**ABSTRACT:** The UCSF 2010 iGEM team aims to combat one of the leading causes of death worldwide: CANCER. Our goal is to turn natural immune cells into Synthetic Killers that can detect cancer cells with GREATER PRECISION, initiate a stronger killing response through ENHANCED SIGNALING, destroy targeted cancer cells more effectively with a BETTER ARSENAL. Successfully engineered Synthetic Killers would be particularly useful in cell-based adoptive immunotherapy of cancer.

**Introduction**

Killer Immune Cells

These cells detect and kill foreign, damaged, or cancerous cells in the body. They include Natural Killer (NK) cells and cytotoxic T cells (CD8+).

Cancerous Cells

Healthy cells that have undergone mutation and grow out of control.

**Killer Cells and Cancer Antigen Detection**

Recognition of surface antigens on target cells by activating and inhibitory receptors control natural killer cell activation.

Why do we want to work with killer immune cells?

They use an interesting detection/response system that we can improve upon through application of synthetic biology. They detect damaged cells and kill them by releasing cytotoxic granules.

What do we want to do this year?

Create synthetic killers specialized in detecting specific cancer cells and effectively killing them without harming normal cells.

**Greater Precision**

Use principles of natural killer cell signaling and Chimeric Antigen Receptor design concepts to construct gate devices.

Use granule address tags (localization motifs) to indicate that it is located in the granules.

**Monoclonal antibodies can be used as modular SENSORS to construct synthetic receptors — “Chimeric Antigen Receptors” or “CARs”**

**Stronger Signaling**

Achieve stronger signaling by convergent kinase activation.

**Better Arsenal**

Synthetically Armed Granules - Localization Tags

**CONCLUSIONS**

**Over this summer...**

- We were able to enable greater precision for Killer Cells by reengineering cells to better identify specific cancers by developing antigen-specific Logic Gates as shown by our ANDN gate.
- By enhancing existing signaling pathways through the use of a synthetic GPCR, we were able to elicit stronger signaling for Killer Cell activation.
- We successfully loaded GFP into granules of Killer Cells as a proof of concept cargo for creating a better arsenal by using granule localization tags.

**These devices have the potential to enhance adoptive cell-based immunotherapy in cancer patients**

**Next Steps:**

Stable expression in Killer Cells (tandem viral vectors)

Examine performance in killing assay

Examine additional gate devices

Look at granule mobilization and release

Identify and examine synthetic “killing” cargo

**Special thanks:**

Lewis Lanier (UCSF)

Michael Milone (U Penn)

Ira Pastan (NCI)

Dario Campana (St. Jude) for providing DNA constructs for scFv against antigen A.

Michael Milone (U Penn), Ira Pastan (NCI), and Dario Campana (St. Jude) for providing DNA constructs for scFv against antigen B.

**Next Steps:**

Identify and examine synthetic “killing” cargo

Examine additional gate devices

Stable expression in Killer Cells (lentiviral vectors)

**Special thanks:**

Lewis Lanier (UCSF) for providing natural killer (NK) cell lines.

Michael Milone (U Penn), Ira Pastan (NCI), and Dario Campana (St. Jude) for providing DNA constructs for scFv against mesothelin and CD19 used to construct model CAR devices.

For further information on our devices and results check out our wiki.