Constant stress and exposure to the harmful effects of environmental factors is an integral part of the modern world. All of those stressors have a negative impact on our skin, what may lead to acne, eczema, rosacea, psoriasis, alopecia, vitiligo and other related skin problems. The first line of defense, which is always ready and prepared to defend the body from environmental factors and function as a barrier between you and the outside world, is skin. The second line of defense are the molecular mechanisms through which stress-induced response intend to counteract the stressor and re-establish body's homeostasis. The hypothalamic-pituitary- adrenal (HPA) axis is our central and fundamental stress response system. We now know that skin posses its own local analog of HPA axis (sHPA), which may be activated by such factors as UV light. It is also well known, that UVB radiation stimulates the production of vitamin $D_3$, but the role of vitamin $D_3$ in the regulation of cutaneous stress response is still poorly understood.

Our preliminary studies showed that vitamin $D_3$ effectively activate the expression of sHPA elements in skin cells (kerationocytes), and therefore may play an important regulatory function not only in the stress response, but also in maintaining the barrier function of the skin. However, the molecular mechanisms through which vitamin $D_3$ acts on the sHPA axis remain unidentified and therefore it is very interesting to investigate this cross-talk a bit more deeply. As most of the cellular effects of vitamin $D_3$ (like induction of epidermal differentiation or formation the permeability barrier) is regulated by the transcription activity of VDR, we would like to investigate the role of VDR and its coactivators (DRIP and SRC) in the expression of sHPA axis elements in keratinocytes. The main part of the project involves silencing gene expression of VDR and its coactivators by siRNA interference technique, which enable us determine their potential role in stimulation sHPA axis by vitamin $D_3$.

We believe that results obtained from this proposal will contribute to our understanding of impact of vitamin $D_3$ on the expression of neuropeptides and their receptors, but also its potential significance in pathogenesis of various skin diseases and development of effective therapies. It is essential to develop more effective therapies to decrease the incidence, alleviate the symptoms and consequences of skin disorders to improve the quality of our lives.