

# PhD Thesis Defense

**Sophie L. Dahl**, MSc in Molecular Biotechnology

## **Renal Erythropoietin-Producing Cells in Health and Disease**

The healthy adult kidney is an important sensor of blood O<sub>2</sub> concentration and the main production site of erythropoietin (Epo). Epo expression is mediated by O<sub>2</sub>-sensing, peritubular, interstitial, renal erythropoietin-producing (REP) cells. In chronic kidney disease (CKD), REP cells lose their ability to produce Epo, causing the development of anemia. As potential causes, transdifferentiation into myofibroblasts and environmental changes due to hyperoxia are considered. Recently, roxadustat, the first hypoxia-inducible factor (HIF) prolyl hydroxylase domain (PHD) enzyme inhibitor stimulating Epo production, was approved for the treatment of CKD patients. To investigate physiological relevant REP cells, we generated a novel transgenic mouse model that allows permanent tagging of REP cells with tdTomato under control of the Epo regulatory region. Our mouse model revealed that REP cells are long-lived, are mainly located at the corticomedullary border but also found in the inner kidney and papilla, and can re-express Epo after a second hypoxic stimulus. In a model of unilateral ureteral obstruction (UUO), Epo expression was completely lost despite proliferating REP cells. Interestingly, myofibroblast transdifferentiation was not the major reason for Epo loss. A single injection of roxadustat could restore Epo production in initially tagged REP cells of the damaged kidney to a similar extent like in the healthy contralateral kidney, demonstrating persistent REP cell functionality in disease. This suggests that hyperoxia rather than transdifferentiation causes Epo loss in the diseased kidney and supports the efficacy of PHD inhibitors in the treatment of renal anemia.

Friday, January 21, 2022, 14:00 h

The event can be attended in person in Y23K52 (2G only) and via ZOOM:

Link: <https://uzh.zoom.us/join>

Meeting ID: 665 9942 8040      Passcode: 098721

<https://uzh.zoom.us/j/66599428040?pwd=cnlpSWc5bkNqV2Y4cm0wT050RGVLU09>