($212 \pm 66.0\ L/m^2$). Serum MTP-PE concentrations declined rapidly in a biphasic manner, with a mean terminal half-life of 2.05 ± 0.40 hrs. PK variability was low (%CV for $AUC_{(0-inf)}$ and C_{max} <30%). Serum IL-6 and TNF-α concentrations increased after dosing and peaked at 4 and 2 hrs, respectively, after infusion start. CRP was elevated in all subjects at 24 hr post-infusion. Heart rate increased following L-MTP-PE infusion with a mean maximum increase of ~31 bpm, sustained 4−8 hrs postdose. Mean changes from baseline in QTcF or QTcI were negative at all time points except 0.5 hrs. Maximum negative values for ΔQTcF and ΔQTcI were −25 and −22 msec, respectively, at 6 hrs postdose. Upper bounds of the 90% two-sided confidence intervals for ΔQTcF and ΔQTcI were <10 msec, with maximal values of 6.9 and 8.6 msec 0.5 hrs postdose. Most frequent adverse events (AEs) were headache (86%), chills (71%), tachycardia (67%), nausea (52%), and pyrexia (43%), all mild-to-moderate in severity. No serious AEs or deaths were reported.

Conclusions: The PK of IV L-MTP-PE was characterized by low variability and a short serum half-life of MTP-PE. PD effects included increases in serum concentrations of IL-6, TNF-α, and CRP. The ECG effects of L-MTP-PE infusion were characterized by an increase in heart rate without prolongation of QTc interval, supporting lack of a clinically relevant effect on cardiovascular repolarization.

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Neuropilin 2 expression on T CD4+ lymphocytes phenotypic study

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Background: The immune system is the only body protection against tumor development. There are 3 cell types involved: dendritic cells (DC), effector T cells and regulatory T cells. As cancer symptoms are detected, tumor immunosurveillance already failed. Neuropilins (Nrp)1 and 2 are transmembrane glycoproteins with no tyrosin kinase activity. They are involved in both axonal and vascular guidance. Nrp2 has been described on DC, but not T cells, unlike Nrp1. Nrp2 has ongenic properties. It enhances cell proliferation and survival through the Akt pathway. Nrp2 interacts with cytoskeleton connectors such as plexins. It may also be involved in TGFβ1 conversion. Those properties suggest Nrp2 as a potential interesting molecule regarding immunity. We were interested in Nrp2 expression on T cells and its involvement in anti-tumor immune response.

Material and method: We used C57Bl/6 ($H\text{-}2^b$) male mice for *in vivo* experiments and to get splenocytes, B16 cells that are human melanoma cells, and EL4 cells that are murin thymoma cells. Humain lymphocytes were obtained from healthy volunteers or humain blood cord. Anti-CD3/CD28 beads, conavaline A and PMA ionomycin were used to activate lymphocytes. Cellular sort kits provided sorted lymphocytes. Cells and molecules were identified thanks to flow cytometry and/or western blotting, and confocal microscopy. si RNA were used via transfection and transduction (lentiviral systems) to obtain no Nrp2 expressing or 100% Nrp2 expressing cells.

Results: We observed that blood cord resting CD4+CD25+ T cells express more Nrp2 than other resting T cells. It was also the case of activated T cells. Tumor environment effect on Nrp2 expression was assessed *in vivo*. Nrp2+ T cells were present in draining lymph node and within the tumor. To develop the previous observation, we cocultured murine splenic T cells with B16 or B16 supernatant. B16 supernatant, even diluted, was efficient enough to increase Nrp2 expression by T cells. In the next stage we used EL4 CD3+CD4+ tumor T cell line to assess Nrp2 repression and its consequences with siRNA technology. We first followed immunological synapse between T cells and DC. We demonstrated that DC-EL4 junctions and actin relocalisation were thiner if EL4 expressed Nrp2. Our next step will focus on hematopoïetic reconstitution with or without Nrp2, and tumor growth in Nrp2 T cells depleted mice. Nrp2 is implicated in TGFβ1 conversion on tumor cell lines, as suggested by its homology with Nrp1, and TGFβ1 ELISA tests are ongoing in different conditions of activated lymphocytes. Nrp2 PCR are ongoing to confirm those results too.

Conclusions: Finally, Nrp2 is an interesting molecule regarding T cells regulation, and anti-tumor immunosurveillance. Its implication in DC-EL4 junction, and possibly in TGFβ1 conversion could make Nrp2 a good tool for immunomodulation.

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Intratumoral and serum interleukin-4 levels in prostate adenocarcinoma

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Background: Interleukin-4 (IL-4) is a pleiotropic cytokine that has been implicated in the aetiopathogenesis of several cancers. Pre-clinical studies in prostate cancer (PC) strongly suggest that IL-4 plays a key role in transition to androgen independence. To test clinical correlation, we have analysed IL-4 levels in serum and in prostate tissue.

Material and Methods: Serum samples were taken from patients with radically-treatable ($n = 30$), androgen sensitive (AS; $n = 29$) and androgen resistant (AR; $n = 30$) PC. Control patients had confirmed benign prostatic hypertrophy ($n = 23$). Serum IL-4 was measured using an ultra-sensitive enzyme-linked immunosorbent assay in a single setting, to minimise inter-assay variation. Since data were not normally distributed, comparison was made using the Kruskal Wallis Test. Frozen blocks from 14 radical prostatectomies performed for PC were sectioned and stained using haematoxylin and eosin. Immunohistochemical (IHC) staining of validated 5μm sections was performed with rabbit anti-human IL-4 IgG, using an Envision™ System. Staining protocols were optimised using IL-4 transfected cells and tonsil. The study protocol was approved by the Guy's and St Thomas' Research Ethics committee.

Results: Median serum IL-4 concentrations were 0.16pg/ml for radical patients, 0.20pg/ml for AS patients, 0.32pg/ml for AR patients and 0.31pg/ml for benign patients. Serum IL-4 was significantly lower in radical patients compared to others combined ($p = 0.009$). Immunohistochemistry revealed greater intensity of IL-4 expression within malignant compared to benign prostate tissue (Figure). Furthermore, IL-4 staining was diffusely found throughout the cytoplasm in malignant epithelium but focally in the apical/peri-nuclear cytoplasm of benign luminal epithelium.

Conclusion: In our series (the largest reported to date), consistent differences in intensity and distribution of IHC staining between malignant and benign tissue were observed. However, these differences were not reflected in serum IL-4 levels, at variance with smaller published data sets. These data emphasize the importance of analysing low level and labile cytokines such as IL-4 in the primary site of disease and are consistent with a role for IL-4 in prostate cancer.

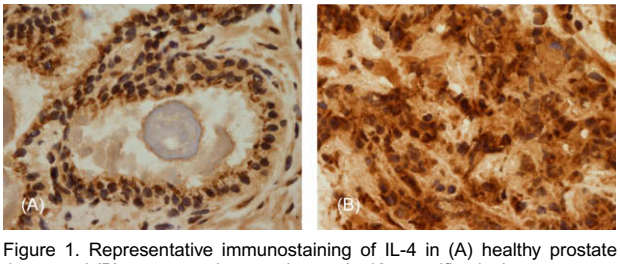

Figure 1. Representative immunostaining of IL-4 in (A) healthy prostate tissue and (B) prostate adenocarcinoma (×40 magnification).