**Neurodegenerative Disorder**
Affects memory, thinking and behavior. Characterized by beta-amyloid plaques and a specific miRNA profile.

**6th Leading Cause of Death**
Affects 5 million Americans. Kills more than breast and prostate cancer combined.

**Current Treatments Ineffective**
Current diagnoses revolve around cognitive and psychological evaluations.

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**β-Amyloid Detection: Native Receptors**

A: LilrB2 and PirB are natural, transmembrane receptors that selectively bind beta-amyloid oligomers (Kim et al. Science 2012). Once bound (1), they recruit the cofactor coflin (2), which is fused to a protease. Upon recruitment to the receptor, the protease cleaves (3), releasing a transcription factor, which can activate a treatment response circuit (4).

**β-Amyloid Detection: B-Cell Receptor**

A: Synthetic B-cell receptor engineered to bind beta-amyloid oligomers (Ostrowski et al., Arch Neurol, 2011). Upon binding (1), BCR is activated, recruiting the cofactor Syk (2). Syk is fused to a protease, cleaving upon recruitment to the receptor (3). Cleavage releases a transcription factor, which can activate a treatment response circuit (4).

**miRNA Detection**

Neurons in Alzheimer’s express a different miRNA profile than healthy neurons. Sensors were built to detect low levels of miRNA (A) and high levels of miRNA (B). Truth table (C) shows overall logic.

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**Treatment**

A: BACE1 is involved in production of beta-amyloid. BACE2 has been shown to degrade beta-amyloid (Abdul-Hay, et al Molecular Neurodegeneration, 2012). The treatment module down-regulates BACE1 and up-regulates BACE2, thereby reducing overall levels of beta-amyloid.

**Delivery**

Potential delivery mechanisms were used to inform decisions regarding our project. Two were explored:

- **Ex-Vivo Delivery**
  Involves extracting cells and engineering them before introducing them back into the patient.
  No risk of random genome integration of circuit.
  No access to chemical pathways within diseased cells.
  No FDA approved treatments; several clinical trials in progress (Wang, Discovery Medicine, 2014).

- **In-Vivo Delivery**
  Involves using a delivery vector (virus or liposome) to deliver therapeutic DNA directly to patient cells.
  Risk of random genome integration of circuit.
  Requires risky procedures to deliver.
  Easy access to diseased cells.
  One approved therapy and several in clinical trials (Wang, Discovery Medicine, 2014).

**Experience with Alzheimer’s and Receptiveness to Gene Therapy**

Hypothesis: People with personal experience with Alzheimer’s disease are more willing to undergo experimental treatments than people who do not have personal experience with the disease.

Neither experience with Alzheimer’s nor knowledge of gene therapy affects respondent’s willingness to receive genetic therapeutics. Respondents prefer less invasive delivery methods. Survey results helped inform our decision to use neuron-specific detection and treatment methods.