# E I N L A D U N G
## zum ZHMB Kolloquium

## Vortrag von

## Prof. Dr. Irina A. Pikuleva

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am

## Freitag, 27.06.2025
## 10:30 – 12:00 Uhr

### Campus Saarbrücken, Gebäude A 2.4 – Seminarraum 0.33

Link für MS Teams: https://tinyurl.com/4tdh68b9

## CYP46A1 as a Pharmacologic Target for Alzheimer's Disease and Other Brain Disorders

CYP46A1 is the CNS-specific cholesterol 24-hydroxylase, catalyzing the conversion of cholesterol into 24-hydroxycholesterol. CYP46A1 is expressed in certain neurons of the brain and retina with the enzyme expression being decreased in many neurodegenerative diseases due to loss of neurons expressing CYP46A1. Therefore, CYP46A1 has emerged as a therapeutic target for various brain disorders. We discovered that CYP46A1 can be allosterically activated by small-dose anti-HIV drug efavirenz and showed that its activation in 5XFAD mice, an Alzheimer's disease model, mitigates multiple disease manifestations. We also identified the CYP46A1 activating efavirenz dose in subjects with early Alzheimer's diseases and tested its safety in this population. Others demonstrate the beneficial effects of CYP46A1 activation, either by pharmacologic or genetic means, on mouse models of Huntington's disease, Parkinson's disease, spinocerebellar ataxia 3, Niemann-Pick type C1 disease, prion infection, depression, epileptic seizers, and glioblastoma. Mechanistically, a variety of apparently unlinked brain processes were affected by CYP46A1 activation, raising a question of how one enzyme can control brain processes beyond cholesterol elimination. To address this question, we developed the "chain reaction" hypothesis, according to which there are primary CYP46A1 activity effects, which in turn can elicit numerous secondary effects. We have identified the major primary and secondary CYP46A1 activity effects, which will be presented in my talk. Our studies also led to some unexpected findings and suggested an additional neurodegenerative disease that may benefit form CYP46A1 activation. Supported by AG067552