Tau Consortium 081518

Biomarkers—Jennifer Yokoyama

* Goal: utilize gene expression in blood immune cells as biomarkers of tauopathy
* Possibility: these immune cells could mirror/report on brain cell biology, or could possibly participate in disease
* Identified >400 genes differentially expressed in FTLD-tau vs FTLD-TDP (including aquaporin 4, which is higher in tau vs TDP
* Moving toward single-cell RNA-seq, already identified NFkB (corroborated by Li Gan’s study)

Biomarkers—Chet Mathis, Neil Vasdev (Ashley Knight’s future PI)

* Goal: evaluate current AD PET probes and determine whether they are able to bind and recognize 4R tau; if results come out negative, synthesize novel 4R probes
* Tested a number of current PET probes on classified tissue from UCSF brain bank
* Assess binding to radiolabeled PET ligand (1nM is the relevant in vivo brain concentration)
* The ligands seem to bind to same site by competition study (?)
* Major setback/needs in the field: very well-defined CTE tissue to test in addition to the other tauopathies

Biomarkers—Thomas Neylan, Christine Walsh, Lea Grinberg

* Sleep biomarkers in tauopathy; considering that different diseases start in different brain regions, it is very possible that different sleep phenotypes might be useful biomarkers
* PSP patients have very disrupted sleep, REM sleep regulation, decreased sleep drive (only ~4hrs sleep)
* At what point over the course of disease do sleep phenotypes emerge?
* Grinberg—sleep distrubances increase at earliest Braak stages of AD
* Sleep/wake promoting nuclei accumulate tau inclusions in CBD/PSP/AD
* Tau burden is not a predictor of neuronal fate (had a hard time interpreting this)
* Clinical trial: test effectivenenss of sleep medications in PSP

Biomarkers—Kate Rankin (from the MAC)

* Informatics tools to integrate clinical data with other types of data(?)

Protein Structure Break Out Session

* Potential for collab with Songhi for changing distances in tau distances upon incubation with hit chaperones—talk to Jason about this
* Do liquid droplets form in the cell/are there high concentration events in the cell that lead to structural transition?
* Songhi: stable WT tau in a droplet + stable RNA🡪could add small amount of heparin or P301L to induce aggregation
* Topic 1: pathways to fibrillization/initiation
* Topic 2: structures of aggregates
* Topic 3: coascervates (?)
* Topic 4: contributions of protein processing
* Topic 5: tau-chaperone interactions
* Songhi: you can make a stable coascervate, and add a seed that won’t initiate in vitro, and then will lead to aggregation🡪Marc’s comment: at a high concentration, he would expect aggregation to happen (in a droplet or not)🡪Songhi: whether this is concentration-dependent, or more, still needs to happen
* Most people are using very heterogeneous heparin
* Songhi’s group has purchases monodisperse heparin, has witnessed length dependence
* Bill: could use chemical dimerizers to bring cargo together in liquid droplets🡪Marc said it didn’t lead to aggregation
* Judith: making synthetic phosphopeptides (by their ms cleavage lengths); or make phosphomutants🡪Markus: best if phosphorylated in vitro, not mutated; haven’t yet alanine scanned to look for most important sites (Hillal Lashual, synthesizes tau peptides and does solid-state synthesis)
* Judith: has phosphosite stoichiometry; she would choose the highest frequency and stoichiometry and put them on one protein
* Stress condensates—why do we see p-granules in tissue, but not these phase transitions?
* Songhi: emphasis on wanting to see dynamic liquid droplet fusion in cells
* Anthony Fitzpatrick: would expect to see liquid droplets also become solid phase (like p-granule example, or lewy bodies)
* Marc: to what extent should we continue what we’re doing and reporting back vs deliberate collaborative projects
* Markus: try NMR with multiple strains/seeds (has been done with other proteins, but not tau)🡪problem, how do we amplify cell material faithfully in vitro; how does mouse tissue look in FLAMES vs PSP tissue
* Bill: what’s the use of starting with a model system, such as K18; are species propagated in a mouse model the same as human? Still need mice for drug discovery
* Anthony: focus is human structures; pharma is already looking at differences between P301L/S etc; other people are focusing on mice, which have shown to have different conformations
* Human tau mouse: variable pathology, etc
* Markus: suggests making three major project proposals
* Marc: wants collab with Anthony, Bill, Judith (emphasis on starting with patient tissue)
* Judith’s mass spec: highest throughput quantitative method to compare brain regions
* Marc: do we recognize the same outliers, etc?
* Markus: better tools to discriminate between pathologies
* Songhi: if patient material can seed in vitro, they can do ESR to determine if the strains narrow or diversify (is a cellular environment needed for this narrowing?)
* Initiation: membrane-binding, RNA granules?
* Markus: NMR of many different tau species/mutations, didn’t see major changes by NMR
* Judith: which chaperones are showing up in the mass spec data?
* Could use HDX +/- seed
* Jim and Bill: possibility of phage display against phosphopeptides identified by Judith; Marc—could also do negative selection against non-phosphotau for isolated B cells from immunized mice
* Barriers: we don’t have pharma resources, but pharma won’t play if it’s too close to clinical relevance
* Next steps: Judith will send around a ppt figure that everyone can add to

Raquel Gardner

* Focus on geriatric TBI
* Even single mild TBI events can contribute to higher risk for neurodegenerative disease
* Risk of dementia after mild TBI increases with age (as opposed to moderate/severe TBI)🡪by later in life, this risk is about the same, no matter the degree of TBI
* Key: must rule out pre-existing neurodegeneration
* CSF and plasma tau are elevated after TBI

Hui Zheng—TFEB-mediated lysosome-nuclear signaling in tau clearance

* TFEB=transcription factor, modulated by phosphorylation, controlled by mTORC1, which sits on lysosomal membrane
* TFEB-responsive genes involve autophagy, lysosomal biogenesis, etc
* Injected TFEB into tau transgenic mouse model—leads to clearance of tau pathology, particularly that of phosphotau (both soluble and insoluble tau)
* How does astroglial TFEB affect uptake and spreading of tau?-->seems to enhance uptake by colocalization with lamp2 as well as overall tau signal; seems to reduce tau spreading by reduction in tau pathology after 2 months
* TFEB expression is correlated with Braak stages