Vassalli et al., (2026) just published a paper entitled **"Narcolepsy is (not) an autoimmune disease"** https://doi.org/10.1038/s41582-026-01232-9 . They propose that hypocretin (orexin) neurons become dysfunctional in narcolepsy because of "immune mediated pathogenic mechanisms" and that "reversible hypocretin gene silencing," not the death of hypocretin containing neurons, is responsible for all human narcolepsy. **But they present no evidence that narcolepsy is not an autoimmune disease, that Hcrt gene silencing occurs in narcolepsy or that "reversal of Hcrt gene silencing" is possible** <PMID: 37126681>.

Hypocretin neurons are located in the hypothalamus. In 2000, we were the first to show that the number of hypocretin neurons is reduced by 95% on average in humans with narcolepsy <PMID:11055430>. Consistent with this, a recent paper indicates that the hypothalamus is reduced in size in human narcolepsy <doi:10.1093/sleep/zsag087>.

Locus coeruleus neurons are located in the pontine brainstem. In 2026 we reported that 46% of locus coeruleus neurons are lost in humans with narcolepsy <PMID 41904178>. We also found microglial cells clustering around surviving hypocretin and locus coeruleus neurons in humans with narcolepsy, and a clear shrinkage of surviving locus coeruleus and hypocretin neurons, all indications of ongoing autoimmune destruction of neurons.

Some evidence for the hypothesized reversibility of narcolepsy would be expected in a paper titled "**Narcolepsy Is (Not) An Autoimmune Disease.**" The title will raise the hopes of people with narcolepsy that a cure is on its way. But the paper does not present any evidence that there is such a thing as "hypocretin gene silencing" or "reversal of hypocretin gene silencing" <PMID: 41904178>.

Vassalli et al. describe hypocretin neurons as being in the "lateral hypothalamus." In fact, these neurons are equally present in the medial and lateral hypothalamus, with high concentrations adjacent to the wall of the third ventricle, the most medial portion of the hypothalamus <PMID: 11055430> <PMID: 9822755> <PMID: 41904178>.

Our recent paper <PMID: 41904178> indicates that the loss of locus coeruleus neurons is the major cause of sleepiness and cataplexy in narcolepsy. The loss of hypocretin neurons can explain the greatly increased incidence of depression in narcolepsy <PMID: 39989723>. Boosting locus coeruleus norepinephrine levels with norepinephrine reuptake inhibitors has been shown to be the most effective treatment for sleepiness and cataplexy in human narcolepsy <PMID 41233821>, <PMID: 41904178> <PMID: 37155728>.

Thomas C. Thannickal[1,2] and Jerome M. Siegel[1,2]
[1]Neuropsychiatric Institute and Brain Research Institute, University of California, Los Angeles, [2]Neurobiology Research, Veterans Administration Greater Los Angeles Healthcare System, North Hills, CA, USA.