# *INVESTIGATING AND EXPLOITING THE SEBOSTATIC POTENTIAL OF PHYTOCANNABINOIDS*

## FINAL REPORT

### Background, Aim

Acne vulgaris – which is characterized by pathologically elevated sebum production, inflammation, and hyperproliferation of the sebaceous glands (SG) – impairs the quality of life of millions worldwide. Despite extensive efforts, we still lack easily applicable, well-tolerated, and universally effective tools to manage these conditions. Hence, there is an emerging demand from both the medical community and the society to identify new therapeutic tools and targets.

We (and others) have previously shown that the emerging endocannabinoid system (ECS), which is fundamentally involved in the regulation of practically all organ systems of the human body, is functionally expressed in multiple compartments of the human skin and controls such key cutaneous processes as e.g. growth, differentiation, metabolism, immune responses, etc. With respect to the SGs, we have previously published that locally produced endocannabinoids (e.g. anandamide, 2-arachidonoylglycerol) dose-dependently induced lipid production in human sebaceous gland-derived immortalized, non-malignant SZ95 sebocytes which establish one of the best available cell culture systems of the human SG. Furthermore, we have also presented that these actions were selectively mediated by constitutively active, metabotropic cannabinoid receptor CB2-coupled signaling mechanisms involving e.g. the MAPK pathway as well as PPAR transcription factors and some of their target genes/molecules.

In addition, as intriguing data which established a solid basis for the current work, we have also found that Cannabidiol (CBD), a major non-psychoactive derivative of *Cannabis sativa*, did not stimulate sebaceous lipid synthesis; instead, quite intriguingly, it markedly inhibited the lipogenic effects of the endocannabinoids on human sebocytes (both in cell and organ cultures). In addition, in further preliminary experiments, we have shown that other non-psychoactive phytocannabinoids also exerted sebostatic effects. Since these unexpected actions were (quite evidently) not mediated by the above CB2-induced signal transduction pathways, the involvement of other signaling mechanisms (including e.g. the ionotropic cannabinoid receptor TRP ion channels) was suggested.

Based on these intriguing data, a novel working hypothesis was established: According to this, it was proposed that non-psychoactive phytocannabinoids may be used to suppress the elevated lipid (sebum) production of SG-derived sebocytes seen under pathological conditions. The major aim of the current work therefore was to probe the validity of this hypothesis and to exploit whether various agents derived from the plant *Cannabis sativa* can be used as efficient “anti-acne” agents.

### Experimental design

There are no proper animal (e.g. murine, rabbit) models which can be used to assess the functional characteristics of the human SGs, as the overall “logic” of the furry animal skin is markedly different from that of the human one. Therefore, the majority of the research was carried out on in vitro cultures of human SG-derived

immortalized, non-malignant SZ95 sebocytes, the best currently available human model system for SGs. In addition, to translate the result obtained on in vitro cultured sebocytes to the in vivo conditions, key effects of the phytocannabinoids was also investigated on full-thickness human skin organ-cultures. In addition, we also planned to assess some effects of the phytocannabinoids in human skin transplant – SCID mouse model. As presented in the previous reports, our preliminary data indicated that we were able to establish and optimize this models. Unfortunately, however, repeated use of this model resulted in very uncertain, heterogeneous, and hardly repeatable data; therefore, quite sadly, we could not perform all of the planned experiments.

However, we were able to employ another model system which originally was not mentioned in the Work plan. Recent data clearly suggest that pathological alterations of epidermal keratinocytes (e.g. hyperproliferation, release of various pro-inflammatory cytokines) markedly contribute to the pathogenesis of acne vulgaris. Therefore, in the course of our experiments, we have also carried out significant amount of experiments of cultured human epidermal keratinocytes.

**Assessment of the desired "triple action" of CBD, as well as the signaling mechanism involved in mediating its effects**

As was introduced above, CBD effectively prohibited the lipogenic effects of endocannabinoids. Of further importance, CBD also prevented the lipogenic actions of other "pro-acne" agents such as arachidonic acid and the combined application of linoleic acid and testosterone. Moreover, by using lipidomics, we also found that CBD not only quantitatively but also qualitatively normalized the augmented lipogenesis of human sebocytes. These data suggested that CBD may act as a "universally effective" lipostatic agent.

However, in order to label CBD as a potential "anti-acne drug", it should ideally counteract the other two key pathological events of acne vulgaris, i.e. hyperproliferation and inflammation of SG-derived cells. Importantly, we were able to provide novel evidence that CBD dose dependently (and quite remarkably) inhibited cellular proliferation of human sebocytes without compromising their viability. Moreover, in parallel to the above lipostatic and sebostatic (but, notably, not sebotoxic) effects, CBD was also proven to be anti-inflammatory as it completely normalized the elevated levels of various pro-inflammatory cytokines (e.g. interleukin IL1α and β, IL6, IL8, tumor necrosis factor TNFα) induced by the above "pro-acne agents" or Toll-like receptor (TLR) activators.

We then attempted to identify the down-stream cellular signaling mechanisms which underlie the "triple action" of CBD. By employing a wide array of techniques of cellular physiology (Ca-imaging, patch-clamping, FLIPR assays), molecular biology (molecular cloning, siRNA technology, quantitative "real-time" PCR), pharmacology (specific and selective agonists and antagonists), and biochemistry (Western blotting), our efforts resulted in the following intriguing findings (summarized in Figure 1):

i) On the one hand, we found that, on human sebocytes, CBD activates the ionotropic cannabinoid receptor transient receptor potential vanilloid-4 (TRPV4) ion channels (but not the also expressed TRPV1 and TRPV3) which effects mediate the

lipostatic and sebostatic actions of CBD. Indeed, when opened by CBD, TRPV4 channels mediate Ca-influx to the cells and the resulted elevation of intracellular Ca-concentration results in multiple cellular consequences including (but not limited to):

- ✓ cell cycle arrest and the down-regulation of the pro-proliferative molecule Ki67
- ✓ inhibition of the activities of the lipogenic signaling pathways, i.e. the MAPK system and PPARγ
- ✓ down-regulation of the "pro-lipogenic" NRIP1, which was identified as an essential factor for triglyceride storage
- ✓ up-regulation of ARHGAP9 which inhibits the "pro-lipogenic" ERK2, part of the MAPK system
- ✓ up-regulation of TRIB3, a key negative regulator of fatty acid synthesis and suppressor of intracellular triglyceride accumulation via inhibiting the transcriptional activity of PPARγ

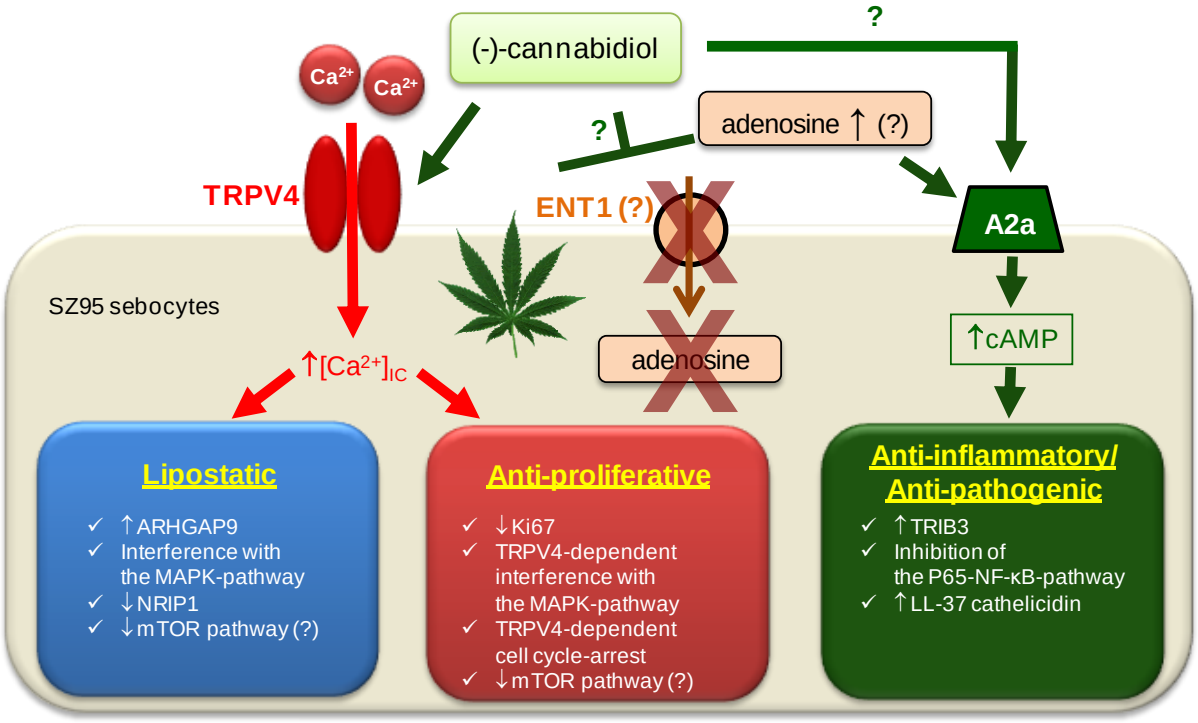


*Figure 1: The complex "triple action" of CBD on human sebocytes*

ii) On the other hand, in parallel to its effect on TRPV4, CBD directly or indirectly (via the increase of extracellular adenosine concentration) also activates adenosine receptor subtype 2a (A2a) which conveys the anti-inflammatory actions of the phytocannabinoid. Namely, A2a activation leads to:

- ✓ inhibition of the release of pro-inflammatory cytokines induced by TLR2 and TLR4 activation
- ✓ inhibition of the activity of the pro-inflammatory NFkB pathway
- ✓ up-regulation of MYBBP1A, a co-repressor of NFkB
- ✓ up-regulation of the anti-microbial peptides IL29 and LL-37 (cathelicidin)

Taken together, these results demonstrate that CBD exert a unique, "triple" anti-acne activity (lipostatic, anti-proliferative and anti-inflammatory actions) in vitro and ex vivo as well, with a quite complex, pleiotropic mechanism of action. Therefore, CBD and

possibly other modulators of the identified signaling pathways might be powerful novel tools in the treatment of acne vulgaris.

**Assessment of cellular effects of other phytocannabinoids on human sebocytes**

We have also performed the functional analyses of other phytocannabinoids on the cellular processes of human sebocytes. As part of our collaboration with GW Pharmaceuticals (the producer and the provider of phytocannabinoids), the assessment of Cannabigerol (CBG), CBG Botanical Drug Substance (CBG BDS: 70.6 w/w% CBG, 0.4 w/w% Cannabigevarin, CBGV, 0.1 w/w% Cannabichromene, CBC; Impurities: ~0.62 n/n% CBGV; ~0.142 n/n% CBC), CBGV, CBGV BDS (47.32 w/w% CBGV, 0.35 w/w% CBC, 0.08 w/w% Tetrahydro-cannabinol), CBC, Cannabidivarin (CBDV), and (-)-Δ9-tetrahydrocannabivarin (THCV) has been initiated and compared to the efficiency and action of CBD.

In initial acute studies (compounds were employed for 24-48 hrs), similar to CBD, all phytocannabinoids exerted dose-dependent sebostatic (i.e. suppression of neutral lipid production induced by arachidonic acid or anandamide without compromising cellular viability) and/or sebotoxic (i.e. both neutral lipid synthesis and viability is decreased) effects. Moreover, we also found that, when applied at suboptimal doses, neither phytocannabinoid was able to augment the sebostatic effects of CBD or Isotretinoin, the currently employed “best” anti-acne agent.

Therefore, chronic assays were also initiated in which human cultures were treated for up to 120 hrs and alterations of the sebum production was daily assessed. Similar to the acute studies, CBD was found to be the most effective anti-lipogenic agent in these assays as well. However, we have also shown that CBG BDS and CBGV BDS also exerted remarkable sebostatic/sebotoxic action when applied for at least 96 hrs. Moreover, suboptimal concentrations of CBG BDS were found to be highly efficient in augmenting the action of suboptimal doses of both CBD and Isotretinoin.

However, in the acute assays, the different phytocannabinoids exerted differential effects on the basal lipogenesis (in these assay, only CBG, CBGV, CBDV, CBC and THCV were assessed, after discussion with our collaborator on potential intellectual property issues). Indeed, at non-cytotoxic doses (i.e. ≤10 μM; 48-hr treatments), the effects of the phytocannabinoids could be categorized into three major groups: “endocannabinoid-like”, i.e. pro-lipogenic (CBG and CBGV), “neutral” (CBDV) and “lipostatic” (CBC and THCV) ones. Indeed, quite surprisingly, CBG and CBGV induced a small (cca. 20-30% as compared to the control), yet significant increase in the sebaceous lipid synthesis. In contrast to CBG and CBGV, CBDV behaved in a more “CBD-like” way having only negligible effects on the basal sebaceous lipid production, whereas CBC and THCV substantially suppressed it.

In the above assays, THCV showed, by far, the best efficacy which was comparable to that of CBD; therefore, in the next phase, our research efforts focused mainly on ThCV. We found that non-cytotoxic concentrations (≤10 μM) of THCV exerted a dose-dependent anti-proliferative action in course of 72-hr treatments. Moreover, at its highest test concentration, it appeared to stop the proliferation completely, demonstrating remarkable sebostatic (i.e. lipostatic + anti-proliferative) activity. It is also noteworthy that, similar to CBD, the cell count did not decrease below the level

of the 24-hr control, indicating a “pure” anti-proliferative action without any cytotoxic activity. Furthermore, THCV was able to fully abolish lipopolysaccharide (TLR4-activator) induced elevations in expression and release of several well-known, “acne-relevant” pro-inflammatory cytokines (i.e. IL-1α, IL-1β, IL6, IL-8, and TNFα) suggesting that it indeed exerted complex anti-acne effects targeting all the three key “sebocyte-specific” steps of the acne pathogenesis.

Taken together, these intriguing data collectively suggest that CBG and CBGV may have potential in the treatment of dry-skin syndrome. Of further importance, our novel findings also implicate that CBC, CBDV and especially THCV (whose efficacy and “triple action” was very similar to those of CBD, see above) show promises to become highly efficient, novel anti-acne agents.

During our work, we also started the identification of the putative mechanisms of actions of selected phytocannabinoids. Since these experiments are still ongoing, we can report only on rather preliminary data. Nevertheless, our findings (obtained using a series of molecular and cellular physiology techniques) suggest that the strong “anti-acne” effects of THCV are most probably mediated by the activation of certain TRP ion channels (TRPV1, V2, V3 or V4) expressed by human sebocytes (since effects of THCV showed striking similarities to those of CBD, the involvement of TRPV4 is most likely).

**Assessment of cellular effects of phytocannabinoids on human epidermal keratinocytes**

As mentioned above, it is generally accepted that epidermal keratinocytes may also play a role in the development of acne vulgaris, e.g. by releasing a multitude of pro-inflammatory cytokines. Moreover, the remarkable anti-inflammatory actions of phytocannabinoids measured on human sebocytes implicated that phytocannabinoids could be efficient, yet safe novel tools in the management of cutaneous inflammations in general. Therefore, we have also assessed effects of certain phytocannabinoids – namely CBD, cannabidiol acid (CBDA), CBDV, CBG, CBGV, and THCV – on the inflammatory response of human epidermal keratinocytes induced by either TRL3 activation, UVB irradiation, or the co-application of Thymic stromal lymphopoietin (TSLP) and *Staphylococcus enterotoxin B* (SEB).

Importantly, all investigated phytocannabinoids exerted certain degrees of anti-inflammatory effects in the different human epidermal keratinocyte models (i.e. significantly prevented the upregulation of synthesis and release of multiple cytokines such as IL6 and IL8); however, their efficacy markedly differed from one another. Namely, in all models, CBD, CBDV, and THCV showed the most remarkable anti-inflammatory effects which were realized already at low μM concentrations. These data further support our concept that phytocannabinoids might be employed as effective anti-inflammatory agents in various forms of inflammatory skin conditions including (but not limited to) e.g. acne vulgaris and atopic dermatitis.

Another “keratinocyte-specific” step of acne pathogenesis is the hyperproliferation of the keratinocytes (similar to that of SG-derived sebocytes). Since we have shown that CBD and THCV exhibited very significant suppression of (hyper)proliferation of human sebocytes, we also tested whether the above phytocannabinoids affect growth of epidermal keratinocytes. For these experiments, we employed

immortalized human keratinocyte cell lines (HaCaT, HPV-Ker) which have highly accelerated growth characteristic. As expected, all phytocannabinoids suppressed (hyper)proliferation of both keratinocyte cell types in a dose dependent manner (significant growth inhibition was achieved already at 1-3 μM concentration), with CBD, CBG and THCV being the most effective ones. These findings, on the one hand, further argue for the potential application of phytocannabinoids in acne. On the other hand, however, these intriguing results also invite further trials to assess the effects of phytocannabinoids in another highly prevalent skin disease, psoriasis, which is characterized by epidermal hyperproliferation and cutaneous inflammation.

**Collaborative work**

As usual in fundamental research in general, during the course of the current projects, multiple collaborations were initiated in which findings of our work were extended and re-visited from different aspects. Below we summarize main results of the most important collaborative efforts:

- ✓ With the Laboratory of László Nagy (Univ. Debrecen, Dept. Biochemistry), we participated in uncovering the role of PPARγ-coupled signaling (which is fundamentally involved in mediating the effects of endocannabinoids in sebocytes) in sebaceous differentiation and lipogenesis;
- ✓ With the Laboratory of Andrea Szegedi (Univ. Debrecen, Dept. Dermatology), we have started the assessment of various pathogenetic steps, the skin barrier alterations, and the role of the ECS in certain inflammatory diseases (e.g. atopic dermatitis, hype-IgE syndrome);
- ✓ With the Laboratory of György Panyi (Univ. Debrecen, Dept. Biophysics), we clarified the role of the ionotropic cannabinoid receptor TRPV2 in the regulation of human dendritic cell functions;
- ✓ With the Laboratories of Zsuzsanna Helyes and Dóra Reglődi (Univ. Pécs), we investigated the role of Pituitary Adenylate-Cyclase Activating Polypeptide (PACAP) in mediating the neurogenic skin inflammation induced by the activation of another ionotropic cannabinoid receptor, TRPV1;
- ✓ With the Laboratory of Lajos Kemény (Univ. Szeged, Dept. Dermatology), we have started the evaluation of various *Propionibacterium acnes* strains (key bacteria involved in the pathogenesis of acne vulgaris) on multiple skin cell populations.

**Impact, Innovation, Future perspectives**

The fundamental research project performed in this OTKA project was initiated with a highly specific goal; namely, to reveal the translational relevance of the application of phytocannabinoids is certain skin diseases. We do believe that our experimental findings that phytocannabinoids inhibit pathologically upregulated lipogenesis of SGs, suppress sebaceous and epidermal proliferation, and exert remarkable anti-inflammatory actions clearly demonstrate that certain *Cannabis sativa*-derived preparations are indeed promising candidates for future use in dermatological practice.

Evidently, with these pre-clinical findings obtained in the best available human models, as part of further R&D innovations, one should initiate and sponsor human trials to explore the actual use of phytocannabinoids in the clinical management of acne vulgaris (and related inflammatory dermatoses). We are more than happy to report that a USA-based company (whose name cannot be revealed yet, due to non-

disclosure agreements and intellectual property protection) has established a long-term relationship with our Laboratory and – besides igniting the "innovation chain" (e.g. further intellectual property issues, feasibility studies, market research and positioning, marketing, etc.) – is in the process of organizing a human clinical trial (hopefully in Hungary). In this trial, first topically applicable, phytocannabinoid-containing formulations will be tested in acne vulgaris patients. If this trial is successfully closed, 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.

Another future perspective is the use of phytocannabinoids (either in topical or systemic formulations) in other skin diseases. During the course of the current OTKA project (due to our publications and presentations at international conferences), several companies have approached us to initiate pre-clinical work in the field. After serious discussions, we are happy to report that, at the beginning of 2015, we signed 2 significant (>200,000 Euro) contracts with GW Pharmaceuticals (UK) and InMed Pharmaceuticals (Canada) to explore the use of phytocannabinoids in certain orphan skin diseases such as e.g. epidermolysis bullosa simplex. Since these companies are markedly interested in not only pre-clinical but also in clinical developments, we strongly hope to be able to report soon on the outcome of these trials in the above diseases.

**Dissemination, Achievements**

In the original Work plan of the proposal, we planned to publish/submit 2 papers during the course of the project, and also start preparing another one on the results of the current work. We believed that this plan was markedly outperformed, as indicated by the below list.

<u>In extenso publications related to the project</u>

1. Oláh A., Tóth I.B., Borbíró I., Sugawara K., Szöllősi A.D., Czifra G., Pál B., Ambrus L., Kloepper J., Camera E., Ludovici M., Picardo M., Voets T., Zouboulis C.C., Paus R., Bíró T. (2014): Cannabidiol Exerts Sebostatic and Anti-Inflammatory Effects on Human Sebocytes. J. Clin. Invest. 124(9):3713-3724. IF: 13,215 – *This paper describes the universal "anti-acne" effect of CBD. We are very proud that we could publish this "story" in one of the most prestigious international translational journals.*
2. Oláh A., Markovics A., Szabó-Papp J., Szabó P.T., Stott C., Zouboulis C.C., Bíró T. (2015): Differential Effectiveness of Selected Non-Psychotropic Phytocannabinoids on Human Sebocyte Functions Implicates Their Introduction in Dry/Seborrheic Skin and Acne Treatment. Exp. Dermatol. (Submitted for publication) IF: 3,762 – *This paper describes the differential effects of various phytocannabinoids on human sebocyte biology, and their potential dermatological applications.*
3. Oláh A., Mihály J., Ambrus L., Markovics A., Tóth B. I. Stott C., Kemény L., Bíró T. (2015): Potent Anti-Inflammatory Effects of Various Phytocannabinoids in Multiple Models of Human Epidermal Inflammation. (Manuscript in preparation) – *This paper summarizes the remarkable anti-inflammatory effects of phytocannabinoids measured on human epidermal keratinocytes.*

*The submission of the paper is halted to explore the possibilities of intellectual property protection and other innovation-related issues with our collaborator GW Pharmaceuticals. After taking care of these matters, the paper is planned to be submitted to either J. Invest. Dermatol. or Exp. Dermatol. As this paper is not submitted yet, it is NOT listed in the publication list at the OTKA website.*

Review articles related to the project

We are also very happy to report that, during the 2012-2015 period, we wrote 7 review papers on the role of the ECS in skin physiology and pathophysiology. Within these publications, we are especially proud to be involved in the writing a Community review (No. 6 in the below list), in which leading researchers of the field summarize recent developments in the ECS; our task was to collect findings on the cutaneous cannabinoid system.

1. Oláh A, Szöllősi AG, Bíró T. (2012): The channel physiology of the skin. Rev Physiol Biochem Pharmacol. 163:65-131. IF: 1
2. Tóth IB, Bíró T. (2013) TRP channels and pruritus. Open Pain J 6:62-80 (Suppl 1: M8) IF: 0
3. Nilius B, Bíró T. (2013): TRPV3: a 'more than skinny' channel. Exp Dermatol. 22(7):447-52. IF: 4,115
4. Nilius B, Bíró T, Owsianik G. (2013) TRPV3: time to decipher a poorly understood family member! J Physiol. J. Physiol. 592(Pt 2):295-304. IF: 5,37
5. Tóth B.I., Oláh A., Szöllősi A.G., Bíró T. (2014): TRP Channels in the Skin. Br. J. Pharmacol. 171(10):2568-2581. IF: 4,842
6. Maccarrone M., Bab I., Bíró T., Cabral G.A., Dey S.K., Di Marzo V., Konje J.C., Kunos G., Mechoulam R., Pacher P., Sharkey K.A., Zimmer A. (2015): Endocannabinoid Signaling at the Periphery: 50 Years After THC. Trends Pharmacol. Sci. 36(5):277-296. IF: 11,539 – *Community review: all authors participated equally in the work*
7. Tóth B.I,. Szallasi A., Bíró T. (2015): Transient Receptor Potential Channels and Itch: How Deep Should We Scratch? Handb. Exp. Pharmacol. 226:89-133. IF: 0

Collaborative publications

The aforementioned results of the new collaborative projects have been published in the below papers:

1. Szöllősi A.G., Oláh A., Tóth I.B., Papp F., Czifra G., Panyi G., Bíró T. (2013): Transient Receptor Potential Vanilloid-2 Mediates the Effects of Transient Heat Shock on Endocytosis of Human Monocyte-Derived Dendritic Cells. FEBS Lett. 587(9):1440-1445. IF: 3,341
2. Dózsa A., Dezső B., Tóth B.I., Bácsi A., Poliska S., Camera E., Picardo M., Zouboulis C.C., Bíró T., Schmitz G., Liebisch G., Rühl R., Remenyik E., Nagy L. (2014): PPARγ-Mediated and Arachidonic Acid-Dependent Signaling is Involved in Differentiation and Lipid Production of Human Sebocytes. J. Invest. Dermatol. 134(4):910-920. IF: 7,216
3. Helyes Zs., Kun J., Dobrosi N., Sándor K., Németh J., Perkecz A., Pintér E., Szabadfi K., Gaszner B., Tékus V., Szolcsányi J., Steinhoff M., Hashimoto H., Reglődi D., Bíró T. (2015): Pituitary Adenylate-Cyclase Activating Polypeptide is Up-Regulated in Murine Skin Inflammation and Mediates Transient Receptor Potential Vanilloid-1-Induced Neurogenic Edema. J. Invest. Dermatol. 135(9):2209-2218. IF: 7,216

4. Mócsai G., Gáspár K., Dajnoki Z., Tóth B., Gyimesi E., Bíró T., Maródi L., Szegedi A. (2015): Investigation of Skin Barrier Functions and Allergic Sensitization in Patients with Hyper-IgE Syndrome. J. Clin. Immunol. (Epub ahead of print) IF: 3,184

PhD Dissertations

Another important achievements of the project are that 2 young scientists have either defended or submitted their PhD theses which were chiefly based on results and publications of the current work:

1. Szöllősi AG: Role of the endocannabinoid system in the regulation of biological processes of the skin (defended PhD thesis, 2014)
2. Oláh A: Role of (endo)cannabinoid signaling in controlling certain pathophysiological processes of the human skin (submitted PhD thesis)

Public relations

Our findings on the “anti-acne” effects of CBD, published in the prestigious J. Clin. Invest., attracted remarkable international and national public press attentions. This interest was realized in numerous appearances in visual, audible, press and electronic media; i.e. multiple television (e.g. RTL Klub) and radio (e.g. MR1 Kossuth Rádió) interviews, many publications in national public journals (e.g. Magyar Nemzet, Népszabadság), and several hundreds of entries at the internet (see e.g. under “kannabidiol & pattanás” key words in Google). We do believe that these appearances perfectly fit to the overall aim of OTKA (NKFIH) and the Hungarian Academy of Sciences to broadly disseminate the scientific findings towards the tax payers and the lay public in general.

Other achievements

According to the directives of the OTKA (NKFIH), in the Final report, we do not list the numerous (>20) international and national conference appearances of the group where oral and poster presentations were reported on the work of the current project. However, we do believe that it is important to mention 2 significant achievements:

1. Attila Oláh, based mainly on our J. Clin Invest. publication and oral presentations at Dermatological meetings, has been awarded by the prestigious Research Award of Galderma (with a research support of 10,000 Euro), a leading pharmaceutical company in the field of acne therapy and skin disease applications in general.
2. Attila Oláh has been selected as Member of the Academy of Future Leaders in Dermatology, a prestigious educational and mentoring program of the European Society for Dermatological Research.

Finally, it is worth mentioning that the PI of the current work was asked by 2 leading journals of the field to write commentaries on recently published papers. Since the “nature” of such commentaries does not permit mentioning any grant support (hence the OTKA number was not indicated), these commentaries are NOT listed among the papers of the final report at the OTKA website. Yet, since they are peer reviewed, we list them here:

1. Bíró T. (2014): Human Sebocytes: The New Leptin Connection? Br. J. Dermatol. 171(6):1288. IF: 4,274
2. Picardo M., Mastrofrancesco A., Bíró T. (2015): Sebaceous Gland – A Major Player in Skin Homeostasis. Exp. Dermatol. 24(7):485-486. IF: 3,762