

## Report from the Tau Front: Cantoblanco 2013

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**Abbreviations:** PrP: Prion Protein; SNCA: Alpha Synuclein; AD: Alzheimer's Disease; APP: Amyloid Precursor Protein; NDD: Neurodegenerative Disease; MAP: Microtubule Associated Protein; MTBR: Microtubule Binding Repeat/Region

### Introduction

The recent interest in tau and its role in neurodegenerative disease (NDD) has been part of a sea change in how we view protein aggregate toxicity in NDD pathogenesis. The longstanding focus on protein aggregate formation as a common mechanism linked to NDD pathogenesis remains largely intact, but there has been a shift away from large cellular and extracellular aggregates [neurofibrillary tangles (NFTs), senile plaques (SPs), Lewy Bodies (LBs) and the like] toward the importance of oligomers and other aggregate intermediates [1-3]. We have also seen an expansion of the hitherto largely cellular focus on toxicity to include interneuronal aspects of the pathogenesis of diverse NDDs, including Alzheimer's Disease, Parkinson's Disease, ALS and non-AD tauopathies such as corticobasal degeneration and Pick's Disease. This has been accompanied by an increasing understanding of the importance of micro RNA and mRNA-mediated mechanisms [4-7] as well as other cellular and intercellular mechanisms and the cytopathogenesis of multiple neurodegenerative syndromes [8-10]. This expansion of research scope at both cellular and intercellular levels of analysis has had particularly notable effects on research into basic and disease-associated functions of tau protein and have elucidated the hitherto shadowy zones separating the traditional cellular focus of tauopathy research (protein aggregate formation) from other important disease features involving cell cycle re-entry [11-14], signal transduction abnormalities [15,16], and the disruption of protein turnover [17] localization [18] and secretion [19-21] mechanisms. Perhaps the largest influence on the direction of recent NDD research has been the idea that oligomer formation may itself be the agent of interneuronal lesion spreading via a "prionlike" mechanism [22-26]. In the case of tauopathy, this concept has tended to both expand and narrow the scope of recent investigations as it focuses attention the link between molecular [templated misfolding] and global (lesion spreading) aspects of tauopathy at the expense of cellular considerations. All of these developments were reflected in the focus of last year's Cantoblanco meeting in Madrid. While that meeting was ostensibly focused on the title subject "Is Tau a prionlike protein?" it also brought together current research on a variety of novel cellular and intercellular facets of tau biology and pathobiology, which I will attempt here to frame in a larger context.

### Back to the Future – Developmental Tau Functions are Relevant Again

The largely neuronal [27] expression of tau during development and the marked localization of tau to the axon initially drew a great deal of attention to the developmental functions of tau and especially its role in the development of axonal identity. Indeed, the best-characterized and most studied function of tau outside of its regulation of MT dynamics [28] before 1991 was its contribution to the generation of

axonal identity in developing neurons [29,30]. Later studies revealed important and MT-independent roles for tau in various other aspects of axonal differentiation, including outgrowth, growth cone motility and myelination [31-33]. The nuclear localization of tau and its ability to selectively bind double stranded DNA [34,35] has led to suggestions that tau may play roles in cell cycle regulation/early developmental fate that are relevant to both AD-associated aberrant cell cycle re-entry and even certain types of carcinogenesis [36]. An additional new function – the involvement of a small amount of tau localized to the postsynaptic density in synaptic plasticity – appears particularly relevant to NDD pathogenesis mechanisms [37].

The sudden interest in tau that came with its identification as the major component of NFTs in the late 1980s produced what might be called a molecular identity crisis for tau that has had important consequences. Tau became a "disease protein" and interest in its normal functions, particularly those functions associated with neuronal development, was largely effaced by the effort to understand the role of tau in NFT formation and AD pathogenesis. In addition, the absence of a link between tau and established secretion pathways restricted interest in tau secretion and tau-related interneuronal disease mechanisms. The recent broadening of research scope to include intercellular aspects of tauopathy pathogenesis was prompted by demonstrations that a) A beta cytotoxicity is largely mediated by tau in both cell culture and murine model systems [38-40] b) the demonstration of tau secretion and uptake [19,21,41-43] and extracellular tau toxicity [44-46] and most of all, c) the application of what might be called the "prionlike hypothesis" [47-49] to account for what appeared to be transsynaptically connected patterns of lesion evolution in AD [50] and other tauopathies [51]. The prior demonstration by Gloria Lee and co-workers that the amino terminal "projection" domain mediates interactions with key signal transduction elements such as fyn kinase [52] now also appears to be a key element in our newly expanded appreciation of the roles played by tau in NDD pathogenesis, since tau-fyn interactions, especially in dendrites [18] now appear to play an essential role in mediating A beta toxicity as well [53]. This, together with links between tau dendritic localization and dendritic cytoskeletal disruption [19,41,54,55], localized tau secretion [19,41] and synaptic dysfunction [56] illustrate the importance of tau localization and possibly of neuronal polarity disruption in tauopathy [57,58]. Finally, demonstrations that N terminal tau fragments can themselves be toxic and can mediate A beta toxicity [59-62] highlight the need to link the molecular and systemic studies of prionlike lesion propagation mechanisms with cellular studies of tau pathobiology.

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## The Meeting

The meeting (comprising oral presentations from 24 invited speakers and 34 posters) was organized around the concept of tau as a “prionlike” protein i.e. capable of communicating toxicity between cells via interneuronal transfer followed by conformation–altering interactions with “normal” tau proteins. Many of the presentations dealt with this topic directly; describing new cellular (Diamond) and/or rodent models of tau lesion spreading or cellular interactors associated with tau misfolding and oligomerization. Attempts were made to integrate aspects of tau function relevant to characteristic features of non AD tauopathies, such as tau splice variants (Zilka) and in injury associated tauopathy (Kayed) and argyrophilic grain disease (Rabano). A major additional theme was directed at imaging and biomarker related diagnostic development and possible therapeutics (Gozes). However, nearly half of the presentations were on topics that were only tangentially related or unrelated to templated misfolding-mediated lesion spreading of tau. Most of these were directed at the as yet poorly understood cellular aspects of tauopathy outlined above that will need to be integrated with the concept of the “prionlike” mechanism of toxicity and/or lesion spreading at the cellular level before the actual relevance and contribution of this mechanism to human NDD pathogenesis can be ascertained. A major advantage of the meeting is that it combined exponents and modelers of “prionlike” tau lesion spreading (Diamond, Buee, Kayed, Zilka, Sergeant, Duff, Avila) with a range of investigators involved in non “prionlike” aspects of tau pathobiology, including key contributors to what we now know about both tau aggregation and hyperphosphorylation (Sahara, Spillantini, Sergeant, Iqbal, Alonso, Mandelkow, Mudher, Avila), tau/MT interactions (Gozes, Alonso, Iqbal), and other NDD relevant aspects of tau function such as A-beta interactions (Gotz, Bloom, Perry) exosomal (Hall) and non-exosomal modes of tau secretion and uptake (Avila, Hanger, Diamond, Duff), tau localization (Gotz, E. Mandelkow), toxicity (E. M. Mandelkow) and turnover (Cuervo, Myeku). While most of the presentations involved studies using conventional cellular and rodent models, exponents of other models that have made important contributions to our understanding of diverse aspects of tauopathy, such as the fruit fly (Mudher) and the sea lamprey (Hall) were also present. Finally, several presentations described recent advances in imaging (Sahara, Duff), immunotherapy (Sigurdssen) and functionally directed therapeutic approaches (Kosik, Gozes, Bhat). In the end, a broad sample of the current perspectives, method and research foci in the field were reflected among the invited speakers and attendees, despite the tight organizational focus of the meeting.

## Summary

Current studies of tau associated dysfunction in NDD are finally starting to integrate our hitherto fragmented view of tauopathy pathogenesis into a more comprehensive picture of how diverse tau functions associated with NDD-associated events (e.g. oligomerization, cell cycle re-entry, apoptotic changes, signal transduction pathway disruption, polarity loss, lesion spreading etc.) can account for global as well as cellular features of neurodegenerative tauopathies. Somewhat ironically, this synthesis has been occurring as a single novel idea – that of toxicity transfers via protein: protein conformational templating – has taken hold in the field. This state of affairs was exemplified by the Cantoblanco tau meeting of 2013, which went significantly beyond its stated focus on “prionlike” spreading mechanisms in tauopathy and crystallized many of the disparate threads of interest and effort that currently make up international tau and tauopathy-directed basic research. This broad, integrative approach combined with a

well defined, but not exclusive, focus on a plausible common disease mechanism of great current interest seems likely to foster synergistic interactions among the participants and represents a distinct break from historical norms in the field. It is both a hopeful metaphor for the current state of tauopathy research and (in the eyes of this participant) a worthy “template” for future progress.

Perhaps we “tauists” are finally applying the lessons we learned during the “war” [63].

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