USC University of Southern California

Zilkha Neurogenetic Institute

NEWS

Fall 2015

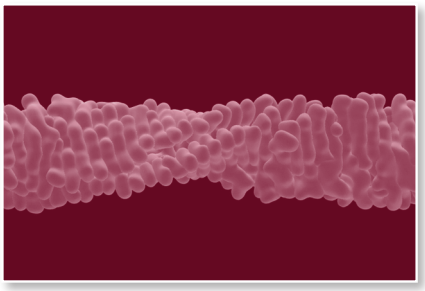
ZNI Faculty Profile

Ansgar Siemer, PhD

Assistant Professor,
Biochemistry and Molecular Biology

How can amyloid fibrils that are usually associated with neurodegeneration, for example in Alzheimer's Disease, have positive functions and in fact be important for memory? The mission of the Ansgar Siemer lab is to determine the atomic structure of both types of amyloid fibrils, to understand what makes functional amyloids beneficial and why disease-associated amyloids are pathologic. To accomplish this goal, his lab uses an emerging technique called solid-state nuclear magnetic resonance (NMR) spectroscopy, which allows investigations of the structure of amyloid fibrils at the atomic level.

Amyloid fibrils form when many proteins of the same type are aligned in a so-called cross-ß structure. Deposits of amyloid fibrils were first described in diseases in the late 1850s, in particular neurodegenerative disorders such as Alzheimer's, Parkinson's, and Huntington's Disease. To date it is not clear how and if these amyloid fibrils are the cause of these disorders. Recently, researchers have become aware of an additional class of amyloid fibrils not found in disease that have positive biological functions. One example is an amyloid formed by the protein Orb2, found in the synapses of fruit flies, where it regulates the formation of long-term memories.



Cross-beta structure of amyloid fibrils

One question the Siemer lab is trying answer is how amyloid fibril formation, which is seen as an accident in the case of amyloid diseases, is turned on and off in the case of Orb2. Another question is why fibril formation is used as a regulatory mechanism in biology and how amyloid formation makes sense mechanistically. Finally, an extremely important question is how functional amyloid fibrils are different from amyloid fibrils found in disease.

Graduate students Maria Conrad-Soria, Sandy Falk and Silvia Cervantes pose with Dr Ansgar Siemer (foreground) and lab technician Thalia Bajakian in front of the solid-state NMR at ZNI.

In order to investigate these differences, Siemer and his group teamed up with Dr Ralf Langen, Professor of Biochemistry & Molecular Biology who also has a laboratory at ZNI. The Langen lab has been working on the structure of amyloid fibrils formed by the protein huntingtin, which are found in patients with Huntington's Disease. When compared on the level of their protein sequence, Orb2 and huntingtin share striking similarities. By analyzing these two proteins, they aim to understand the differences between benign and pathological amyloids.

Much of what we know about protein structure today comes from two techniques: Crystallography, which is used to determine the structure of protein crystals, and solution NMR spectroscopy, which provides insight into soluble proteins. But how can we determine the structure of proteins that are neither in solution nor in a crystalline state? While still an emerging technique, solid-state NMR can help determine structures of proteins that are neither in solution nor in a crystalline state. Indeed, most of what we know about the atomic resolution structures of amyloid fibrils today comes from solid-state NMR data.

During his graduate and postdoctoral work, Ansgar Siemer was already contributing to the structural knowledge of amyloid fibrils using solid-state NMR. He worked on

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In addition to being a co-Investigator on Dr Ralf Langen's NINDS R01, recently Dr Ansgar Siemer was awarded his own 5-year R01 grant from NIGMS. The study aims to determine the structure of the protein Orb2, which is a key player in long-term memory in fruit flies and show how Orb2 interacts with lipid membranes. Knowing the structure of functional amyloids and understanding how aggregation is regulated will lead to a better understanding of toxic amyloids and may ultimately help find a cure for neurodegenerative amyloid diseases like Alzheimer's Disease.

ZNI Faculty Profile: Ansgar Siemer, PhD

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identifying the structure of fibrils formed by the HET-s prion protein while obtaining his PhD in the lab of Beat Meier at the Swiss Federal Institute of Technology (ETH) in Zurich, Switzerland. Later, while a postdoctoral fellow in the lab of Ann McDermott at Columbia University, he characterized the human amyloid formed by the proteins RIP1-RIP3. While at Columbia, Dr Siemer established a collaboration with Nobel laureate Eric Kandel, and worked on the amyloid formed by the protein CPEB, an Orb2 homologue in the sea snail Aplysia.

Since establishing his own laboratory at ZNI in 2012, Dr Siemer and his research group have made significant progress. Not only have they been able to show that the N-terminus of the Orb2 isoform A—which is crucial for long-term memory—forms part of the Orb2 amyloid fibril core, but they have also demonstrated that the structure of the amyloid fibrils formed by Orb2 and huntingtin are strikingly different. These results are an important step toward understanding how some amyloid fibrils regulate memory formation and others cause disease. Investigations of these differences at the atomic level will help researchers and clinicians identify therapies and ultimately cures for neurodegenerative diseases in the future.

ZNI Graduate Student, Brian Zingg, Awarded NIH Fellowship

Brian Zingg, a graduate student working in the laboratories of Dr Huizhong Tao and Dr Li Zhang, will receive a Ruth L. Kirschstein National Research Service Award by the National Institute on Deafness and other Communication Disorders (NIDCD), part of the National Institutes of Health. The F31 fellowship provides three years of support for predoctoral students working toward a PhD or equivalent degree in the biomedical, behavioral and clinical sciences.

Zingg's project, entitled "Functional Properties of Subclasses of Layer 5 Projection Neurons in the Auditory Cortex," will further explore how sound information is processed in the brain. Specifically, Brian's research will explore the role of the auditory cortex in sound processing, in particular the sources from which the auditory cortical projections arise as well as the nature and timing of the feedback signals that these projections provide.

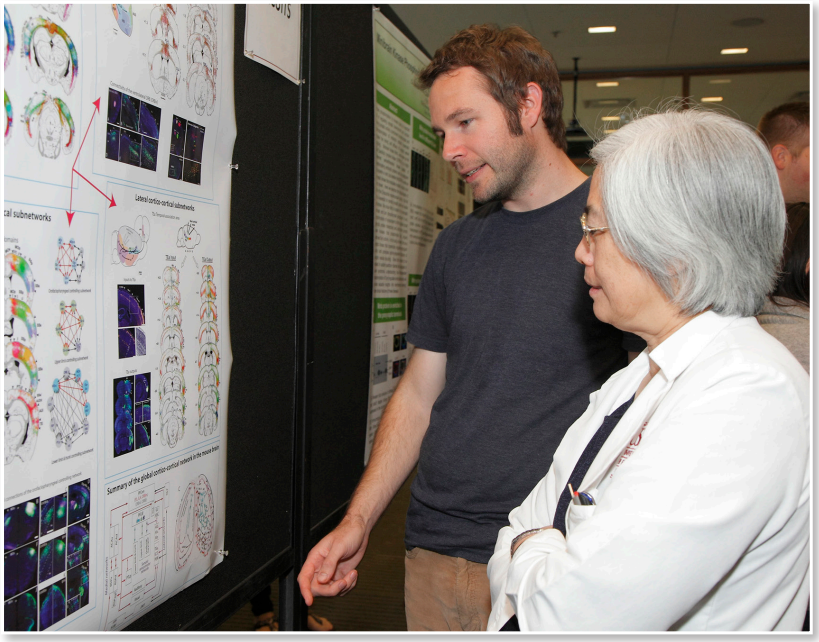

Photo by Steve Cohn

Brian Zingg and Dr Helena Chui, review a poster of data presented at the Annual Zach Hall event (Nov 2014)

The aim of the proposed studies is to generate new insights for understanding the normal physiology and organization of the auditory system, which may provide a means for identifying circuit components that go awry in psychiatric and neurological disorders.

NMR Spectrometer Comparison: What's the Difference?

Did you know that Protein Structure Laboratory in ZNI actually houses two Nuclear Magnetic Resonance (NMR) spectrometers? Both are large, multi-ton, highly specialized instruments that utilize the magnetic properties of atomic nuclei in order to assist researchers in better understanding the physical and chemical properties of atoms and molecules. Each NMR uses a strong magnetic field to detect the absorption and release of electromagnetic radiation by proteins. Spectral resolution and sensitivity increases with the strength of the magnetic field. Most atoms have their own radio frequency (resonance frequency or chemical shift); the NMR detects these frequencies, allowing scientists to obtain information about the chemical environment of the individual atoms, including distances between atoms, the dynamics between different atoms, and helping capture the atomic resolution 3D structure of a molecule, opening the door for computer-aided drug development.

Here are some differences between the two:

	Solid State NMR	Liquid State NMR
Speed	600 MHz spectrometer, where 1 MHz = 1 million cycles per second	700 MHz spectrometer, similar to frequency of T-Mobile cellular network
Scientific Approach	The ssNMR deploys a Magic Angling Spinning (MAS) technique, where the sample is spun at a very high speed at a specific angle. The very high resolution enables data collection on chemistry, structure and dynamics in the solid state.	The liquid state NMR uses a signal detection system, optimized to examine proteins in aqueous solution and in lipid membranes. This allows the study of proteins at conditions that closely resemble their cellular environment.
Contributions to research	The solid state NMR allows study of amyloid fibrils at atomic resolution, which is not possible through X-ray crystallography or by using liquid-state NMR.	Solution NMR reveals the structures of molecules and their interactions, even weak and transient, helping characterize functional processes in solution as well as directly in living cells.
Fun Fact!	The solid state NMR is called Xena Fourier Princess, a name chosen after a highly competitive contest at ZNI.	To keep the magnet superconducting at a temperature of -269° C, it is cooled by 500 liters of liquid helium and 400 liters of liquid nitrogen.

Zilkha Welcomes new Lead Development Officer – Christopher Sickels

Christopher Sickels

We are pleased to announce that Chris Sickels has joined the Zilkha Neurogenetic Institute and Keck Medicine Advancement Staff as the Sr. Director of Development for Brain Sciences. Chris comes to USC from Hunterdon Medical Center Foundation and Hunterdon Healthcare System where he served as an Executive Vice President, Senior Vice President & Chief Operating Officer. Previously, Chris also worked at NYU-Langone Medical Center in NYC and the University of Medicine and Dentistry of New Jersey in Newark where he served as the Sr. Director of Development for Neurosciences at both institutions. Chris has had 25 years of experience in academic medicine and healthcare philanthropy and will be working with Dr Zlokovic and other ZNI Faculty on all major philanthropic endeavors. Chris can be contacted at **(626) 710-3266** and/or **sickels@usc.edu**.

New Website for ZNI

As part of a pilot program within the Keck School of Medicine, ZNI spent the last 18 months working with a team from Health Sciences Public Relations & Marketing to refresh the look and feel of our website.Faculty and staff contributed new content to appeal to current and prospective graduate students and postdoctoral fellows, faculty and their collaborators, as well as the community at large, including updates on the various research programs and areas of study at the Institute. The site features new visuals, an electronic repository of our publications, and a news feed of announcements and upcoming events.

Drop by www.usc.edu/zni, take it for a test drive and kindly let us know what you think!

Grant Funding at ZNI

Over the summer, four ZNI researchers were awarded a second R01 grant from the NIH. The Research Project Grant (R01) is the original and historically oldest grant mechanism used by NIH. R01s can be investigator-initiated or can be in response to a program announcement or request for application.

NIH funding levels have not been keeping pace with inflation over the last several years. Fewer dollars going to more research programs has made an already difficult process, much more competitive. To maintain their laboratories, 30 ZNI researchers submit an average of 8-10 proposals a month. The hard work is paying off, as ZNI scientists currently hold 67 research grants (49 federal, 18 from foundations) with an annual portfolio over $17M/year. As of September 2015, 40 more grants submitted by ZNI investigators are still pending, which if awarded would bring in an additional $50M.

Dr Ralf Langen now holds two R01s, one from the National Institute of Neurological Disorders and Stroke (NINDS) and another from the National Institute of General Medical Sciences (NIGMS). Dr Janos Peti-Peterdi received in July a second R01 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Dr Huizhong (Whit) Tao recently was awarded a second R01 from the National Eye Institute (NEI). And in addition to his existing National Institute on Aging (NIA) R01, Dr Berislav Zlokovic was awarded in 2015, renewals for three separate R01 research projects, one from National Institute on Aging (NIA) and two from NINDS.

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