Capitalizing on progress to date, TARCC researchers are aggressively pursuing a number of important cutting-edge research objectives aimed to improve the efficiency of early diagnosis, elucidate the disease mechanisms that are at work in Alzheimer's and enable more effective disease prevention.

- **Development of a serum protein-based tool for predictive diagnosis of Alzheimer's disease.** A simplified version of the TARCC blood test, first developed using serum samples from TARCC participants in 2010 has been independently validated in plasma collected from participants in the Alzheimer's Disease Neuroimaging Consortium (ADNI). The TARCC blood screener represents many firsts for the potential diagnosis of Alzheimer's, First, no other such test has ever been cross-validated in an independent group of subjects, all the more impressive in light of a recent Wall Street Journal article detailing the difficulties of reproducing study results. Second, this version of the screener works with different sorts of blood draws making it easier for clinics to implement. Third, to date, no previous attempts at identifying blood-based screening tools have utilized markers across blood fractions. This blood-based test for detecting Alzheimer's disease holds the potential for earlier and more accurate detection of Alzheimer's. Because of the length of time that Alzheimer's develops prior to the onset of symptoms, early diagnosis would be of great benefit to the development of novel treatment therapies and perhaps lead to improved methods to delay or prevent the onset of Alzheimer's disease.
- **Discovery of new genes associated with the development of Alzheimer's disease.** TARCC researchers are conducting a genetic scan of the entire complement of human chromosomes to identify novel genes that are associated with the development of Alzheimer's disease. The discovery of novel genes that are associated with Alzheimer's is likely to lead to the development of new drugs and therapies that will improve the quality of life of Alzheimer's patients and ultimately prevent this devastating disease. Thus far, genetic data have been generated for over 800 TARCC participants using the Affymetrix 6.0 panel, which includes 1.8 million genetic markers that cover two separate data sets. The first data set contains more than 906,600 single nucleotide polymorphisms (SNPs), the most common form of genetic variation, where a single base differs among individuals. The second data set includes more than 946,000 probes for the detection of copy number variation (CNV). CNV genetic variants result because some genes are duplicated and not all people have the same number of copies of each. The TARCC CNV data have been used in one publication and another submitted publication, as well as two funded grants. The first of these grants was from the Alzheimer's Association in the amount of $100,000. The second grant, which is ongoing, is from the National Institutes of Health (NIH) in the amount of $853,565. The SNP data have been used for two presentations at international meetings on Alzheimer's disease; they are also being used to support three collaborative research projects. In addition, these genetic data are being used in support of the TARCC biomarker project. This effort aims to determine if there are genetic changes that impact concentration of blood proteins that have been linked to Alzheimer's disease. Preliminary analysis indicates that multiple genetic variants are significantly associated with the concentrations of the serum proteins that most diagnostic in the TARCC blood test.

- **Discovery of genetic variants within inflammatory genes that are associated with the development of Alzheimer's disease.** The identification of inflammatory genes that are important to the development of Alzheimer's disease would allow the development of treatments that are aimed at reducing levels of chronic inflammation. Because a number of FDA-approved anti-inflammatory drugs are currently on the market, rapid and effective progress could be made in this arena if specific inflammatory genes are identified as important Alzheimer's risk factors.
- **Evaluation of the roles of altered cholesterol and insulin metabolism in the development of Alzheimer's disease.** If cholesterol, altered insulin metabolism are shown to be important Alzheimer's risk factors, therapies aimed at moderating these factors would be indicated.
- **Resolving the relationship between cardiovascular risk factors, inflammation and Alzheimer's disease.** Identification of inflammation as the key mechanism of action whereby cardiovascular risk factors increase the risk for Alzheimer's would enable physicians to prescribe more effective heart disease medications to prevent or delay onset of Alzheimer's disease.
- **Evaluation of the roles of key cardiovascular risk factors in the development and progression of Alzheimer's disease.** If elevated blood levels of homocysteine or Lp-PLA2 (two key markers of risk for cardiovascular disease) are shown to be important Alzheimer's risk factors, therapies aimed at moderating these factors would be indicated.

- **Evaluation of depression and depressive symptoms at various stages of cognitive decline.** Results from this study would allow clinicians to more accurately predict risk for depression among their patients who are at various stages of cognitive decline.

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