Going new places using an old MAP: tau, microtubules and human neurodegenerative disease
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The microtubule-associated protein tau was originally identified as a protein that co-purified with tubulin in vitro, stimulated assembly of tubulin into microtubules and strongly stabilized microtubules. Recognized now as one of the most abundant axonal microtubule-associated proteins (e.g. MAP1B) in establishing microtubule stability, axon elongation and axonal structure. Missense and splice-site mutations in the human tau gene are now known to be causes of inherited frontotemporal dementia and parkinsonism linked to chromosome 17, a cognitive disorder of aging. This has provided direct evidence for the hypothesis that aberrant, filamentous assembly of tau, a frequent hallmark of a series of human cognitive diseases, including Alzheimer's disease, can directly provoke neurodegeneration.

Introduction
Twenty three years have now passed since one of us (DW Cleveland) first purified the microtubule-associated protein (MAP) tau as a potent inducer of tubulin assembly into microtubules [1]. Originally, tau was determined to be a heterogeneous population of four to six polypeptides with many common chemical properties [2]. Subsequent discoveries (including the seminal discovery that genes have introns!) confirmed that tau indeed comprises six isoforms and revealed that these isoforms derive from a single gene via alternative splicing at two different loci within the mRNA (Figure 1). Isoform diversity arises from one of three possibilities: inclusion of exon 2, exons 2 and 3 or neither of this pair of exons which encode 29 or 58 amino acids near the amino terminus. Any of those three possibilities can then be attached to RNAs that contain or exclude exon 10, which encodes a further 31 amino acids, including one of four microtubule-binding motifs. All six isoforms are expressed in normal, adult human brain. It has now become very clear from inherited neurodegenerative diseases (see below) that the inclusion of exon 10 has a profound influence (at least in humans) on aberrant, filamentous tau assembly, which is independent of its role in microtubule function. We focus here on recent developments uncovering aspects of tau's normal role in neuronal function and on how very modest point mutations and seemingly innocuous intronic mutations can provoke neurodegenerative tauopathies.

Tau's role in axonal structure
Since its initial isolation, several attempts have been made to clearly define tau's role in the neuron. As tau was initially isolated through its microtubule stabilizing properties [1], it seemed logical to assume that in vivo it would stabilize microtubules, thus providing structural support for axons. Several key in vitro experiments supported an essential role for tau in axonal elongation and maintenance. An initial series of antisense oligonucleotides added to cultured neuron-like cells suppressed tau accumulation and neurite outgrowth, suggesting a key role in neuronal growth, presumably by affecting microtubule properties (e.g. [3]). This result was not supported by targeted disruption of the tau gene in mice, however. Although subtle differences in microtubule organization were detected in small caliber axons, mice that were chronically deficient in tau were essentially normal, and worse, neither neurite growth properties nor microtubule stability were altered by total absence of this prominent axonal MAP in primary neuronal cultures from such mice [4]. The genetics and in vitro manipulations could only be reconciled by postulating that there was sufficient plasticity and redundancy among the remaining MAPs to hide a required function of tau during normal development in the whole animal.

These results have now been revisited by gene targeting of one of the two other prominent axonal MAPs, MAP1B. Although this produced what was initially seen to be a surprisingly normal animal [5], mating of the MAP1B and tau null animals proved that deficiency in both axonal MAPs is invariably lethal by four weeks of age [6**]. Moreover, once analyzed in a nearly homogenous genetic background (e.g. the MAP1B disruption in C57B1/6J), absence of MAP1B revealed dysgenesis in axon tracts and lethality in a proportion of animals. Both phenotypes were more severe with simultaneous loss of tau. A likely explanation for the dysgenesis of axons tracts is deficiencies in axonal elongation, and this is seen in cultured neurons derived from the double MAP1B and tau deletions. Additionally, a slight retardation in neuronal migration was observed in older, layered structures of the brain (e.g. the hippocampus). Thus, it is now clear that this pair of axonal MAPs functions synergistically.
Tau suppresses microtubule dynamics

From the initial description of tau’s effect on stimulating microtubule assembly, it was known that tau can strongly stabilize the final polymer, producing microtubules that cannot be disassembled even at low temperature [2]. Microtubules are known, from the pivotal discovery of Mitchison and Kirschner [7], to be dynamically unstable, with a few microtubules growing while adjacent ones disassemble catastrophically. It seems likely that tau binding to the walls of such microtubules would reduce the switching from growth to rapid disassembly (‘catastrophe’), although this has not been directly tested. However, microtubules with both ends free (as may be the case in axons) display an alternative behaviour — treadmilling — with subunits adding to one end and an equivalent number dissociating from the other. In a recent set of experiments, Panda et al. [8•] identified conditions in vitro where treadmilling was the major contributor to microtubule dynamics. The addition of tau, in ratios greater than or equal to 1 molecule of tau to 15 molecules of tubulin (about half the maximal amount that can bind [2]), reduced the treadmilling rate, as might have been expected for a component bound to the microtubule wall.

Tauopathies: a role for tau in human neurodegenerative diseases

The accumulation of filamentous tau independently of tubulin is a well established hallmark of several neurodegenerative diseases, collectively known as tauopathies. Tauopathies comprise a heterogeneous group of age-dependent cognitive disorders, which, in some examples, arise from a dominantly inherited gene defect. Examples include Pick’s disease, progressive supranuclear palsy (PSP), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), and Alzheimer’s disease, the last of which represents the most abundant human cognitive neurodegenerative disease. Although the precise brain areas most strikingly affected differ in each disease, as do the more detailed phenotypic and pathologic presentations, they all display prominent filamentous deposits of hyperphosphorylated tau, accompanied by neuronal loss in the affected regions. In Alzheimer’s disease, for example, although much attention has been focused on the extracellular deposits of a fragment of amyloid precursor protein (APP) (and the effects of mutations in the presenilins in processing of APP), the prominent intracellular pathology in the neurons at risk are tangled, insoluble filaments, which are apparently comprised primarily of aggregated tau (see [9] for a review). Divining pathogenesis from pathology is always a tricky business but such findings raise an obvious question: to what degree are such aggregates intrinsic to dysfunction and degeneration, or at the other extreme, are they simply innocent bystanders of a neuron self-destructing?

Identification of mutations in tau in human dementia

The recent discovery of 18 different tau mutations (detailed in Figure 1) as the primary cause of a set of dominantly inherited cases of FTDP-17 was a seminal

Figure 1

Schematic diagram of the longest human tau isoform with the approximate locations of FTDP-17 mutations. Alternatively spliced exons 2 and 3 are represented as gray boxes. Thirteen different missense, silent and deletion mutations occurring in exons 9, 10, 12 and 13 are identified. Additionally, the structure of the critical stem-loop formed from the 5’ portion of exon 10 and intron 10 is expanded. Five intronic mutations and two exonic mutations (with corresponding amino-acid changes) that destabilize the stem-loop structure are shown. Exon 10 residues are shown in capital letters and intron 10 residues are shown in lower case letters. *Indicates microtubule-binding domains.

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insight for understanding neuronal degradation and death. Errors in tau, accompanied by misaccumulation into tau-containing filaments in neurons (and sometimes in the surrounding astrocytes, which also make tau), are directly linked to initiation of neuronal failure. From a flurry of nearly simultaneous initial reports from several teams of investigators [10–15], two different classes of mutations have been identified.

**Identification of missense tau mutations**

The first class of tau mutations (Table 1) is an expected one, in which a single missense mutation alters one amino acid within tau isoforms that carry the affected exon. Many of the reported missense mutations occur in highly conserved residues within or near to one of the microtubule-binding domains. To date, mutations have been reported in exons 9, 10, 12 and 13. Mutations within exons 9, 12 and 13 affect all tau isoforms, whereas those in exon 10 affect only the three tau isoforms bearing four microtubule-binding repeats (referred to as 4R tau). Several groups have explored the consequences of these missense mutations. They found that exonic, missense mutations reduce tau’s abilities to bind to microtubules and promote microtubule assembly in vitro [12,16,17,18**–19], although it should be realized that in most cases such differences are at best minimal. Adding some weight to this idea is the finding that expression of the V337M mutant in insect-derived SF9 cells induced the formation of processes with greatly reduced and disorganized microtubules when compared to cells expressing wild-type tau [20]. However, the degree to which massive overexpression of mutant, or for that matter wild-type, tau recapitulates properties associated with dominantly inherited disease is not at all clear.

The inherent ability of the mutants to self assemble into tau filaments was examined in vitro using three missense mutations: P301L, V337M and R406W. Each forms filament thereby facilitating tau filament formation. tau, and these in turn could expose tau’s self interaction properties (raising the concentration of available soluble forms) of which could be two-fold: primary sequence differences could reduce tau’s abilities to bind to microtubules and promote microtubule assembly, and these in turn could expose tau’s self interaction motif thereby facilitating tau filament formation.

**Identification of splicing defects in tau mRNAs**

The second class of mutations was not really expected — and is arguably the more interesting. These mutations are single base pair alterations occurring within intron 10 or silent nucleotide changes in the adjacent exon 10 sequence (see Figure 1 and Table 1). At first it was perplexing how mutations that do not affect the tau polypeptide sequence could provoke dominantly inherited disease, but measurement of the accumulated isoforms in autopsy samples of patients with these mutations has demonstrated that the mutations increase the level of 4R tau isoforms in both soluble and insoluble pools [12,24]. The use of DNA transfection of gene constructs in which exon 10 and its surrounding introns have been introduced into test genes (a technique frequently referred to as exon trapping), has shown that the FTDP-17 mutations increase the proportion of tau mRNAs in which exon 10 is retained [18**–19,25,26**,27,28**–31**].

An emerging model for how this may be achieved is shown in Figure 1. The presence of a stem–loop structure beginning within the final codons of exon 10 and continuing into intron 10, lowers the efficiency of exon 10 inclusion, presumably by partially blocking access of splicing components. The effects of FTDP-17 mutations in destabilizing this stem–loop structure possibly allow for increased U1 snRNP binding and, consequently, increased inclusion of exon 10 [28**].

Although prediction of RNA structures is notoriously unreliable, two experimental approaches indicate that the predicted structure is likely to be correct for tau mRNA. First, direct thermodynamic stability and an accompanying structure (solved by NMR) have proved that the stem–loop can form and that mutations destabilize it [29**]. Second, the gold standard for RNA structure prediction is demonstrating that pairs of base substitutions that retain the predicted structure also retain the properties of the wild-type RNA sequence. Such an approach has shown that a combination of the initial single base pair alterations with additional compensatory ones to restore the predicted stem–loop pairing does indeed restore the initial pattern of splicing [18**,25].

**Identifying the toxicity arising from the missense and splicing mutants**

The collection of mutations in tau greatly affects the resulting tau filaments and the cells that accumulate filamentous tau. This might ultimately influence the clinical pathology (Table 1). What is becoming clear is that the two classes of mutations result in morphologically distinct filaments. Mutations that alter the binding of tau to microtubules produce a range of structures from narrow twisted ribbons to paired helical filaments and can be composed of all six isoforms (Table 1). Additionally, these accumulations occur primarily in neurons (Table 1). Splicing mutations that alter the ratio of tau with four microtubule-binding domains (4R) to types with only three microtubule-binding domains (i.e. 3R) ratios generally result in wide twisted ribbons composed entirely of 4R tau (Table 1). These mutations lead to filament formation in both neurons and glia (Table 1).

Although the two classes of mutations differentially affect tau, both lead to FTDP-17. A possible explanation for the pathological convergence of seemingly divergent mutations could be that both classes of mutation increase the pool of unbound tau. As missense mutations modestly
decrease the affinity of tau for microtubules, the mutations seem likely to yield an increased pool of unbound tau. Because the splicing mutations increase the synthesis of 4R tau at the expense of 3R, this would yield an increased level of ‘free’ tau from such mutants if the increase in available 4R tau, with its expanded microtubule-binding domain, completely saturated the available microtubule-binding sites. Unfortunately, assuming that 4R tau binding

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Class</th>
<th>Location</th>
<th>Purposed disease</th>
<th>NFT-containing cells</th>
<th>Filament morphology</th>
<th>Tau composition of filament</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intron439AG</td>
<td>Possible splicing</td>
<td>Intron 4</td>
<td>Progressive supranuclear palsy</td>
<td>Neurons and glia</td>
<td>Not determined</td>
<td>Not determined</td>
<td>[25]</td>
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<tr>
<td>K257T</td>
<td>Functional</td>
<td>Exon 9</td>
<td>Pick’s disease</td>
<td>Neurons</td>
<td>Narrow, irregularly twisted ribbons</td>
<td>All six isoforms with 3R predominant</td>
<td>[43]</td>
</tr>
<tr>
<td>G272V</td>
<td>Functional</td>
<td>Exon 9</td>
<td>FTDP-17/Pick’s disease</td>
<td>Neurons</td>
<td>Not determined</td>
<td>Not determined</td>
<td>[13,44]</td>
</tr>
<tr>
<td>N279K</td>
<td>Splicing</td>
<td>Exon 10</td>
<td>Pallido-ponto-nigral degeneration</td>
<td>Neurons and glia</td>
<td>Possibly twisted ribbons</td>
<td>4R isoforms</td>
<td>[10]</td>
</tr>
<tr>
<td>Δ280K</td>
<td>Splicing</td>
<td>Exon 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Not determined</td>
<td>Not determined</td>
<td>[18,**45]</td>
</tr>
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<td>Splicing</td>
<td>Exon 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Possibly wide twisted ribbons</td>
<td>Not determined</td>
<td>[18**]</td>
</tr>
<tr>
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<td>Splicing</td>
<td>Exon 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Not determined</td>
<td>Not determined</td>
<td>[27]</td>
</tr>
<tr>
<td>P301L</td>
<td>Functional</td>
<td>Exon 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Narrow twisted ribbons</td>
<td>4R isoforms + small amounts of the abundant 3R isoform</td>
<td>[10,11,13]</td>
</tr>
<tr>
<td>P301S</td>
<td>Functional</td>
<td>Exon 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Narrow twisted neuronal</td>
<td>Predominantly neuronal</td>
<td>[46]</td>
</tr>
<tr>
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<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Not determined</td>
<td>Not determined</td>
<td>[19]</td>
</tr>
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<td>Exon 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Straight and twisted filaments</td>
<td>Not determined</td>
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<td>FTDP-17</td>
<td>Neurons</td>
<td>Pair helical filaments</td>
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<tr>
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<td>Pick’s disease</td>
<td>Neurons</td>
<td>Predominantly straight</td>
<td>3R and 4R isoforms</td>
<td>[48]</td>
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<tr>
<td>R406W</td>
<td>Functional</td>
<td>Exon 13</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Paired helical filaments</td>
<td>All six isoforms</td>
<td>[13]</td>
</tr>
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<td>Intron 9</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Straight, pair helical Filaments and twisted ribbons</td>
<td>Not determined</td>
<td>[45]</td>
</tr>
<tr>
<td>Intron10s313a</td>
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<td>Intron 10</td>
<td>FTDP-17/Familial multiple systems tauopathy with presenilie dementia</td>
<td>Neurons and glia</td>
<td>Straight, pair helical Filaments and twisted ribbons</td>
<td>4R isoforms</td>
<td>[15,49]</td>
</tr>
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<td>Intron10c12u</td>
<td>Splicing</td>
<td>Intron 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Wide twisted ribbon</td>
<td>4R isoforms</td>
<td>[50]</td>
</tr>
<tr>
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<td>Splicing</td>
<td>Intron 10</td>
<td>FTDP-17</td>
<td>Neurons and glia</td>
<td>Possibly wide twisted ribbons</td>
<td>4R isoforms</td>
<td>[13]</td>
</tr>
<tr>
<td>Intron10c14u</td>
<td>Splicing</td>
<td>Intron 10</td>
<td>FTDP-17/Familial progressive subcortical gliosis</td>
<td>Neurons and glia</td>
<td>Possibly wide twisted ribbons</td>
<td>4R isoforms</td>
<td>[10,13]</td>
</tr>
<tr>
<td>Intron10c16u</td>
<td>Splicing</td>
<td>Intron 10</td>
<td>FTDP-17/Familial progressive subcortical gliosis</td>
<td>Neurons and glia</td>
<td>Wide twisted ribbons</td>
<td>4R isoforms</td>
<td>[13,51]</td>
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to microtubules is stronger than 3R tau, one would predict that the unbound, excess tau would probably be the 3R isoform, a notion that is entirely inconsistent with most autopsy evidence. Since analysis of brain samples at autopsy has yielded neurofibrillary tangles (NFTs) comprised predominantly of 4R tau [12,13], it seems most likely that the increase in unbound 4R tau is the key underlying property. Yet how does a mutation that gives rise to increased levels of 4R tau, without significantly increasing the overall pool of available tau, satisfy this condition? One explanation, which is not completely satisfactory, is that either 3R tau binds to microtubules more avidly in vivo than 4R tau or that 4R binding enhances the binding of 3R, thereby lowering soluble 3R. If this were true, the increased expression of 4R, at the expense of 3R, would produce a pool of 4R tau that could not bind to microtubules and thus be free to form the observed NFTs.

On a different but related front, a truncated form of the Cdk5 kinase activator tau, called p25, accumulates in neurons of Alzheimer’s patients. Binding of p25 to Cdk5 constitutively activates Cdk5 and alters substrate specificity [32••]. Curiously, the p25–Cdk5 complex hyperphosphorylates tau, whereas FTDP-17 mutations decrease the association of protein phosphatase 2A with tau [33••]. Taken together, the data suggest that in FTDP-17 there exists a pool of free tau that is readily phosphorylated by a constitutively active kinase, possibly contributing to filament formation.

To a neuron an increased pool of free tau could have severe consequences. Overexpression of human tau in lamprey anterior bulbar cells leads to the development of tau filaments, which is associated with the loss of microtubules and synapses [34••]. Unexpectedly, when the cells were stained for the presence of tubulin, the majority of detectable tubulin was associated with the tau filaments. In differentiated, mammalian neuroblastoma cell lines (N2a cells), tau overexpression suppressed kinesin-dependent transport of vesicles and mitochondria, as well as altering the shape of the endoplasmic reticulum [35]. Thus, the toxicity associated with tauopathies may be due to tau filaments sequestering free tubulin, thereby preventing microtubule maintenance and secondary choking of distal processes due to reduced kinesin-based transport.

**Modeling tau mutants in mouse models: what has been learned?**

With the discovery of tau mutations as the primary cause of FTDP-17, the key issue is how do the mutant taus (or the increased ratio of 4R to 3R tau in the splicing mutants) provoke neuronal degeneration. Six sets of transgenic mice have now been generated, with the hope of recapitulating aspects of the degenerative pathway.

The most direct attempts have been the mimicking of the splice site mutants, that is, increasing the synthesis of the 4R tau variant by using the appropriate human tau 4R cDNA linked to a promoter active in neurons. The first attempt used a Thy-1 promoter transgene, but this produced animals that expressed tau at only ~10% above that of non-transgenic animals [36]. Subsequent attempts, also using the same promoter and human 4R cDNA transgenes, produced much higher levels of human tau expression in mice (between 1.5 [37••,38•] and 6 times [39•] the normal tau levels), but even with this range of over-accumulation of human 4R tau, no tau-containing NFTs were reproduced. Moreover, although FTDP-17 is seen primarily as a disease of the cortex with involvement of the basal ganglia and substantia nigra, much of the severe pathology in these mice is associated with the spinal cord, with the prominent phenotype being motor neuron dysfunction and resultant muscle weakness [37••–39•]. Inclusions in neurons of both the brain and spinal cord are seen and apparently consist of tau (including phosphorylated epitopes characteristic of those generated during human disease), neurofilaments, mitochondria and vesicles, suggesting impairment in axonal transport.

Although the FTDP-17 splice variants appear to yield an increase in 4R tau, two groups have examined the consequences of the opposite shift in tau isoform accumulation: selective increases in the 3R tau isoform [40,41•]. The rationale here was perhaps mindful that in several examples of other disorders the tau filaments are apparently enriched in 3R tau (Table 1). Use of the mouse prion promoter produced animals with 5–15 times the normal level of tau, age-dependent increases in insoluble tau, motor neuron degeneration, and, in the mouse lines with the highest level of expression, death by three months [41•].

Notwithstanding the careful work in these five examples of high level overexpression of tau isoforms in mice, the relevance of these models to the disease mechanism in tauopathies such as FTDP-17 is unclear. Certainly it can be concluded (to no surprise) that too much tau is detrimental to neurons, but neither the characteristic pathology nor neuronal selectivity of the human disease has been mimicked very faithfully.

A more promising example has emerged from the construction of mice expressing a P301L mutant tau transgene [42••]. Using a mouse prion protein promoter linked to wild-type or P301L tau cDNAs, mouse lines were established that accumulate the mutant human tau to levels equivalent to the endogenous tau in hemizygotic animals (homozygotes express twice the level of hemizygotes). These animals developed NFTs and Pick-body-like lesions in many regions of the brain, and displayed pretangles in the cortex,
hippocampus and basal ganglia. Importantly, development of NFs was gene-dose and age dependent, with tau accumulation in the brain detectable as early as two months. Behaviorally, P301L mice develop defects that are consistent with the clinical disease — neglecting personal hygiene. Additionally, as seen in the earlier tau transgenics, these animals also display prominent motor deficits associated with motor neuron loss. These phenotypic changes, presumably due to progressive tau filament accumulation, begin to occur at approximately 4.5 months for homozygotes. These animals highlight the relevance of tau mutations in disease progression. They express considerably lower levels of tau compared to earlier transgenic animals (see [37–39]), yet P301L mice develop NFs, which do not occur in the higher expressing wild-type tau transgenic animals, in cells that are affected by disease. In mice, the accumulation of tau into filaments is progressive; although this, for various reasons, has not been satisfactorily documented in tauopathies, it is widely accepted to be the case in human diseases. Moreover, lower expression levels of mutant tau produced phenotypic changes that are associated with FTDP-17. Although earlier work certainly underscores the consequences of expressing too much tau, or for that matter any protein, the P301L mouse is the only effort to date that offers an initial model of the mechanisms of tau-mediated human disease.

Conclusions
Isolated 23 years ago, tau has been slow to reveal its secrets. Genetic studies in mice have demonstrated a role for tau in microtubule biology, albeit one redundant with other axonal MAPs. The discovery of mutations in tau associated with inherited FTDP-17, on the other hand, has led to unequivocal evidence that aberrant tau can provoke neurodegenerative disease in humans.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
* • of special interest
** • • of outstanding interest
19. This thorough report provides a detailed analysis of cis-acting elements that regulate tau exon 10 splicing and the effects FTDP-17 mutations have on these elements. Compensatory base changes offer very strong evidence for a stem-loop structure whose presence lowers the efficiency of tau exon 10 inclusion during splicing.
24. Examination of the assembly properties of three FTDP-17-linked tau missense mutants reveals that all three assemble into filaments in vitro at faster...
rates than that of wild-type tau. This is consistent with this aberrant assembly playing part in mutant-mediated neuronal toxicity.


Using a series of tau peptides combined with electron microscopy and CD spectra, this report identifies a minimal interphase motif required for tau filament assembly. The structural evidence supports a model in which paired helical filament assembly is initiated by a short fragment that adopts a local β-sheet structure.


This paper provides strong support for the hypothesis that 5’-splice site mutations affect the stability of a critical stem-loop structure within the 5’-most portion of intron 10 and adjacent sequences in exon 10. Disruption of this stem-loop structure is proposed by the authors to allow easier access to the splicing machinery, thereby increasing the efficiency with which exon 10 is included in the final mRNA.


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This report describes that expression of tau in lamprey neurons results in straight filaments accumulation and dendritic degeneration. Most interestingly, tau filaments immunolabel with anti-tubulin antibodies which is, to date, the only indication that tau filaments may sequester free tubulin.


35. Ishihara T, Hong M, Zhang B, Nakagawa Y, Lee MK, Trojanowski JQ, Lee VM: Overexpression of tau results in axonal spheroids, but does not produce neurofibrillary tangles or degeneration by the age of 18 months.


The authors suggest that FTDP-17 mutations reduce protein phos- phatase 2A binding to tau. This paper offers a mechanistic explanation for tau hyperphosphorylation associated with tauopathies.


This paper reports that expression of tau in lamprey neurons results in straight filament accumulation and dientritic degeneration. Most interestingly, tau filaments immunolabel with anti-tubulin antibodies which is, to date, the only indication that tau filaments may sequester free tubulin.


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These authors report the construction of transgenic mice expressing 4R human tau at levels up to six times higher than the endogenous mouse tau. This produces motor neuron deficiencies but does not produce neurofibrillary tangles similar to those seen in FTDP-17.


This report offers the best animal model to date of FTDP-17 pathology, with expression of one of the FTDP-17-linked, missense tau mutant proteins. Aspects of FTDP-17 pathology in many regions of the brain are documented.


Using a transgene containing the entire human tau gene, transgenic mice are produced that express all six human tau isoforms at levels up to 3.5 times more than that of endogenous mouse tau. This does not, however, produce insoluble tau or degeneration.


