.30-13.00	Talk <b>Dominique Eladari</b> , INSERM, Paris, France “Pendrin is involved in thiazide-sensitive NaCl absorption in the kidney”
13.00-14.30	Lunch
14.30-16:00	<b>Chair: Ivana Valenti</b> , Università degli Studi di Bari, Italy
14.30-15.00	Talk <b>Christine Petit</b> , Institut Pasteur, Paris, France
15.00-15.30	Talk <b>Kenji Izuhara</b> , Saga Medical School, Saga, Japan “Pendrin and Airway Inflammation”
15.30-16.00	Talk <b>Silvia Dossena</b> , PMU, Salzburg, Austria “Functional characterization of human pendrin”
16.00-20.00	<b>Idea Translation and Relax</b>
20.00-22.00	Dinner
22.00-23.00	<b>Chair: Markus Paulmichl</b> , PMU, Salzburg, Austria
22.00-22.30	Talk <b>Amiel Dror</b> , Tel Aviv University, Israel “The rolling stones: A mineralization deficiency in the Slc26a4loop mouse inner ear leads to deafness and balance disorder”
22.30-23.00	Talk <b>Karen Avraham</b> , Tel Aviv University, Israel “Identification of SLC26A4 mutations in the deaf population by deep sequencing”
23.00-23.10	<b>Closing Remarks</b>
23.10-	“Spirits”

## Sunday 10 April 2011

08.00-09.00	Breakfast
	<b>Round Table and Discussion for future EU project</b>
09.00-12.00	<b>Chair: Markus Paulmichl</b> , PMU, Salzburg, Austria
9.00-9.30	<b>Presentation FFG: Funding Opportunities in the EU</b> Talk <b>Ylva Huber</b> , FFG, Vienna, Austria “Funding opportunities in the 7th EU framework programme (FP7) and beyond”
9.30-12.00	<b>Round Table and Discussion</b>
12.00-14.00	Lunch
14.00	Departure

## 5. Final List of Participants

### List of Participants 2011-06-30

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**6. Statistical Information**

<b>Statistical information participants ESF Workshop 8-10/04/2011</b>
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28.07.2011

<b>Participants</b>	<b>Country</b>	<b>Male/Female</b>
<b>Convenor</b>		
Markus Paulmichl	Austria	M
<b>Co-Convenor</b>		
Karen Avraham	Israel	F
<b>ESF Representative</b>		
Josef Syka	Czech Republic	M
<b>FFG Representative</b>		
Ylva Huber	Austria	F
<b>Land Salzburg Representative</b>		
Gerfried Brandstetter	Austria	M
<b>Local Organiser / Secretary</b>		
Elisabeth Mooslechner	Austria	F
<b>Participants</b>		
Seth Alper	USA	M
Robert Diasio	USA	M
Silvia Dossena	Austria	F
Amiel Dror	Israel	M
Jacques Dumont	Belgium	M
Dominique Eladari	France	M
Kenji Izuhara	Japan	M
Peter Kopp	USA	M
Florian Lang	Germany	M
Adam Lee	USA	M
Charity Nofziger	Austria	F
Christoph Nowak	Singapore	M
Gerd Rasp	Austria	M
Giovanna Valenti	Italy	F
Philine Wangemann	USA	F
Viktor Weichbold	Austria	M