Univerza v Ljubljani
Medicinska fakulteta

Javna agencija za raziskovalno dejavnost Republike Slovenije

Research project N1-0066

Development of novel estrone derivatives for targeted intracrine modulation of estrogen biosynthesis and transport

Principal Investigator: Katja Kristan

Funding: 1. 11. 2017 – 31. 10. 2020

Project group: SICRIS

Project description:

Hormone-dependent cancers include breast, endometrial and ovarian cancers and comprise more than 35% of all cancers in women. Breast cancer is the most common type of cancer in women, while endometrial and ovarian cancers represent the most frequent gynecological cancer and the most deadly hormone-dependent cancer, respectively. The enormous numbers of patients and deaths that are attributed to these hormone-dependent diseases demonstrate the uttermost importance of novel therapeutic strategies. Estrogen-dependent receptor-mediated cell proliferation associated with increased number of mutations is the generally accepted mechanism associated with development of estrogen-dependent cancers. Breast, endometrial and ovarian cancers predominately affect women after the menopause, when estrogen synthesis occurs in peripheral tissue. Estrogen biosynthetic enzymes control occupancy and activation of corresponding estrogen receptors and represent important targets for development of selective intracrine modulators (SIM). The current estrogen depriving therapies are not optimal and lead to estrogen-refractory disease. The novel strategies including combinations of SIM or dual inhibitors of estrogen biosynthetic enzymes and SERM are needed to improve the success of cancer therapy. The project will investigate steroid based compounds synthetized in the collaborating group of Dr. Erzsébet Mernyák from Department of Organic Chemistry, University of Szeged, Hungary, as potential SIM. We will use recombinant enzymes, and model cell lines of hormone-dependent cancers together with state-of-the-art approaches for investigation of cellular proliferation, invasion and migration in real time. The aims of the project are to examine effects of these compounds: i) on recombinant enzymes HSD17B1 and AKR1C3 and off target enzyme HSD17B2; ii) on biosynthesis of active estrogens in model cell lines of breast cancer, endometrial cancer and ovarian cancer and iii) on proliferation, invasion and migration of model cell lines in real time. The project will join expertise of the collaborative group in organic chemistry and particularly steroid synthesis with expertise of the group from UL MF in molecular endocrinology and in the steroid biosynthesis and action.

Bibliography: SICRIS