As proposed in our project we continued our research on the hypothesis that abnormal keratinocyte functions are essential part of psoriasis pathomechanism and other skin resident cells (such as fibroblasts) may contribute to disease development by providing an abnormal matrix and cytokine milieu for keratinocytes. Numerous data suggest that the normal looking skin of psoriatic patients (non-lesional skin) differ from the normal looking skin of healthy individuals. Our research focuses on determining those differences that are essential in making the psoriatic non-lesional skin prone to develop and perhaps maintain the the psoriatic lesional phenotype. While working on these tasks we had to investigate so far unknown basic mechanisms regarding resident skin cells (mainly keratinocytes and fibroblasts).

In our present OTKA proposal we set four major aims.In AIM I we investigated keratinocyte cell cycle regulation, our findings is finally published in a paper accepted last fall and appeared in **Experimental Cell Research {347 (2019) 290-303}.**

In AIM II we worked on finding the potential regulatory problems behind the previously described fibronectin (FN) and oncofoetal fibronectin (EDA+FN) altered expression in the psoriatic non-lesional skin. Results of these investigations were published in the **British Journal of Dermatology {174 (2016) 533-541}.**

In AIM III Our aim was to investigate upstream regulatory molecules that may contribute to the molecular differences of healthy and psoriatic non-involved skin. *In silico* analysis was performed on previously identified 58 genes that show different gene expression and cytokine induction responses in healthy and psoriatic non-lesional epithelium (Szabó *et al*, 2014). First we focused on regulatory factors predicted to regulate most of the investigated genes (TCF3, SP1, FOX04, ELK1, MAZ, AP1, ZEB1, NFkB, BACH2, CHX10, ETS2, PITX2, SRY). Further bioinformatic screening has been used to select particular transcription factors, in particular AP-1 (c-Jun), which typically regulates the group of genes involved in the immune response (IL-23A, IL-6, IL-10, MMP9, LIFR); and FOXO4, which is associated with the set of genes involved in the construction and maintenance of homeostasis of the extracellular matrix (FN1, LAMC2, BAMBI, INHBA, ABLIM3). Although previously performed ChIP-Seq data sets clearly suggest the regulatory role of c-Jun and FOXO4 on the investigated gene set, the selected transcription factors have not been studied in primary cells and/or in the psoriasis sample, therefore we will perform ChIP on epithelial and fibroblast cells from healthy and psoriatic skin samples followed by Q-PCR to validate the interaction between the selected transcription factors and the promoter regions this part of our project is not completed yet, but we anticipate its completion soon and have ordered all materials needed.

In AIM IV we were interested to see whether patients with psoriasis would have enhanced anti-alfa6 integrin antibodies present in their sera as a reflection of their abnormal dermo-epidermal extracellular matrix structure. Previous studies on non-lesional and lesional psoriatic skin described basement membrane alterations in the disease. We completed this part of the study and published the results in the **Journal of Dermatology {44 (2017) 370-374}.**

While we worked on our proposed AIMs we participated in some other project-related studies. Our international collaboration studies resulted in two papers on pustular psoriasis (AP1S3 mutations cause skin autoinflammation by disrupting keratinocyte autophagy and up-regulating IL-36 production **J Invest Dermatol 136 (2016) 2251-2259** and Clinical and genetic differences between pustular psoriasis subtypes **J Allergy Clin Immunol** in press).

Small contributions were also made in other projects related to psoriasis pathomechanisms. Results of these are published in the following papers:

Splicing factors differentially expressed in psoriasis alter mRNA maturation of disease-associated EDA+ fibronectin. **Mol Cell Biochem 436 (2017) 189-199**
PRINS Non-Coding RNA Regulates Nucleic Acid-Induced Innate Immune Responses of Human Keratinocytes. **Front Immunol. 29 (2017)1053**
Differential Inflammatory-Response Kinetics of Human Keratinocytes upon Cytosolic RNA- and DNA-Fragment Induction. **Int J Mol Sci. 8 (2018)19**
Nuclear Factor κB Activation in a Type V Pityriasis Rubra Pilaris Patient Harboring Multiple CARD14 Variants. **Front Immunol. 3 (2018) 1564**