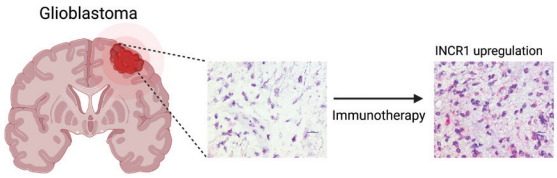

Figure 1. INCR1 is upregulated in patients treated with immunotherapy.

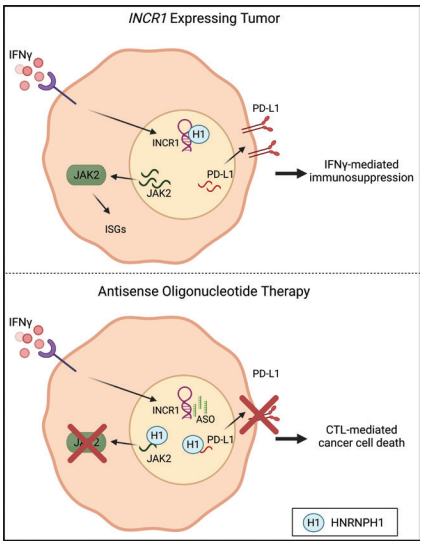

Figure 2. INCR1 regulates tumor interferon signaling.

Antisense Oligonucleotides for Cancer Immunotherapy

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Dr Mineo's work is focused on developing a new approach to treatment of glioblastoma. His work brings together his understanding of the tumor microenvironment with his expertise in long noncoding RNA, his work uses gene therapy to manipulate tumor cells in a way that will make them more susceptible to attack by immunotherapies. Dr Mineo has demonstrated the effectiveness of this strategy in animal models and is working on pre-IND studies.

Cancer is the second leading cause of death worldwide. Despite the significant advances in tumor targeted therapy and the development of novel drugs, there remain a large number of cancer patients who do not respond to therapy. In addition, personalized treatments available may be toxic for some patients. As a result, there is an urgent need to identify new therapeutic options. The need for novel therapies is even higher in certain cancers, such as glioblastoma, in which the standard of care has not advanced beyond maximum possible resection, radiation, and chemotherapy. For these patients, the median survival remains only few months. Immunotherapies have been shown to be effective in some types of cancer, such as melanoma, but remain mostly ineffective in glioblastoma, which is characterized by a highly immunosuppressive microenvironment.

Understanding the molecular mechanisms of resistance may pave the way for more effective immunotherapeutics that overcome current limitations. We have recently identified the interferon-stimulated noncoding RNA 1 (INCR1) as a novel long non-coding RNA transcribed from the PD-L1 locus, and showed that INCR1 is highly inducible in tumor cells stimulated with interferon-γ. We demonstrated that INCR1, through the interaction with the ribonucleoprotein HNRNPH1, regulates tumor interferon signaling and the expression of different immunosuppressive molecules. Moreover, we showed that silencing INCR1 could improve effectiveness of different immunotherapies, such as CAR T and IL-12 therapy. INCR1 functions can be therapeutically blocked using antisense oligonucleotides (ASOs), which are currently FDA-approved for the treatment of a variety of disorders. We recently designed ASOs targeting INCR1, and showed their ability to inhibit the expression of INCR1 and reduce the levels of immunosuppressive molecules. Therefore, our results suggest the use of ASOs targeting INCR1 as potential immunotherapeutic strategy for the treatment of cancer.