Nearly all tissues in our body have resident immune cells. These cells are involved not only in immunity, but also surveillance, and tissue maintenance (Figure 1). Resident immune cells can change according to what they stumble upon in the environment of the tissue. For instance, if they encounter a bacterium, they change so that they can capture and eat the bacteria (Figure 2, green to red). This can also happen when they encounter some sort of object which does not belong in the spaces surrounding the cells of the tissue, and they change so they can capture and eat this strange object. They can also change when they sense damage, to repair it (Figure 2, green to yellow). In addition to changing to meet a challenge, they also secrete signals to tell other immune cells what they have found, and to tell the cells of the tissue they are helping that they have found something. These signals are called cytokines. The combination of changes and types of cytokines released by the resident immune cells are called phenotypes. There is great diversity in how resident immune cells can change. Luckily, we have some simple definitions in the classification of phenotypes. In the case of handling bacteria and foreign bodies, resident immune cells assume the inflammatory phenotype, sometimes called M1 (Figure 2, red). When resident

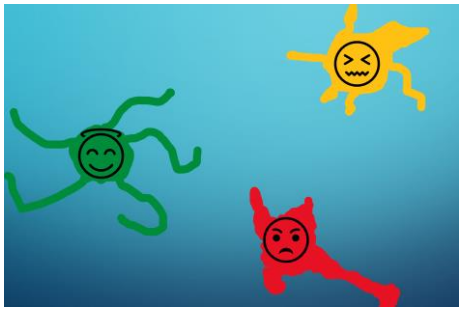

Figure 2. Resident Immune Cells (RICs) can change into different functional modes, called phenotypes.

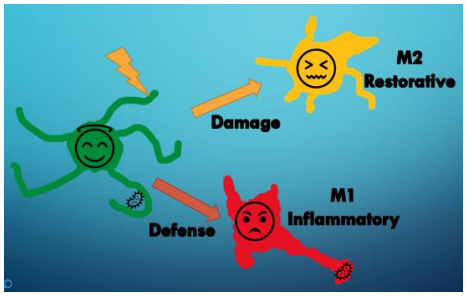

Figure 1. Resident Immune Cells (RICs) sense the environment and change according to the challenge. In the case of a bacterium, assume inflammatory M1. In the case of damage or tissue adaptation, M2, restorative.

immune cells find damage, to repair it, they assume the restorative phenotype, which has another name in immunology, termed M2 (Figure 2, yellow).

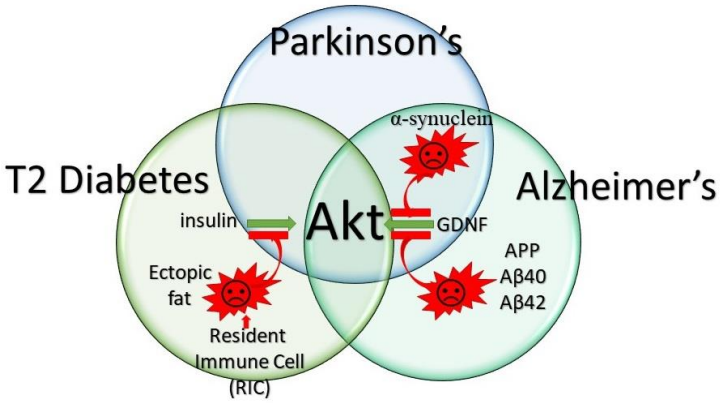

Figure 3. Intersections of diabetes, Parkinson's, and Alzheimer's, suggest parallel mechanisms leading to trophic factor resistance.

Most of the time the response of resident immune cells is beneficial, but sometimes the effects of resident immune cells are not so great (Figure 3, red RICs). We may be able to apply what we have learned about the role of resident immune cells for some diseases, like diabetes, which is well known, to other diseases. Parkinson's or Alzheimer's disease share several disease characteristics with diabetes. For instance, all three diseases, strange deposits are found, referred to as ectopic deposition or aggregates, a situation which does not appear in healthy tissues (Figure 3). The resident immune cell response to finding this junk, is to become inflammatory and attempt to clear the aggregations. However, this has consequences to the cells of the tissue they support. The inflammatory cytokines impair certain signaling pathways in these tissues (Figure 3). In diabetes the insulin signaling pathway is impaired, which we call insulin resistance (Figure 3, green bubble). A protein called A-k-t (Akt) is normally activated as part of the insulin response. In the case of nerve cells though, a different hormone activates Akt, one that can be secreted by microglia, called glial derived neurotrophic factor (Figure 3, blue and aqua bubbles). Some of the treatments effective in diabetes are also helpful in treating Parkinson's and

Alzheimer's. For instance, exercise, insulin, and diabetes medications, not only improve diabetes, but also are helpful for Parkinson's and Alzheimer's disease. The above-described treatments, improve Akt signaling (figure 3 and 4).

We want to find out if a similar situation to diabetes occurs in Parkinson's. In Parkinson's disease, do we find that Akt activation is lesser in response to glial derived neurotrophic factor compared to normal nerve cells? The proposed study asks the first part of this question. Do microglia cells clear the aggregations (composed of a damaged protein called alpha-synuclein) found in Parkinson's disease and change, do they ingest damaged alpha-synuclein, and then become inflammatory? Secondly, if they do, can the products produced by the microglia (containing the inflammatory cytokines), applied to nerve cells, impair Akt activation when glial derived neurotrophic factor is present?

By answering these questions, we will gather the necessary preliminary data to apply for a larger proposal to submitted to the National Institute of Health. This idea will need thorough exploration, because to our knowledge, has not been proposed yet by other established investigators. If our hypothesis is correct there will be more options for treatment of diseases which involve aggregation.

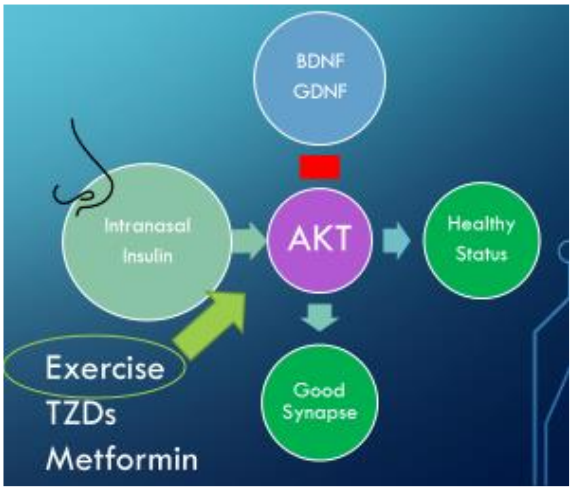

Figure 4. Interventions which improve Akt signaling in diabetes, also are effective in enhancing Akt signaling in the brain. Thus, when neurotrophic factor signals are inhibited by inflammatory signals, Akt can be activated by alternative methods, such as intranasal insulin, exercise, insulin sensitizers (TZDs), and alternative Akt activators like metformin.

Our preliminary exercise data shows that in a rat model of Parkinson's we can restore measures of motor coordination to that of controls. We also have data which suggests that the microglia phenotypes are different in the Parkinson's treated versus the Parkinson's with exercise treated rats. The exercise seems to promote the M2 phenotype. These data suggest that we may be on to something here. Follow the link below to support the project. Included is the official abstract of the proposal.

Intersections of diabetes and Parkinson's disease suggest parallel mechanisms leading to trophic factor resistance. S. Groshong, Jason, University of St. Thomas (St. Paul, MN), 11 Nov 2021. Experiment

Insulin and exercise improves diabetes, AD and PD. In diabetes, resident immune cells (RICs) secrete inflammatory cytokines upon ingestion of fat deposits, inhibiting Akt signaling. Glial derived neurotrophic factor (GDNF) also activates Akt. Perhaps a similar mechanism occurs in the CNS, involving RIC exposure to alpha-synuclein aggregates. We will attempt to replicate this in vitro and characterize RIC inflammatory status, then expose neuronal lines to RIC and monitor Akt inhibition.