**Triple Negative Breast Cancer (TNBC)** is an aggressive, heterogeneous subtype of breast cancer (BC) accounting for 20% of BC cases1. Unlike other subtypes of BC which are characterized by the presence of estrogen receptors, progesterone receptors, or HER2 amplification, TNBC is characterized by the lack of all three of these markers. **Claudin-Low (CL) TNBC** is a subtype of TNBC making up 7-14% of invasive breast cancers diagnoses2. CL tumors are prone to epithelial to mesenchymal transition (EMT) as well as exhibiting stem-cell like characteristics, two hallmarks of cancer marking high metastasis rates2,5. The low proliferation rate of the subtype sets it apart from most tumors, making it difficult to treat with cytotoxic drugs2. CL TNBC has a poor prognosis and a clear need for new treatment options.

**Tumor reversion** is the biological process by which tumor cells lose a significant fraction of their malignant phenotype7. Tumor reversion has been observed *in vitro, in vivo, and ex vivo for* over a century (SOURCE). In particular, tumor reversion has been achieved in vitro with the CL cell line MDA-MB-231, and *in vivo* in a mice xenografted with MDA-MB-231 cells8-13.

At the cellular level, the development of cancer can be seen as a systems-level dynamical process driven by a tumorigenic intracellular signaling network. Attractors of this network correspond to cell phenotypes14. **Cancer attractors** are attractors presenting a malignant phenotype that are pre-existing in the network but not typically accessible and therefore not occupied by cells14. They can be accessed through genetic mutations or changes in the tumor microenvironment. **Tumor reversion can be viewed as an optimal control problem in dynamical systems where the objective is to shift the system away from a cancerous attractor and towards normal-like attractors.**

**Structure-based control methods** study the controllability of systems based solely on the structure of the network15-18. Attractor-based control methods focus on the controllability of the system by restricting the target states to attractors. Recently, structure-based attractor-based methods for non-linear systems have been proposed17,18(Fig 1). The newly proposed Feedback Vertex Set Control (FC) framework is especially suited for systems with non-linear dynamics8. The objective of FC is to identify combinations of network nodes that drive the network from an arbitrary initial state to any desired dynamical attractor of the system through an override of their initial state.

**Objectives:** Develop and apply a computational systems biology pipeline for the construction and control of an intracellular signaling network of reversion of Claudin-Low Triple Negative Breast Cancer. The ultimate goal is to identify and experimentally validate combinations of therapeutic targets to aid in the reversion of CL TNBC.

**Objectives:**

* Develop and apply a computational systems biology pipeline for the construction and control of an intracellular signaling network
* Identify and experimentally validate combinations of therapeutic targets to aid in the reversion of Claudin-Low Triple Negative Breast Cancer