Specific Aims – Background and Gap

Schizophrenia is a chronic, heritable brain disease characterized by numerous symptoms causing cognitive, perceptual, and behavioral impairments in those affected (1). The disease can manifest in many ways; however, studies have shown that schizophrenic individuals have decreased grey matter in the frontal and temporal lobes of their cerebral cortexes compared to healthy individuals (2). Furthermore, it has been observed that these regions contain fewer and sparser dendritic spines (2), which normally function in synaptic storage and electrical transmission between neurons. Complement component 4A (C4A) is a cleaved protein encoded by the C4A gene which is located on chromosome 6 and functions in classical complement activation and synaptic pruning (1). Complement activation in the brain caused by increased C4A gene copy number has been observed in both Alzheimer’s disease (3) and Schizophrenia (1), but *the mechanism by which mutated C4A proteins target dendritic spines during the classical complement pathway is still unknown.*

**References:**

1. Sekar, A., Bialas, A. R., de Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., … McCarroll, S. A. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature*, *530*(7589), 177–183. http://doi.org/10.1038/nature16549
2. Garey, L., Ong, W., Patel, T., Kanani, M., Davis, A., Mortimer, A., … Hirsch, S. (1998). Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *65*(4), 446–453.
3. Zorzetto, M., Datturi, F., Divizia, L., Pistono, C., Campo, I., De Silvestri, A., … Ricevuti, G. (2016). Complement C4A and C4B gene copy number study in Alzheimer's disease patients. *Current Alzheimer Research*, Epub ahead of print.

Ideas:

C4A is overexpressed in the brains of schizophrenic patients and localizes to neurons and their synapses (does this only happen at dendritic spines?), so what is signaling the C4A to activate the complement pathway in these regions? What is the C4A targeting?

This can lead to new drug targets for treatment and/or prevention of schizophrenia