Glioblastomas are the most common primary brain tumors among adults. Yet, despite decades of basic research and clinical innovations, the median survival is merely slightly more than one year from diagnosis. In recent years, we have witnessed extraordinary progress in treating other solid tumors due to the stellar growth of novel therapies that are based on instructing and boosting patients' immune system responses, collectively known as immunotherapies. Yet the high hopes of immunotherapy had not come to fruition in the case of glioblastoma. The primary reason for this failure is thought to be a prevailing environment within these tumors that suppresses the immune system activity that allows tumor cells to evade eradication by immune cells. In such a situation, a promising approach should use an agent that combines the ability to destroy the bulk of the tumor while boosting a well-timed immune response that would attract immune cells into the depth of the tumor to mop up the last pockets of resistance and preventing tumor's recurrence in the future.

Engineered therapeutic agents known as oncolytic viruses that have been developed for glioblastoma therapy with some success possess such characteristics. They could thus provide the desired combinatorial effect, merging cytotoxicity (i.e., the ability to recognize and kill tumor cells) and boosting immune signaling. Unfortunately, the conditions prevailing in the tumor environment blunt their effectiveness. Among them, a *force majeure* title belongs unequivocally to hypoxia, i.e., low oxygen concentration. Hypoxia is an inherent, inescapable feature of glioblastoma, and its gradual buildup during the disease progression cannot be controlled and prevented. To make matters worse, response to hypoxia is a widespread mechanism, ubiquitous in any cell, and thus, impossible to block without harming healthy, beneficial cells. We aim to overcome this obstacle by targeting discovered by us hypoxia-induced factor that is, in fact, particular to tumor cells.

The candidate molecule (HIF1A-AS2) came to our attention during our decade-spanning research efforts to characterize the largest yet poorly comprehended part of the human cell transcriptome (i.e., all RNA species present in a cell at a given time) – non-protein-coding RNAs (ncRNAs). Unlike mRNAs, ncRNAs do not carry information encoding proteins but rather act as fine-tuning agents overseeing complicated cellular processes. ncRNAs are unique from a cancer cell biology standpoint because of their strict cancer cell-type-specific patterns of expression, thus providing promising candidates for tumor-specific targeting. HIF1A-AS2 expression is prevailing in hypoxic regions of the tumor, and in vitro, it is selectively maintained in low oxygen conditions. We assume that this mechanism enables tumor cells with survival skills, thereby allowing them to withstand hostile conditions while making them resistant to therapeutic intervention and evading immune system surveillance.

We demonstrated that the experimental knockdown (i.e., inactivation) of HIF1A-AS2 resulted in weak and lagged activation of hypoxia response, while its strict tumor-specificity makes the targeting neutral for non-malignant cells, including immune cells. Moreover, HIF1A-AS2-dependent blunting of hypoxic response led to improved and prolonged effectiveness of oncolytic virus therapy. The effect was further propagated by releasing nanometer-sized vesicles shed by virus-infected tumor cells, which efficiently turns on the immune response. Capitalizing on that knowledge, we propose to use these extracellular vesicles naturally secreted by cells to deliver the message to both cancer and immune cells. Thus we hypothesize that breaching through a HIF1A-AS2-enforced hypoxic firewall will significantly augment oncolytic virus immunotherapy.