MPI-NAT SEMINAR SERIES

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Therapeutic and structural insights into the integrated stress response, a pathway of medical relevance for neurodegenerative diseases

Life depends on ability to survive challenges. Our work focusses on vital signaling pathways that evolved to ensure cell survival in the face of challenges or stresses. I will present my scientific journey going from the discovery of components of the integrated stress response (ISR) to pioneering strategies that harness such pathways to enhance cellular resilience. This modality is generically applicable to improve fitness in diverse diseases, including the age-related neurodegenerative diseases. Some of the small molecules we reported have progressed to human clinical trials: Guanabenz was found efficacious in a Phase 2 trial in ALS and phase 2 trials are ongoing with Sephin1, after successful Phase 1 and Phase 2a trials.

Expanding our toolbox, we recently made the unexpected discovery that broadly used ATP-competitive inhibitors of one eIF2 kinase can paradoxically activate a related one and thereby activate a pathway they were designed to inhibit. These findings have broad relevance.

Our work is driven by understanding fundamental cellular processes which in turn, bring therapeutic opportunities. Going full circle, the small molecules we discovered also raise fundamental questions. The work on Guanabenz, Sephin1 and Raphin1 has stimulated our interest on the termination of the ISR controlled by dedicated phosphatases. We have deployed a combination of approaches to characterize these poorly understood enzymes and to elucidate the mechanism by which the phosphatases of the ISR recruit their large substrate. This revealed the mechanisms terminating ISR signaling, a question that had been unresolved for 50 years.

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Friday, 19.6.2026, 11 am
Ludwig Prandtl Hall

Hosts: Marina Rodnina & Sonja Lorenz & Niels Fischer

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