aggregates, may be future non-Aβ routes to therapy in Alzheimer disease.


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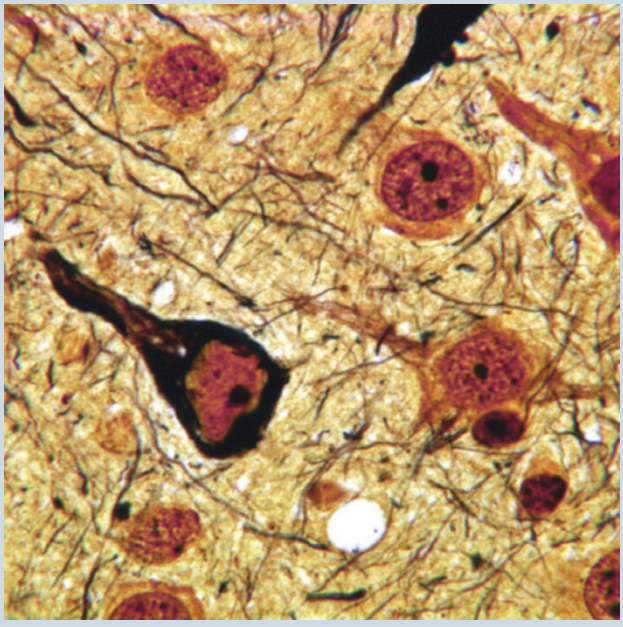
## The author's perspective



Courtesy of Martin Ramsden

Like many others studying Alzheimer disease a decade ago, I was unsure about the role of tau in disease pathogenesis. My interest was piqued in 2000 when tangle-forming transgenic mice expressing tau variants developed neurodegeneration, a prominent aspect of Alzheimer neuropathology that was lacking in the amyloid plaque–forming transgenic mice I was studying. Because of my interest in how Alzheimer-related molecules alter brain function, I turned my attention to how tau impairs memory. First, I needed to create a model that would permit us to study memory function, as the existing mouse models had brainstem pathology that interfered with memory testing. Mike Hutton gave me the tau constructs we needed to generate the rTg4510 line, which directly competed with his own colleagues' attempts to make a similar mouse. Our early years generating mice with regulatable transgenes were not overtly productive, but they were intrinsically worthwhile. In some years all we did was come to the conclusion that a particular methodology was not very good, but even these failures represented a step forward, in a different direction. In 2002, when we eventually developed the rTg4510 mouse, it became the platform for a meeting of minds in the labs of Mike, Brad Hyman and our group. This was critical because the work could not have been carried out by only one of our groups. At one point, I thought the whole project had gone awry because I was expecting memory function to deteriorate as neurofibrillary tangles accumulated. I was depressed for a while because the data went against my preconceived ideas. However, my spirits lifted when I realized that the data suggested the existence of tau*, a molecule which, like Aβ*56, could impair memory function independently of amyloidosis or neuronal death. My lab is currently searching for tau*. I wake up every day wondering whether Aβ*56 and tau*, when found, will truly be good diagnostic and therapeutic targets. We are proceeding ahead methodically. I expect a period of quiet in terms of publications from my laboratory while we regroup to meet the technical demands that these new questions pose. Our ability to weather the next phase of exploration will depend upon our financial supporters' understanding that the best science requires the temperament to take major risks, the tenacity to solve great problems and, importantly, time.

*Karen H. Ashe, University of Minnesota Medical School*

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[a]Number of citations as of 13 June 2006. Table includes all clinical trials (including Phase 1 trials), epidemiological studies, case reports and biomarker studies that have the terms 'Alzheimer' or 'Alzheimer's' in their title, abstract or keywords, and that have been cited at least 25 times. Data source: *Scopus*