PROJECT PROPOSAL: ***Nutrigenomic influences of metformin and Omega3 fatty-acids on the clinical, metanolical and immunological profile of medium-severe psoriasis patients***
PROPUNERE DE PROIECT: ***Influențe nutrigenomice ale metforminului și acizilor grași Omega3 asupra profilului clinic, metabolic și imunologic la pacienții cu psoriazis mediu-seve.***

A. Curriculum Vitae of the project leader

Personal information:

First name(s)/Surname(s): Voiculescu Vlad-Mihai
Nationality: Romanian, Date of birth: November 25, 1982
Gender: Male
Address(es): 7A J. S. Bach street, ap. 4, 020202, Bucharest, Romania
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Work experience:

2018 – present: Lecturer of Dermatology and Venerology "Carol Davila" University of Medicine and Pharmacy, Bucharest
2016 - present: Senior consultant of Dermatology and Venerology, Elias Universitary Emergency Hospital, Bucharest
2015 - present: Assistant Professor of Dermatology and Venerology, "Carol Davila" University of Medicine and Pharmacy, Faculty of Medicine
2015 – present: Member of the scientific editorial board for The Journal of the Romanian Society of Dermatology and Venerology
2014 - present: Reviewer for Acta Endocrinologica (Bucharest)
2013 - 2016: Specialist in Dermatology and Venerology Elias Universitary Emergency Hospital
2009 - present: secretary of the committee of both specialist and senior consultant national examination in Dermatology and Venerology
2008 - 2015: Junior Teaching Assistant in Dermatology and Allergology, "Carol Davila" University of Medicine and Pharmacy
2009-2011: Medical consultant in clinical dermatological related issues over the internet, Adecco resurse umane srl, Romania Type of business or sector: Medicine
2002 – 2007: Student representative in the Faculty of Medicine executive board

Education and training:

2016: Senior consultant of Dermatology and Venerology, , Elias Universitary Emergency Hospital

2015 - 2018: Assistant Professor of Dermatology and Venerology “Carol Davila” University of Medicine and Pharmacy, Bucharest

2015: Doctor in medical sciences, PhD: "Genetic and biochemical markers that impact evolution of psoriasis with metabolic syndrome patients”

2009 - 2014: PhD-student “Carol Davila” University of Medicine and Pharmacy

2013: Specialist in Dermato-Venerology, Elias Universitary Emergency Hospital

2008-2012: Dermatology and Venereology resident, University Emergency Hospital, Bucharest

2001-2007: Medical Doctor (student) “Carol Davila” University of Medicine and Pharmacy, Bucharest

Professional membership:

2015 - present: member of Romanian Society of Dermatology Board of Directors

2013 - present: member of EADV Alumi Club

2011 - present: IDS member

2010 - present: EADV Junior Member (no. J 9648)

2008 - present: member of Romanian Society of Dermatology

2008 - present: member of the Bucharest Association of Physicians (CMB)

Awards and postgraduate courses:

2013 - Michael Hornstein Memorial Fellowship, EADV Spring Symposium, Kracow 2013

2012 - Summer School - Dermatopathology, part 2, 25-29 June, LKH Graz (AT)

2011 - Summer School - Dermatopathology, part 1, 11-15 July, LKH Graz (AT)

2001: 3rd prize winner in the National Olympics of Biology

2000: 1st prize (1st place) winner in the National Olympics of Biology

Personal skills and competences:

Mother tongue: Romanian

Other languages: English (C1/Proficent), French (B1/Advanced), Greek (C1/Beginner)

Communication and pedagogical skills acquired through my duties as a medical doctor and teaching assistant.

Computer skills (advanced) in Windows, Office (Microsoft Word, Power Point, Excel); Adobe Photoshop; QuarkExpress; Internet

I am a holder of a Romanian category B driving license

Additional information:

Humanitarian – volunteer and participant as a consulting physician to „Opening Eyes" (a medical testing programme for children with Down syndrome), part of Special Olympics, Buzau, 2009

PERSONAL INTERESTS - Art photography. Practiced many sports particularly tennis, football and swimming. I enjoy traveling and experiencing different cultures.

Significant and representative scientific achievements

The research field of the project leader has done research in two directions: skin inflammatory diseases (mainly psoriasis, because some family members are affected by this disease) and skin cancers. In both directions the main approach was from a clinical and molecular manner. The first direction led to the achievement of a PhD diploma in Medicine (in 2015), with a thesis entitled "Genetic and biochemical markers that impact evolution of psoriasis with metabolic syndrome patients". Also, this research interest led to the winning in the beginning of 2015 of a 2 year-research grant entitled (Genetic and molecular correlations regarding treatment response in patients with psoriasis and metabolic syndrome), in the "Young researcher Competition" by "Carol Davila" University of Medicine and Pharmacy. This led to a communication within the 2016 National Congress of Dermatology and to two original articles that are in the process of submitting.

The other direction was more rewarding to date since it led to a publication in an international peer-reviewed journal (2016 IF of 2,173) of a number of three articles on proteomics of skin cancers. This first three articles received prices in the national competition "Premierea rezultatelor cercetarii - articole 2016", funded by UEFISCDI, code PN-III-P1-1.1-PRECISI-2016-13308

The project leader has been also invited to hold oral presentations about the researched topics at the Romanian National Congress in 2016.

The present project proposal would actually be a follow-up of the PhD thesis and of the "Young researcher" grant, in which we would like to have a better insight of the genetic and molecular mechanisms that influence treatment response in complicated psoriasis patients.

B. Nutrigenomic influences of metformin and Omega3 fatty-acids on the clinical, metabolical and immunological profile of medium-severe psoriasis patients.

Abstract

Following the clinical observation that medium - severe psoriatic (Ps) patients with metabolic disturbances (metabolic syndrome (metS)) that were given Omega3 essential fatty acids as a dietary supplement (and/or other immunomodulating agents, eg. metformin) have had a better clinical response to the specific anti-psoriatic treatment, we propose to study the clinic, metabolic and immunologic profiles of these patients given their genetic traits in order to identify and define specific subtypes of patients that would benefit from the nutrigenomic approach.

Research project description

Issues

Psoriasis is a chronic inflammatory disorder of unknown origin characterized by an underlying immunological disruption that has a high social and economical impact and with a substantial negative impact on patients' quality of life. The medium and severe types affect 2-3% of the general population, with mild and discrete forms affecting as much as up to 8-10% [1].

Abnormal keratinocyte proliferation and differentiation of the epidermis and systemic or local inflammation are common features of the disease results in the formation of chronic erythematous and scaly lesions.

Also, an overproduction of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), will ultimately lead to insulin resistance and the development of metabolic syndrome, type 2 diabetes mellitus, intimal proliferation, atherosclerosis, and nonalcoholic fatty liver disease (NAFLD) [2]. Therefore psoriatic patients have an increased risk of cardiac disease, an important and previously unidentified cause of morbidity and mortality.

Metabolic syndrome has been described and defined as the ensemble of cardiovascular risk factors, including central obesity, atherogenic dyslipidemia, hypertension, and glucose intolerance, influenced by lifestyle, genetic predisposition and the environment. Metabolic syndrome triples a patient's risk of developing type 2 diabetes mellitus and doubles the risk of developing cardiovascular disease [3].

This syndrome is characterized by a fundamentally TH1 inflammatory response, much the same as in psoriasis, which suggests a potentially shared inflammation mechanism. Another possible

explanation for predisposition to the development of metabolic syndrome by patients with psoriasis lies with behavioral habits or in the psychological impact of the disease. Also it is possible that it is the actual metabolic syndrome that promotes development of psoriasis. This syndrome is a strong predictor of cardiovascular diseases, diabetes and stroke [4].

Omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), reduce symptoms in many inflammatory skin diseases, limiting the spreading of the inflammatory process [4]. In the skin, the main route for the synthesis of leukotrienes is 15-lipoxygenase, giving rise to 15-hydroxyeicosatetraenoic acid. Moreover, the epidermis can convert the leukotriene A4 (produced by the polymorphonuclear leukocytes) into leukotriene B4, one of the main inflammation mediators.

The intake of EPA and DHA leads to the formation of hydroxylated metabolites through 15-lipoxygenase, 15-hydroxyeicosapentaenoic acid, and 15-hydroxydocosahexaenoic acid. Both substances are potent inhibitors of the 5-lipoxygenase of mononuclear cells, thus limiting the synthesis of proinflammatory leukotrienes LTB4, LTC4, and LTD4.

Several studies have been performed to evaluate the efficacy of the daily supplementation of EPA and DHA in patients with psoriasis [5], with an improvement observed in their mean Psoriasis Area and Severity Index (PASI) score, as well as in clinical symptoms, particularly in pruritus. Yet, to this date, no studies did a more than brief description of the immunological and genetic profiles of these patients.

Metformin, a biguanide-class drug, has proven efficacy in the treatment of prediabetes and leads to a pronounced and sustained weight loss in overweight individuals. We expect that addition of metformin to other therapies can lead to positive effects with respect to the PASI score, reduction of the weekly doses of the concentional drugs and of elevated cardiovascular risk factors in patients with metabolic syndrome and psoriasis [6].

Although there is no cure for psoriasis, some biological therapies targeting specific immune components have recently proven to be highly effective [7]. Earlier biological agents, including efalizumab and alefacept, primarily disrupt the activation and migration of T cells, whereas agents like infliximab, etanercept, and adalimumab target TNF-α. Recently, agents like ustekinumab and ABT-874, which target the p40 subunit of both IL-12 and IL-23, have been developed, as well as new anti-IL-17 agents and anti-IL-23p19 agents [7] and [8]. However, approximately 20%–30% of psoriasis patients fail to respond to biological therapies [9]. Therefore, valuable biomarkers for the diagnosis, prognosis, and treatment of psoriasis are of great significance for clinicians in designing effective and personalized therapies.

Despite all this, there are a number of limitations to the current approach. In the past years many attempts to define a valid profile or biomarker had been made with little to no success. In part this is due

to the fact that both psoriasis and metabolic syndrome are multifactorial diseases with no apparent cause yet discovered. Also, researched had focused only at one kind of profile at a time, none developed an integrative and exhaustive study yet. We propose a different approach, selecting all the useful parameters from each group of profiles and investigate them combined with a novel investigation of miRNAs.

Several studies have identified valid biomarkers of psoriasis from cytokines, specific proteins or microRNAs (miRNAs) [10]. However, there are still no specific biomarkers that can accurately predict the progression of disease and therapeutic effects. miRNAs are a large family of highly conserved small non-coding RNAs that regulate diverse biological processes by modulating gene expression at the post-transcriptional level [11]. Numerous studies have reported that the abnormal expression of miRNAs plays an important role in the pathogenesis of some skin diseases, such as psoriasis, scleroderma, atopic dermatitis, and lupus [12]. In a very recent study (aug. 2016) Zhibo Yang et al. showed that miRNA-146a and miRNA-99a are potential biomarkers in vulgar psoriasis for disease activity and treatment outcome [13].

In Romania, the first cause of mortality is cardiac disease and therefore prevention requires early identification of individuals at risk of developing cardiovascular disease in patients that are clinically asymptomatic. Metabolic syndrome may be a strong predictor for developing heart disease but psoriasis lesions on the skin surely represent an earlier sign of future cardiac burden This can prove a useful sign so that intensive preventive therapies can be taken to slow the progression of disease.

Considering the above mentioned aspects of metabolic interference with psoriasis, we aim to use as adjuvant therapy Omega3 essential fatty acids (alone or in conjunction with metformin).

Objectives

The diagnosis of psoriasis is primarily focused around the clinical morphologic evaluation of a skin lesion, as there are no other clearly-defined diagnostic criteria. The differential diagnosis of psoriasis is abundant and depends on the clinical subtype. Histopathological analysis of a skin biopsy specimen is currently the most common and efficient diagnosis method. Nonetheless, a skin biopsy is invasive and the pathological alterations are not obvious in early stages of psoriasis. Therefore, there is an urgent need to develop non-invasive diagnostic tests or biomarkers with high sensitivity and specificity for psoriasis.

The main objectives are to:

1. assess the effects of the association of omega3 and/or metformin in psoriasis and metabolic syndrome

2. define the clinic, metabolic, immunologic and genetic profiles of the patients that responded to the add-on therapy in search of potential immunologic and genetic biomarkers of the disease activity and treatment response.

Secondary objectives are:

- to investigate the possible mechanisms through which Omega3 fatty acids and metformin determine an improvement in psoriasis activity (either by direct action or by ameliorating metS or both)

- to evaluate the role as novel biomarkers for miRNA-146a and miRNA-99a (as stated by Zhibo Yang et al. 2016) for the Romanian population and

- to increase the awareness of participants regarding their skin condition which actually is affecting their organism beyond the skin.

The project brings an original approach to discovering potential biomarkers by creating different profiles of the patients (clinic, metabolic, immunologic and genetic) and integrating all the resulted data. **To our knowledge no such extensive studies have been made to this day!**

Another important approach is to address the participants in groups, explaining in a more detailed yet easy to process manner the true extent and implications of their disease, hoping that this will greatly improve their adherence to the present study (short-term) and to the anti-psoriatic treatment (long-term).

Impact

Psoriazis is a chronic disease that accumulates a psychoemotional burden (DLQI study pso patients worse than neoplastic patients) [14] as well as systemic complications, especially in the cardiovascular spectrum. A consistent number of psoriatic patients present with metabolic syndrome manifestations, a known risk factor for heart disease. Therefore, when meeting the objectives of the current study, we will be able to outline the clinical and biological profiles of patients who suffer from both psoriasis and metabolic syndrome, and also choose an adequate treatment (preventive or not).

The correct identification of patients that could benefit from immunomodulatory therapies may lead to the creation of a maintenance treatment scheme, in order to prevent relapses. Using complementary treatments such as Omega3, we may be able to either prevent cardiac disease as well as metabolic syndrome, or defer the installation of these diseases. We may also be able to treat psoriasis improving therapeutic response. There is no available treatment that may prevent cardiac disease in these patients, but Omega3 and/or metformin use may prevent such disorders, especially in those reporting a family history of cardiac events. Moreover preventing cardiovascular disease may reduce systemic inflammatory complications and visceral burden.

Improving quality of life in psoriatic patients has a number of benefits including, increasing productivity and patient compliance. Also self-esteem improves greatly inversely-related to DLQI and is an important contributor to the social and work status of patients.

The studied cytokine network (TNF alpha, IFN gamma, IL17, IL22, VEGF, IL10, Oxidative Stress/ABTS, adiponectin, leptin, resistin) and genetic traits (MiRNA – 146a and MiRNA – 99a), in combination with clinical parameters and routine blood tests, will permit the contouring of possible risk and response patterns.

MiRNAs, an extensively studied class of molecules in inflammatory disease, but less studied in psoriasis, has the capacity to influence the transcription of certain genes. This is an acenstral mechanism, with almost perfectly preserved sequences. Therefore, in the eventuality of MiRNA confirmation as a biological marker for clinical and treatment response outcome may be a step forward regarding personalized medicine in this category of patients. Furthermore, the efficacy of certain molecules or combination molecules in diminishing systemic inflammation and psoriatic profiles can ultimately determine the lowering of the global healthcare burden and, also, the adverse effects of conventional medications, such as methotrexate, cyclosporine.

This study will open new research directions in the field of personalize medicine because it integrates data from many different aspects of disease (clinical, metabolical, immunological and genetic).

Methodology

Subjects and method

This study will be performed with patients from a tertiary dermatological clinic (at "ELIAS" University Emergency Hospital Bucharest, the project leader's current workplace).

Sixty patients will be included. A preliminary examination of all participants will consist of medical history, including details of systemic diseases, drug administration, cigarette smoking, trauma and exposure to ultraviolet radiation. The selection will be made according to the inclusion and exclusion criteria (defined below). Selected participants will be divided in three groups:

1. Psoriasis patients without metabolic syndrome (metS),
2. Psoriasis patients with metS and
3. Non-psoriatic patients with metS.

All groups will be gender and age matched. Each group will consist of 20 participants.

Inclusion criteria:

- Stable psoriasis activity for 3 months (regardless of treatment type). All patients will be monthly evaluated by PASI, DLQI, BSA (and this should not vary more then 25%).

- For selected participants => Metabolic syndrome (defined by modified ATP III criteria – at least 3 of the following components: 1. Abdominal obesity (waist circumference >90cm in men or >80 in women), 2. Triglycerides >150 mg/dl, 3. HDLc <40 mg/dl for men or <50 mg/dl for women, 4. BP (blood pressure) > 130/85 mmHg or receiving drug treatment for elevated BP, 5. Fasting plasma glucose >100 mg/dl or impaired glucose tolerance (defined as two-hour glucose levels of 140 to 199 mg per dL on the 75-g oral glucose tolerance test) or T2DM.
- PASI>5
- DLQI>5
- Age>18 yo

Exclusion criteria: known drug allergies to metformin and drug excipient of medications administered, psoriatic arthritis, pustular psoriasis, gutatte psoriasis, mild psoriasis (PASI < 5, DLQI < 5), poorly-controlled diabetes mellitus (Hb A1c>9mg/dl), concomitent infectious diseases, concomitent neoplastic diseases, pregnancy, presence of systemic autoimmunity.

The study will consist of 3 stages for the study (each with secondary activities):

Stage 1: Patient selection: All presenting patients with psoriasis will be admitted in the Dermatology ward of Elias University Emergency Hospital and will receive a general evaluation that will include clinical parameters (BMI, BP, waist/thigh circumference ratio, PASI, DLQI, BSA) and biological parameters (CBC, fasting glucose, HbA1c, cholesterol, triglycerides, HDL, LDL, liver and renal function tests). They will be screened for metS and organized in groups of 20. This stage will last 6 months. During this time **disease stabilizing** will be attempted (no variation in PASI, BSI and DLQI more than 25%) and if successful the participant will be included in one of the three groups.

Secondary activity: **Group information** - The groups will participate in awareness raising sessions (at least 7-8 participants) regarding their disease and, more importantly, its systemic complications in order to raise adherence to the study. These sessions will be held at ELIAS University Emergency Hospital, in the Lecture Hall, with minimal logistical costs (approximately 25 euros/session). This stage will last 1-2 months, and will be repeated before each of the following stages.

When the groups are completed an **evaluation** of previously mentioned clinical and biological parameters will be made and also measurement of serum TNF alpha, IFN gamma, IL17, IL22, VEGF, ROS/ABTS, adiponectin, leptin, resistin, IL10 and miRNAs (miRNA-146a and miRNA-99a) will be conducted. These special parameters (cytokines and miRNAs will be analyzed from serum of the patients stored at -80 degrees C at a -80 freezer in SUU ”Elias” Hospital which will be acquired in the project)

Stage 2: All patients will receive O3 capsules, 1000mg/day, after the main meal of the day, in order to facilitate absorbtion. This stage will last 3 months. All previously mentioned clinical and biological parameters, including serum dosing of cytokines and MiRNA will be repeated.

Group information for the next stage and clinical serum **measurement of followed parameters** will be made at the end of this stage.

Stage 3: All the patients will be administered metformin added to the existing treatment (antipsoriasis treatment + omega3 + metformin) 15 mg/day (a low dose enough to assess the immunological activity and to prevent the occurrence oh hypoglycemia) for a period of 3 months. Serum **measurement of followed parameters** will be made at the end of this stage.

After Stage 2 ant Stage 3 partial accumulated data will be statistically analyzed and communicated. In the last 2 months of the project all data will be integrated, analyzed and communicated in high impact factor journals and/or international scientific meetings (Congresses, Conferences)

From our past experience the most difficult part of the project will be the constitution of groups and maintaining patients' interest in the project. Therefore we see as mandatory the informed group sessions with two important roles: first to raise the level of understanding of psoriasis (and its compications) among patients and more importantly to maintain the adherence of the pacients to treatment and the study.

All serum samples that need storing will be stored in the hospital (ELIAS) at -80 degrees C and will be transported at the right time to the laboratory using special recipients with carbonic ice (to keep the low temperature). Cytokine assays will be performed at "C.I. Parhon" National Institute of Endocrinology, **Laboratory of molecular, cellular and structural endocrinology (**https://erris.gov.ro/ENDOCED). The laboratory has all needed infrastructure for the project:

- Automated Immunoassay Analyzers and semi-automated ELISA platform, for cytokine/adipokine assays.
- Thermocycler PCR (Eppendorf) and real-time PCR machines (Viia 7, Applied Biosystems, Quant Studio - Thermo Fisher Scientific) for quantitative measurement of miRNA. MiRNa will be quantitative determined on Viia7 (with TaqMan probes).

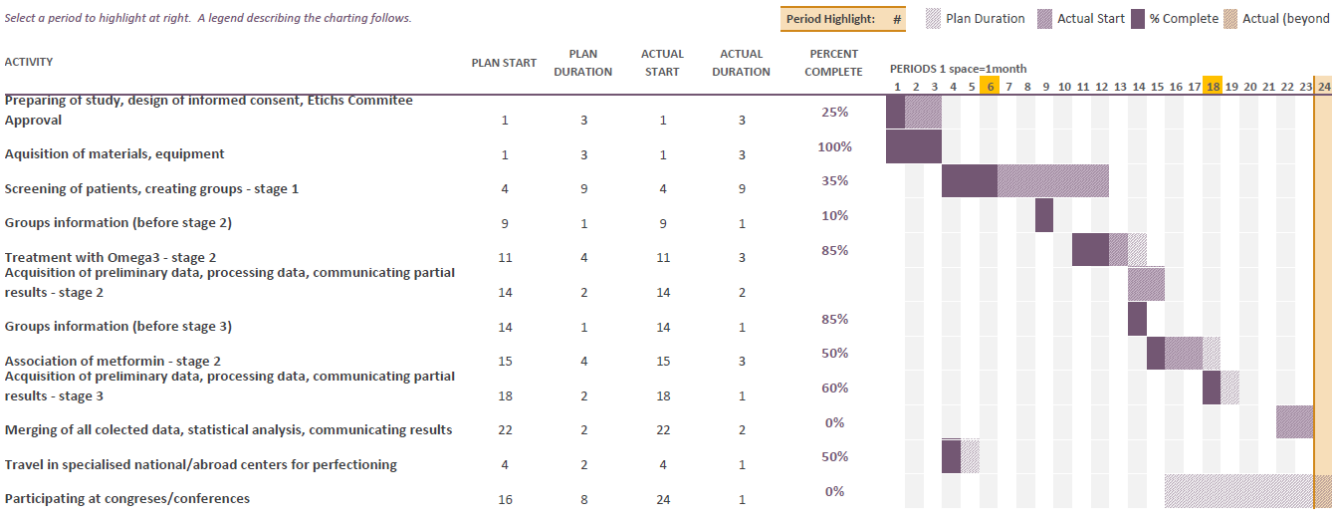

Fig.1. Gantt diagram representing the project activities in 24 months.

Statistical analysis.

Continuous variables will be reported as mean values ± standard deviation, the categorical ones as percentages. Comparing the values from 2 dependent samples (paires) will be performed by using the parametric t test or its nonparametric equivalent Wilcoxon signed rank test. The association between categorical presumptive risk factors and outcome will be assessed calculating odds ratios with 95% confidence intervals. Multivariable analysis will be used in order to compare the concomitant contribution of multiple factors in the occurrence of an event: linear regression for continuous variables and binary logistic regression for dichotomous ones. The ROC curve analysis will be used to identify cut-off values of variables associated with outcomes. Areas under the ROC curves of different models will be calculated and compared. A 2-tailed p value <0.05 will be considered statistically significant. All data analysis will be performed using the commercially available statistical analysis software package SPSS for Windows, version 14.0 (SPSS Inc., Chicago, Illinois).

Ethical aspects.

At admittance, patients will sign an informed consent regarding their diagnosis and medical procedures, and also available therapeutic options. The study is in accordance with international (Helsinki declarations, revised in 2013) and national norms (Patient's rights law, nr. 46/2003). Patient data was confidential, with distinct encoding, including patient names, address, and telephone number. Written informed consent will be obtained from all participants according to the ethics committee guidelines and Good Clinical Practice regulations. The Ethical Board of UMF "Carol Davila" will be requested for approval of the study.

Resources and budget

In view of the above mentioned work plan, the team members will be involved as follows: Dr. Voiculesc Vlad-Mihai – in scientific coordination and project management, examination protocols pacient recruitment, pacient screening, selecting the groups, in data analysis, writing of abstracts and articles, presenting data, organizing groups' informed sessions.

We intend to submit and publish our results in peer-reviewed international journals with high impact factor (IF >2,5)

The **available infrastructure** (http://erris.gov.ro/ENDOCED) relevant for the proposed project consists of:

- Automated Immunoassay Analyzers and semi-automated ELISA platform, for cytokine/adipokine assays.
- Thermocycler PCR (Eppendorf) and real-time PCR machines (Viia 7, Applied Biosystems, Quant Studio - Thermo Fisher Scientific) for quantitative measurement of miRNA.

We intend to acquire the following:

- ELISA kits for TNF alpha, IFN gamma, IL17, IL22, VEGF, IL10, Oxidative Stress/ABTS, adiponectin, leptin, resistin). Estimated costs: 3600-4000 Euro (8x"96-gauge ELISA plates", each one costing aprox. 450-500 Euro, depending on the studied cytokine)
- miRNA: MiRNA – 146a and MiRNA – 99a and control (all material, including isolation kits, Taq-Man probes, etc). Estimated costs: 1000 Euro

Budget Breakdown (euro, for the whole project)

Budget chapter (expenses)	**Total budget 2018 - 2019**
Personnel	0
Logistical	5000
Travel	0
Indirect	0
TOTAL	5000

! VERY IMPORTANT: additional costs will be supported by "C.I. Parhon" National Institute of Endocrinology, **Laboratory of molecular, cellular and structural endocrinology (ENDOCED)**, in terms of man-power, and man-hours, and of materials (they already have MiRNA – 146a and MiRNA – 99a TaqMan probes, only needing miRNA isolating kits)

Risk analisys:

Although the solution proposed in this project has some elements that were previously researched, it contains elements of utmost novelty and importance such as evaluating metformin as an immunomodulatory drug in psoriasis and also the study of miRNAs as potential biomarkers of evolution, severity and treatment response.

Potential risks are: delaying of funding, small number of patients included in the study, delaying in acquisition of materials, lack of statistical power. The risks can be easily overcome through collaboration with other Dermatological Clinics in Bucharest and Romania (through my position as Board Member of SRD), through timely ordering of the materials and through a rigorous selection of patients.

Results:

Expected outcomes of the project are:

a. Original articles, a total of 3-4, that I intend to publish in high impact factor peer-reviewed journals: Molecular Metabolism (ISSN: 2212-8778, CiteScore: 5.78, Impact Factor: 6.799, 5-Year Impact Factor: 6.824), Best Practice & Research: Clinical Endocrinology & Metabolism (ISSN: 1521-690X, CiteScore: 5.17, Impact Factor: 4.466, 5-Year Impact Factor: 5.218), Metabolism (ISSN: 0026-0495, CiteScore: 5.02, Impact Factor: 5.777, 5-Year Impact Factor: 4.258) Molecular and Cellular Endocrinology (ISSN: 0303-7207, CiteScore: 3.82, Impact Factor: 3.754, 5-Year Impact Factor: 3.803)

b. Including the results in and/or modifying present national psoriasis guides and protocols

c. Participating at National and International Congreses (EADV, AAD, ESDR, JDP, etc) with either posters or, more important, oral presentations that will allow for best dissemination of the results.

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