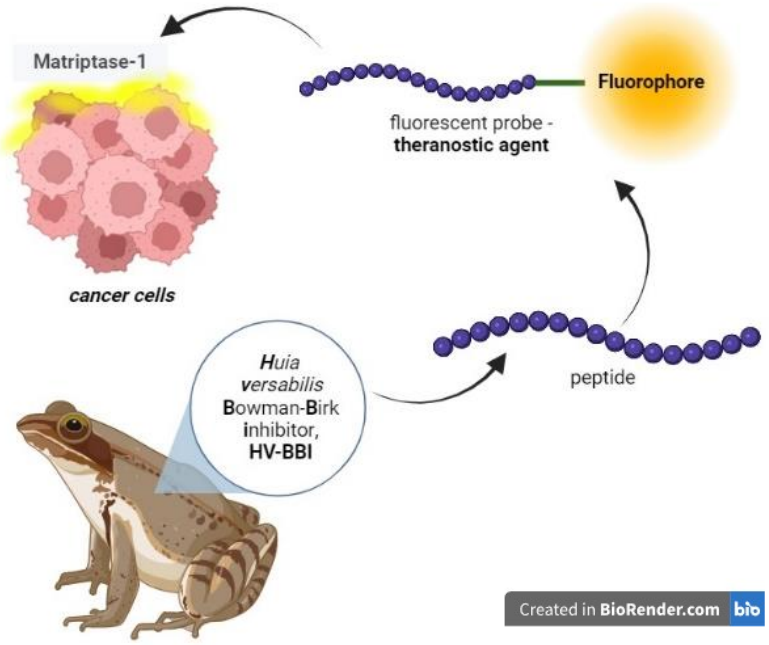

Each of many biochemical reactions essential for cell life is catalyzed by a unique protein. These proteins are enzymes and they catalyze or speed up biochemical reactions. Enzymes are involved in numerous biochemical processes like food digestion, breakdown of toxic, foreign substances, repair of damages etc. Proteases are involved in proteins and peptides degradation to deliver the stock of free amino acids to synthesize another proteins. This activity may be easily associated with digestion process, but peptidases play significant roles in numerous other physiological procedures, such as blood coagulation, iron absorption, activation of growth factors, but also pathological states such as cancer progression. Since enzymes are involved in such important facets of cellular life it is important to control their activity, to maintain the stable state of organism. The activity of enzyme can be physiologically downregulated (by inhibitors) or upregulated, according to the accurate metabolic needs of cell. Inhibitors are important tools to control proteases activity in case of abnormal activity.

The main object of interest in this project is matriptase-1 (MT1) belonging to the type II transmembrane serine proteases (TTSPs) and sharing significant structural similarity with matriptase-2 (MT2). In healthy organism, MT1 is primarily expressed on the surface of various epithelial cells and affects the formation and integrity of epithelial tissues. MT1 is also involved in epithelial-derived cancers, including breast, prostate and ovary and its increased MT1 activity often correlates with poor disease prognosis.

The main purpose of this project is to find highly potent and selective peptidic inhibitor of MT1. This task is particularly challenging, due to close resemblance to its structural “twin” MT2, which is a regulator of iron homeostasis and its presence was not detected in case of malignant tumors but rather these correlated with good prognosis. The problem in finding selective inhibitors of these two enzymes is reflected in limited number of papers reporting such compounds. Both enzymes share very similar structure and, thus, very similar preferences for substrates and inhibitors.

Our group has wide and long experience in developing inhibitors of various proteases. Recently our attention was drawn by peptide isolated from skin of Bamboo Leaf Odorous frog, *Huia versabilis*, (*Huia versabilis* Bowman-Birk inhibitor, HV-BBI). Its shortened analog turned out to be very strong MT1 inhibitor, with about 1000-fold selectivity for MT1 over MT2. These are preliminary, unpublished data and our project assumes further assay and development of new series of such strong inhibitors of this protease. Our experimental work will be supported by computing assay performed by group of Prof. Boudreault from University of Sherbrooke in Canada. Beside examination of inhibitory activity of synthesized compounds we plan to assess their resistance to digestion by ubiquitous proteases, as well as to reductive environment and improve these attributes when necessary.

Inhibitors characterized by best qualities, i.e. strong inhibition of MT1 over other proteases, high stability in serum and resistance to reductive environment will be further transformed into fluorescent probes combining possibility of detecting MT1, allowing monitoring its bio-distribution simultaneously inhibiting its activity. Development of such fluorescent probes is exceptionally important both for diagnosis and treatment of particular cancers.