

**Presentation:**

Toll-like Receptors and Cancer

**Speaker:**

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**Abstract:**

DNA and RNA from both microbes and damaged host cells can be recognized by the immune system. Specialized receptors such as Toll-like receptors (TLR) and helicases sense nucleic acids as a "danger" signal and trigger a potent type-I interferon and cytokine response. The specificity of the signal relies on the cellular and intra-cellular distribution of the receptors, particular motifs and structures within the nucleic acids, as well as the existence of "chaperone" systems such as antibody-nucleic acid complexes. The endosomal receptor TLR9 can be stimulated by synthetic single stranded DNA oligodeoxynucleotides containing CpG motifs. Stimulating the immune system using TLR9 agonists has broad prophylactic and therapeutic applications. In particular, the TLR9 agonist PF-3512676 has shown potent activity in mouse tumor models when used as monotherapy. Interestingly, its activity is even enhanced when combined with the chemotherapeutic drug paclitaxel, and the anti-tumor effect of the combination requires CD8 T cells. We therefore focused our investigations on the effects of paclitaxel on the immune system, and in particular on regulatory T cells (Treg). We found that paclitaxel could decrease the numbers of Treg in mice, although it also depleted other T cells. However, paclitaxel preferentially affected the cycling fraction of Treg, which is more important than in other T cells at the steady state. Furthermore, after paclitaxel treatment, the remaining Treg showed decreased Foxp3 expression and inhibitory function. However, in the EL-4-ovalbumin tumor model, paclitaxel treatment did not enhance the frequency of tumor-antigen specific cytotoxic CD8 T cells induced by PF-3512676 in the periphery. A higher frequency of tumor-antigen specific CD8 T cells was nevertheless found within the tumor in mice treated with paclitaxel, together with a higher proportion of CD62L<sup>lo</sup> cells in spleen. These results suggest that chemotherapeutic drugs and TLR9 agonists may cooperate in complex and still poorly understood immune networks. In the clinic, PF-3512676 is being investigated for cancer treatment, in particular in association with chemotherapy. Results of a phase II study in NSCLC are presented.