Research

Research Program

Our research focuses on the problem of selective vulnerability. Recently, we have used frontotemporal dementia (FTD) and Alzheimer's disease (AD), the most common causes of dementia among patients under 65 years of age, as model disorders for understanding selective vulnerability at the network and cellular levels. Ongoing research explores selective vulnerability in FTD, AD, corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and amyotrophic lateral sclerosis (ALS).

Our laboratory blends diverse methods and provides a rich training environment for aspiring researchers interested in studying neurodegenerative disease in humans. Dr. Seeley is a new member of the UCSF Neurosciences Program [1] and is happy to receive inquiries from prospective UCSF graduate students, postdoctoral fellows, and visiting scholars.

Participate in Research

If you are interested in participating in Memory and Aging Center research, please visit the Research page at the Memory and Aging Center website below [2].

Von Economo Neurons and Fork Cells

Our lab identified the von Economo neurons (VENs) and fork cells, large layer 5 projection neurons, as early neuronal targets in the behavioral variant of FTD. VENs are found exclusively in anterior cingulate (ACC) and frontoinsular (FI) cortex, and their numbers have expanded greatly in humans, apes, cetaceans, and elephants. Fork cells are a related neuron subtype found primarily in the FI. We propose that some aspect of VEN and fork cell biology confers FTD-related selective vulnerability to the ACC and FI, and that understanding this phenomenon may provide clues toward finding new FTD treatments. Longer term, we hope to use VEN and fork cell degeneration in FTD as a model for the broader study of selective vulnerability.
Ongoing Projects

Neuroimaging

Modern neuroimaging studies of patients with degenerative disease provide the critical anatomical maps that guide neurodegenerative disease research. We use network-sensitive structural and functional MRI techniques to chart the brain regions affected early in each disease. Asymptomatic mutation carriers provide an important window into these early stages. We also use imaging to study disease progression. To date, our findings suggest that disease progression may represent spread of disease along network connections, perhaps due to prion-like corruption of natively folded (or unfolded) proteins. Additional ongoing studies seek additional more direct support for this hypothesis.

Neuroanatomy and Pathology

Because quantitative neuropathological experiments require meticulous, labor-intensive experiments that yield rich information about few, restricted brain regions, we use the neuroimaging to pinpoint networks and provide a map for our quantitative pathology
studies. Neurohistological methods then enable us to delve deeper, into the microstructure of the brain as it undergoes progressive degeneration. In addition, modern single cell profiling approaches allow us to pursue questions of neuron type-specific identity and vulnerability. The molecular genetics of neurodegeneration provides candidate pathways for further exploration in human tissues and other model systems. The overall goal of these studies is to understand how selective vulnerability works, paving the way for discovery of novel therapeutics that protect, restore, or even replace susceptible neurons.
Clinicopathological Correlation

Dr. Seeley founded the UCSF Neurodegenerative Disease Brain Bank (NDBB) in 2008. The NDBB, housed within the Seeley Lab, contains brain tissue specimens from over 600 patients with neurodegenerative disease, and UCSF research conducted on this cohort has helped contribute to our understanding of clinicopathological correlations in FTD (image at left available for download). The NDBB also serves as a valuable tissue resource for the neurodegeneration research community.

The combination of imaging and pathology expertise and resources in our lab also provides a fertile environment for studies that relate imaging measures obtained during life to pathological observations made at autopsy.

Slide courtesy W.W. Seeley, UCSF

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