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Pilot Project Proposal  
(Not to exceed two pages)

**Name of Project:** The seven signals toolbox: Leveraging Synthetic Biology to Define the Logic of Stem-Cell Programming

**Proposer and Contact Information:**

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**Background:**

The astonishing diversity of cell types and organ structures in the human body are largely generated from the action of just seven signals: the Hedgehog, Wnt, TGF- $\beta$ , receptor tyrosine kinase, Notch, JAK/STAT and nuclear hormone pathways. These pathways are activated in many combinations and temporal patterns to drive the differentiation of stem cells into hundreds (perhaps thousands) of cell types during embryogenesis. We refer to the many possible patterns of pathway activation as signaling space. Differentiation space is a term that describes the range of possible cell states in the progression of stem cells to differentiated cells.

**Technical Idea:**

Mapping the signaling space of the seven core developmental pathways to differentiation space would enable the generation of many human cell types from HGP2 stem cells *in vitro*. To achieve this goal, we will develop a genetic toolbox for the precise temporal modulation of the seven pathways in any combination using optogenetic or chemical control. In addition, we build a complimentary toolbox of reporters for the rapid phenotypic profiling of these cells.

**Utility and “Fit” For GP-write:**

This project will not only trace a map for the artificial control of development, it will also generate tools that facilitate the control cell of differentiation *in vitro*. Ultimately, a precise control of cell differentiation is a crucial step toward the use of HGP2 lines in cell therapies, tissue replacement or even organ transplants.