A system for the anterograde tracing of synaptic connections in mammals.

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Abstract:
The human brain consists of trillions of neural connections, giving rise to the neural networks underling all behaviors and cognition. Mapping the presence of these connections is challenging, relying on either complex physiological tests or retrograde viral techniques, and there is pressing need for an efficient way to label the neurons postsynaptic to any given neuronal population. The call is for building anterograde tracing tools that can reveal the downstream circuits from defined neuronal populations both in the intact mouse and in organoids.

Rationale & Hypothesis:
Here, we propose to build a molecular tool for the robust and specific anterograde tracing of synaptic connections in mammals by using a synthetic biology approach involving custom receptor-ligand pairs across a synapse that triggers unique intracellular cascades to activate gene expression. We hypothesize that this approach will allow for the creation of an AAV-deliverable anterograde transsynaptic tracer that allows for mammalian circuit tracing

Research Plan:
To achieve our goal, we will focus on the following work packages (WP):
WP1: Molecular design of the tool
WP2: Tool validation in-vitro by primary neurons engineering
WP3: Testing the system in a mouse model for mapping visual circuits
WP4: Testing the system in photosensitive brain organoids

Integration of Expertise of Partners:
Siciliano's lab focus on the development of approaches derived from synthetic and systems biology in order to design optimized DNA or RNA-based genetic circuits for cell therapy. Rompani's lab studies the function of visual circuits in the mouse thalamus, and he is an expert in functional imaging and tracing systems in-vivo. Expertise from both labs is essential, since in the Siciliano lab we can develop the tools and perform in vitro tests, while in vivo validation and optimization will be done in the Rompani lab, as well as relying on the knowledge of transynaptic viruses in the Rompani lab. We believe that the combination of both labs' expertise is instrumental for the development of a novel tool to trace neural networks in-vivo.