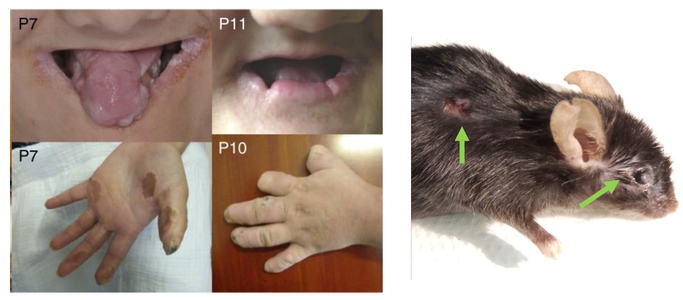
Prdm12 deficiency impairs sensory nervous system function and organization

Tomislav Kokotović[1], Ewelina M Lenartowicz [1], Michiel Langeslag [2], Christopher Fell [1] and Vanja Nagy [1]

[1] Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD), Vienna, Austria; [2]Department of physiology, Medical University of Innsbruck, Innsbruck, Austria

Introduction

PRDM12 is a member of a larger family of PR-domain containing transcriptional regulators. PRDM12 engages with DNA and G9a methyl-transferase to ultimately dictate cell-fate decisions during early sensory neuronal development. Mutation in any part of *PRDM12* gene causes complete insensitivity to acute and chronic pain in humans, a condition named Congenital Insensitivity to Pain (CIP). These patients also suffer from recurrent skin infections, most commonly caused by *S. aureus*. In order to investigate molecular background of the observed phenotype, several conditional knockout mouse models have been developed and phenotyped on a behavioral, microanatomical and electrophysiological level.



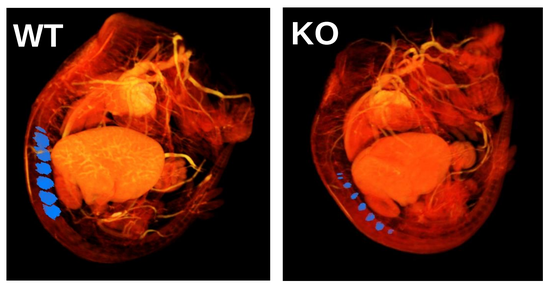
Objective: Exploring behavioral, (micro)anatomical and electrophysiological phenotype of *Prdm12*-deficient murine models of Congenital Insensitivity to Pain.

Goals:

1. Behavioral phenotyping of the developed conditional knockout murine models
2. Microanatomical phenotyping of the sensory nervous system in *Prdm12*-deficiency
3. Electrophysiological properties of individual *Prdm12*-deficient nociceptors

Classical knockout model

Prdm12 classical KOs

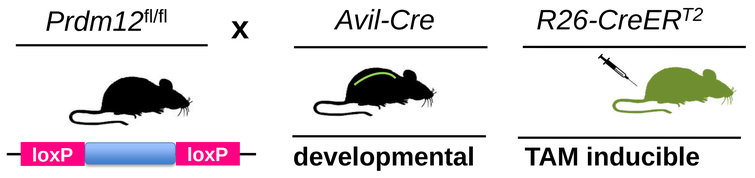


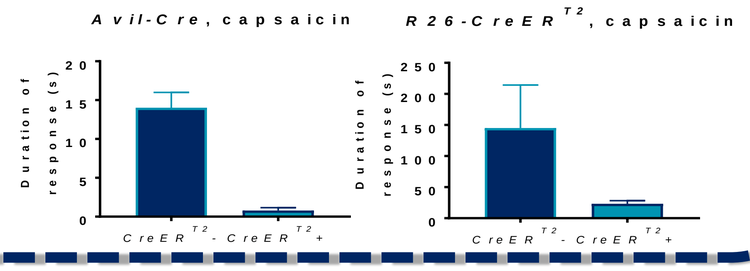
MicroCT of E14.5 embryos

In collaboration with Brian Metscher

Conditional knockout models

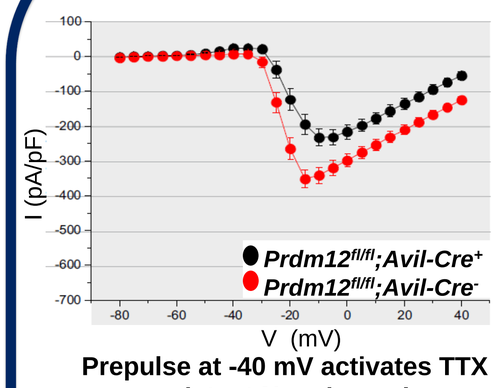
Conditional knockout models



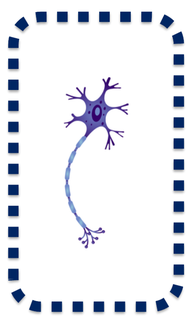


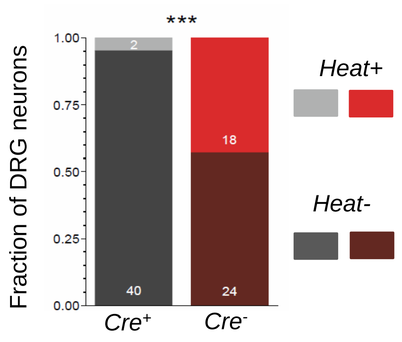
Electrophysiological phenotype

Single cell electrophysiological studies

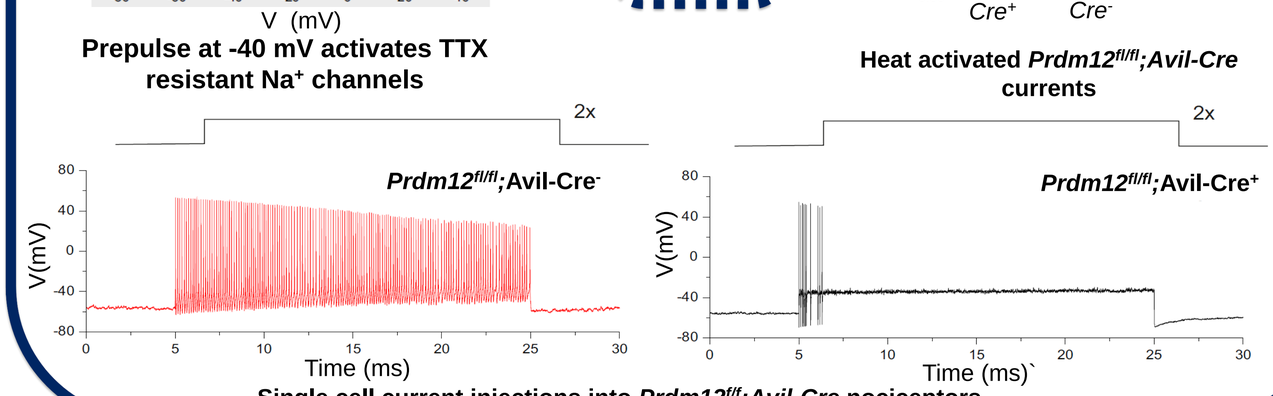


Prepulse at -40 mV activates TTX resistant Na^+ channels





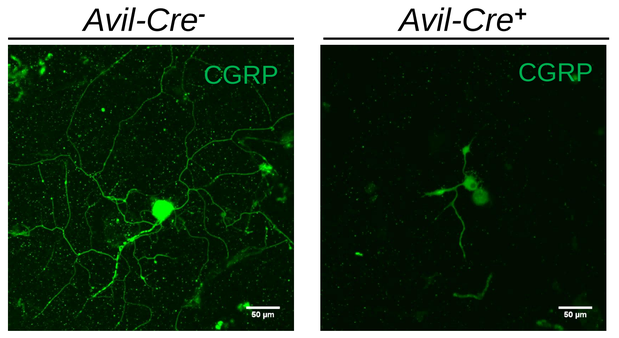
Heat activated *Prdm12fl/fl;Avil-Cre* currents



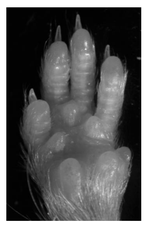
Single cell current injections into *Prdm12f/f;Avil-Cre* nociceptors

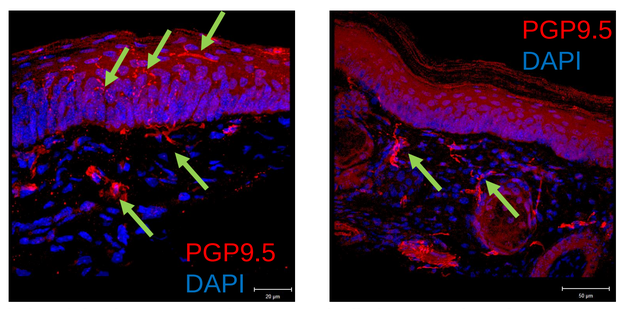
(Micro)anatomical Phenotype of the *Prdm12fl/fl* ; Avil-Cre

LacZ/PRDM12; sensory ganglia expression*



Prdm12 – deficient (*Avil-Cre*$^+$) nociceptor show impaired microanatomy and neurite outgrowth





Inervation pattern of the hindpaw; *Prdm12* – deficient animals (*Avil-Cre*$^+$) lack epidermal sensory innervation

*in collaboration with Eric Bellefroid

Conclusions

1. ***Avil-Cre;Prdm12$^{fl/fl}$* and *R26CreER^{T2};Prdm12$^{fl/fl}$* conditional knockout models phenocopy behavioral phenotype of insensitivity to pain.**
2. **Nocicpetors in developmental advilin *Prdm12*-deficient model show impaired innervation of the skin and absence of sensory fibers in the epidermis.**
3. ***Prdm12*-deficient nociceptors show impaired electrophysiological properties, suggesting impaired voltage-gated sodium channels.**

Chen, YC., et., 2015, Transcriptional regulator PRDM12 is essential for human pain, Nature genetics, 47, 803-808.
Nagy V., et al., 2015, The evolutionary conserved transcription factor PRDM12 controls sensory neuron development and pain perception, Cell Cycle, 14:12, 1799-1808.