and progenitor cell properties, and by further understanding their biology, we hope to identify those cells that are more aggressive and resistant to conventional therapies.

Our project is focused on identifying and characterizing critical populations of tumor cells within high-grade gliomas of the proneural subclass. We hope that in the future, insights gained from this project will inform the optimization of current therapies and the development of therapeutic approaches that are more targeted to these cell populations.

Elena Bazzoli

A New Model for the Mesenchymal Subtype of Human Gliomas

High-grade gliomas are aggressive and uniformly fatal tumors, composed of a heterogeneous population of cells, including many with stem-cell-like properties. Acquisition of stem-like traits might be responsible for glioma initiation, growth, and recurrence. We investigated the role of the transcription factor myeloid Elf-1-like factor (MEF, also known as ELF4) in glioma. We found that MEF is highly expressed in both human and mouse glioblastoma multiformes and its absence impairs gliomagenesis in a PDGF-driven glioma mouse model. We show that modulation of MEF levels in both mouse primary brain cells and glioma cell lines has a significant impact on stem-like characteristics such as neurosphere formation and side population. Taken together, our studies have implicated MEF as a new oncogene involved in gliomagenesis by promoting stem cell characteristics. Given its role in promoting features of aggressiveness, MEF could potentially be a novel therapeutic target in the clinical care of patients suffering from gliomas.

Further work will be necessary to address whether modulation of MEF levels could have an impact on sensitizing glioma cells to standard treatments such as chemotherapy and radiotherapy.

Ranjit Bindra

High-Throughput Screening for Novel DNA Repair Inhibitors in Glioma Cell Lines

Our drug screen has yielded several interesting drugs to radiosensitize glioma cells in vitro. One of our lead hits from this study, mibefradil, is of particular interest because it was previously marketed as an FDA-approved anti-hypertensive agent. Furthermore, recent studies suggest that it has anti-glioma activity both in vitro and in vivo, and the drug is currently being tested in a clinical trial with patients who have recurrent glioma. We are now further developing mibefradil as a novel radiosensitizer for the treatment of adult and pediatric glioblastoma multiforme (GBM). Specifically, we plan to initiate a phase I clinical trial testing this drug with radiation therapy in patients with recurrent GBM.

Barbara Oldrini

Dissecting the Mechanism of EGFR Signal Termination by the PTEN Tumor Suppressor

EGFR represents a compelling therapeutic target in glioblastoma multiforme. Tumors with *EGFR* mutation and PTEN loss are resistant to first-generation EGFR kinase inhibitors. Using a global mass spectrometric approach we discovered RanBP6 is a novel EGFR-interacting protein and EGFR regulator. The interaction between EGFR and RanBP6 is PTEN dependent.

Tatsuya Ozawa

The Exploration of Druggable Target for the NF1 Loss / Mesenchymal Subgroup of Gliomas

Mouse models based on genetic alterations identified in human gliomas are a very valuable tool to not only better understand brain tumor biology but also to explore potential novel therapeutic targets. Recent large-scale analysis of molecular profiling of glioblastomas has revealed that neurofibromatosis type 1 (NF1) gene mutation/loss is common in sporadic human glioblastomas as well as in NF1 patients and is strongly associated with one of four main subgroups that are classified based on molecular profiles. In order to examine a molecular mechanism of glioma formation mediated by NF1 loss, I have established a novel NF1 loss-mediated glioma mouse model with RCAS/tv-a system. Gliomas were induced with similar penetrance compared to previously published NF1 loss mouse models generated with different methods. In addition, the molecular profile and the signaling pathway of tumors caused resembled human counterpart and appeared as a promising druggable target for brain tumors, specifically those with *NF1* mutation. Thus, my project itself is facing clinical application. Once the candidate pathway is confirmed as a therapeutic target, it may be translated into the clinic.

My mouse model differs from previously established NF1 mouse models as this model utilized the RCAS/tv-a system, which allows us to easily examine the functionality between a gene of interest and glioma formation. This model is therefore useful for expanding our understanding of the underlying molecular biology behind gliomas, which will be beneficial not only for glioma patients belonging to the NF1 subgroup, but also potentially for all glioma patients.

Massimo Squatrito

Investigating the Role of Chk1 in Gliomagenesis and Therapy Response

One of the aims of this project has been to analyze the role of the Chk1 checkpoint kinase in the response of gliomas to therapy. Our preliminary evidence suggests that Chk1 inhibition increases glioma sensitivity to ionizing radiation, the current standard therapy used in glioblastoma multiforme (GBM) patients. Although the data is still preliminary for treatment of gliomas, Chk1

inhibitors are currently used in various clinical trials for other tumor types.

A better understanding of the molecular mechanisms that protect the cells from the response to a specific DNA damaging therapy is required to develop new treatments that could overcome this resistance. Increasing the response to the current standard therapies in GBM patients will allow affected patients to have extended survival.