Can the bactericidal and immunomodulatory effects of ceragenins be used in the development of new methods of treating *acne vulgaris*?

Acne vulgaris is one of the most common inflammatory skin diseases seen worldwide, affecting all ethnic races, with a peak incidence between the ages of 15 and 20. The resulting clinical and psychological sequelae of the disease are significant. *Acne vulgaris* has many negative effects on young adolescents. It causes discomfort, emotional stress, disfigurement and even permanent scarring to the skin. It may also cause anxiety and embarrassment in patients and may diminish the patient's physiological and social well-being. *Acne vulgaris is* characterized by open and closed comedones and lesions with inflammatory nodules, pustules and papules, which typically affect the face, chest and back. *Acne vulgaris* is a chronic disease that requires long-term antibiotic therapy for satisfactory results. These antibiotics should not be used in monotherapy because of the high risk of resistance, and treatment duration should be 8 to a maximum of 12 weeks. A retrospective study conducted in the U.S. with *acne vulgaris* patients showed that most of them took these substances for 6 months or longer. The results of this study also indicate overuse of antibiotics and late recognition of treatment failure in patients with severe inflammatory acne. The main factor responsible for the failure of *acne vulgaris* therapy is the ability of *Cutibacterium acnes* to form a biofilm. This biofilm is clinically relevant because it increases the pathogenicity of *C. acnes* by allowing the commensal organism to transform into a pathogen. Studies of biofilm formed by *C. acnes* in affected sebaceous follicles consisted mainly of the IA phenotype of *C. acnes* and showed increased expression of Christie-Atkins-Munch-Peterson mRNA (CAMP). Genetic analysis showed that *C. acnes* isolates have five unique genes with known functions (acsA, clpS, dppB, rcsB, ytpA) whose expression is increased in *acne vulgaris*. In particular, rcsB (response regulator RcsB) is positively involved in biofilm formation in many different bacterial species. RcsB increases the expression of genes that promote biofilm formation while regulating various metabolic functions in *Escherichia coli*.

The project aims to investigate whether synthetic ceragenins (CSA)-analogs of natural antimicrobial peptides- can eradicate the biofilm formed by C. acnes and reduce the inflammatory response of human skin cells. The application of CSAs in the present project may provide new opportunities for the treatment of *acne vulgaris*. Evaluation of ceragenins antimicrobial activity against planktonic and biofilm forms will be examined using bacterial survival assays (counting formed colonies-bacteria- CFU). In addition, the expression of genes relevant to the disease *acne vulgaris*, and inflammation (NF-kB pathway) will be determined using qRT-PCR after ceragenins treatment. The immunomodulatory effect of ceragenins will be assessed by examining the secretion of cytokines and chemokines in cultures of skin cells-keratinocytes 2D and 3D (treated with heat-inactivated suspension of *C. acnes*) using cytokine array kits.

Data obtained from studies on the antimicrobial activity of CSAs against *C. acnes* may identify a new therapeutic target- the eradication of bacterial biofilm by neutralizing bacterial virulence factors and stimulating the expression of genes involved in biofilm formation in patients with *acne vulgaris*. In addition, the results obtained during this project may significantly increase our knowledge of the effect of CSA on the keratinocyte response (immunomodulatory effect) during *acne vulgaris*.