Basic research and small molecule drug screenings − coupled with in vivo treatment response will be instrumental for the development of new therapeutic modalities.

Gaining insights into the pathways that determine this poor treatment response will help to define new therapeutic targets for treatment of brain tumours.

The central focus of our Group is to uncover the genetic alterations present in GBM patients that are responsible for the aggressiveness of this tumour type, with particular interest in the identification of the signalling pathways that lead to poor treatment response.

GBM mouse models in order to identify genes involved in therapy resistance of gliomas. We reason that these studies will help to define new therapeutic targets for treatment of brain tumours.

MBGM genomic rearrangements contribute to chemotherapy resistance in gliomas

Temozolomide (TMZ) is an oral alkylating agent used for the treatment of glioblastoma and is now becoming a chemotherapeutic option for patients diagnosed with high-risk, low-grade gliomas. The therapeutic benefits of TMZ depend on its ability to methylate DNA, which takes place at the N-7 and O-6 positions of guanine and the N-3 position of adenine. Although the minor product O-6-methylguanine (O6-meG) accounts for less than 10% of the total alkylation, it exerts the greatest potential to induce apoptosis. The O-6-methylguanine-DNA methyltransferase (MGMT) is responsible for the direct repair of the O6-meG lesion by transferring the alkyl group from guanine to a cysteine residue. Epigenetic silencing, due to promoter methylation of the MGMT gene, prevents the synthesis of this enzyme and consequently increases tumour sensitivity to the cytotoxic effects induced by TMZ and other alkylating compounds.

MGMT genomic rearrangements contribute to chemotherapy resistance in gliomas

By analysing a large cohort of IDH wild-type and mutant recurrent gliomas treated with TMZ, we have discovered that a subset of patients carries distinct MGMT genomic rearrangements. By leveraging CRISPR/Cas9 technology, we generated some of these MGMT rearrangements in glioma cells and demonstrated that the MGMT genomic rearrangements contribute to TMZ resistance, both in vitro and in vivo. Lastly, we showed that such fusions can be detected in tumour-derived exosomes and could potentially represent an early detection marker of tumour recurrence in a subset of patients treated with TMZ.

Figure (a): MGMT fusions are mutually exclusive with other known TMZ resistance mechanisms. (b): Schematic representation of the identified fusions.


** Awards and Recognition **

Miguel Jiménez Alcázar has been awarded an EMBO long-term fellowship.

** Publications **
