Tau Consortium 081318

Adam Boxer—clinical trials in PSP

* Most recent anti-tau monoclonal Ab in clinical trials
* Majority of anti-tau Ab are against N-term of tau (one funded by UCSF Parkinson center)
* Salsalate—identified by Li Gan
* N-term Ab: N-term of N inserts, against tau fragments (?)
* Basket trial: different tauopathies/phenotypes, but all based in tau; includes 6 tauopathies
* How to choose the right anti-tau (compared to failures for anti-aBeta)? These are just N-term, there are also some conformational Ab; unclear what will work

Jennifer Crum-Bailey and Bill Seeley—mystery case

* FTD-ALS diagnosis, onset age 46-50
* All negative in genetic tests
* Passed away at age 55
* See TDP-43

Stem Cell Session—Sally Temple

* Includes Martin, Aimee Kao (UCSF/MAC), and Ken Kosik (UCSB)
* Have isogenic controls for P301L/S, V337M, and R406W
* We have some of these lines(?)
* Increase in CHIP and 70 accumulation in A152T, P301L, and R406W iPSC lines
* Single cell scRNA analysis of organoids by Ken Kosik’s lab

Stem Cell Session—Justin Ichida

* Microglial activation during neurodegeneration
* When co-culturing V337M neurons with microglia, microglia become amoeboid, shift in cytokines, etc
* With microglia in culture, mutant MAPT iPSC neurons have a lower survival rate
* C9 expansion🡪increase in APOE
* Ivermectin increases the neuron survival in co-culture, shifts microglia into anti-inflammatory state
* AcuraStem—stem cell based drug discovery for ALS and FTD, this is a new company, hits include kinase inhibitors (PIKfyve)

Stem Cell Session—Celeste Karch

* RNAseq and transcriptomics to determine downstream events of MAPT mutations that are implicated in pathogenesis
* Model: R406W, validated in 406W patient brains
* Identified 61 genes that change upon mutation in IPSCs and brains, many are direct interactors (unclear if this is STRING analysis, PPIs, or other)
* SNAP25 and SYT1 as most central hits
* Generally, implicates alteration in GABA receptor function and downregulation in GABR genes
* None of the genes replicated in FTD-TDP43 or AD PSEN brains
* Lysosomal disfunction also implicated

Mechanisms Break-out group

* Can we have early diagnosis of PSP? 🡪 1-5 in 10,000, biomarker would have to be very cheap and very specific
* Are there clear premotor/preclinical PSP symptoms? 🡪 perhaps psychiatric
* Do mechanisms prize goals seem useful? 🡪 is it worth doing other things besides lowering tau levels?
* Missing link outside of genetics: environmental component
* Goal: polygenic risk scores for all tauopathies; however, these will overlap
  + Rare variants, transcriptomics, imaging data🡪multimodal risk profiling
* most meaningful biomarkers are rooted in biology🡪which direction to start with, mechanism, or drill down from biomarker?
* Causality, initiation events🡪invertebrate models
* Lots of discussion about animal/cell models; or should it be prioritized to do experiments across multiple models
* Stem cells as the best option to get around differences in gene expression in mouse tissue🡪but we need animal models to test drugs
* Caveats: IPS again, mouse gene expression🡪emphasis on mouse models for particular phenotypes, rather than models for the full disease
* What are the appropriate standards of evidence? Findings in mouse models need to be replicated in mice? Worms? What’s needed to move to the clinic, in terms of convergent evidence?
* Examples from other fields: replicating in 3 labs for efficacy of rapamycin, metformin, etc in mice; also mice have genetically heterogeneous background
* Future goals: table of pros/cons for different models
* Small Chilean rodent with naturally occurring tauopathy—specimen was caught from the wild; genetically controlled animals couldn’t replicate these findings
* If the disease is primarly environmental, how do we make good models? Predictions?
* There’s very little investment into studying environmental roles🡪Steve Haggarty is doing this with his IPSC lines
* Goal: identify the second hit and avoid it🡪problem: second hit could be many many things, unless it’s a “sledgehammer” like the compromised groundwater in France

Mechanisms Session—Karen Duff

* Is clinical diversity a result of strains? Particularly is FTD heterogeneity due to strains, as opposed to AD (see Diamond paper)
* Tau particularly colocalizes with excitatory neurons in AD, which are a subtype that are lost in AD (also seen for FTD)
* Do certain strains populate different parts of the brain?
* Developed sensor lines (like Diamond lab strains/clones) that originated in CBD patient brain samples
* Microscopy with Steve Finkbeiner
* Postdoc positions available

Mechanisms Session—Tim Miller

* Many tau mutations in exon 10 lead to increase in 4R tau
* Using antisense oligonucleotides change splicing and increase amount of 4R tau—is 4R particularly toxic?
* Increase in 4R tau associated with increased phospo-tau, seizures, etc
* Increase in 4R also confers changes to astrocytes
* Oligos that decrease 4R tau have already been characterized

Mechanisms Session—Aimee Kao

* Case study: behavioral FTD without genetic markers
* Total tau accumulates upon knockout of TSC1
* TSC=lysosomal storage disease
* TSC1/2 inhibit mTOR🡪mTOR inhibits lysosome biogenesis and autophagy
* In pulse chase, TSC1 heterozygous knockout show accumulation of tau
* Al Burlingame did PTM mass spec for phosphorylation of tau, 4 phosphosites specific to TSC1 hets
* New acetylation at K343 between two KFERQ sequences in the R4 repeat
* Changes in acetylation may be due to changes in activity of both acetyltransferase (P300) and deacetylase (SIRT1)
* P300 inhibitor brings tau levels back to normal/control in TSC1 hets

Mechanisms Session—Lennart Mucke

* Melanie’s in his lab (A152T), I gave them fibrils!
* Which pathomechanisms are most important for phenotypes/different tauopathies?
* Cool slide about the different functions, drugs, phenotypes, etc surrounding tau

Mechanisms Session—Hui Zheng

* Skipped
* About the transcription factor TFEB

Drug Discovery Session—Ana Maria Cuervo

* Modulation of CMA
* Pathogenic tau seems to inhibit autophagy
* Therapeutic goal: enhance autophagy
* Tau gets stuck/can’t translocate into lysosomes
* KFERQ-Dendra as marker for CMA activity?
* Accumulated tau (due to CMA blockage) may then go into endosomes
* Lamp2a knockout mice show higher amount of contralateral tau than WT mice (suggesting impaired CMA promotes release and spread of tau)
* Addition of extracellular tau fibrils seems to decrease CMA activity in both neurons and astrocytes
* First genetic approach to see if increasing CMA is a good therapeutic option
* Lamp2a decreases with age—knocking it in seems to reverse mouse phenotypes🡪next need to cross the mice to see if this is true in the context of tauopathy
* Collab with martin’s lab to discover more genetic targets, targeted chaperone approaches with our lab
* See company Selphagy for CMA activator work
* How would external tau affect CMA—through endosomes or signaling via membrane receptors?

Drug Discovery Session—Li Gan

* Intercellular trafficking of tau; goal is to block trafficking of toxic species
* Could travel through neurons or glia
* Compared spread in injection with WT vs SIRT1 mice (HDAC), or knocked out/inhibited p300 (acetyltransferase) reduced spread of tau (my name was on that slide!)
* How does tau affect microglia—transcriptomic changes, distinct changes by LPS activation
* Fibrils and monomers activate NFkB in microglia
* Inactivation of microglial NFkB reduced tau spreading, as well as vice versa with NFkB activation
* More tau retained in microglia with NFkB inhibited, and vice versa, in pulse chase expt
* Microglia release 25kDa fragment
* Ac-K174 tau Ab—even without the microglia present, there is acetylation; monomers and fibrils of rec tau acetylated; seems like a fair proportion of total tau by western blot (~40%?)
* Also found acetylation at 274, 280, others by Krogan lab mass spec

See steve elledge cell paper from a few weeks ago for neo c-term

Drug Discovery Session—Stephen Haggarty

* Targeting tau degradation with bifunctional ligands to recruit E3 ligases (PROTACs)
* Collab with Nathanael Gray lab (at Dana Farber)
* Observed the hooke effect (conc of molecule can’t get too high or else it will bind to each target separately instead of forming a ternary complex)
* By proteomics, still causing degradation of many other proteins, still need SAR to increase specificity for tau
* The half of the molecule designed to bind tau Is supposed to be conformationally/pathologically selective, so that it wouldn’t recognize healthy tau controls (this has only been tested for tau mutants A152T, P301L, and R406W, not for different WT strains)
* Tau may actually be a natural substrate for cereblon E3 ligase at one site
* Next gen is working with VHL E3 ligase, although not as high a level of degradation
* Compounds may cross the blood brain barrier

Drug Discovery Session—Kenneth Kosik

* Repurposing of farnesyl transferase inhibitor for treatment of tauopathies
* Focus on hitting tau pathways (upstream or downstream) rather than hitting tau directly
* RASD2 (Rhes protein) gene was most implicated gene in RNAseq studies of IPSCs with tau mutations
* Changes nest shredding phenotype in P301L mice, also changes the behavior of turning in circles quickly and continuously
* Drug treatment also decreases NFTs in cortex and hippocampus by MC1 staining
* Seemed to decrease phosphotau but not total/other tau, same effect with eliminating sarkosyl insoluble tau
* Seems to activate 3 autophagy pathways (CMA, macroautophagy, lysosomal autophagy)
* Molecule alters Rhes localization (no longer farnesylated and associated to plasma membrane)
* Does the drug work through Rhes? Seems like it by siRNA or overexpression
* Model: Rhes in cytoplasm activates lysosomes to clear tau