



## **Marie Curie Host Fellowships for Early Stage Research Training:**

Interdisciplinary, international PhD-program of the  
Center for Systems Neuroscience Hannover  
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Project No. 7:

### **Mechanisms and treatment of pharmacoresistance in a rat model of temporal lobe epilepsy**

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#### **Aim of the project:**

More than 30% of patients with epilepsy have inadequate control of seizures despite the choice of an adequate antiepileptic drug (AED) and carefully monitored treatment. Pharmacoresistant epilepsy is a major health problem, associated with increased morbidity and mortality, and accounting for much of the economic burden of epilepsy. A striking obstacle in developing new strategies for treatment of pharmacoresistant epilepsy is that mechanisms of pharmacoresistance are only poorly understood. Despite the problem of intractable epilepsy, there are only few models specifically dedicated to identify effective therapeutic agents for resistant epilepsy or to study mechanisms of drug resistance. Thus, new methods for evaluating the therapeutic potential of novel compounds for the treatment of refractory epilepsy are urgently needed. An animal model of epilepsy allowing selection of pharmacoresistant and pharmacosensitive subgroups of animals would be particularly valuable to study mechanisms of intractability and to develop more efficacious treatment strategies.

Over recent years, the group of W. Löscher has developed such animal models. The specific aim of this project is to further characterize these models by studying mechanisms of pharmacoresistance and potential strategies to counteract or prevent this resistance. Experimental methods used in this project include experimental neurophysiology, immunohistochemistry, laser scanning microscopy, and behavioral pharmacology.

#### **State of the field:**

In about one third of patients with epilepsy, the seizures persist despite the choice of an adequate antiepileptic drug (AED) and carefully monitored treatment. In most of these patients, neither monotherapy with other AEDs nor combination therapy with two or more AEDs lead to seizure control, so that these patients are considered resistant to AED therapy. The mechanisms underlying such pharmacoresistance are only poorly understood. Research

on these mechanisms and development of more efficacious therapies is hampered by a lack of adequate experimental models of intractable epilepsy. An animal model of epilepsy allowing selection of pharmacoresistant and pharmacosensitive subgroups of animals would be a valuable tool to study mechanisms of intractability and to develop more efficacious treatment strategies.

**Previous work of Löscher's group in this field:**

Over the last 20 years, Löscher's group has developed rat models of temporal lobe epilepsy, allowing to select subgroups of rats that are either responsive or nonresponsive to treatment by AEDs. We have started to characterize the mechanisms underlying drug resistance in these models, resulting in the observation that AED nonresponders have an increased expression of drug efflux transporters in the blood-brain barrier (cf., Löscher and Potschka, 2005). Thus, inhibitors of such transporters could be a valuable strategy to prevent or counteract drug resistance.

**Literature:**

Löscher, W. and H. Potschka:

Drug resistance in brain diseases and the role of drug efflux transporters.

*Nature Rev.Neurosci.*, 6, 591-602, 2005.

This project is part of the main research area "Characterization of genetically induced brain alterations in animal models" of the ZSN.