FL-118 Executive Summary

FL-118 has been in research and development for over ten years at Roswell Park and has demonstrated unprecedented promise to be an effective precision, targeted medicine for late stage metastatic pancreatic cancers and other cancers such as head and neck, and colorectal. The drug's development priority has been on solving the primary shortfalls inherent with available FDA approved chemotherapy drugs for advanced and aggressive metastatic pancreatic cancer, specifically acquired cancer drug treatment resistance, patient over-toxicity and treatment failure.

Pancreatic cancer is known for its agility to mutate as it metastasizes. These metastases are characterized by damaged genes producing greater or lesser amounts of particular proteins that help the damaged cells survive. The result is cancer cells that are unable to die through a natural cell death process called apoptosis. FL-118 is designed to target these proteins that prevent or inhibit apoptosis. Simply put, FL-118 restores this death process so that cancer cells can die through apoptosis. This is accomplished through the regulation of the cancer gene transcriptional and post-transcriptional process for expression of proteins or regulation of protein stability (i.e. the inhibition of oncogenic proteins or enhancement of tumor suppressor proteins in the transcriptional level, mRNA level, and/or protein levels.)

The more aggressive the cancer has become, the more anti-cancer cell death proteins FL-118 has to target and the better the drug works. In fact, extensive laboratory testing over these past years using only FL-118 without anything else, has confirmed the total elimination of treatment-resistant human pancreatic tumors in certain animal model cases. In this regard, the tumor suppressor protein p53 has been found to be at the core of this treatment resistance. Indeed, p53 is called the guardian of the human genome and when the p53 gene is turned off in cancer cells, cancer cells will be free to proliferate without anything to stop or control it. In highly aggressive cancers with many cancer-associated gene mutations, p53 is known to be either non-existent (null expression) or dysfunctional (non-functional p53 protein).

FL-118 has been confirmed to activate p53, independent of ATM (Ataxia-Telangiectasia Mutated protein kinase). What this means is that FL-118 is able to effectively bypass the ATM-controlled p53 pathway. This uniqueness may be associated with the fact that without p53, FL-118 is more effective at killing cancer cells. Furthermore, FL-118 is able to effectively bypass typical drug treatment resistance resulting from overexpression of the drug-efflux pump proteins ABCG2/BCRP (Breast Cancer Resistant Protein) and Pgp/MDR1 (Multi-Drug Resistant Protein 1), which transport drugs through the cell membrane and out of the cancer cell. This is why FL-118 accumulates in human tumor tissue after oral administration in animal models. Therefore, FL-118 is effective against late-stage cancers, which have a dysfunctional or nullified p53 and have become resistant to DNA-damage drug treatments such as chemotherapy. Furthermore, FL-118 effectively inhibits the expression of ERCC6 proteins which are used by cancer cells to repair their own damaged DNA to prevent their death due to DNA damage.

Chemotherapy “targets” fast growing cells that are characteristic of cancer. But there are many normal cells in the body that are also fast growing and chemotherapy cannot properly discriminate between fast growing cancer cells and fast growing normal cells. Therefore, chemotherapy toxicity to normal cells can limit the dosages and cycles that can be given to many patients. Additionally chemotherapy is also unable to kill quiescent (dormant or not growing) cancer cells, an example being the Cancer Stem Cell (CSC). However, FL-118 targets multiple cancer-associated specific gene proteins that cancer cells use to prevent apoptosis, namely survivin, mcl-1, XIAP, cIAP1, and MdM4. In cancer cells these proteins exist quite differently from normal cells (low or negative). Thus, FL-118 can selectively kill both growing and quiescent cancer cells, while exhibiting minimal toxic effects on normal cells and tissues. This is consistent with the findings from oral administration of FL-118 in dogs; even at the maximum tolerated dose (MTD), FL-118 was well tolerated. There has been no significant body weight loss and no other relevant clinical observations to report. In short, FL-118 is relatively safe and is now going to enter formal clinical trials in CY 2020.

Most current pancreatic cancer treatments seem to eventually fail because they are unable to adequately kill cancer stem cells which often develop into metastatic tumors. Survivin, a protein, is known to be expressed across most tumor cell types, but is rarely present in normal, non-malignant adult cells. By knocking out survivin, microtubule formation is disrupted, massive apoptosis results and stem cells are unable to form spheres. This means that treatment with FL-118 is envisioned to be significantly longer lasting than existing treatments and potentially even a cure. Of note is that even if FL-118 is unable to permanently eradicate all the cancer cells, it could turn a terminal disease into a chronic managed disease.

In the laboratory, FL-118 has demonstrated high effectiveness for colorectal, head and neck and pancreatic cancer tumors in vitro and in-vivo. One final note, while FL-118 is intended to be a monotherapy for late stage pancreatic cancer, lab testing has indicated that some pancreatic cancer tumors without the target dysfunctional genes exhibit much less sensitivity to the drug. In this case, FL-118 in combination with a pancreatic cancer chemotherapy drug such as gemcitabine will be needed. In fact, lab testing has validated that some tumors that are not sensitive to either FL-118 or chemo monotherapy, become highly sensitized when the two treatments are used in a combination protocol.