Improving intra-tumor drug distribution of anti-cancer nanoparticles by data-informed mathematical modeling

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Project aims

The aim of this project is to develop and validate a mathematical model of the biophysics of drug transport for a nanoparticle in order to optimize its distribution properties.

Description of the project

Background

One of the major challenge in anti-cancer chemotherapy is the very high toxicity associated with cytotoxic agents (such as the folfirinox triplet in the treatment of colorectal cancer). To overcome this issue, nanoparticles conjugated with cancer cell specific antibodies are being developed that ensure delivery of the drug to the therapeutic target only. However, intra-tumor penetration of antibody nanoconjugates (ANC) properties are not fully understood and could be improved. In collaboration with a team of pharmacologists (R. Fanciullino and J. Ciccolini, SMARTc team, Inserm U_911, Marseille) experimentally developing two new ANCs, the goal of the PhD is to develop and validate against the experimental data a mathematical model of the drug penetration in order to inform on ANC parameters (size, antibody graft rate, etc...) that will ensure optimal drug delivery.

Methodology

In parallel to in vitro experiments conducted on 3D tumor spheroids, a dedicated mathematical model of intra-tumor ANC transport will be constructed to inform and optimize the development of the compound. Based on previous research efforts that developed relevant mathematical models for poroelastic description of 3D tissue [Deville et al., 2017], the PhD student will build and validate a computational model for the distribution of the nanoparticles. Mathematically, the resulting model will consist in a system of coupled partial differential equations. Numerical resolution of these equations will be performed using schemes already developed within the MONC team for resolution of such models [Deville et al., 2017].

Some biophysical parameters present in these equations are physiologically relevant and amenable to experimental determination. While several of them are already available in the literature [Jain, 1987, Welter and Rieger, 2013], some will be specific to the case of nanoparticles and to the cell line. These parameters will be directly calibrated from experimental measurements and the validity of the model will be assessed by comparing model predictions to the experimental data (see Figure 1).

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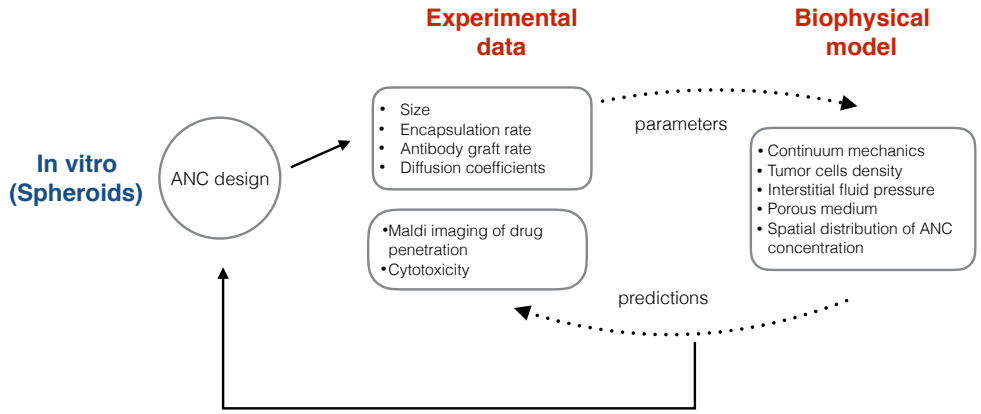

Figure 1 – Scheme of the integration between experiments and mathematical models.

Project interest and applications

The project will have direct implications in the development of this new anti-cancer agent that will be further evaluated in a phase I clinical trial.

Required knowledge and background of the candidate:

The candidate should have a strong interest for applications of mathematical modeling to concrete problems, especially in the fields of medicine and biology. He should have a knowledge of deterministic modeling tools (ordinary differential equations and partial differential equations) and numerical programming skills. Basic knowledge in cell biology is not required but will be appreciated.

References

[Deville et al., 2017] Deville, M., Natalini, R., and Poignard, C. (2017). A continuum mechanics model of enzyme-based tissue degradation in cancer therapies. *submitted*.

[Jain, 1987] Jain, R. K. (1987). Transport of molecules in the tumor interstitium: a review. *Cancer Res*, 47(12):3039–3051.

[Welter and Rieger, 2013] Welter, M. and Rieger, H. (2013). Interstitial Fluid Flow and Drug Delivery in Vascularized Tumors: A Computational Model. *PLoS ONE*, 8(8):e70395–23.