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Eltrombopag as first line treatment for acute radiation syndrome

Yuhchyau Chen, Jane Liesveld, Lin Gan and David Wu James P. Wilmot Cancer Center, USA In the event of nuclear terrorism, nuclear warfare or nuclear power plant accidents, there is a critically unmet need in the treatment of life threatening bone marrow suppression as part of the Acute Radiation Syndrome (ARS). Thrombocytopenia and associated bleeding after acute radiation exposure is often lethal. Currently no safe and effective thrombopoietic agents exist for ARS. The only treatment for thrombocytopenia is through frequent platelet transfusions. In mass radionuclear incidents, our nation's supply of fresh platelets will be threatened and depleted rapidly.

Eltrombopag (Eltrombopag olamine, SB-497115-GR), an oral thrombopoietic agent and a TPO non-peptide mimetic holds great promise in post-radiation bone marrow recovery. It is a small molecule and an oral thrombopoietic factor that acts as a thrombopoietin-receptor (*c-mpl*) agonist. *In vitro*, it stimulates the growth of TPO-dependent cell lines via JAK2 and STAT signaling pathways and stimulates isolated human CD34+ (stem/primitive progenitor) cells to become megakaryocytes and produce platelets. The drug interacts with the transmembrane (TM) domain of the TPO receptor *c-mpl* and induces proliferation and differentiation of megakaryocytes, thus increasing platelet production. Ex vivo experiments with platelets from humans, and *in vivo* studies of healthy subjects, have shown that treatment with eltrombopag does not adversely affect platelet function The most frequent drug-related adverse events are all of low grade severity, including dry mouth, headache, abdominal pain and nausea.

Eltrombopag has been approved by FDA for the treatment of idiopathic thrombocytopenic purpura (ITP). Pre-clinical investigation models for testing eltrombopag in rescuing ARS are limited due to strict species specificity of the drug to only humans and chimpanzees. We present our study design and the process towards the development of eltrombopag for ARS countermeasure.