­

**Peter W. Baas, PhD**

**Professor, Department of Neurobiology and Anatomy**

**Director, Graduate Program in Neuroscience**

July 19, 2024

iScience

Online Submissions

Re: Manuscript entitled “Tau and MAP6 establish labile and stable domains on microtubules”

To the Editors:

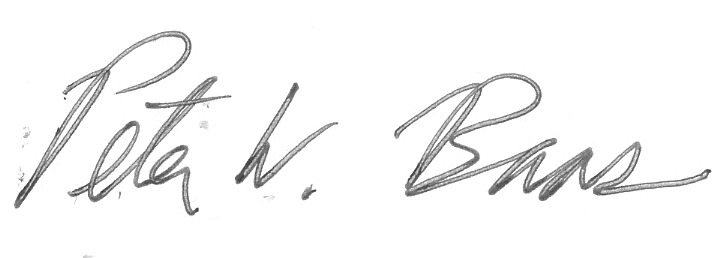
I’ve been studying the domain structure, polarity orientation, stability properties and composition of axonal microtubules for over thirty years. Much of my work has been on tau, which is among the most well-known of microtubule-associated proteins (MAPs) in the axon because it is so abundant, influences microtubules so profoundly, and goes awry in virtually every neurodegenerative disease or injury scenario of the brain. Hundreds of research papers over the years touted that tau is a key microtubule stabilizing protein until I published evidence in 2019 that tau actually does the opposite – which is to allow axonal microtubules to assemble long labile domains. The manner by which tau functions in this capacity seemed to be its interplay with another MAP, namedly MAP6, a relatively poorly studied protein but with much more certain microtubule-stabilizing properties. These two proteins seemed to have a yin-yang relationship to regulate the stability properties of microtubules. But could they somehow account for individual microtubules each having a stable domain and a labile domain? That was the question left on the table. A related question was whether the findings in that work broadly apply to axons or just developing axons in the culture dish.

Here, we first documented that these findings about tau being responsible for ensuring axonal microtubules have a robust labile fraction were extended to adult neurons. This is more than just a confirmation of what we would have assumed to be the case, because adult neurons are famous for having very stable microtubules. To document that they too, like developing neurons, consist of roughly half the total microtubule mass being able is critically important new information that will surprise many.

The lion’s share of the paper than goes on to take a reductionist approach to ascertain whether the properties of tau and MAP6, within themselves, can organize individual microtubules into stable and labile domains. These studies were done by expressing tau and MAP6 constructs in simple fibroblasts, and then conducing a number of experiments on them. Finally, we cap off the work with computational modeling, using various parameters of tau and MAP6 in tunable fashion to reveal further how they are able to segregate into distinct domains on individual microtubules.

I believe this work represents an important, timely and well-rounded story that will be of broad interest in your readership. There is basic science as well as disease relevance, and a few surprises that should garner attention from both fields. I am attaching a short manuscript we recently submitted to Journal of Cell Science with some related findings.

Sincerely,



Peter W. Baas, PhD