Colorectal cancer (CRC) is the type of cancer with one of the highest incidences worldwide. Despite improvements in treatment strategies, the prognosis of patients with the spread of cancer cells into other organs than the original remains poor. Thus, novel therapeutic approaches focus on identifying factors inhibiting cancer cell spread. Platelets, small cells circulating in the blood, are key players in many physiological processes and pathological states, including cancer. Activated platelets release extracellular vesicles (EVs called platelet-derived microparticles; PMPs), which, due to their small sizes, can reach sites that can extend beyond the typical platelets' reach example, lymphatic vessels to facilitate tumor progression and metastasis. PMPs are the most abundant microparticles present in the blood, and their number is increased in cancer patients Cancer cells release the cancer-extracellular vesicles (for CRC; CRC-EVs), which platelets could incorporate to form so-called tumor "educated" platelets (TEP), which can contribute to metastatic incidents. Cancer cells communicate with platelets by stimulating them to release PMPs and, in turn, take the vesicles up. PMPs can be taken up by cancer cells to transfer their cargo or signals and change their properties. PMPs are mostly believed to be "bad" players that facilitate cancer progression and metastasis, but they can be altered to become a "good" weapon. Increasing interest is focused on the engineering of the blood cells (platelets, red blood cells) to deliver the therapeutic component at the specific site of interest. PMPs formed from such engineered platelets can be even more effective in carrying factors to cells located in places physically not available for platelets.

In the proposed project, we want to establish how to modify the incorporation of PMPs and CRC-EVs into cancer cells and platelets, respectively, to decrease CRC progression. We will also address the possibility of using PMPs as a carrier of antibodies used in immunotherapy that is known to suppress metastasis. We will verify our hypothesis by answering the following questions:

1. Can we modulate the uptake of PMPs or CRC-EVs by cells using inhibitors, and whether blocking of EVs uptake inhibit metastasis in mouse models of CRC?
2. Whether the antibodies used in immunotherapy, conjugated with platelets and released on PMPs, will bind to colorectal cancer cells. Moreover, we are also asking whether these antibodies conjugated with platelets can reduce the recurrence and metastasis of CRC.

Our work plan for part 1 of the project comprises *in vitro* and *in vivo* studies. We will use a panel of CRC cell lines of various phenotypes. We will use the different inhibitors to study the incorporation of PMPs or CRC-EVs. Then, we plan to evaluate which pathway of PMP uptake by CRC should be inhibited to diminish cancer cells' metastasis potential. This *in vitro* part of the study will also serve as background for *in vivo* study in the xenograft mouse model of colorectal cancer.

For part 2, we also plan *in vitro* and *in vivo* studies. We will prepare the platelets with conjugated anti-PD-L1 antibodies and verify their effectiveness in the mouse model of CRC. We believe our results may shed some light on the new potential anti-cancer therapy based on the,,good face" of the platelets and PMPs effect.