P.A.T.R.ol 4 Cure = Pseudomyxoma Angiogenesis Translational Research

Testing 4 anti-angiogenic drugs with animal models for PMP to propose a cure.

Marc Pocard - UMR 1275 Project financed by NORD association

Goal of this project: Validation of new therapeutic approaches for PMP, through animal models and use of anti-angiogenic agents.

Rationale and Objectives:
i) our laboratory is part of the European consortium "PMP4cure". In 2012 NORD funding had help us for the creation of one animal model of PMP disease (PATRoL project). We master the art of passing on animals of various human cancers, in the research Unit. This technique has been applied to rare cancers. It requires close coordination with the department of surgery to provide optimal surgical specimen and the service of pathology for validating these models. Ethical considerations are required to offer by the patient the opportunity to use tumour fragment to create models. Using that model we have demonstrated that an anti-angiogenic treatment (Bevacizumab) could control PMP growth in nude mice. We demonstrated that in case of incomplete PMP resection, Beva decrease the PMP growth. (Dohan A, Lousquy R, Eveno C, et al. Orthotopic animal model of pseudomyxoma peritonei: An in vivo model to test anti-angiogenic drug effects. Am J Pathol. 2014 Jul;184(7):1920-9.)

ii) Because of these results we have proposed to the oncologists to give for patient affected by PMP and not amenable to surgical complete cytoreductive surgery, Bevacizumab treatment. However, secondary effects are important with small bowel spontaneous perforation and more often wound healing difficulty including secondary fistula opening on old scar, resulting in gelatine evacuation trough the abdominal wall. Secondary effects are so important that we stop giving Bevacizumab in our clinical practice.

Hypothesis: However 4 different anti-angiogenic drugs exist for colon cancer (Beva, Ramucirumab, Regorafenib and Aflibercept). It is possible to test various treatment and 5FU chemotherapy in these animal PMP models.

Experiments: We planed to test for 4 different anti-angiogenic drugs effect on PMP models on: spontaneous tumor growth after graft – re evolution after incomplete cytoreductive surgery on mice – effect on wound healing using a specific animal model associating PMP and 5FU chemotherapy. Result is based on mice PCI evaluation after 4 weeks of treatment.

We have the possibility to perform MRI to follow the tumor progression on mice.
We have the possibility to evaluate angiogenesis using blood test on mice (PlGF, VEGF, Tie2, Notch etc) and DNA blood detection, to confirm anti tumor effect.
We have our model of PMP (if necessary new could be done with surgical unit collaboration) and a model offered by Pr K Flatmark from Norvay, all using human PMP grafted on nude mice.

We postulated that one of the different antiangiogenic drugs is able to control as efficient as AntiVEGFR2 (Beva) PMP pathway and affected less the wound healing, offering a chance for the patients.