Towards Precision Medicine, April 2nd 2018: Jing Zhang, Professor and Shaw Endowed Chair, UW Pathology

Dr. Jing Zhang gave an overview of the rapidly advances in central nervous system (CNS) specific biomarker discovery for Alzheimer's and Parkinson's diseases, with an eye to the area's fundamental contribution to a precision medicine approach.

In general, the best AD biomarker is PET imaging and cerebrospinal fluid (CSF) analysis for amyloid beta and tau (amyloid β peptide 1–42, total tau, and phosphorylated tau [p-tau]), with 85% - 90% diagnostic accuracy for AD. In PD, PET and CSF analysis for alpha-synuclein and amyloid beta are the best available. However, the fact that mixed pathologies often underlie clinical dementia limits the ability of CSF biomarkers to discriminate AD from related disorders.

Value of CSF Biomarkers to Differential Diagnosis
Consider that Zhang's group has found that in typical clinical AD, only 1/3 of cases are "pure" AD, 40% - 60% will have Lewy bodies, and others have vascular changes and TDP-43. In recently published work, Zhang and collaborators investigated whether biomarkers for other concomitant pathologies (e.g., CSF α-synuclein [α-syn] for Lewy body pathology) are needed to improve the differential diagnosis. In 367 participants, they found that CSF total α-syn, when combined with amyloid β peptide 1–42 and either total tau or phosphorylated tau, improved the differential diagnosis of AD versus FTD, Lewy body disorders, ALS, or other neurological disorders. Suggestive of high relevance to a precision medicine, the diagnostic accuracy of the combined models attained clinical relevance and was largely validated in neuropathologically confirmed cases. (**https://doi.org/10.1016/j.jalz.2018.02.015**)

In the above study, they chose α-syn as the biomarker of interest because of their previous finding that α-syn increases in MCI AD, but decreases in PD. They saw that both increased tau and α-syn was more characteristic of AD; but in the mismatch situation of increasing p-tau but decreasing α-syn, they observed that when the mismatch was higher, the progression from MCI to AD occurred more quickly, illustrating that the presence of α-syn matters in AD diagnosis.

Zhang and collaborators also found that amyloid beta, tau, and p-tau all decrease abnormally *before* the development of clinical PD in familial and idiopathic LRRK2 mutation carriers, revealing that the development of autosomal dominant or familial PD, like familial FTD and AD, can be tracked during the asymptomatic period.

The search for CNS-derived blood based biomarkers.
While CSF is the best biomarker available, spinal taps are too invasive to realistically serve as a tool for diagnosis and preclinical detection for general clinical use. So, the field has become invested in peripheral (blood) biomarkers of AD and PD disease, but to very little success or replication as of now. According to Zhang: 1. Not everything in the brain crosses the blood brain barrier (BBB) into the blood; 2. The molecules of interest in the blood are not uniquely originating from the CNS; for example, tau can come from muscle. To use these measurements of pathology as useful biomarkers, the field needs to know that the blood-based tau, amyloid or α-syn actually came from the brain.

For a couple of years, the Zhang Lab has been exploring CNS derived blood based biomarkers for PD in mice and humans. In 2013, they confirmed their hypothesis that if exosomes (vesicles that transport cargo and waste between cells) can communicate between cells, then exosomes cross BBB and can be detected in the blood. They looked for exosome that specifically express the nervous system molecular marker L1CAM, which stays on the surface of the exosomes in blood. Confirmed by mass spectrometry, the exosome containing L1CAM can be pulled from blood uncontaminated by the peripheral nervous system.

Upon measuring α-syn in CNS-derived L1CAM exosomes, they found the level of blood α-syn increased in the PD patient cases (even though it is decreased in CSF), suggesting that the mechanisms of transport of α-syn from cell to CSF and from cell to blood are likely regulated differently. Similarly, in 2016 they found that, in contrast to AD patients, L1CAM exosomal tau was significantly higher in PD patients than controls and correlated with cerebrospinal fluid tau. They concluded that tau is readily transported from the brain to the blood and that mechanisms of CNS tau efflux are likely different between AD and PD. **(Paper: https://www.ncbi.nlm.nih.gov/pubmed/27234211)**

The Zhang Lab is currently trying to replicate a 2016 UCSF study that measured p-tau (not total tau) in L1CAM exosomes from a blood draw in people without dementia, finding a dramatic increase in CNS derived exosomes captured in blood 10 years before

the development of eventual clinical AD symptoms.
(**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4925777/**) Zhang's group did not find such results when measuring total tau. He notes and that the exosome biomarker story is expanding quickly in the field, for example, towards the use of exosome biomarkers in serum to predict symptoms.

Red cells
The Zhang Lab has found that the periphery contains much more α-syn than does CSF, with the highest concentration in red blood cells (99% of total α-syn in blood). They do not know why red blood cells carry so much α-syn, but they cultured the red cells of PD cases vs. control cases, then collected exosomes and injected them into mice. They observed that those particles can cross the BBB; they co-localize with microglia; and activation in PD is much greater than in controls. Now, they are intensely focused on the bold idea that PD starts in the periphery in red blood cells, not the brain.

While others have already proposed that Lewy body pathology can spread from the spinal cord to CNS, and from gut to CNS, Zhang specifically proposes that the spread goes from red blood cells, across BBB, and into CNS, contributing to development or progression of PD. They are now working to understand the mechanisms involved in the transport.

Zhang takes the broad view that, with the support of the ADRC Clinical Core and Udall Center, blood based CNS-specific biomarker discovery will make it possible to treat people according to their specific profile of pathological findings in very early stages of disease-the hallmark of a precision medicine approach.