

## C3 / Padres Pedal the Cause 2020

“Precision Interception of Gastric Cancers”

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## SCIENTIFIC ABSTRACT

Despite the knowledge of a treatable trigger, i.e., the carcinopathogen *Helicobacter pylori* (*Hp*) and known pre- neoplastic states, e.g., multi-atrophic gastritis, intestinal metaplasia (IM) and low- to high-grade dysplasia (L/HGD) that increase the risk of progression to Gastric Cancers (GCs), medical treatment to intercept such progression has not emerged. A transdisciplinary team of researchers comprised of engineers, cancer biologists, chemists, and physician-scientists have joined forces to find novel therapeutic solutions for intercepting GCs using: **1)** a novel set of mathematical tools for **target discovery** from *human* transcriptomics, and **2)** reverse- engineered *human* stem-cell based disease models for **target validation**.

The *primary objective* of this proposal is to secure funds to generate key preliminary data to eventually form a NCI-funded GC consortium. The likelihood of success is high because that team can leverage a newly built GC-map for the development of ~ 3-6 network-rationalized therapeutics that specifically intercept continuum states which otherwise progress to GC.

Our **Specific Aims** are: **1:** *Network-guided target Identification and prioritization*; **2:** *Target validation using pre-clinical animal models of GC initiation and progression*; **3:** *Phase '0' proof-of-concept trials testing the efficacy of drugs for intercepting GC initiation and progression using human organoid-based disease models*.

Use of these human Phase '0' model systems are expected to increase the success rate of translating our findings rapidly to the clinic. This program is uniquely poised to **deliver** novel therapeutic solutions that target pre-neoplastic states in GC. Success by any measure will decisively **impact** the management of those at highest risk of GCs.

## LAY ABSTRACT

A team of researchers comprised of engineers, cancer biologists, and physician scientists have joined forces to intercept the devastating disease that is Gastric Cancer (GC). GCs often present as advanced disease and kill silently. Fortunately, this disease has well known triggers, e.g., the cancer-causing bug, *Helicobacter pylori* (*Hp*) and some poorly understood, but definite pre-cancerous states that are typically not treatable by surgery but could be specifically intercepted with medical treatment. Currently, no such treatment exists; this team seeks to change just that.

This team is deploying a new set of mathematical tools for **finding precise drugs that prevent GCs** and utilizing *human* stem-cell based disease models for **target validation**. The team has already created the first-ever map of how GCs begin and has defined the most important steps of GC progression that

could be precisely intercepted with drugs. Going forward, their goal is to validate ~3-6 new drugs, some aimed for prevention and others for halting metastatic disease.

*There are 2 reasons why this team is likely to succeed where others have failed: First, when it comes to **drug discovery in GC**, this team employs **precise and unbiased** AI-based approaches to expose previously unknown and undefined intermediate stages before GCs and reveal how to stop progression. *Second*, when it comes to **drug testing**, this team has developed human models that are reverse engineered with the GC-causing bug, the stomach lining and the immune cells to mimic the **human “stomach-in-a-dish”**. These human-relevant models are expected to enable rapidly translation of discoveries.*