# PEDIATRIC NEURO-ONCOLOGY RESEARCH

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## SUMMARY & MISSION STATEMENT

We investigate cellular mechanisms and molecular control of tissue invasion in paediatric brain tumours and explore novel intervention methods to target tumor cell dissemination. Our long-term goal is to develop intervention strategies allowing for specific inhibition of the pathophysiological, pro-invasive tumor cell phenotype without affecting physiological functions of the brain.

## OVERVIEW

Metastatic dissemination of tumour cells and distant growth still constitute a major obstacle to effectively treat malignant primary brain tumours such as Medulloblastoma (MB) in children. MB metastasize both locally in the cerebellum and distantly to the leptomeninges of the brain and the spinal cord.

Our working hypothesis is that tissue invasion prior to distal dissemination in metastatic and recurrent MB is driven by aberrant activation of pro-invasive signalling pathways in the tumour cells, and that the specific blockade of synergistically acting pathways will prevent invasion and restrict brain tissue infiltration and recurrence.

To characterize such pathways and to identify and validate relevant target molecules, we use functional screening approaches in 3D cell culture models and organotypic brain slice culture, which mimic a physiologically-relevant tissue environment.

We identified FGF and HGF receptor tyrosine kinases as key regulators and drivers of tumor cell invasion. Using cell biological and biochemical approaches in 2D and 3D *in vitro* and *ex vivo* models, we currently decode aberrantly activated pro-migratory signalling pathways downstream of these receptors, to understand the molecular control of tissue invasion and to develop novel targeting strategies to restrict cell dissemination in malignant brain tumours.

## SELECTED CANCER RELATED PUBLICATIONS

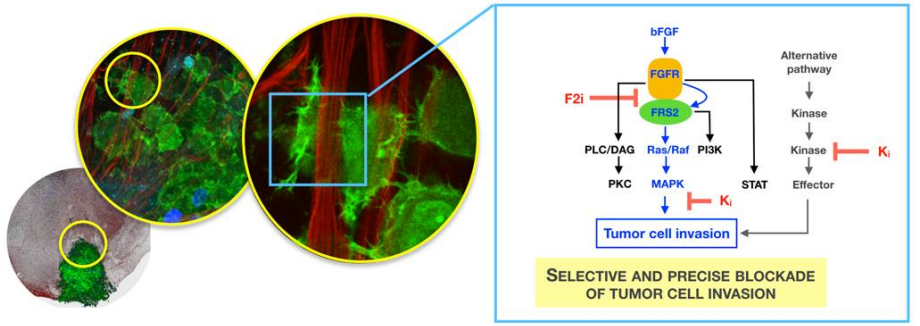
TGF-β determines the pro-migratory potential of bFGF signalling in medulloblastoma. Karthiga Santhana Kumar, Anuja Neve, Ana S. Guerreiro Stucklin, Claudia M. Kuzan-Fischer, Elisabeth J. Rushing, Michael D. Taylor, Dimitra Tripolitsioti, Lena Behrmann, Daniel Kirschenbaum, Michael A. Grotzer and Martin Baumgartner. **Cell Rep.** 2018, accepted

MAP4K4 controlled integrin beta1 activation and c-Met endocytosis are associated with invasive behavior of medulloblastoma cells. Dimitra Tripolitsioti, Karthiga Santhana Kumar, Anuja Neve, Jessica Migliavacca, Charles Capdeville, Elisabeth J. Rushing, Min Ma, Noriyuki Kijima, Ashish Sharma, Martin Pruschy, Scott McComb, Michael D. Taylor, Michael A. Grotzer & Martin Baumgartner. **Onctarget** 2018, in press

Investigation of brain tissue infiltration by medulloblastoma cells in an ex vivo model. Anuja Neve, Karthiga Santhana Kumar, Dimitra Tripolitsioti, Michael Grotzer and Martin Baumgartner. **Scientific reports** 2017, 7: 5297.

Computer-assisted quantification of motile and invasive capabilities of cancer cells. Karthiga Santhana Kumar, Max Pillong, Jens Kunze, Isabel Burghardt, Michael Weller, Michael A. Grotzer, Gisbert Schneider and Martin Baumgartner. **Scientific reports** 2015, 5:15338.

The Ser/Thr kinase MAP4K4 drives c-Met-induced motility and invasiveness in a cell-based model of SHH medulloblastoma. Karthiga Santhana Kumar, Dimitra Tripolitsioti, Min Ma, Jasmin Grählert, Katja B Egli, Giulio Fiaschetti, Tarek Shalaby1, Michael A Grotzer1 and Martin Baumgartner. **SpringerPlus** 2015 4:19.




**Imaging of cerebellum infiltration by medulloblastoma (MB) cells in organotypic cerebellum slice cultures revealed the formation of filopodia-like invasive protrusion at the invasion front (green: LA-EGFP expressing MB tumour cells, red: anti-GFAP, blue: EdU-positive nuclei). Box: Invasion and formation of filopodia-like invasive protrusions in MB tumour cells is driven by FGFR-FRS2 signalling and by additional growth factor-activated kinase signalling pathways. Specific targeting of these kinases may be an efficient means for preventing tumor cell invasion and dissemination.**