

**Projekt: Discovery of new leads modulating voltage gated potassium ion channels as emerging cancer targets**

**Trajanje projekta:** 2017 - 2020

**Koordinator:** University: KU Leuven, Pharmaceutical and Pharmacological Sciences (prof. dr. Jan Tytgat)

**Vodja projekta na UL FFA:** prof. dr. Lucija Peterlin Mašič

### **Povzetek projekta:**

Rak ostaja glavni razlog obolevnosti, smrtnosti in ekonomskih izgub na svetu. Uporaba konvencionalnih protitumornih učinkovin je pogosto omejena zaradi številnih neželenih učinkov in razvoja rezistence. Napetostno odvisni kalijevi ionski kanali so bili obsežno preučevani v povezavi z ekscitabilnostjo celic, nedavno pa je bila dokazana njihova vloga v specifičnih funkcijah kot so proliferacija, angiogeneza in celična migracija. Ether-à-go-go-1 (hEag1, Kv10.1, KCNH1) je predstavnik napetostno odvisnih kalijevih kanalov in je prvi ionski kanal, ki so ga povezali z onkogenezo in razvojem tumorjev. Ciljanje kalijevih kanalov hEag1 predstavlja novo terapevtsko strategijo iskanja novih protirakavih učinkovin. Znanstveni cilj predlaganega Projekta je priprava novih protirakavih spojin vodnic in validacija ter modulacija rakave tarče hEag1 s potencialom za zdravljenje ne-Hodgkinovega limfoma. Predlagani Projekt pokriva celoten cikel zgodnjega odkrivanja novih učinkovin: molekulsko modeliranje, sintezo, testiranje na ionskih kanalih ter platformo za protitumorno vrednotenje novih učinkovin. Koordinator projekta je prof. dr. Jan Tytgat, KU Leuven, Pharmaceutical and Pharmacological Sciences, Toxicology and Pharmacology, vodja projekta UL FFA je prof. dr. Lucija Peterlin Mašič.

### **Project summary:**

Cancer remains an important cause of mortality and economic losses worldwide. Conventional cancer therapies are often limited by severe side effects and resistance development. For an improved cancer therapy approach, a permanent need for the discovery of new-generation, refined anticancer agents is needed, as well as the elucidation of novel cancer targets.

This project will focus on the genetic, biological and chemical data available in cancer research of selected cancer types, and forward this knowledge into the design and synthesis of new leads for emerging 'drug-able' cancer targets, in particular the voltage gated potassium ion channels human Ether-à-go-go-1 (hEag1) and human Shaker-type 1.3 (hKv1.3), for the treatment of non-Hodgkin lymphomas and solid tumours.

It is generally known that Kv1.3 channels regulate the membrane potential of human T lymphocytes and provide the electrochemical driving force for Ca<sup>2+</sup> influx, which is necessary for important downstream effector functions such as cytokine production and proliferation, often implicated in the development of cancer.

The Eag1 channel is also a member of the voltage gated potassium channel family (but not Shaker-type) and is expressed mainly in the brain, at low levels in placenta, testis and adrenal gland, and only transiently in myoblasts. Recently, several studies have suggested that Eag1 is selectively expressed in various tumour tissues: Eag1 plays important roles in cancer proliferation, malignant

transformation, invasion, metastasis, recurrence, and prognosis. Therefore, it has become a new molecular target for tumour diagnosis, prognosis evaluation, and cancer-targeted therapy. The aim of this CELSA project will thus be to develop new selective and high affinity small molecule modulators for the emerging cancer targets hKv1.3 and hEag1, using drug-design methods with the aid of new homology models of human Kv1.3 and Eag1 channels.

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