"**Brain targeting of 9c,11tConjugated Linoleic Acid, a natural calpain inhibitor, preserves memory and reduces Aβ and P25 accumulation in 5XFAD mice**" by Binyamin et al.

Lay summary

We have shown in previous manuscripts that GranaGard, a nanoformulation of pomegranate seed oil (NanO-PSO), can delay the onset of genetic CJD in a transgenic mouse model. We have also learned about the mechanism of action of this reagent and established it can reduce death of brain cells by protecting mitochondria, which constitutes the "engine" of cells. However, it does not reduce PrP^{Sc} accumulation (at least not at the more advanced stages of disease).

In this paper, we wanted to establish what is the "active molecule" in this food supplement, and whether the nanoformulation of pomegranate seed oil GranaGard is composed of will indeed target the active agent to the brain. Next, we wanted to test the effect of GranaGard on a mouse model of AD, which shares many of the pathological properties GranaGard seems to correct in the gCJD model.

To this effect we first administrated GranaGard as compared to regular pomegranate seed oil (PSO) to wt mice for several weeks or months. Subsequently, we collected livers and brains of these mice and tested extracts of these organs for the presence or Punicic Acid (PA), the main component of PSO, and for conjugated linoleic acid (CLA), the know metabolite of PA. We found that it is the metabolite CLA and not the PA that gets to the brain, and that this happens only when the nanoformulation of PSO (GranaGard) was administrated to the mice.

Interestingly CLA, the metabolite of PA, was shown previously to be a Calpain inhibitor, which is a group of reagents looked upon these days as targets for treatments in all neurodegenerative diseases, including AD, Parkinson and prion diseases.

To this effect, we administrated GranaGard to 5xFAD mice, considered as a model for AD. After 7 and 10 months, we performed cognitive tests on treated and untreated AD and wt mice, and showed in several tests that GranaGard treated mice conserved their memory much better while aging. Surprisingly, this was also the case for wt mice in some but not all of the tests. Concomitantly, we looked into the levels of Abeta aggregation in these mice and found they were significantly reduced in the GranaGard treated AD mice. Also the levels of COX-IV1, a crucial mitochondrial enzyme, increased after GranaGard treatment, as we previously showed for CJD mice.

Finally, we looked into the levels of P25, considered as the marker for Calpain activity. We found that P25 was elevated with age both in AD and in gCJD mice, and that in both cases, GranaGard treatment reduced P25 levels.

We conclude that GranaGard, which is a safe food supplement may prevent/delay the onset of neurodegenerative conditions, such as AD and CJD