

Title	Development of target-specific metallodrugs
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Project description:

Although highly effective toward a number of solid tumors, platinum anticancer drugs cause severe toxic effects on normal tissues and induce the appearance of resistance phenomena. These drawbacks have stimulated an extensive search to develop alternative metal-based drugs with improved pharmacological properties and targeting different tumor-specific biomolecules (besides DNA).

By taking into consideration that the unique electronic structure of transition metals offers great versatility in tuning the properties of a given target-specific ligand, this project aims at the development of transition metal-based compounds able to target specific proteins that are over-expressed or even unique to selected cancer cell types as well as able to target specific abnormalities of certain tumor types.

The project will encompass the following steps: i) Design, synthesis and characterization of new metal-based derivatives; ii) Evaluation of target interaction at molecular level; iii) Assessment of target modulating activity and in vitro antitumor potential in selected cancer cells; iv) Investigation on cancer cell effects and signaling; v) Preliminary evaluation of the in vivo antitumor activity.

Besides primarily aimed at identifying structure-activity relationships (SARs) and selecting Lead compounds, these studies also provide mechanistic investigations for the recognition of biological and molecular determinants accounting for their antitumor activity.

Publications:

- 1 Montagner D., Fresch B., Browne K., Gandin V., Erxleben A. (2016) A Cu(II) complex targeting the translocator protein: in vitro and in vivo antitumor potential and mechanistic insights. *Chem Commun (Camb)*, 53, 134-137.
- 2 Raveendran R., Braude J.P., Wexselblatt E., Novohradsky V., Stuchlikova O., Brabec V., Gandin V., Gibson D. (2016) Pt(IV) derivatives of cisplatin and oxaliplatin with phenylbutyrate axial ligands are potent cytotoxic agents that act by several mechanisms of action. *Chem Science*, 7, 2381-2391.
- 3 Harper B.W.J., Petruzzella E., Sirota R., Faccioli F.F., Aldrich-Wright J.R., Gandin V., Gibson D. (2017) Synthesis, characterization and in vitro and in vivo anticancer activity of Pt(IV) derivatives of [Pt(1S,2S-DACH)(5,6-dimethyl-1,10-phenanthroline)]. *Dalton Trans.*, DOI: 10.1039/C7DT01054K.

Collaborations/Network:

- Dr D.Montagner, Dept. of Chemistry, National University of Ireland, Maynooth, Ireland;
- Prof. D.Gibson, The Hebrew University of Jerusalem, School of Pharmacy- Institute for Drug Research;