

Mini-project proposal

Project title: Modelling of dose-response studies for novel organometallic anticancer complexes

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Project outline:

We work on the discovery of new anticancer drugs based on transition metals such as ruthenium and osmium amongst others. We have established structure-activity relationships and successfully investigated their mechanisms of action for several years. Ruthenium arene complexes, for example, have shown a high cytotoxic activity profile in a panel of human cancer cell lines. Their mechanism of action seems to involve DNA as the primary target site, showing preference for purine bases, in particular guanines. Emerging osmium compounds are promising drug candidates which also bind to DNA. The DNA targeting of these complexes can be tuned to show a preference for guanine bases.

In addition to optimising drug design, we are fortunate to be able to carry out cell screening ourselves through collaboration with the department of Biological Sciences.

Striving to overcome current chemotherapeutic drawbacks, including the emergence of drug resistance, we plan to design cytotoxicity assays involving combinations of drugs with different mechanisms of action using our cancer cell lines.

We plan to investigate how a small selection of our complexes combines with a set of reference agents including, for instance, cisplatin, a widely-used DNA damaging anticancer agent. Specifically, we aim at establishing whether selected combinations of drugs individually acting via different mechanisms exhibit different cytotoxic effects when compared to these agents alone. Does the order in which treatments are administered have any effect on the outcome? Do we observe either significantly enhanced or reduced activity as a result of the combination?

We wish to create and validate dynamic models relating multiple dose levels and schedules to their observed levels of cytotoxicity so as to explore rapidly possible synergistic or anti-synergistic effects of combinations of two or more drugs with different mechanisms of anticancer action. The development of these models will include a phase of explorative data analysis using non-parametric fitting of the observed relative cytotoxicity levels and non-parametric testing. These will provide overall quantitative measures of evidence against a null hypothesis of no difference among the cytotoxic effects of the chosen drug combinations. A second phase of the analysis will implement statistical pharmacokinetic (PK) models, such as dynamic dose-response models, so as to provide a full probabilistic description of the relation between cytotoxicity and drug combinations.

The student will gain an appreciation of the relevance of the project, and the several factors affecting the statistical results that the data will provide. To achieve this, the student will understand the way in which the cytotoxicity data are obtained, from the preparation of the experiment, to every step of the protocol, to gaining the results and analysis of the data. Then, the student will provide original contributions for the design and validation of the aforementioned statistical models for comparing the effects of multiple dose levels and schedules of a combination of at least two drugs. The project has the potential to contribute to new cancer therapies.

References

- Bugarcic, T.; Habtemariam, A.; Stepankova, J.; Heringova, P.; Kasparkova, J.; Deeth, R. J.; Johnstone, R. D. L.; Prescimone, A.; Parkin, A.; Parsons, S.; Brabec, V.; Sadler, P. J. **The Contrasting Chemistry and Cancer Cell Cytotoxicity of Bipyridine and Bipyridinediol Ruthenium (II) Arene Complexes.** *Inorganic Chemistry*, **2008**, *47*, 11470.
- Dougan, S. J.; Habtemariam, A.; McHale, S. E.; Parsons, S.; Sadler, P. J. **Catalytic organometallic anticancer complexes.** *Proceedings of the National Academy of Sciences of the United States of America*, **2008**, *105*, 11628.
- Van Rijt, S. H.; Peacock, A. F. A.; Johnstone, R. D. L.; Parsons, S.; Sadler, P. J. **Organometallic Osmium(II) Arene Anticancer Complexes Containing Picolinate Derivatives.** *Inorganic Chemistry*, **2009**, *48*, 1753.
- Kostrohunova, H.; Florian, J.; Novakova, O.; Peacock, A. F. A.; Sadler, P. J.; Brabec, V. **DNA Interactions of Monofunctional Organometallic Osmium(II) Antitumor Complexes in Cell-Free Media.** *Journal of Medicinal Chemistry*, **2008**, *51*, 3635.
- Wakefield, J. **The Bayesian Analysis of Population Pharmacokinetic Models.** *Journal of the American Statistical Association*, **1996**, *91*, 62.
- Wakefield, J.; Bennett, J. **The Bayesian Modeling of Covariates for Population Pharmacokinetic Models.** *Journal of the American Statistical Association*, **1996**, *91*, 917.
- Wakefield, J. **An Expected Loss Approach to the Design of Dosage Regimens Via Sampling-Based Methods.** *The Statistician*, **1994**, *43*, 13.