Univerza v Ljubljani

CELSA
Central Europe Leuven Strategic Alliance

Project: Exploiting structural insights in IP3 receptor function to develop novel, allosteric inhibitors of IP3 receptor channels (SINFONIC)

Duration: 1 Oct 2023 – 30 Sept 2025

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Project summary:

IP3 receptors (IP3Rs) are a class of ion channels, i.e. proteins that flux ions across cellular membranes. IP3Rs mediate the release of calcium ions (Ca2+) from the endoplasmic reticulum, the main intracellular Ca2+ store, thereby fulfilling key functions critical for cell physiology. Deregulation of these channels including excessive IP3R activity has been implicated in a plethora of diseases. For instance, several cancer cells appear addicted to IP3Rs for their survival. Unfortunately, our arsenal of tools to selectively inhibit IP3R function in living cells and cell systems is outdated and heavily relies on (natural) products that also impact several other Ca2+-transport systems, thereby limiting cell biological studies as well as hampering therapeutic translation of such tools. Through this project integrating very recent insights in IP3R structure & modulation, we aim to change this and therefore have the ambition to develop the first in-class IP3R inhibitors. We believe the time is ready to tackle this problem. First, recent structural studies revealed unique regions in IP3Rs key for channel opening. Second, molecular studies revealed that exactly those regions are targeted by IP3R-accessory proteins (such as anti-apoptotic Bcl-2 proteins) that inhibit channel opening. These insights now pave the path for the first rational design of specific, allosteric IP3R inhibitors tailored towards targeting these exact regions important for IP3R-channel opening. These tools will not only be invaluable to advance IP3R research in cell biology but may also serve as lead compounds to target excessive IP3R-channel function driving pathogenesis. The KU Leuven and University of Ljubljana partners have complementary expertise in IP3Rs, protein interactions & Ca2+ signaling and computer-aided drug design to target ion channels, respectively. They will join forces to tackle this problem and to develop a novel and unprecedented set of IP3R-inhibitory small molecules.

Web page: Research Portal - Exploiting structural insights in IP3 receptor function to develop novel, allosteric inhibitors of IP3 receptor channels (SINFONIC) (kuleuven.be)