EXPLOITATION OF THE THERAPEUTIC POTENTIAL OF THE SKIN CANNABINOID SYSTEM IN ATOPIC DERMATITIS

Note: As of February 1, 2020, the original PI of the project, prof. Tamás Bíró, ceased to work at the University of Debrecen. Hence, with the written agreement of all senior participants, dr. Attila Oláh took over the supervision of the project for the last period (i.e., February 1, 2020 – December 15, 2020). It should also be noted that, due to the world-wide escalation of the COVID-19 pandemic situation, the national and international conferences at which we planned to present our data in course of the last year of the project, have been cancelled.

BACKGROUND

Although **atopic dermatitis** (AD) is not directly life-threatening disease, it is estimated to affect **~15-30%** of the **children** as well as **~2-10%** of the **adults**. It impairs quality of life of millions worldwide, hence, it results in **significant financial and psychological burden to the society** (Bieber 2008; Griffiths et al. 2017). Since research efforts of the past decades failed to unravel the fine details of its pathogenesis, **we still lack universally effective tools to manage it**. Thus, there is an **emerging demand** from both patients and the medical community to better understand its pathogenesis, which would hold out the promise of identifying novel therapeutic targets.

Despite of the existing open questions regarding its pathogenesis, it is widely accepted that AD is characterized by a **complex disorganization** of multifaceted **cutaneous barrier functions**. This includes regulation of proliferation and differentiation of epidermal keratinocytes (Greb et al. 2016; Kubo et al. 2012; Oláh et al. 2012; Schmuth et al. 2015), as well as the disturbance of the keratinocyte ↔ professional immune cell cross-talk (Greb et al. 2016; Kubo et al. 2012; Kuo et al. 2013b; Oláh et al. 2012; Schmuth et al. 2015). Thus, **epidermal keratinocytes are definitely key players** in the process, since their appropriate differentiation is crucially important in the development of the physicochemical barrier (Oláh et al. 2012), and they can also regulate cutaneous immune responses via the production of various cytokines and chemokines (Karsak et al. 2007).

Importantly, the endocannabinoid system (ECS), and, in a wider sense, the complex cutaneous cannabinoid signaling, were already shown by us and others to be deeply involved in regulating biology of the human skin (Oláh and Bíró 2017; Tóth et al. 2019). Moreover, we also demonstrated that "non-classical" **cannabinoid signaling** (e.g., via an adenosine A_{2A} receptor-coupled pathway), activated by several non-psychotropic plant-derived cannabinoids, led to significant **anti-inflammatory** actions and complex cellular anti-acne effects in human sebocytes (Oláh et al. 2016b; Oláh et al. 2014). Of further importance, in a previous study, we have demonstrated the existence of **a functional relationship between** one of the most important endocannabinoid (eCB)-degrading enzymes, fatty acid amide hydrolase (**FAAH**) (Tóth et al. 2019), and the highly **AD-relevant** (Kuo et al. 2013a) Toll-like receptor 2 (**TLR2**) **signaling**. Namely, we found that the protein (but not mRNA) expression and activity of **FAAH** can be **up-regulated by TLR2** activation in human epidermal keratinocytes (Oláh et al. 2016a).

These findings collective implicated that cannabinoid signaling indeed played a key role in the epidermal (barrier) homeostasis and that certain "barrier-forming" mechanisms, which were shown to fundamentally operate in AD, may have modulated the activity of the skin ECS. **Thus, in the current project, we intended to unveil novel aspects of the complex cannabinoid signaling and certain related pathways in the cutaneous (patho)physiology, with a special emphasis on their putative involvement in AD.**

RESULTS

1. Identification of novel tools that may be efficient in alleviating AD-related barrier disturbance

Appropriate differentiation of the epidermal keratinocytes is a key player in the cutaneous homeostasis. Disturbance of this strictly regulated process is a key contributor to the development of AD. We could demonstrate that two polyols, namely glycerol and xylitol, can promote differentiation of cultured primary human epidermal keratinocytes, and they exerted moderate anti-inflammatory effects as well (Páyer et al., *Exp. Dermatol.*, 2018; Scimago: Q1 in Dermatology; IF: 2.868), supporting the concept that they could be beneficial in the clinical management of diseases accompanied by barrier-impairment and inflammation, e.g. AD.

Besides, anti-inflammatory efficiency of an *Echinacea purpurea*-derived alkylamide-rich extract exhibiting potent CB_2 cannabinoid receptor agonism was tested *in vitro* in one of our keratinocyte-based inflammatory model systems, as well as *in vivo* in targeted clinical trials enrolling AD patients. In this study, we demonstrated that the above *Echinacea* extract exerted anti-inflammatory action in human keratinocytes. Moreover, when applied in appropriate topical formulation, it also alleviated symptoms of AD patients, and improved the structure of the epidermal lipid barrier (Oláh et al., *J. Dermatol. Sci.*, 2017; Scimago: D1 in Dermatology; IF: 3.675).

2. Role of the "classical" cannabinoid signaling in human keratinocytes

First, we collected paraffin-embedded histological samples from patients suffering from AD from both lesional and non-lesional sites, as well as from healthy individuals, and optimized highly standardized, reliable staining protocols to assess *in situ* FAAH and occludin expression in human epidermis by using immunohistochemistry. Next, we performed the histological comparison of FAAH expression in lesional and non-lesional skin of four AD patients as well as appropriate healthy controls. Intriguingly, although our preliminary data obtained on 2D keratinocyte cultures suggested that FAAH may be down-regulated, we found that FAAH tended to be up-regulated in the lesional epidermis of AD patients compared to the non-lesional sites and the appropriate healthy controls, too. Although due to the inter-individual variability, this up-regulation did not reach the level of statistical significance, it highlighted the possibility that the FAAH-mediated loss of the homeostatic anti-inflammatory eCB tone may contribute to the onset of the pathological inflammatory processes in AD. In order to get a deeper insight to the putative role of eCB-dysregulation in the development of cutaneous inflammatory processes, we analyzed skin samples of 4-4 subjects suffering from rosacea and psoriasis (PSO), i.e. two additional inflammation-accompanied skin diseases. Intriguingly, we found that FAAH was tended to be up-regulated in rosacea, but remained hardly altered in lesional epidermis of PSO patients.

Mitochondrial activity of the keratinocytes is known to contribute to the regulation of their proliferation, differentiation as well as immunological behavior (Bidaux et al. 2016; Bidaux et al. 2015; Feichtinger et al. 2014; Hamanaka and Chandel 2013). Given that eCB signaling is a key endogenous suppressor of mitochondrial activity in various cell types (Maccarrone et al. 2015), we decided to assess its role in fine-tuning epidermal mitochondrial activity. By using several complementary experimental approaches (selective gene silencing as well as receptor specific agonists and inverse agonists; immunoelectron microscopy of healthy human skin; immunohistomorphometry and *in situ* enzyme activity assays in organ-cultured full-thickness human skin; fluorescent/luminescent high-throughput screening methods on primary, normal human epidermal keratinocytes), we showed that homeostatic eCB signaling is an important negative regulator of the epidermal mitochondrial activity. Moreover, we could also confirm that the most important target of the eCB signaling, i.e. CB_1 cannabinoid receptor, is expressed not only in the cell membrane ($cmCB_1$), but also in the mitochondria ($mtCB_1$) of the epidermal keratinocytes. Importantly, our data suggest that the two receptor sub-populations most probably play differential

roles in regulating two major aspects of epidermal keratinocytes' biology, i.e., inflammatory responses and differentiation. These findings were presented at multiple national and international meetings in the form of 2 posters and 5 lectures, among which, 2 were invited, keynote lectures about the mitochondrial effects of the cutaneous cannabinoid signaling (for details, see the "*List of the project-related publications*" chapter below).

3. Effects of phytocannabinoids and semi-synthetic phytocannabinoid-derivatives in cutaneous inflammation

Cutaneous inflammation and itch are key players in AD. Thus, we also started the investigation of synthetic and semi-synthetic *Cannabis*-derived phytocannabinoids in alleviating inflammation, which would be very much desired in the clinical management of AD.

First, in order to get a deeper insight to the putative anti-inflammatory effects of the complex cannabinoid signaling, we probed the effects of the most studied non-psychotropic phytocannabinoid, (-)-cannabidiol (CBD), as well as its fluorinated semi-synthetic derivatives (provided by our collaborators) in several *in vitro* inflammatory models. We found that certain fluorinated compounds exerted superior anti-inflammatory efficiency compared to unmodified CBD. Besides CBD, we also decided to assess putative anti-inflammatory efficiency of a "non-classical" phytocannabinoid, namely the highly selective CB_2 agonist (Gertsch et al. 2008) β-caryophyllene (BCP) in human *in vitro* inflammatory keratinocyte model systems, and we found that it exerted remarkable anti-inflammatory effects.

In order to increase the translational relevance of our findings, next, we continued the investigation of the anti-inflammatory effects of BCP, CBD, as well as of the fluorinated semi-synthetic derivatives of the latter in several *in vivo* inflammatory mouse models (oxazolone-induced allergic contact dermatitis and croton oil-induced irritative dermatitis).

We found that both CBD, as well as its semi-synthetic derivatives were efficient in suppressing oxazolone-induced ear swelling in male Balb/c mice following topical application. As an intriguing observation, we also found that CBD was more efficient when applied at a lower (1 μM) concentration than at its higher (10 μM) dose. Importantly, a fluorinated, semi-synthetic analogue of CBD ("HUF101") was more potent than CBD in suppressing oxazolone-induced ear swelling, but neither myeloperoxidase activity, nor plasma extravasation was ameliorated by the cannabinoids. Importantly, topically applied BCP was also found to be effective in suppressing oxazolone-induced ear swelling.

Intriguingly, although CBD could reduce the croton oil-induced ear swelling as well, HUF101 and BCP were unable to suppress it, arguing that the three cannabinoids might activate distinct, independent (or only partially overlapping) anti-inflammatory pathways. Thus, our data highlight that they may be optimal for the treatment of inflammatory conditions of different origin. Data of these experiments were presented at several international and national meetings in the form of 10 posters, 7 oral presentation, and 2 related citable abstracts. Moreover, preparation of an *in extenso* manuscript is in progress.

4. Exploration of the role of the ionotropic cannabinoid receptor TRPV3

To better understand the complex role of the endocannabinoid system in regulating cutaneous inflammation, we also investigated the expression pattern and functional role of an ionotropic cannabinoid receptor belonging to the transient receptor potential ion channel superfamily (namely TRPV3). We found that activation of this channel led to a pro-inflammatory response in human keratinocytes; therefore, its antagonism augurs to be beneficial in alleviating cutaneous inflammatory processes (Szöllősi et al., *J. Invest. Dermatol.*, 2018; IF: 6.29; Scimago: D1 in Dermatology). Importantly,

we could also demonstrate that TRPV3 was overexpressed in the epidermis of patients suffering from AD as compared to healthy individuals. Moreover, isolated keratinocytes of AD patients exhibited a more pronounced response upon TRPV3 agonist treatment. Taken together, these data strongly argue that TRPV3 antagonism holds out the promise to become a novel anti-inflammatory strategy in AD and maybe in other inflammatory dermatoses as well (Vasas et al., in revision at the *J. Invest. Dermatol.*)

5. Effects of the cannabinoid signaling in human sebocytes

Sebaceous gland dysfunction has recently been recognized as an important factor in the pathogenesis of AD (Pappas 2009; Shi et al. 2015), and we have previously shown that some eCBs are central orchestrators of sebaceous lipid synthesis (Dobrosi et al. 2008). Thus, we also investigated the impact of the eCB signaling on the biology of human sebocytes. We found that the major eCB synthesizing and degrading enzymes were expressed in human sebaceous glands, and the elevation of the eCB-tone led to significant anti-inflammatory actions, and a moderate increase of the sebaceous lipogenesis, which could be beneficial in alleviating symptoms of AD (Zákány et al., *J. Invest. Dermatol.*, 2018; IF: 6.29; Scimago: D1 in Dermatology).

As an intriguing side-finding of the above study, we found that human sebocytes were able to metabolize two "eCB-related" substances, namely palmitoylethanolamine (PEA) and oleoylethanolamide (OEA). This highlighted the possibility that besides the "classical" eCBs, PEA and OEA may also be involved in regulating sebocyte functions. Importantly, we found that the most important receptor of OEA, namely GPR119, was indeed expressed in human sebocytes *in vitro*, as well as in human sebaceous glands *in situ*. Moreover, we could also demonstrate that OEA promoted differentiation of human sebocytes (elevated sebaceous lipogenesis and initiation of early apoptotic processes), and induced pro-inflammatory actions. Next, we unveiled several details of the mechanism of its pro-lipogenic actions. We found that lipogenic effect of OEA was dependent on the activation of GPR119, as well as of ERK1/2, JNK, CREB, and Akt/PKB pathways, but was independent of the activation of PPARα (another possible cellular target of OEA) or STAT5 (Markovics et al., *J. Invest. Dermatol.*, 2020; IF: 7.143 [JCR 2019]; Scimago: D1 in Dermatology).

Besides the above papers, our sebaceous gland-related data were also presented at numerous national and international meetings in the form of 5 posters and 2 related citable abstracts.

6. Role of the cannabinoid signaling in human hair follicles

Besides sebaceous glands, we also aimed to investigate human hair follicles, because, from a perspective of the future clinical administration, exploration of the effects of cannabinoid signaling on this member of the pilosebaceous unit is of great importance. We found that CBD exerted differential effects in a concentration-dependent manner, namely its low micromolar concentrations triggered the onset of the regressive catagen phase most likely via the activation of TRPV4 ion channels. However, when applied at nanomolar concentrations, CBD had no significant effect on the hair cycle, but exerted anti-inflammatory actions via activating adenosine receptors (Szabó et al., *J. Invest. Dermatol.*, 2020; IF: 7.143 [according to JCR 2019]; Scimago: D1 in Dermatology). Besides the above paper, these data were also presented at one international conference in the form of 1 poster and 1 related citable abstract.

7. The role of the opioid signaling in human keratinocytes

κ-opioid receptor (KOR) is a recently recognized player in the human epidermal homeostasis, and its expression was shown to be reduced in lesional skin of patients suffering from PSO (Kupczyk et al. 2017). Importantly, we found that the KOR activator nalfurafine exerted remarkable anti-inflammatory

effects in human keratinocytes in a KOR-dependent manner, implicating that its pharmacological activation could be a valid approach in the management of inflammation-accompanied skin diseases. Encouraged by these promising data, we optimized staining protocols to assess expression of KOR and prodynorphin (PDYN; the precursor of the major endogenous ligands of KOR), and assessed their expression in the epidermis of patients suffering from AD, PSO, or rosacea. Importantly, in contrast to the available literature data, we found that neither KOR, nor PDYN was significantly down-regulated in the above diseases, arguing that, at least in a subset of the patients, KOR remains a druggable target to alleviate cutaneous inflammation. These data have been presented at numerous national and international meetings in the form of 3 posters and 1 related citable abstract. Moreover, preparation of a manuscript summarizing our data is in progress.

Additional collaborative projects

During the four years of the project, additional experiments were also performed which were not planned in the original proposal but, according to our opinion, were highly important and relevant to the complexity of our work.

1. **Investigation of the functional expression of TRPV channels**

From the perspective of the potential clinical administration of endocannabinoid system-targeting medications, it is crucially important to unveil potential side-effects. Importantly, we successfully described the expression and functional presence of TRPV3 as well as 3 other, closely related ionotropic cannabinoid receptors (TRPV1, -2 and -4) on human podocytes, indicating that in case of systemic administration of TRPV3 antagonists (or other cannabinoid ligands which target any of these ion channels), one should also take into consideration the potential impact on the glomerular filtration barrier (Ambrus et al., *Br. J. Pharmacol.*, 2017; IF: 6.81. Pharmacology: Q1).

2. **Exploration of the cutaneous anti-inflammatory effects of selective serotonin reuptake inhibitors**

Since in a recent publication disturbance of the cutaneous serotoninergic signaling has been suggested contributing to the development of AD symptoms (Rasul et al. 2016). Moreover, since cannabinoid signaling was found to interact with the serotoninergic pathways in the brain; we also decided to assess the effects of selected selective serotonin reuptake inhibitors (SSRIs) in a keratinocyte model system. We found that fluoxetine (but, intriguingly, not the other tested SSRIs or serotonin) exerted remarkable anti-inflammatory actions, and prevented the release of the itch-mediator endothelins from human keratinocytes. Importantly, findings of these experiments provided an important additional, highly "AD-relevant" experimental end-point (i.e., the endothelin release), which was investigated within the confines of the main project. Next, we intended to unveil the mechanism of the beneficial anti-inflammatory actions. We found that fluoxetine slightly increased $[Ca^{2+}]_{IC}$, and, most likely via inhibiting certain phosphodiesterases, elevated cAMP level in human keratinocytes. Having excluded the involvement of several signaling pathways, we performed RNAseq that revealed the fluoxetine-induced modulation of several signaling pathways (e.g., HIF-1, MAPK, and mTOR) that may be responsible for the anti-inflammatory actions. While the necessary confirmatory experiments are currently being performed, **we started the preparation of an *in extenso* manuscript** summarizing our data. Some of the above findings have already been presented at various national and international meetings, in the form of **3 posters and 1 related citable abstract**.

3. Effects of nicotinic acid on human sebocytes

We also investigated the effects of nicotinic acid (NA; a member of the vitamin B3 complex) on sebocytes' biology. Interestingly, NA was proven to suppress "pro-acne" agents-induced excessive sebaceous lipogenesis via activating hydroxycarboxylic acid receptor 2 (HCA_2), making this receptor a novel and previously unknown regulator of sebaceous lipogenesis, which may therefore also contribute to the development of AD. These findings were presented at 1 national and 2 international conferences in the form of 3 poster presentations and 2 citable abstracts, and 1 *in extenso* manuscript has also been published (Markovics et al., *JCMM*, 2019; IF: 4.868; Scimago: Molecular Medicine: Q1).

4. Effects of honokiol on human sebocytes

Within the confines of a newly established international collaboration, we assessed the effects of the plant-derived tribbles homolog 3 (TRIB3; a key cannabinoid target gene in sebocytes) activator honokiol (HNK) in human sebocytes, and found that HNK exerted complex anti-acne effects. More precisely, we found that non-cytotoxic concentrations of HNK were able to suppress both the basal as well as the arachidonic acid-induced, "acne-mimicking" sebaceous lipogenesis. Of great importance, lipostatic effect of HNK was not restricted to AA, but it was also able to prevent the effects of other lipogens (anandamide, linoleic acid+testosterone, and palmitic acid), indicating that, similar to CBD, it most likely activates a universal lipostatic pathway. Moreover, HNK was found to exert significant anti-proliferative and anti-inflammatory effects as well, making it an ideal anti-acne drug candidate. Unfortunately, due to the escalation of the COVID-19 pandemic, investigation of its qualitative effects on the sebaceous lipidome, as well as the exploration of its mechanism of action has not been completed yet. However, our recent RNAseq analysis revealed significant HNK-induced modulation of several promising target genes (e.g., retinoic acid receptor B, mir7-1, etc.) that may be involved in mediating the beneficial anti-acne effects of HNK. The above results were presented at multiple national and international conferences in the form of 3 posters and 1 related citable abstract. Moreover, we started the preparation of a manuscript summarizing the above findings.

Non-experimental project-related activity:

We published two reviews summarizing the currently available knowledge on the cutaneous cannabinoid signaling (Oláh and Bíró, EBioMedicine, 2017; IF: 6.183. Medicine (miscellaneous): D1; Tóth et al, Molecules, 2019; Scimago: Q1 in Pharmaceutical Science; IF: 3.267; Citations: 66), and one about its immunological role (Oláh et al., *Fr. Immunol.*, 2017; IF: 5.511. Immunology: Q1). Moreover, within the confines of a book chapter, we provided a concise overview of the endogenous factors involved in the development and maintenance of the acidic cutaneous pH (i.e., the "acid mantle"), disturbance of which is well-known to be involved in the pathogenesis of AD (Bíró et al., 2018; In. *pH of the Skin: Issues and Challenges*).

IMPACT, INNOVATION, FUTURE PERSPECTIVES

The current basic research project performed with the support of the K_16 grant of the NRDIO aimed to unveil delicate details of the complex cannabinoid signaling and its putative translational potential in AD, and, in a wider sense, in inflammation-accompanied skin diseases in general. We believe that our above detailed results have the potential to encourage further R & D & I activities and subsequent future clinical trials.

We are happy to report that a German company (whose name cannot be revealed yet due to the non-disclosure agreement) has recently expressed its interest in establishing a long-term relationship with

our laboratory, and intends to initiate the innovation chain (e.g., management of intellectual property issues, feasibility studies, market research and positioning, marketing, etc.). If this relationship does indeed result in successful future clinical trials, it can be strongly hoped that our pre-clinical and clinical research efforts (besides resulting in definite commercial and economic values/income) will eventually result in obvious social impact, since the application of these novel products may improve quality of life of millions in Hungary and worldwide.

DISSEMINATION OF THE FINDINGS, MAJOR ACHIEVEMENTS

Although it was not part of the official work plan, we strongly believe that dissemination of our latest findings towards the society is crucially important. Thus, in the past years we regularly joined to the **Researchers' night events**, where we had the chance to present our most intriguing data in layman's terms to the public.

In the original work plan of the proposal, we planned to publish/submit **2 original papers** as well as **1 review paper** in course of the project, and to present our data at **1 national** and at **1 international meeting each year**. We believe that this plan was markedly outperformed, as during the course of this 4-year project, **11 *in extenso* manuscripts** were published in high-ranked journals. Moreover, our data were presented in the form of **12 lectures and 31 posters** at various national and international conferences. The detailed list of our publications that are related to the current project can be found below.

LIST OF THE PROJECT-RELATED PUBLICATIONS

***In extenso* publications (11 [IF: 60.048 according to JCR 2019]; all of which are last- or co-last-authored by either the former or the current PI; citations are given according to Google scholar [02/25/2021]):**

1) **Oláh A***, **Bíró T** (2017): Targeting Cutaneous Cannabinoid Signaling in Inflammation - A "High"-way to Heal? *EBioMedicine* **16(2017):**3-5. doi: 10.1016/j.ebiom.2017.01.003. *Corresponding author. **IF: 6.183.** Medicine (miscellaneous): **D1**; Citations: **14.** *This review paper focuses on summarizing the anti-inflammatory properties of the cutaneous cannabinoid signaling.*

2) **Oláh A**, Szabó-Papp J, Soeberdt M, Knie U, Dähnhardt-Pfeiffer S, Abels C, **Bíró T** (2017): *Echinacea purpurea*-derived alkylamides exhibit potent anti-inflammatory effects and alleviate clinical symptoms of atopic eczema. *J. Dermatol. Sci.* **88(1):**67-77. doi: 10.1016/j.jdermsci.2017.05.015. **IF: 3.675.** Dermatology: **D1;** Citations: **29.** *This paper demonstrates the (most likely CB_2-dependent) anti-inflammatory effects of an Echinacea purpurea extract both in vitro and in vivo in clinical trials.*

3) Szöllősi AG, Vasas N, AngyalÁ, Kistamás K, Nánási PP, Mihály J, Béke G, Herczeg-Lisztes E, Szegedi A, Kawada N, Yanagida T, Mori T, Kemény L, **Bíró T** (2018): Activation of transient receptor potential vanilloid 3 regulates inflammatory actions of human epidermal keratinocytes. *J. Invest. Dermatol.* **138(2):**365-374. doi: 10.1016/j.jid.2017.07.852. **IF: 6.29.** Dermatology: **D1;** Citations: **28.** *This paper demonstrates that TRPV3 is expressed in a functionally active form in primary human epidermal keratinocytes, and its activation leads to a pro-inflammatory response.*

4) Ambrus L, Kelemen B, Szabó T, **Bíró T**#,&, Tóth BI# (2017): Human podocytes express functional thermosensitive transient receptor potential vanilloid (TRPV) channels. *Br. J. Pharmacol.* **174(23):**4493-4507. doi: 10.1111/bph.14052. #***Shared last-authorship.*** &***Corresponding author.*** **IF: 6.81.** Pharmacology: **Q1;** Citations: **8.** *This paper demonstrates the functional expression of multiple TRPV ion channels in human podocytes.*

5) Páyer E, Szabó-Papp J, Ambrus L, Szöllősi AG, Andrási M, Dikstein S, Kemény L, Juhász I, Szegedi A, **Bíró T**#, **Oláh A**# (2018): Beyond the Physico-Chemical Barrier: Glycerol and Xylitol Markedly yet Differentially Alter Gene Expression Profiles and Modify Signaling Pathways in Human Epidermal Keratinocytes. *Exp. Dermatol.* **27(3):**280-284. #***Shared last authorship.*** **IF: 2.868; Dermatology: Q1; Citations (Google scholar): 7.** *This paper describes the anti-inflammatory and pro-differentiating effects of two polyols (glycerol and xylitol) in human epidermal keratinocytes.*

6) **Oláh A**, Szekanecz Z, **Bíró T** (2017): Targeting cannabinoid signaling in the immune system: "High"-ly exciting questions. *Fr. Immunol.* **8:**1487. doi: 10.3389/fimmu.2017.01487. **IF: 5.511.** Immunology: **Q1;** Citations: **67.** *This review paper focuses on summarizing the immunological effects of the cannabinoid signaling.*

7) Zákány N*, **Oláh A***, Markovics A, Takács E, Aranyász A, Nicolussi S, Piscitelli F, Allarà M, Pór Á, Kovács I, Zouboulis CC, Gertsch J, Di Marzo V, **Bíró T**#,&, Szabó T# (2018): Endocannabinoid tone regulates human sebocyte biology. *J. Invest. Dermatol*. **138(8):**1699-1706. doi: 10.1016/j.jid.2018.02.022. **IF: 6.29** ***Shared first-authorship.*** #***Shared last-authorship.*** &***Corresponding author.*** Dermatology: **D1;** Citations: **12.** *This paper describes the expression and functional roles of the major members of the ECS in human sebocytes in vitro and sebaceous glands in situ.*

8) Tóth KF, Ádám D, **Bíró T***, **Oláh A***,& (2019): Cannabinoid signaling in the skin: Therapeutic potential of the "c(ut)annabinoid" system. *Molecules* **24:**918. doi: 10.3390/molecules24050918**. IF: 3.267** *#***Shared last authorship.*** &***Corresponding author.*** Pharmaceutical Science: **Q1;** Citations: **66.** *This review paper summarizes the available knowledge on the cutaneous cannabinoid signaling.*

9) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, **Bíró T[#], Oláh A[#]** (2019): Nicotinic acid suppresses sebaceous lipogenesis of human sebocytes via activating hydroxycarboxylic acid receptor 2 (HCA_2). *J. Cell Mol. Med.* **23:**6203–6214. doi: 10.1111/jcmm.14505. **IF: 4.868** ***[#]Shared last authorship.*** Molecular Medicine: **Q1;** Citations: **8.** *This paper describes the lipostatic and anti-proliferative effects of nicotinic acid, and provides evidence that they are mediated via activating a previously unknown regulator of sebocyte function, namely hydroxycarboxylic acid receptor 2 (HCA_2).*

10) Szabó IL, Lisztes E, Béke G, Tóth KF, Paus R, **Oláh A[*]**, **Bíró T[*]** (2020): The phytocannabinoid (-)-cannabidiol (CBD) operates as a complex, differential modulator of human hair growth: Anti-inflammatory submicromolar versus hair growth inhibitory micromolar effects. *J. Invest. Dermatol*. **140:**484-488. doi: 10.1016/j.jid.2019.07.690. **IF: 7.143 (according to JCR 2019)** ***[*]Shared last authorship.*** Dermatology: **D1;** Citations: **6.** *This paper describes the differential effects of the non-psychotropic phytocannabinoid cannabidiol on human hair follicles.*

11) Markovics A, Angyal Á, Tóth KF, Ádám D, Pénzes Zs, Magi J, Pór Á, Kovács I, Törőcsik D, Zouboulis CC, **Bíró T[*]**, **Oláh A[*]** (2020): GPR119 is a potent regulator of human sebocyte biology. *J. Invest. Dermatol.* **140(10):**1909-1918.e8. doi: 10.1016/j.jid.2020.02.011. **IF: 7.143 (JCR 2019);** ***[*]Shared last-authorship.*** **Dermatology: D1; Citations (Google scholar): 1.** *This paper describes the role of the novel cannabinoid receptor GPR119 in the regulation of human sebocyte biology*.

Book chapters: 1

1) **Bíró T**, **Oláh A**, Tóth BI, Szöllősi AG (2018) Endogenous Factors That Can Influence Skin pH. In. Surber C, Abels C, Maibach H (eds.) *pH of the Skin: Issues and Challenges*. Curr Probl Dermatol. Basel, Karger, vol. 54, pp. 54–63. doi: 10.1159/000489518. Citations: **1.** *In this book chapter we provide a concise overview of the endogenous factors involved in the development and maintenance of the acidic cutaneous pH (i.e., the "acid mantle"). Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

Submitted manuscripts in the revision phase: 1

1) Vasas N, Angyal Á, Pénzes Zs, Kistamás K, Nánási PP, Molnár Sz, Szegedi A, **Oláh A**, Tóth BI, Szöllősi AG, **Bíró T**: Transient receptor potential vanilloid 3 expression is increased in non-lesional skin of atopic dermatitis patients. ***In revision at the Journal of Investigative Dermatology*** **(IF: 7.143 [JCR 2019]).**

Citable abstracts: 11

1) Szabó IL, Herczeg-Lisztes E, Szöllősi AG, **Bíró T**, **Oláh A** (2017): (-)-cannabidiol differentially influences hair growth. *J. Invest. Dermatol.* **137(Number 10S Supplement 2):**S238. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

2) **Oláh A**, Alam M, Chéret J, Kis G, Hegyi Z, Szántó M, Bai P, Lerchner J, **Bíró T**, Paus R (2017): CB_1 is a novel regulator of epidermal mitochondrial functions. *J. Invest. Dermatol.* **137(Number 10S Supplement 2):**S210. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

3) Tóth KF, Szabó-Papp J, Pénzes Zs, Kilić A, Soeberdt M, Abels C, **Bíró T**, **Oláh A** (2017): The selective serotonin reuptake inhibitor fluoxetine exerts anti-inflammatory actions on human

epidermal keratinocytes. *J. Invest. Dermatol.* **137(Number 10S Supplement 2):**S214. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

4) Mihály J, Miltner N, Tubak V, Mechoulam R, Russo E, **Bíró T** (2017): Assessment of the anti-inflammatory effects of fluorinated semi-synthetic phytocannabinoids in human in vitro inflammatory keratinocyte model systems. *J. Invest. Dermatol.* **137(Number 10S Supplement 2):**S271. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

5) Miltner N, Béke G, Angyal Á, Kemény Á, Pintér E, Helyes Zs, **Bíró T**, Mihály J (2018): Assessment of the anti-inflammatory effects of cannabidiol and its fluorinated derivative in in vitro and in vivo models of atopic dermatitis. *J. Invest. Dermatol.* **138(5):**S224. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

6) **Oláh A**, Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, **Bíró T** (2018): Nicotinic acid suppresses sebaceous lipid synthesis of human sebocytes via activating hydroxycarboxylic acid receptor 2 (HCA2). *J. Invest. Dermatol.* **138(5):**S224. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

7) Tóth KF, Markovics A, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, **Bíró T**, **Oláh A** (2018): Endocannabinoid-like molecule oleoylethanolamide promotes sebaceous lipid synthesis. *J. Invest. Dermatol.* **138(5):**S224. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

8) Ádám D, Tóth KF, Sárkány F, Soeberdt M, Abels C, **Oláh A**, **Bíró T** (2018): Activation of κ-opioid receptor (KOR) suppresses pro-inflammatory response of human epidermal keratinocytes. *Exp. Dermatol.* **27(Supplement 2):**38.

9) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, **Bíró T**, **Oláh A** (2018): Sebaceous lipogenesis of human sebocytes is suppressed by nicotinic acid via the activation of hydroxycarboxylic acid receptor 2 (HCA2). *Exp. Dermatol.* **27(Supplement 2):**27.

10) Tóth KF, Markovics A, Ádám D, Pénzes Zs, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, **Bíró T**, **Oláh A** (2018): GPR119 is a potent novel regulator of human sebocyte biology. *Exp. Dermatol.* **27(Supplement 2):**36.

11) Tóth KF, Ádám D, Arany J, Faragó P, Arbiser JL, Zouboulis CC, **Bíró T**, **Oláh A** (2019): The putative tribbles homolog 3 (TRIB3) activator honokiol suppresses lipogenesis, and exerts anti-proliferative as well as anti-inflammatory effects on human sebocytes. *J. Invest. Dermatol.* **139(9S) Supplement 2:**S319. *Note that due to publisher's restriction,* ***we were not allowed to mention any grants*** *supporting our work.*

Posters and lectures presented at national and international meetings: 43

1) Markovics A, Magi J, Tóth KF, Angyal Á, Sós KE, Zouboulis CC, Benyó Z, **Bíró T**, **Oláh A** (2017): A nikotinsav biológiai hatásainak vizsgálata humán szebocitákon. *47th. Membrane-Transport Conference (Sümeg, Hungary; 05/16/2017-05/19/2017)* *https://www.remedicon.hu/261/47-membran-transzport-konferencia* **POSTER presentation.**

2) Magi J, Markovics A, Tóth KF, Angyal Á, Pór Á, Kovács I, Zouboulis CC, **Bíró T**, **Oláh A** (2017): A novel endokannabinoid oleoil-etanolamid hatásainak vizsgálata humán szebocitákon. *47th. Membrane-Transport Conference (Sümeg, Hungary; 05/16/2017-05/19/2017)* *https://www.remedicon.hu/261/47-membran-transzport-konferencia* **POSTER presentation.**

3) Miltner N, Mihály J, Zara B, Hollósi E, Ádám D, Jambrovics K, Mechoulam R, Russo E, **Bíró T** (2017): Újszerű szemi-szintetikus fitokannabinoidok gyulladáscsökkentő hatásának vizsgálata RAW 264.7 sejtekben. *Annual meeting of the Hungarian Physiological Society (Debrecen, Hungary; 06/13/2017-06/16/2017)* https://www.remedicon.hu/263/a-magyar-elettani-tarsasag-a-magyar-kiserletes-es-klinikai-farmakologiai-tarsasag-es-a-magyar-mikrocirkulacios-es-vaszkularis-biologiai-tarsasag-kozos-vandorgyulese/nyitolap **POSTER presentation**

4) Mihály J, Miltner N, Zara B, Hollósi E, Ádám D, Tubak V, Mechoulam R, Russo E, **Bíró T** (2017): Fluorinált szemi-szintetikus növényi kannabinoidok vizsgálata gyulladásos humán keratinocita modellrendszerekben. *Annual meeting of the Hungarian Physiological Society (Debrecen, Hungary; 06/13/2017-06/16/2017)* https://www.remedicon.hu/263/a-magyar-elettani-tarsasag-a-magyar-kiserletes-es-klinikai-farmakologiai-tarsasag-es-a-magyar-mikrocirkulacios-es-vaszkularis-biologiai-tarsasag-kozos-vandorgyulese/nyitolap **POSTER presentation**

5) Tóth KF, Szabó-Papp J, Pénzes Zs, Kilić A, Soeberdt M, Abels C, **Bíró T**, **Oláh A** (2017): Szelektív szerotoninvisszavétel-gátló farmakonok hatásainak vizsgálata keratinocitákon. *Annual meeting of the Hungarian Physiological Society (Debrecen, Hungary; 06/13/2017-06/16/2017)* https://www.remedicon.hu/263/a-magyar-elettani-tarsasag-a-magyar-kiserletes-es-klinikai-farmakologiai-tarsasag-es-a-magyar-mikrocirkulacios-es-vaszkularis-biologiai-tarsasag-kozos-vandorgyulese/nyitolap **POSTER presentation, awarded by poster award.**

6) Alimohammadi S, Magi J, Markovics A, Tóth KF, Angyal Á, Pénzes Zs, Pór Á, Kovács I, Zouboulis CC, **Bíró T**, **Oláh A** (2017): Novel aspects of the endocannabinoid signaling in human sebocytes. *Annual meeting of the Hungarian Physiological Society (Debrecen, Hungary; 06/13/2017-06/16/2017)* https://www.remedicon.hu/263/a-magyar-elettani-tarsasag-a-magyar-kiserletes-es-klinikai-farmakologiai-tarsasag-es-a-magyar-mikrocirkulacios-es-vaszkularis-biologiai-tarsasag-kozos-vandorgyulese/nyitolap **POSTER presentation.**

7) **Oláh A**, Alam M, Chéret J, Kis G, Hegyi Z, Szántó M, Bai P, Szabó IL, Szegedi A, Lerchner J, Vidali S, Zimmer A, **Bíró T**, Paus R (2017): Role of mitochondrial CB_1 in human epidermal keratinocytes. *Annual meeting of the Hungarian Physiological Society (Debrecen, Hungary; 06/13/2017-06/16/2017)* https://www.remedicon.hu/263/a-magyar-elettani-tarsasag-a-magyar-kiserletes-es-klinikai-farmakologiai-tarsasag-es-a-magyar-mikrocirkulacios-es-vaszkularis-biologiai-tarsasag-kozos-vandorgyulese/nyitolap **ORAL presentation.**

8) **Oláh A**, Alam M, Kis G, Hegyi Z, Lerchner J, Vidali S, Zimmer A, **Bíró T**, Paus R (2017): CB_1 regulates mitochondrial functions of human epidermal keratinocytes *in situ* and *in vitro*. *The 27th Annual Symposium of the International Cannabinoid Research Society (ICRS) Montréal, Canada; 06/29/2017-06/27/2017.* http://www.icrs2017.org/ **ORAL presentation.**

9) **Bíró T**, Mechoulam R, Guimarães FS, Maccarrone M, Russo E (2017): Fluorinated cannabidiol derivatives as novel, highly effective therapeutic alternatives. *The 27th Annual Symposium of the International Cannabinoid Research Society (ICRS) Montréal, Canada; 06/29/2017-06/27/2017.* http://www.icrs2017.org/ **ORAL presentation.**

10) Szabó IL, Herczeg-Lisztes E, Szöllősi AG, **Bíró T**, **Oláh A** (2017): (-)-cannabidiol differentially influences hair growth. *47th Annual Meeting of the European Society for Dermatological Research (ESDR) (Salzburg, Austria; 09/27/2017-09/30/2017)* http://www.esdr2017.org/ **POSTER presentation.**

11) Mihaly J, Miltner N, Tubak V, Mechoulam R, Russo E, **Bíró T** (2017): Assessment of the anti-inflammatory effects of fluorinated semi-synthetic phytocannabinoids in human in vitro inflammatory keratinocyte model systems. *47th Annual Meeting of the European Society for Dermatological Research (ESDR) (Salzburg, Austria; 09/27/2017-09/30/2017)* http://www.esdr2017.org/ **POSTER presentation.**

12) **Oláh A**, Alam M, Chéret J, Kis G, Hegyi Z, Szántó M, Bai P, Lerchner J, **Bíró T**, Paus R (2017): CB_1 is a novel regulator of epidermal mitochondrial functions. *47th Annual Meeting of the European Society for Dermatological Research (ESDR) (Salzburg, Austria; 09/27/2017-09/30/2017)* http://www.esdr2017.org/ **POSTER presentation.**

13) Tóth KF, Szabó-Papp J, Pénzes Zs, Kilić A, Soeberdt M, Abels C, **Bíró T**, **Oláh A** (2017): The selective serotonin reuptake inhibitor fluoxetine exerts anti-inflammatory actions on human epidermal keratinocytes. *47th Annual Meeting of the European Society for Dermatological Research (ESDR) (Salzburg, Austria; 09/27/2017-09/30/2017)* http://www.esdr2017.org/ **POSTER presentation.**

14) **Oláh A**, Alam M, Chéret J, Kis G, Hegyi Z, Szántó M, Bai P, Lerchner J, **Bíró T**, Paus R (2017): CB_1 is a novel regulator of epidermal mitochondrial functions. *47th Annual Meeting of the European Society for Dermatological Research (ESDR) (Salzburg, Austria; 09/27/2017-09/30/2017)* http://www.esdr2017.org/ **ORAL presentation.**

15) **Oláh A** (2017): The endocannabinoid system as a novel regulator of mitochondrial activity in human epidermis. *47th Annual Meeting of the European Society for Dermatological Research (ESDR) (Salzburg, Austria; 09/27/2017-09/30/2017)* http://www.esdr2017.org/ **ORAL presentation; invited keynote lecture.**

16) Miltner N, Mihály J, Tubak V, Mechoulam R, Russo E, **Bíró T** (2017): Assessment of the anti-inflammatory effects of fluorinated semi-synthetic phytocannabinoids in human in vitro inflammatory keratinocyte model systems. *46th annual meeting of the Hungarian Immunological Society; Velence, Hungary; 10/18/2017-10/20/2017)* *https://www.remedicon.hu/267/magyar-immunologiai-tarsasag-46-vandorgyulese* **POSTER presentation.**

17) Tóth KF, Szabó-Papp J, Kilić A, Soeberdt M, Abels C, **Bíró T**, **Oláh A** (2017): Investigation of the effects of selective serotonin reuptake inhibitors on human keratinocytes. *46th annual meeting of the Hungarian Immunological Society; Velence, Hungary; 10/18/2017-10/20/2017)* *https://www.remedicon.hu/267/magyar-immunologiai-tarsasag-46-vandorgyulese* **POSTER presentation.**

18) Miltner N, Mihály J, Zara B, Hollósi E, Jambrovics K, Mechoulam R, Russo E, **Bíró T** (2017): Assesment of the anti-inflammatory effects of novel semi-synthetic phytocannabinoids in murine RAW 264.7 cells. *19th International Summer School on Immunology (FEBS) (Hvar; Croatia; 09/22/2017–10/01/2017)* *http://www.febs-immunology-course.org/* **POSTER presentation.**

19) Mihály J, Miltner N, Tubak V, Mechoulam R, Russo E, **Bíró T** (2018): Anti-inflammatory effects of novel semi-synthetic phytocannabinoids in human in vitro inflammatory keratinocyte model systems. *16th EAACI Immunology Winter School, Basic Research in Allergy and Clinical Immunology, Saas-Fee, Switzerland, 01/25-01/28/2018.* **POSTER presentation.**

20) Miltner N (2018): Fitokannabinoidok potenciális gyulladáscsökkentő hatásának feltérképezése in vitro egér gyulladásos modellrendszerben. *A jog tudománya, a mindennapok joga I. nemzetközi konferencia Debrecen, 2018.10.11.* **ORAL presentation.**

21) Mihály J (2018): Növényi kannabinoidok anti-inflammatorikus hatásának vizsgálata bőrben. *A jog tudománya, a mindennapok joga I. nemzetközi konferencia Debrecen, 2018.10.11.* **ORAL presentation.**

22) **Oláh A**, Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, **Bíró T** (2018): Nicotinic acid suppresses sebaceous lipid synthesis of human sebocytes via activating hydroxycarboxylic acid receptor 2 (HCA2). *5th International Investigative Dermatology (IID) Meeting, 2018. 05.16-19., Orlando, Florida, USA* *http://iid2018.org/* **POSTER presentation.**

23) Tóth KF, Markovics A, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, **Bíró T**, **Oláh A** (2018): Endocannabinoid-like molecule oleoylethanolamide promotes sebaceous lipid synthesis. *5th International Investigative Dermatology (IID) Meeting, 2018. 05.16-19., Orlando, Florida, USA http://iid2018.org/* **POSTER presentation.**

24) Miltner N, Béke G, Angyal Á, Kemény Á, Pintér E, Helyes Zs, **Bíró T**, Mihály J (2018): Assessment of the anti-inflammatory effects of cannabidiol and its fluorinated derivative in in vitro and in vivo models of atopic dermatitis. *5th International Investigative Dermatology (IID) Meeting, 2018. 05.16-19., Orlando, Florida, USA http://iid2018.org/* **POSTER presentation.**

25) Miltner N (2018): Assessment of the anti-inflammatory effects of novel semi-synthetic phytocannabinoids in human in vitro pro-inflammatory keratinocyte model systems. *EADV-ESDR Summer Research Workshop, Advanced molecular biology tools in dermatological research, 06/04-08/2018, Naples, Italy https://www.eadv.org/eadv-school/221* **ORAL presentation.**

26) Miltner N, Mihály J, Tubak V, Mechoulam R, Russo E, **Bíró T** (2018): Investigation of anti-inflammatory effect of β-caryophyllene in human in vitro inflammatory keratinocyte model systems. *13th EFIS-EJI Tatra Immunology Conference (Strbske Pleso, Slovakia; 06/9-06/13/2018) https://tatra.img.cas.cz/* **POSTER presentation.**

27) Tóth KF, Faragó P, Ádám D, Sárkány F, Markovics A, Arbiser JL, Zouboulis CC, **Oláh A**, **Bíró T** (2018): A tribbles homolog 3 (TRIB3) aktivátor honokiol vizsgálata humán szebocitákon. *Annual meeting of the Hungarian Physiological Society (Szeged, Hungary; 06/27/2018-06/30/2018)* http://www.regio10.hu/hu/?mod=webshop_cnt&cla=webshop_cnt&fun=showconflist&conf_id=4492 **POSTER presentation.**

28) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, **Bíró T**, **Oláh A** (2018): A nikotinsav a „hydoxycarboxylic acid receptor 2" (HCA2) aktiválásával csökkenti a humán szebociták faggyúlipid-termelését. *Annual meeting of the Hungarian Physiological Society (Szeged, Hungary; 06/27/2018-06/30/2018)* http://www.regio10.hu/hu/?mod=webshop_cnt&cla=webshop_cnt&fun=showconflist&conf_id=4492 **POSTER presentation.**

29) Sárkány F, Ádám D, Tóth KF, Faragó P, Soeberdt M, Abels C, **Oláh A**, **Bíró T** (2018): A κ opioid receptor (KOR) hatásainak vizsgálata humán epidermális keratinocitákon. *Annual meeting of the Hungarian Physiological Society (Szeged, Hungary; 06/27/2018-06/30/2018)* http://www.regio10.hu/hu/?mod=webshop_cnt&cla=webshop_cnt&fun=showconflist&conf_id=4492 **POSTER presentation.**

30) Tóth KF, Markovics A, Ádám D, Pénzes Zs, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, **Bíró T**, **Oláh A** (2018): A novel endokannabinoid oleoil-etanolamid hatásainak vizsgálata humán szebocitákon. *Annual meeting of the Hungarian Dermatological Society (Budapest, Hungary; 11/29/2018-12/01/2018) https://www.convention.hu/Rendezveny/Reszletek/MDT18/Koszonto* **POSTER presentation.**

31) Ádám D, Tóth KF, Sárkány F, Faragó P, Soeberdt M, Abels C, **Oláh A**, **Bíró T** (2018): A κ opioid receptor (KOR) hatásainak vizsgálata humán epidermális keratinocitákon. *Annual meeting of the Hungarian Dermatological Society (Budapest, Hungary; 11/29/2018-12/01/2018) https://www.convention.hu/Rendezveny/Reszletek/MDT18/Koszonto* **POSTER presentation.**

32) Miltner N, Mihály J, Tubak V, Mechoulam R, Russo E, **Bíró T** (2018): Investigation of anti-inflammatory effect of β-caryophyllene in human in vitro inflammatory keratinocyte model systems. *Annual meeting of the Hungarian Dermatological Society (Budapest, Hungary; 11/29/2018-*

12/01/2018) *https://www.convention.hu/Rendezveny/Reszletek/MDT18/Koszonto* **POSTER presentation.**

33) Ádám D, Tóth KF, Sárkány F, Soeberdt M, Abels C, **Oláh A**, **Bíró T** (2018): Activation of κ-opioid receptor (KOR) suppresses pro-inflammatory response of human epidermal keratinocytes. *3rd Inflammatory Skin Disease Summit (Vienna, Austria; 12/12/2018-12/15/2018)* *http://www.isds2018.org/* **POSTER presentation**.

34) Markovics A, Tóth KF, Sós KE, Magi J, Gyöngyösi A, Benyó Z, Zouboulis CC, **Bíró T**, **Oláh A** (2018): Sebaceous lipogenesis of human sebocytes is suppressed by nicotinic acid via the activation of hydroxycarboxylic acid receptor 2 (HCA2). *3rd Inflammatory Skin Disease Summit (Vienna, Austria; 12/12/2018-12/15/2018)* *http://www.isds2018.org/* **POSTER presentation**.

35) Tóth KF, Markovics A, Ádám D, Pénzes Zs, Angyal Á, Magi J, Pór Á, Kovács I, Zouboulis CC, **Bíró T**, **Oláh A** (2018): GPR119 is a potent novel regulator of human sebocyte biology. *3rd Inflammatory Skin Disease Summit (Vienna, Austria; 12/12/2018-12/15/2018)* *http://www.isds2018.org/* **POSTER presentation**.

36) Miltner N, Mihály J, Mechoulam R, **Bíró T** (2019): Assessment of the potential anti-inflammatory effect of phytocannabinoids in an in vitro inflammatory mouse model system. *17th EAACI Immunology Winter School, Basic Immunology Research in Allergy and Clinical Immunology, 2019.01.24-27., Trysil, Norway* **POSTER presentation.**

37) Tóth KF, Ádám D, Kis NG, Hegyi Z, Pénzes Zs, Gyetvai Á, Paus R, **Bíró T**, **Oláh A** (2019): A sejtfelszínen és mitokondriálisan kifejeződő CB1 receptor szubpopulációk szerepének vizsgálata epidermális keratinocitákon. *Annual meeting of the Hungarian Physiological Society (Budapest, Hungary; 06/05/2019-06/08/2019)* *http://www.eqcongress.hu/kongresszusadat/fame/* **POSTER presentation**.

38) Tóth KF, Ádám D, Arany J, Faragó P, Arbiser JL, Zouboulis CC, **Bíró T**, **Oláh A** (2019): The putative tribbles homolog 3 (TRIB3) activator honokiol suppresses lipogenesis, and exerts anti-proliferative as well as anti-inflammatory effects on human sebocytes. *49th Annual Meeting of ESDR (Bordeaux, France; 09/18/2019-09/21/2019)* *http://esdrmeeting.org/* **POSTER presentation**.

39) Tóth KF, Faragó P, Ádám D, Sárkány F, Arany J, Arbiser JL, Zouboulis CC, **Bíró T**, **Oláh A** (2019): A tribbles homolog 3 (TRIB3) aktivátor honokiol vizsgálata humán szebocitákon. *Annual meeting of the Hungarian Dermatological Society (Budapest, Hungary; 11/28/2019-11/30/2019)* *https://convention.hu/Rendezveny/Reszletek/MDT19/Koszonto* **POSTER presentation.**

40) **Oláh A** (2019): Cannabinoids and skin: The "c(ut)annabinoid" system as a novel player in regulating cutaneous mitochondrial biology. *10th Targeting Mitochondria Conference (Berlin, Germany; 10/27-29/2019)* https://www.targeting-mitochondria.com/ - **ORAL presentation (invited, keynote lecture).**

41) Miltner N (2019): Fitokannabinoidok potenciális gyulladáscsökkentő hatásának feltérképezése in vitro egér gyulladásos modellrendszerben. *DOSZ XXII. Tavaszi Szél Konferencia* *http://dosz.hu/hirek/xxii_tavaszi_szel_konferencia_programfuzet* **ORAL presentation.**

42) Miltner N (2019): Fitokannabinoidok potenciális gyulladáscsökkentő hatásának feltérképezése in vitro egér gyulladásos modellrendszerben. *X. Sántha Kálmán Tudományos Kerekasztal Debrecen, 2019.04.17.* **ORAL presentation.**

43) Miltner N (2019): Fitokannabinoidok potenciális gyulladáscsökkentő hatásának feltérképezése in vitro egér gyulladásos modellrendszerben. *A jog tudománya, a mindennapok joga II. nemzetközi konferencia Debrecen, 2019.04.04.* **ORAL presentation.**

REFERENCES (REFERENCES OF THE PIS ARE HIGHLIGHTED AS RED)

Bidaux G, Borowiec A, Gordienko D, Beck B, Shapovalov GG, Lemonnier L, et al. Epidermal TRPM8 channel isoform controls the balance between keratinocyte proliferation and differentiation in a cold-dependent manner. Proc. Natl. Acad. Sci. U. S. A. 2015;112(26):E3345-3354

Bidaux G, Borowiec A-S, Prevarskaya N, Gordienko D. Fine-tuning of eTRPM8 expression and activity conditions keratinocyte fate. Channels Austin Tex. 2016;10(4):320–31

Bieber T. Atopic dermatitis. N. Engl. J. Med. 2008;358(14):1483–94

Dobrosi N, Tóth BI, Nagy G, Dózsa A, Géczy T, Nagy L, et al. Endocannabinoids enhance lipid synthesis and apoptosis of human sebocytes via cannabinoid receptor-2-mediated signaling. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 2008;22(10):3685–95

Feichtinger RG, Sperl W, Bauer JW, Kofler B. Mitochondrial dysfunction: a neglected component of skin diseases. Exp. Dermatol. 2014;23(9):607–14

Gertsch J, Leonti M, Raduner S, Racz I, Chen J-Z, Xie X-Q, et al. Beta-caryophyllene is a dietary cannabinoid. Proc. Natl. Acad. Sci. U. S. A. 2008;105(26):9099–104

Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, et al. Psoriasis. Nat. Rev. Dis. Primer. 2016;2:16082

Griffiths CEM, van de Kerkhof P, Czarnecka-Operacz M. Psoriasis and Atopic Dermatitis. Dermatol. Ther. 2017;7(Suppl 1):31–41

Hamanaka RB, Chandel NS. Mitochondrial metabolism as a regulator of keratinocyte differentiation. Cell. Logist. 2013;3(1):e25456

Karsak M, Gaffal E, Date R, Wang-Eckhardt L, Rehnelt J, Petrosino S, et al. Attenuation of allergic contact dermatitis through the endocannabinoid system. Science. 2007;316(5830):1494–7

Kubo A, Nagao K, Amagai M. Epidermal barrier dysfunction and cutaneous sensitization in atopic diseases. J. Clin. Invest. 2012;122(2):440–7

Kuo I-H, Carpenter-Mendini A, Yoshida T, McGirt LY, Ivanov AI, Barnes KC, et al. Activation of epidermal toll-like receptor 2 enhances tight junction function: implications for atopic dermatitis and skin barrier repair. J. Invest. Dermatol. 2013a;133(4):988–98

Kuo I-H, Yoshida T, De Benedetto A, Beck LA. The cutaneous innate immune response in patients with atopic dermatitis. J. Allergy Clin. Immunol. 2013b;131(2):266–78

Kupczyk P, Reich A, Hołysz M, Gajda M, Wysokińska E, Kobuszewska A, et al. Opioid Receptors in Psoriatic Skin: Relationship with Itch. Acta Derm. Venereol. 2017;97(5):564–70

Maccarrone M, Bab I, Bíró T, Cabral GA, Dey SK, Di Marzo V, et al. Endocannabinoid signaling at the periphery: 50 years after THC. Trends Pharmacol. Sci. 2015;36(5):277–96

Oláh A, Ambrus L, Nicolussi S, Gertsch J, Tubak V, Kemény L, et al. Inhibition of fatty acid amide hydrolase exerts cutaneous anti-inflammatory effects both in vitro and in vivo. Exp. Dermatol. 2016a;25(4):328–30

Oláh A, Bíró T. Targeting Cutaneous Cannabinoid Signaling in Inflammation - A "High"-way to Heal? EBioMedicine. 2017;16:3–5

Oláh A, Markovics A, Szabó-Papp J, Szabó PT, Stott C, Zouboulis CC, et al. Differential effectiveness of selected non-psychotropic phytocannabinoids on human sebocyte functions implicates their introduction in dry/seborrhoeic skin and acne treatment. Exp. Dermatol. 2016b;25(9):701–7

Oláh A, Szöllősi AG, Bíró T. The channel physiology of the skin. Rev. Physiol. Biochem. Pharmacol. 2012;163:65–131

Oláh A, Tóth BI, Borbíró I, Sugawara K, Szöllõsi AG, Czifra G, et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. J. Clin. Invest. 2014;124(9):3713–24

Pappas A. Epidermal surface lipids. Dermatoendocrinol. Taylor & Francis; 2009;1(2):72–6

Rasul A, El-Nour H, Lonne-Rahm S-B, Fransson O, Johansson C, Johansson B, et al. Serotonergic Markers in Atopic Dermatitis. Acta Derm. Venereol. 2016;96(6):732–6

Schmuth M, Blunder S, Dubrac S, Gruber R, Moosbrugger-Martinz V. Epidermal barrier in hereditary ichthyoses, atopic dermatitis, and psoriasis. J. Dtsch. Dermatol. Ges. J. Ger. Soc. Dermatol. JDDG. 2015;13(11):1119–23

Shi VY, Leo M, Hassoun L, Chahal DS, Maibach HI, Sivamani RK. Role of sebaceous glands in inflammatory dermatoses. J. Am. Acad. Dermatol. 2015;73(5):856–63

Tóth KF, Ádám D, Bíró T, Oláh A. Cannabinoid Signaling in the Skin: Therapeutic Potential of the "C(ut)annabinoid" System. Mol. Basel Switz. 2019;24(5):918