Application for the GRAPPA pilot research grant 2023 for the rheumatology-dermatology collaborative project

Immunological maps to guide phenotyping of psoriasis patients at different risk levels to develop psoriatic arthritis by integration of clinical, molecular (multi-OMICs) and innovative imaging assessment using NIR-fluorescence optical imaging technique as indicator for changes in vascularization as preliminary marker for inflammatory processes in psoriatic arthritis.

Applicant:
Caroline Gross, MD
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Mentors:
Michaela Koehm (MD) (and Prof. Frank Behrens, PD Andreas Pinter)

Scientific Abstract
The prevalence of psoriatic arthritis (PsA) in patients suffering from Psoriasis vulgaris (PsO) is considerably higher than in the overall population. As there is currently no known prediction technique considering the transition from PsO to PsA (apart from patients already showing symptomatic status), this project will investigate the use of near-infrared fluorescence optical imaging technique (NIR-FOI) examining the finger and wrist area on both hands as a promising tool to facilitate early detection of PsA. NIR-FOI allows the detection of disturbances in the microcirculation in the examined joints, representing subclinical signs of inflammation.
Therefore, psoriasis patients (n=30) defined as at-risk to develop PsA (e.g, nail involvement) will be included and screened by use of NIR-FOI to assess vascularisation status, supplemented by standardized ultrasound (PsASon22). Patients will be further characterized by means of clinical and molecular (lipidomics, proteomics, metabolomics) assessments and results will be compared after stratification according to NIR-FOI status. Immunological maps will be created from the integrated data to identify specific patient profiles regarding the risk profiles of PsA.
This project will help to better understand the transition process from PsO to PsA, will provide clinical and molecular patient characterizations, thereby facilitating an early intervention for patients at-risk.

Lay Summary
Some people suffer from a skin disease called psoriasis vulgaris, which is caused by a malfunction of the immune system of the own body. Affected patients suffer from inflammation, leading to, for instance, painful spots and flaky skin. Not few of these patients are expected to develop another disease called psoriatic arthritis with additional symptoms like joint swellings, inflammation of the entheses and reduced ability for movements. So far, there is little known to predict which patients are likely to get psoriatic arthritis in the future, although it would be very useful to understand preceding processes in the body. This knowledge would be important to improve the quality of life of affected people because an early treatment (before new symptoms even occur) prevents irreparable harm.
The approach of this study is the implementation of a innovative and easy to use imaging technique using harmless infrared light to detect changes in the blood flow of joints. The findings of this examination can identify the beginning of very small inflammations, possibly defining the onset of psoriatic arthritis. In order to receive a full picture of the patients at-risk for developing psoriatic arthritis, in this project, patients with psoriasis will additionally be examined physically, by ultrasound and by blood analysis. In the end, all information will be combined in order to build a detailed patient profile, characterizing typical features of people likely to develop psoriatic arthritis. The collected and categorized data will be very helpful to better understand the transition from psoriasis to psoriatic arthritis and potentially help patients at risk to receive early treatment.

Background
Psoriasis vulgaris (PsO) is associated with a disease of the musculoskeletal system (psoriatic arthritis [PsA]) (including inflammation of the peripheral joints, the axial skeleton and the entheses) in up to 30% of cases. PsA usually occurs as a manifestation of the musculoskeletal system years after skin manifestation; in rare cases, joint involvement precedes skin involvement (1). The prevalence of PsA in the overall population is between 0.3% and 1% (1). However, the prevalence of PsA in patients with PsO is considerably higher, ranging from 6% to 42% (2,3).
Although risk factors for development of PsA were identified (e.g., nail involvement of PsO), little is known which patients will develop PsA and when in the disease course to adapt clinical monitoring for very early detection of PsA and fast treatment to avoid structural changes and impairment of function.

In early stages of PsA, not yet clinical manifest PsA, changes in synovial vessels with altered microcirculation are accompanied by increased expression of pro-angiogenetic factors (4). Therefore, imaging techniques that map changes in microcirculation may represent an advance in the early diagnosis of patients with psoriatic arthritis.
Near-infrared fluorescence optical imaging technique (NIR-FOI) uses the detection of changes in the microcirculation at the hands to reveal inflammations and thus has the potential to demonstrate pathological changes in early stages of the inflammatory process.
NIR-FOI is a ICG tailored method for imaging of the finger and wrist area of both hands. After optical excitation with dark red light at a wavelength (λ) of 740 nm by high-power light emitting diodes (LED), fluorescence signals in the near-infrared spectral range (> 800 nm) are captured from the hand by means of a highly sensitive camera. The fluorescence signals are detected at different periodic points in time. The total duration of a measurement is 6 minutes. The NIR-FOI system is CE certified and approved for the visualization of microcirculation disturbances in Europe (5–7) . Beside a semi-quantitative assessment of NIR-FOI findings, which is limited to experienced operators, an automated objective assessment technique was developed by Zerweck et al in our research group. (8).
Koehm et al. (9) showed, that screening with NIR-FOI in patients already suffering from arthralgia accelerated the rate of detection of PsO patients with development of PsA within 2 years by approx. 10,8% (yearly incidence rate according to literature approx. 8,6%).
Nevertheless, clinical symptoms such as arthralgia are named as an already symptomatic status of the musculoskeletal disease (prodromal phase according to Scher et al. (10)). Thus, the medical need to identify patients in the subclinical phase of psoriatic disease, where soluble biomarkers and changes in vascularisation are evident, is of high relevance.
In this pilot research project, psoriasis patients defined as at-risk to develop PsA according to a list of attributes will be included and screened by use of NIR-FOI to assess vascularisation status. The clinical and molecular (lipidomics, proteomics, metabolomics) characteristics to deeply characterize these patients will be compared after stratification according to NIR-FOI status. Immunological maps will be created from all available information and included into the deep characterization of patient profiles and analysis of their risk profile for PsA.

Methods
Patients with plaque type psoriasis will be screened to be included in this pilot research project (n=30). Similar sample sizes have been recommended in the literature for pilot and feasibility studies to conduct initial screening, and to test study procedures and methods (11). The at-risk population will be defined as dermatologic confirmed moderate to severe plaque-type psoriasis, fulfilling 2 out of 5 criteria of the following: Presence of Nail Matrix Psoriasis, early onset of PsO (onset of PsO ≤ 30 years), positive family history of PsA, disease duration of PsO (≤ 20 years), absence of PsO-involvement of palms/soles.
For the clinical phenotype the following parameters will be assessed: severity of PsO (body surface area (BSA), Psoriasis Activity severity index (PASI), nail psoriasis), comorbidities (including cardiovascular diseases and depression), assessment of musculoskeletal inflammation (tender and swollen joint count (TJC/SJC (68/66)), Leeds Enthesitis Index (LEI), dactylitis), associated manifestations (uveitis, Inflammatory Bowel Syndrome (IBD)). Besides clinical examination, NIR-FOI and standardized ultrasound (PsASon22) will be performed. Molecular profiles will be identified by measuring lipidomics, proteomics, metabolomics in blood samples. Results will be used to profile patients by creating immunological maps. With this approach, profiles of patients will be generated beyond clinical classifications. PsA diagnosis will be documented and the classification of PsA will be correlated to the clinical, imaging and molecular attributes with special focus on vascularization status assessed by NIR-FOI.

The analytical aim is to identify key features for immunological mapping to identify early subclinical PsA development in PsO patients which can then be applied in clinical routine care to intercede PsA development. Statistical analysis will as such focus on learning instead of classical testing methods and will be a two-step process to achieve overall phenotyping: (1) Single assessment of clinical, imaging and OMICS data by using correlation analyses, clustering and regression methods for variable reduction (e.g., mass spectrometry, volcano plots, odds ratios, lasso/elastic net with (G)LMM, SVM, SME, cluster analysis) to identify predictors within single assessments, groupings within the different data types and to reduce data dimensions. (2) Combinational analysis will focus on identifying correlations between clinical, imaging and OMICS data while considering findings of step (1). Classification and clustering methods of machine learning (e.g., PCA, random forests) will be applied and compared to combine different data types and to assess the best statistical method to define immunological maps. All statistical models and outcomes will also be assessed for scientific importance by clinical and bioanalytical experts to ensure logical use of variables and interpretability. If statistical tests are applied, a global significance level of 5% will be used for the family-wise error rate.

Expected results

Within this pilot research project, immunological maps of PsO patients at-risk for development of PsA but asymptomatic at inclusion will be created by integration of clinical data, sensitive imaging with special focus on vascularization status measured by NIR-FOI defined as subclinical signs of inflammation, and OMICS analysis. Based on the immunological maps and the underlying clinical and molecular characteristics, PsO patients can be stratified to individual groups, facilitating identification of patients at different risk levels. Additioanlly, the combined clinical and molecular data will increase the knowledge about the transition process from PsO to PsA and will give important insights into these specific patient characteristics relevant for best practice at dermatologic and rheumatologic patient care.

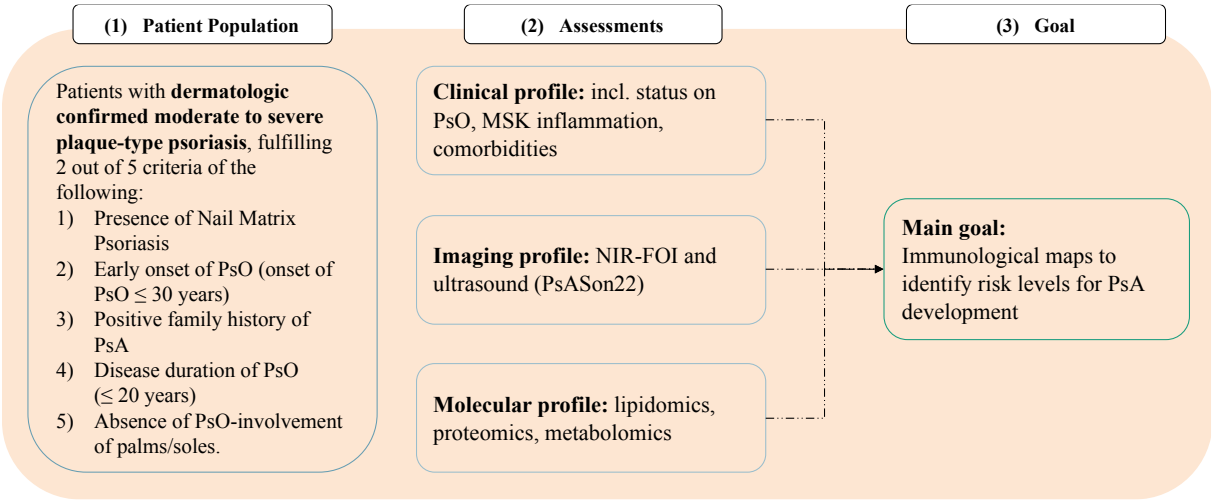

Figure 1: Project overview.

Significance for psoriatic disease

The pilot research project will give important and detailed insights in the characteristics and profiles of asymptomatic PsO patients at different risk levels to develop musculoskeletal inflammation (PsA) and will increase the understanding of the pathophysiologic pattern underlying the transition from PsO to PsA. Results of this project will allow risk stratification by immunological mapping and will facilitate early identification of PsA. Moreover, the information obtained from the project can be used to characterize patient groups for prospective translational research projects in the future beyond clinical classification.

References

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Budget Calculation and justification

	2023 [€]	2023 [$]
Scientist, Coordinator (part-time; 6 months)	15738	16777
Biomarker analysis (multi-OMICs: lipidomics, proteomics, metabolomics, imaging)	14619	15584
Material and administrative costs (fluorescent color agent, ethical committee)	2494	2639
Sum	**32851**	**35000**

Curriculum vitae

Name:	**Dr. med. Caroline Gross**
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Present Assignment:	
Since 01/2022	Resident physician in rheumatology University Hospital Frankfurt am Main Theodor-Stern Kai 7, 60590 Frankfurt
Working experience:	
01/2020 – 12/2021	Resident physician in internal medicine Hochtaunus-Kliniken gGmbH Zeppelinstraße 20, 61352 Bad Homburg von der Höhe
Education:	
03/2021	Doctoral thesis "the impact of a virtual reality simulation-assisted informed consent process on patient satisfaction and procedure related anxiety"
12/2019	license to practise medicine
10/2013 – 12/2019	Study of human medicine, J.W. Goethe-University Frankfurt

21.02.23 C. Gross

Date, Signature

Bio Sketch Mentor: Michaela Koehm MD

Michaela Koehm studied “Medicine” at the Goethe University in Frankfurt/Main. She performed her doctoral dissertation at the Institute of Forensic Toxicology by conducting a clinical interventional trial in the indication field of adult forms of ADHS under treatment with Methylphenidate (Ritalin). After receiving her approval, she started working at the division of Rheumatology at the University Hospital Frankfurt to complete her education to be a specialist in Internal Medicine and Rheumatology in 2017.

Her scientific track record focuses on psoriatic arthritis and methods for early detection and clinical development of treatments and treatment regimes in psoriatic disease. For this, she leads a team of medical writers, biostatisticians, and scientists in the Fraunhofer Institute for Translational Medicine and Pharmacology in Frankfurt/Main and was involved in the design and conduction of the MUST study, which Lancet Rheumatology published recently (Koehm et al., Lancet Rheumatology, 2023).

Moreover, Dr. Koehm co-leads the work package, which focuses on early diagnosis of PsA in the IMI consortium HIPPOCRATES, which started in 2022. She is involved as a senior rheumatologist in interdisciplinary care of psoriasis and psoriatic arthritis patients in close collaboration with specialists in the fields of dermatology and gastroenterology in an innovative division at University Hospital Frankfurt/Main, named “Translational Rheumatology, Immunology – Inflammation Medicine.” Besides this, she is responsible for rheumatological education at the Goethe University Frankfurt.

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Support Letter for Caroline Gross, MD, an applicant for the GRAPPA pilot research grant in the field of dermatologic and rheumatologic research

Dear Ladies and Gentlemen of the GRAPPA research committee,

I, Frank Behrens, Director of the Division of Translational Rheumatology, Immunology – Inflammation Medicine of the University Hospital Goethe-University Frankfurt/Main, Germany, am writing on behalf of Caroline Gross, MD, to express support for her grant application for the rheumatology-dermatology collaborative project of the GRAPPA pilot research grant for her research project titled *Immunological maps to guide phenotyping of psoriasis patients at different risk levels to develop psoriatic arthritis by integration of clinical, molecular (multi-OMICs) and innovative imaging assessment using NIR-fluorescence optical imaging technique as indicator for changes in vascularization as preliminary marker for inflammatory processes in psoriatic arthritis*, whose goal is to characterize psoriasis patients on different risk levels for development of psoriatic arthritis (PsA) by clinical, molecular and innovative imaging markers to integrate the results to develop immunological maps which will help to deeply phenotype patients at-risk for psoriatic arthritis early.

This project aims to answer a fundamental question for optimizing treatment within the indication of psoriatic disease as the understanding of at-risk profiles of patients with later PsA development is limited. Integrating data from innovative techniques may add insight into pathophysiological pathways usable in the clinical routine care setting.

Your support will enable us to recruit a pilot patient cohort that Caroline Gross will deeply characterize to integrate data and develop immunological maps giving clear guidance to at-risk levels and profiles. Specifically, NIR-FOI will identify early changes in micro vascularisation, named the first signs of specific inflammatory processes in PsA. The first results of the value of NIR-FOI in the identification of at risk-patients for PsA were shown in our research group recently (Koehm et al., 2022). The method, with a particular focus on objective measurement of NIR-FOI, was optimized as published in 2022 (Zerweck et al., 2022). It is a promising tool easy to use for screening PsO patients in the outpatient setting.

Caroline Gross started working in 2022 in the Translational Rheumatology, Immunology – Inflammation Medicine division at University Hospital Frankfurt/Main. She showed early a deep interest in the interdisciplinary care of patients with psoriasis and psoriatic arthritis. Her support helped build up and strengthen the collaborative network between rheumatologists and dermatologists at our institution and in the Rhine-Main area. Besides her work in routine clinical care, Caroline Gross showed a high interest in clinical and translational research. So, she joined the working group of Michaela Koehm, MD, which focuses on the early diagnosis of PsA for individualized treatment and care of PsA patients. She is involved in an observational study that characterizes patients with PsA by lipidomic profiles and will publish first data at ACR 2023.

Your support of this specific topic will gain a deeper understanding of the transitional process of psoriasis to psoriatic arthritis as a starting point to evaluate the use of innovative assessment methods (multi-OMICs, innovative imaging techniques) to improve patient care.

I confirm to support Caroline Gross with all equipment and resources she needs from our facility in case of a positive result in the application process. I am available to answer any questions you may have.

Sincerely,

Prof. Dr. Frank Behrens

Director