LSU Health Sciences Center NEW ORLEANS

School of Medicine

*Neuroscience Center of Excellence*

# Chancellor's Award Lecturer *in Neuroscience*

## Co-Sponsored by the Local Chapter of the Society for Neuroscience (GNOSN)

# Cell and Animal Models of Tau Pathology and Neurodegeneration

Pathological changes of Tau in axons and dendrites (hyperphosphorylation, missorting, aggregation and others) are among the earliest signs of neurodegeneration in Alzheimer disease and other tauopathies. Incipient changes are observed from the second decade of life onwards, before the occurrence of amyloid plaques and dystrophic neurites, and they spread in a stereotypic pattern. We are developing cell and animal models to study the progression of Tau pathology, the interaction with Aβ, and the effects of aggregation inhibitor compounds. Several cell and mouse models are based on the concept of regulatable expression of either "pro-aggregant" or "anti-aggregant" Tau. The expression of Tau can be switched on or off by doxycyclin (tet-on or tet-off systems). The expressed Tau variants are based on mutations observed in FTDP-17. The pro-aggregant form contains the deletion mutant ΔK280 in the repeat domain, the anti-aggregant form contains in addition two Ile>Pro mutations in the repeat domain. In both cell and mouse models, neurodegeneration occurs only when pro-aggregant Tau is expressed, whereas cells or mice with anti-aggregant Tau are nearly normal. This implies that the toxicity of Tau resides in the ability to form β-structure, and that there is a remarkable correlation between the in vitro aggregation behavior of Tau and its effects in cells and animals. In pro-aggregant mice with tau aggregates, loss of synapses and neurons, we find learning and memory deficits which can be rescued when the expression of the toxic pro-aggregant tau is switched off. We are pursuing this concept on several levels: (a) regulatable transgenic mice (pro- or anti-aggregant, expressing repeat domain or full-length Tau, (b) brain slices derived from the transgenic mice, (c) regulatable neuroblastoma cell models, and have started collaborations to establish analogous models in C. elegans (collaboration E. Schmidt & R. Baumeister, Univ. Freiburg) and Drosophila (collaboration L. Partridge, MPI Aging Res. Cologne). While mice represent closer approximations to the Tau pathology in AD and FTD, the cell models, C. elegans and Drosophila will allow more efficient screening of Tau anti-aggregation compounds and other therapeutic agents that are being developed (collab. B. Bulic, CAESAR). - Supported by MPG, EU FP7 (Memosad), Metlife Fnd, BMBF (KNDD).

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**12:00 p.m.**
**November 11, 2011**

**8th Floor**

**Neuroscience Center of Excellence Conference Room**

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