POPULAR SCIENTIFIC SUMMARY

Phototoxicity is the most common type of skin-related adverse drug reactions. It is defined as an acute, light-induced, non-immune toxic reaction following skin exposure to a photosensitizing compound, either topically or systemically. Symptoms of drug-induced phototoxicity usually appear up to several hours after exposure to sunlight and include erythema, swelling, blisters, exudation, peeling, burning, itching, and hyperpigmentation of the skin. Currently, the number of photosensitization cases is constantly increasing. The reasons for this can be found in excessive exposure to sunlight, dictated by the aesthetic value of a tan, as well as the increasing number of photosensitizing substances in food, dietary supplements, as well as pharmaceutical and cosmetic products. The risk of phototoxic reactions concerns several hundred currently used drugs including antibiotics, chemotherapeutics, nonsteroidal anti-inflammatory drugs, drugs used in the pharmacotherapy of cardiovascular diseases (diuretics, antiarrhythmics, antihypertensive drugs), drugs acting on the central nervous system (neuroleptics, antidepressants), antidiabetic and anticancer drugs.

Studies of drug phototoxicity are an important part of the safety assessment of medicinal products. Nowadays, the 3T3 Neutral Red Uptake (3T3 NRU) test is the most recommended and appropriate *in vitro* method to assess phototoxic potential. Although this test detects phototoxic properties of an evaluated substance, however, it has some serious limitations. The recommendation to use UVB filters is one of them. Moreover, the 3T3 NRU test does not determine the cellular, molecular and biochemical mechanisms and effects of the phototoxic action accurately. It also does not take into account the role of melanin biopolymers that can take part in phototoxic reactions. Melanin protects cells against the harmful effects of UV radiation and neutralizes free radicals. Besides, due to the formation of complexes with drugs, melanin affects their efficacy, and also their toxicity as well as the occurrence of adverse reactions.

The purpose of the project is the development of an entirely innovative *in vitro* model for the assessment of phototoxicity of drugs with different affinity to melanin using a sunlight simulator. The model will involve factors occurring *in vivo*, like the presence of melanin biopolymers and the exposure to reproduced natural sunlight radiation. The developed model will involve for the first time human normal cell lines of the skin with different content of melanin.

The project involves investigations of selected phototoxic drugs with different affinity for melanin biopolymers, e.g. fluoroquinolones, tetracyclines, psoralens, and nonsteroidal anti-inflammatory drugs. The pharmacological and cytotoxic properties of these drugs will be evaluated and taken into account due to a potential role in the development of phototoxic reactions. The research will be carried out with the use of normal human skin cells with different content of melanin biopolymers, i.e., human dermal fibroblasts, human epidermal melanocytes lightly pigmented and darkly pigmented. The multi-directional experimental panel will involve studies of the mechanisms of cytotoxic and phototoxic effects at the cellular, molecular, and biochemical levels. Detailed researches will be related to the evaluation of oxidative stress, inflammation, and the process of melanogenesis. The planned experiments and analyzes will be carried out using the various advanced laboratory techniques: image cytometry, fluorescence wide-field, and confocal microscopy, colorimetric and fluorimetric tests, RT-qPCR, western blot, and immunoenzymatic assays ELISA.

The assumptions and goals of the project involve the complexity of the pathophysiological basis of phototoxicity as well as multi-directional studies leading to the assessment of the risk of the cutaneous adverse effect. The innovation of a new model includes the use of differently pigmented cells, irradiation with the advanced sunlight simulator, and concerning multidirectional aspects of pharmacological properties of drugs. The new elements introduced to the model of phototoxicity assessment will cause the test to reflect a lot of *in vivo* conditions to a greater extent. Moreover, the proposed comprehensive experimental panel will allow for the first time elucidation of the role of melanin and the mechanisms of phototoxicity. Besides, the project will expand the current state of knowledge of the character and properties of the phototoxic reaction itself. Analysis of cytotoxicity and phototoxicity will help to identify the causes of skin adverse effects during therapy with drugs binding to melanin.