

BBB Seminar (BMED380)



Thursday, November 7. 14:30 at the BBB, Auditorium 4

From basic research in fruit flies to patients with impaired coenzyme A biosynthesis in less than 5 years

Ody Sibon

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Dr. Sibon's PhD (University of Utrecht, The Netherlands) and postdoctoral training (University of Stony Brook, NY, USA) provided her with a background in fundamental cell and developmental biology. In 1998, Sibon started as a P.I. at the University Medical Center in Groningen, The Netherlands. Her interest is to unravel coenzyme A (CoA) metabolism in health and disease. She found evidence for alternative routes for cells and organisms to maintain CoA homeostasis via the uptake of CoA precursors other than the well-known precursor: vitamin B5. Sensitive detection methods for CoA-derivatives were developed and models to manipulate CoA homeostasis were generated. She tested the usage of alternative CoA-precursors in animal models of various CoA-linked diseases. Diseases characterized by inborn errors of CoA biosynthesis, including PKAN (neurodegenerative disease), CoPAN (neurodegenerative disease) and PPCS-deficiency (dilated cardiomyopathy).

Dr. Sibon used the fundamental knowledge to explore possibilities to generate bypass molecules for the defective CoA biosynthesis steps, like the vitamin B5 derivative "4'-phosphopantetheine" and successfully tested them in PKAN Drosophila and mouse models. Together with prof. Hayflick at the Oregon Science and Health University, she developed 4'-phosphopantetheine further via a non-for-profit manner into a medical product which fulfils all the standards allowing testing in a clinical trial. As a result, at the Oregon Science and Health University, a clinical trial with 4'-phosphopantetheine is successfully finished and Sibon is currently the coordinator of the first ongoing PKAN clinical trial with 4'-phosphopantetheine in the Netherlands.

The aim is to finally bring 4'-phosphopantetheine to the market as a cost-effective product for PKAN. This seminar will elaborate on the trajectory from fundamental research in fruit fly models towards the development of a medical product for the rare-Coenzyme A-linked disease PKAN.

Key papers:

1) Srinivasan, et al., Extracellular 4'-Phosphopantetheine is a source for intracellular Coenzyme A synthesis. *Nature Chemical Biology* 2015 Oct;11(10):784-792. **2)** Ody C.M. Sibon & Erick Strauss. Coenzyme A: make it or (re) uptake it. *Nature Reviews in Molecular Cell Biology* (2016) 10:605-606. **3)** Roald Lambrechts et al., Linkage of CoA and pyruvate dehydrogenase reveals a pathway affected in neurodegenerative diseases. *EMBO MOL MED* 2019 Dec;11(12):e10488. **4)** Jeong et al., 4'-Phosphopantetheine corrects CoA, iron and dopamine metabolic defects in mammalian models of PKAN. *EMBO MOL MED* 2019 Dec;11(12):e10489.

Chairperson: Mathias Ziegler, Department of Biomedicine