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Rue Gabrielle-Perret-Gentil 4
CH – 1211 Genève 14

**Subside de l'Association Frédéric Fellay**

Département
d'oncologie

Direction et
administration

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T direct : 022 372 98 52

**Projet : "Immunologie des tumeurs cérébrales"**

Prof. Pierre-Yves Dietrich, Dr Paul R Walker

## Rapport Scientifique Final - Décembre 2018

The overall objectives of this project have been to perform in-depth analysis of glioblastoma cells to assess their potential sensitivity – or resistance - to immunotherapy. These cells are either long-term established glioblastoma cell lines (LN18, U87, U251, SB28), or short term cell lines derived from tumour biopsies from patients eligible for participation in immunotherapy clinical trials in Geneva (Ge835, Ge904).

As previously reported, different glioblastoma cell lines show quite different sensitivities to being killed by different mediators, including the immune cytotoxic molecule Fas ligand (FasL), as well as different chemotherapy compounds. These observations are consistent with glioblastoma heterogeneity between patients, and will clearly need to be taken into account in future precision or personalised therapies. Although our initial studies have been in vitro, we have moved closer to in vivo conditions by analysing many responses under conditions of limited oxygen availability that occur in vivo, i.e. hypoxia. By performing metabolic analyses of glioblastoma cells (including oxygen consumption and viability/proliferation), we identified different metabolic profiles that could be modulated with the drug metformin, a human-approved drug for diabetes that is currently under investigation for cancer therapy. We are now identifying mutational status in our glioblastoma cell lines in order to determine whether particular mutations impact on the functional responses we see.

The continued aim of all of our studies has been translational, i.e. to explore glioblastoma characteristics and mechanisms that impact on therapy responsiveness. In view of the expertise in the laboratory, and in clinical oncology research in Geneva, the focus is on immunotherapy. This is such a rapidly developing field that preclinical approaches have to correspond with new clinical opportunities. One of the most pressing clinical questions in glioblastoma immunotherapy is how to take advantage of the therapeutic power of immune checkpoint blockade based immunotherapies. Therefore, in addition to the previously described in vitro experimentation, we have also worked on designing better pre-clinical models for glioma immunotherapy. Early clinical data for immune checkpoint blockade in human glioblastoma suggested therapy resistance in most patients, which was in contrast to preclinical results in some models.

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We therefore took advantage of the SB28 glioblastoma cell line (of murine origin) that we have been investigating throughout this project, and we have made comparisons of the mutational load of this tumour, in comparison with human glioblastomas, and with the more commonly used mouse model (GL261) which provided pre-clinical data for the first clinical trials in glioblastoma with this approach.

Our results show that SB28 recapitulates the low mutational load and poor immunogenicity of human glioblastoma, and importantly, shows resistance to immune checkpoint blockade therapy in vivo, whereas the more highly mutated GL261 model is therapy responsive. These results have now been published (*Genoud et al, Oncoimmunology, 2018;7(12):e1501137. doi: 10.1080/2162402X.2018.1501137*; publication attached).

Overall, funding of this project by the *Association Frédéric Fellay* has enabled advances in two areas. First, it has highlighted the futility of immune checkpoint blockade as monotherapy for the majority of glioblastoma patients. This has guided the design of a new clinical trial starting in Geneva which will not use immune checkpoint blockade alone, but will combine it with vaccination (IMA950-106). Second, our studies have highlighted that ultimate success or failure of glioblastoma therapy occurs at the tumour site, with its very particular (and hostile) microenvironment. Therefore, future improvements in glioblastoma therapies need to further identify those local factors (which will include hypoxia) that are limiting the success rate of our currently investigated treatments.

**Professor Pierre-Yves Dietrich**
Chairman of the Department of Oncology
Full Professor

**Paul R. Walker, PhD PD MER**

clementine.debisschop@hcuge.ch | T. +41 (0)22 372 92 52 | F. +41(0)22 372 98 86 | hug-ge.ch