Charles University

Second Faculty of Medicine

Summary of the Dissertation Thesis

Monogenic susceptibility to infectious pathogens

Monogenně podmíněné vnímavosti k infekčním patogenům

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Disertační práce byla vypracována v rámci prezenčního studia doktorského studijního programu Biologie a patologie buňky na Ústavu imunologie 2. lékařské fakulty Univerzity Karlovy

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dne ..... v ..... od .....hod.

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TABLE OF CONTENT

ABSTRAKT (CZ)

Moderní přístupy ke studiu monogenních vrozených poruch imunity, podpořené v posledních dekádách bezprecedentním rozvojem genetických metod, odkrývají nové, dosud neprobádané funkční aspekty imunitního systému. Nemoci s nápadným klinickým fenotypem, leč víceméně normálními základními imunologickými nálezy, jako jsou poruchy vrozené či intrinsické imunity se selektivně zvýšenou náchylností k jedinému infekčnímu agens, poskytují vzácnou příležitost ke studiu interakcí imunitního systému člověka s patogeny. Tato práce se zaměřuje na imunopatologické, genetické a klinické aspekty takových onemocnění, konkrétně na chronickou mukokutánní kandidózu způsobenou hypermorfními (gain-of-function, GOF) mutacemi ve *STAT1* genu, které způsobují poruchy Th17 asociovaných imunitních mechanismů, a vrozenou náchylností k mykobakteriálním onemocněním (Mendelian susceptibility to mycobacterial diseases, MSMD) způsobenou poruchami signální dráhy IL-12, IL-23/IFNy. Práce dále přispívá k objasnění role IL-6 signalizace v protistafylokokové imunitě a zabývá se novým onemocněním dětského věku PIMS-TS (Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2), jako život ohrožujícím důsledkem imunopatologie spuštěné jediným konkrétním patogenem, který se s vysokou pravděpodobností vyvíjí v důsledku individuální, dosud neznámé genetické predispozice. Poznatky prezentované v této práci bylo možné v několika případech přenést přímo do klinické praxe, např. použití JAK inhibitorů u pacientů se STAT1 GOF a úpravu dávkování podle nově vyvinutého STAT fosfoflow protokolu, doporučení k očkování proti SARS-CoV-2 u STAT1 GOF pacientů, profylaxi a léčbu IFNγ u pacientů s AD parciálním deficitem IFNγR1, individuální terapeutická doporučení pro pacienta s unikátní kombinovanou poruchou IFNγ a NOD2 signalizace nebo

identifikaci prediktorů závažnosti u PIMS-TS a doporučené terapeutické strategie u tohoto onemocnění.

Klíčová slova: vrozené poruchy imunity, infekce, Candida, mycobacterium, SARS-CoV-2, IL-12, IL-23, IFNγ, MSMD, Th17, STAT1, IL-6, PIMS-TS, MIS-C

ABSTRACT (ENG)

The modern approach to studies of monogenic inborn errors of immunity, driven by unprecedented advances of genetic tools, opens vast undiscovered areas of immune system components and functions. In particular, the diseases with striking clinical phenotypes with normal or near normal baseline immunophenotype, such as disorders of innate and intrinsic immunity with susceptibility to single pathogen, provide a unique window into the host-pathogen interactions. This thesis covers various novel aspects of immunopathology, genetics and clinical facets behind some such diseases, namely chronic mucocutaneous candidiasis due to hypermorphic (gain-of-function, GOF) *STAT1* mutations, which hamper Th17-associated immune activities, and Mendelian susceptibility to mycobacterial diseases (MSMD) due to impairment of IL-12, IL-23/IFNγ signalling pathway. Moreover, it contributes to the mounting evidence that IL-6 signalling is non-redundant in anti-staphylococcal immunity. Finally, it explores the novel Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) as a single pathogen-driven life-threatening immunopathology, which likely develops due to individual, yet unknown, genetic predisposition. The findings presented in this thesis were in several cases translated directly into the patients' clinical management, for example the use of JAK inhibitors in STAT1 GOF patients and the use of newly developed STAT phosphoflow protocol for dose adjustments, the recommendations on vaccination against SARS-CoV-2 in STAT1 GOF patients, the prophylaxis and treatment with IFNγ in patients with AD partial IFNγR1 deficiency, individualized therapeutic recommendation for a patient with unique combined impairment of IFNγ and NOD2 signalling, or the identification of severity predictors in PIMS-TS and its recommended management strategies.

Key words:

inborn errors of immunity, infections, Candida, mycobacterium, SARS-CoV-2, IL-12, IL-23, IFNγ, MSMD, Th17, STAT1, IL-6, PIMS-TS, MIS-C

INTRODUCTION

Inborn errors of immunity (IEI) are rare heritable diseases which provide a unique window into the human immune system composition and orchestration of its operational processes, which are not fully understood yet. Diseases with striking clinical phenotypes and known genetic background teach us much about the host-pathogen interactions and the evolution of immune defence mechanisms under the millennia-long microbial pressure.

Spearheaded by the teams of J.L. Casanova, L. Abel, and A. Alcaïs, genetic variants rendering carriers vulnerable to single type, or a narrow spectrum of pathogens have been extensively studied since the 1990'. The diseases affect mechanisms of innate or intrinsic immunity and share several hallmark features, namely:

- severe/prolonged/treatment-refractory course of primary infection with a particular pathogen (that would usually not pertain such severe symptoms)
- recurrent/persistent infections with single pathogen despite adequate treatment
- unincreased susceptibility to other microbes
- normal/near normal basic immunologic parameters

This thesis covers various novel aspects of such inborn errors of immunity with pronounced susceptibility to single pathogen in otherwise healthy individuals. Specifically, chronic mucocutaneous candidiasis (CMC) due to hypermorphic (gain-of-function, GOF) *STAT1* mutations, which hamper Th17-associated immune activities, and Mendelian susceptibility to mycobacterial diseases (MSMD) due to impairment of IL-12, IL-23/IFNγ signalling pathway are addressed. The thesis also contributes to the mounting evidence that IL-6 signalling is non-redundant in anti-staphylococcal immunity. Finally, a serendipitous event allowed the author to explore the novel Paediatric

inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) as a single pathogen-driven life-threatening immunopathology, which most likely develops due to individual, yet unknown, genetic predispositions.

AIMS

Primary objectives

A) To describe selected clinical, immunologic, and genetic aspects of patients with **STAT1-gain-of-function chronic mucocutaneous candidiasis** and translate the findings into their clinical management

B) To describe selected clinical, immunologic, and genetic aspects of patients with **Mendelian susceptibility to mycobacterial diseases** and translate the findings into their clinical management

C) To report a proof-of-principal case that **systemic *Staphylococcus aureus* infection in individuals with disturbed IL-6 signalling** may arise due to the presence of IL-6 autoantibodies

D) To contribute to investigations concerning the novel severe **Paediatric inflammatory multisystem syndrome – temporally associated with SARS-CoV-2** (PIMS-TS; also MIS-C - Multisystemic inflammatory syndrome in children)

Secondary objectives

E) To increase awareness of IEI with selective microbial susceptibility, encourage referrals of suspect individual to immunologists and promote national cooperation

F) To connect with the international network of clinicians and researchers working in the fields of rare IEI to maximize the benefit of collective experience

METHODS

Patients

The majority of patients described in this thesis are followed by the author at the Department of Immunology, Motol University Hospital in Prague and Department of Paediatrics, Thomayer University Hospital, Prague. Some individuals are regularly followed at other departments across the country. Informed consents with inclusion in the respective research projects were obtained from the participants and/or by the participants' legal guardians in accordance with the Declaration of Helsinki.

Data on demographics, clinical manifestations, routine laboratory features and other investigations, therapeutic management, and outcomes were collected from the medical records and obtained via patient/parent interview or communications with other healthcare providers of the patients. International data sharing was based on personal communications of the author of this thesis.

Laboratory methods

Laboratory, analytic and statistical methods were used according to the individual aim of each presented study and performed at the Department of Immunology, Motol University Hospital in Prague, Childhood Leukaemia Investigation Prague laboratory and the genetic laboratory in Centre for Cardiovascular Surgery and Transplantation, Masaryk University, Brno. Some genetic evaluations were performed in Laboratoire de Génétique Humaine des Maladies Infectieuses, Institut National de la Santé et de la Recherche Médicale et Université Paris Descartes, France.

The laboratory methods are described in detail in the manuscripts which substantiate this thesis. In general, these included flow cytometry methods, immunoassays and various techniques of DNA and RNA sequencing.

RESULTS

1.1 PRIMARY ENDPOINTS - PUBLICATIONS DIRECTLY SUPPORTING THE THESIS

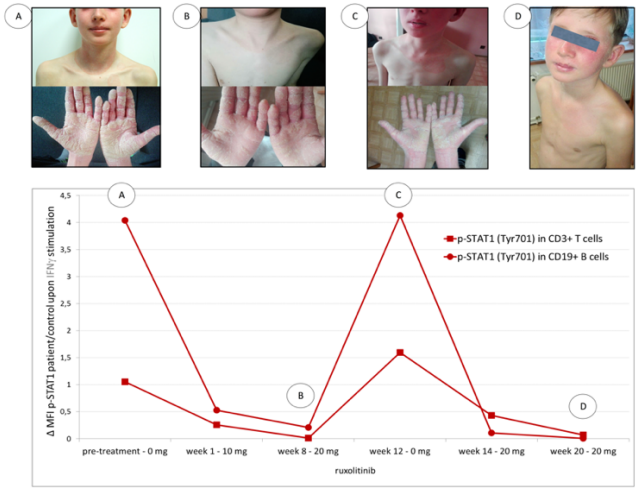
1. Utility of ruxolitinib in a child with chronic mucocutaneous candidiasis caused by a novel STAT1 gain-of-function mutation
2. Impact of JAK inhibitors in pediatric patients with STAT1 Gain of function (GOF) mutations-10 children and review of the literature
3. Immunogenicity and Safety of COVID-19 mRNA Vaccine in STAT1 GOF Patients
4. Mutual alteration of NOD2-associated Blau syndrome and IFNγR1 deficiency
5. Manifestations of cutaneous mycobacterial infections in inborn errors of IL-12, IL-23/IFNγ immunity
6. Mendelian susceptibility to mycobacterial disease: The first case of a diagnosed adult patient in the Czech Republic
7. Anti-IL6 autoantibodies in an infant with CRP-less septic shock
8. Nationwide observational study of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the Czech Republic
9. EAACI statement and guideline on the pathogenesis, immunology, and immune-targeted management of the Multisystem inflammatory syndrome in children (MIS-C) or Pediatric inflammatory multisystem syndrome (PIMS-TS)
10. B cells, BAFF and interferons in MIS-C

1.1.1 UTILITY OF RUXOLITINIB IN A CHILD WITH CHRONIC MUCOCUTANEOUS CANDIDIASIS CAUSED BY A NOVEL STAT1 GAIN-OF-FUNCTION MUTATION

Bloomfield M, Kanderová V, Paračková Z, Vrabcová P, Svatoň M, Froňková E, Fejtková M, Zachová R, Rataj M, Zentsová I, Milota T, Klocperk A, Kalina T, Šedivá A. Utility of Ruxolitinib in a Child with Chronic Mucocutaneous Candidiasis Caused by a Novel STAT1 Gain-of-Function Mutation. ***J Clin Immunol***. 2018 Jul;38(5):589-601. (IF=4.85, Q1)

In this article, the author and her colleagues reported a novel STAT1 mutation to underlie features of extensive chronic mucocutaneous candidiasis. We established the hypermorphic effect of the mutation by employing single-cell STAT phosphoflow assay, which was developed by the authors. Moreover, the paper was one of the first to described the utility of targetted therapy of STAT1 GOF with JAK inhibitor ruxolitinib in pediatric settings, and the first to monitor the clinical effect of the compound in parallel to the cellular responses to JAK inhibitor. The optimized phosphoflow protocol was then used for treatment monitoring prior to this child HSCT and for dose adjustements in three other STAT1 GOF patients who received JAK inhibitor.

<u>Achieved key objectives = A, E</u>



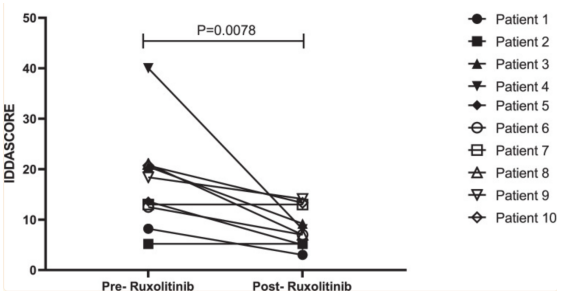
Representative figure: Clinical progress paralleled to IFNγ-induced p-STAT1 (Tyr701) activation during ruxolitinib treatment of STAT1$^{c.617T>C}$ patient

1.1.2 IMPACT OF JAK INHIBITORS IN 10 PEDIATRIC PATIENTS WITH STAT1 GAIN-OF-FUNCTION MUTATIONS (STAT1 GOF) AND REVIEW OF THE LITERATURE

Deyà-Martínez A, Rivière JG, Roxo-Junior P, Ramakers J, **Bloomfield M**, Guisado Hernandez P, Blanco Lobo P, Abu Jamra SR, Esteve-Sole A, Kanderova V, García-García A, Lopez-Corbeto M, Martinez Pomar N, Martín-Nalda A, Alsina L, Neth O, Olbrich P. Impact of JAK Inhibitors in Pediatric Patients with STAT1 Gain of Function (GOF) Mutations-10 Children and Review of the Literature. *J Clin Immunol.* 2022 Jul;42(5):1071-1082. (IF 8.32, Q1)

This international collaborative study arose from the applicant's communications with colleagues from Spain and Brazil and concerned the experience with efficacy and safety of precision treatment of paediatric STAT1 GOF patients with JAK inhibitors. Prior to this publication, such reports had been scarce, limited to individual reports. Based on our collective experience, this group of authors formed recommendations regarding dosing, monitoring, and follow-up care and envisaged paths for future clinical research, such as drug level monitoring or the identification of treatment-response biomarkers. The group has since become involved in the European Society for Immunodeficiency (ESID) and European Society for Blood and Marrow Transplantation (EBMT) multicentric retrospective study on JAK inhibitors treatment in patients with inborn errors of the JAK/STAT pathways.

Achieved key objectives = A, F



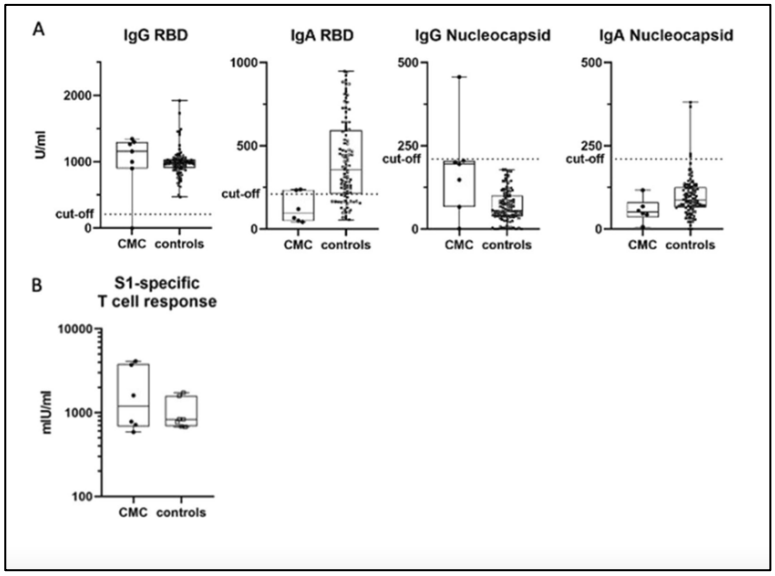
Representative figure: Effect of JAK inhibitor ruxolitinib on Immune deficiency and dysregulation activity (IDDA) score in STAT1 GOF pediatric patients

1.1.3 IMMUNOGENICITY AND SAFETY OF COVID-19 mRNA VACCINE IN STAT1 GOF PATIENTS

Bloomfield M, Parackova Z, Hanzlikova J, Lastovicka J, Sediva A. Immunogenicity and Safety of COVID-19 mRNA Vaccine in STAT1 GOF Patients. *J Clin Immunol.* 2022 Feb;42(2):266-269. (IF 8.32, Q1)

The emergence of COVID-19 brough on serious concerns about its course in patients with STAT1 GOF. At the time when only three records of COVID-19 infection and only two records of mRNA vaccinations in STAT1 GOF existed worldwide, we reported seven STAT1 GOF patients with an uneventful course of COVID-19 vaccination (including data on antibody and T-cell mediated responses), and/or SARS-CoV-2 infection, including two patients receiving JAK inhibitor. Additionally, two of the patients described in this publication harbour previously unreported mutations, which expanded the known STAT1 GOF- associated variant pool.

Achieved key objectives = A, E



Representative figure: Immune responses to SARS-CoV-2 mRNA vaccine in STAT1 GOF patients after the second vaccine dose

1.1.4 MUTUAL ALTERATION OF NOD2-ASSOCIATED BLAU SYNDROME AND IFNγR1 DEFICIENCY

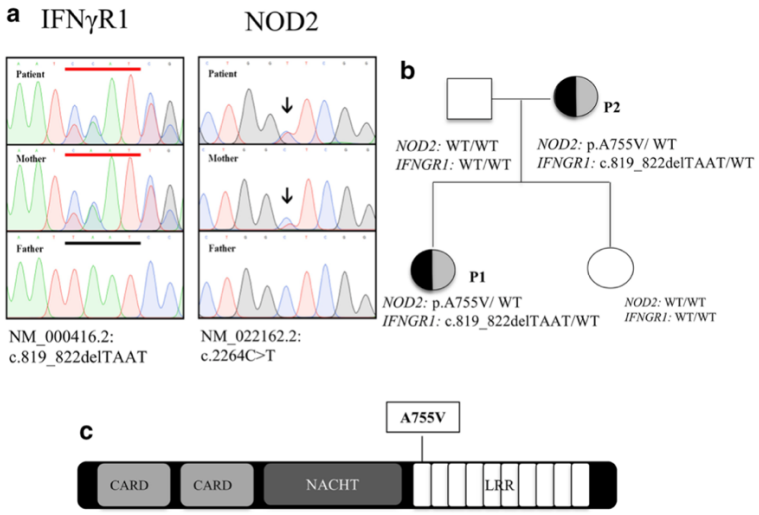
Parackova, Z*., **M. Bloomfield***, P. Vrabcova, I. Zentsova, A. Klocperk, T. Milota, M. Svaton, J.-L. Casanova, J. Bustamante, E. Fronkova, and A. Sediva. 2019. Mutual alteration of NOD2-associated Blau syndrome and IFNγR1 deficiency. *J. Clin. Immunol.* 2020; 40:165–178.
*Authors contributed equally (IF=6.78, Q1)

In this work, we followed an extraordinary experiment of nature – a unique kindred harbouring heterozygous mutations in two innate immune mechanisms of antimicrobial defences - IFNGR1 (associated MSMD) and NOD2 (associated with Blau syndrome). Together, they resulted in a combined phenotype of milder MSMD and atypical Blau syndrome. This was intriguing, because NOD2 Blau syndrome, an auto-inflammatory granulomatous disease of unknown pathophysiology, was hypothesized to involve abnormal response to IFNγ. These two pathways have, however, not been previously mechanistically linked.

Utilizing an array of NOD2 and IFNγ pathways-probing molecular methods, we demonstrated a functional crosstalk, which suggested that IFNγ is an important driver in the NOD2 hyperreactivity in Blau syndrome, independently of IFNγR/STAT1-mediated signalling.

Our two years long effort eventually enabled intelligence-based selection of optimal therapy for the patient. Moreover, the hereby described observations contributed to the notion of therapeutic targeting of IFNγ signalling in Blau syndrome BS.

Achieved key objectives = B, F



Representative figure: DNA sequencing chromatograms, the pedigree and segregation of the *NOD2* and *IFNGR* mutations, and the NOD2 protein structure highlighting the aminoacid substitution in the proband

We were honoured that this work was co-authored by Prof. J.L.Casanova and received personal appreciation from doctor Edward B. Blau:

Dear colleagues,
I am the Edward B. Blau …and I must tell you your article … is one of the most fascinating that I have read in many a year.
The clinical presentation, diagnosis and treatment are first rate. The laboratory work was also of the highest order.
I have always been interested in what stimulates the (deficient) NOD2 system … to go onto unchecked granuloma formation.
I have thought it might be … benign Mycobacterium. Please extend my congratulations on a splendid piece of work to your colleagues.

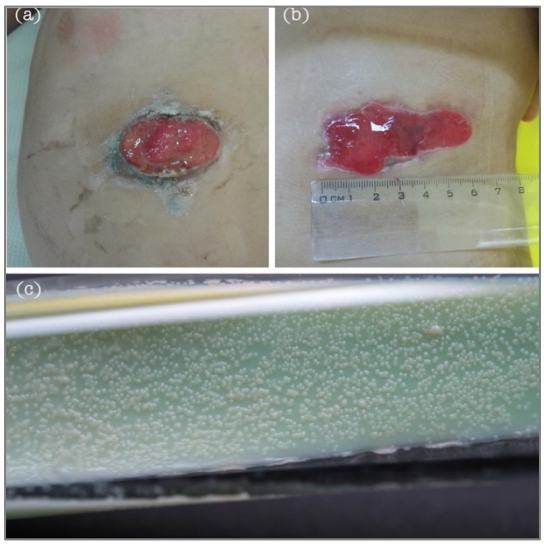
Very sincerely yours,
Edward B. Blau, M. D.
Marshfield, WI, USA

1.1.5 MANIFESTATIONS OF CUTANEOUS MYCOBACTERIAL INFECTIONS IN INBORN ERRORS OF IL-12, IL-23/IFNy IMMUNITY

Dolezalova K, Strachan T, Matej R, Ricna D, **Bloomfield M.** Manifestations of cutaneous mycobacterial infections in inborn errors of IL-12, IL-23/IFNγ immunity. *European Journal of Dermatology*. 2022; 7;32(4):1-10. (IF 2.80, Q2)

Individuals with disturbed IL-12, IL-23/IFNy circuit often present with cutaneous infections with non-tuberculous mycobacteria. The mycobacteriosis in MSMD may, however, adapt an atypical or severe course, lacking the classic granulomatous nature. Collaborating with Czech and Slovakian paediatric TB specialists, geneticists and the pathologist, two main objectives of this article were to increase awareness of MSMD and to highlight the characteristics of NTM infections and the pitfalls of their diagnosis in imunocompromised patients. Specifically, infections with M. marinum and BCG in AD partial STAT1 deficiencies, infections with M. avium-intracellulare, M. abscessus-immunogenum and BCG in AD partial IFNyR1 deficiency, and infections with M. abscessus-intracelulare and BCG in fatal AR complete IFNyR1 deficiency were depicted. Moreover, one of the presented family harboured a previously unreported mutation in STAT1 gene, thus enriching the known disease-associated genotypes. Also, one of the children was successfully treated with IFNy.

Achieved key objectives = B, E, F



Representative figure: *Mycobacterium avium-intracellulare* scrofuloderma of the thorax due to autosomal recessive complete IFNyR1 deficienc

1.1.6 MENDELIAN SUSCEPTIBILITY TO MYCOBACTERIAL DISEASES:THE FIRST CASE OF A DIAGNOSED ADULT PATIENT IN THE CZECH REPUBLIC

Prucha M, Grombirikova H, Zdrahal P, **Bloomfield M,** Parackova Z, Freiberger T. Mendelian Susceptibility to Mycobacterial Disease: The First Case of a Diagnosed Adult Patient in the Czech Republic. *Case Reports Immunol.* 2020 Dec 19; 8836685. (without IF)

This case study represents an example of a successful national collaboration. It describes a 42-year-old woman, who suffered from severe obscure mycobacterial infections most of her life. Only in her adulthood, she was referred to a genetic evaluation and found to harbour IFNGR1 mutation by the team of geneticists, who specialize in IEI. The loss-of-function consequence of the variant was validated by the author of this thesis and her colleagues. Based on previous experience and literary accounts, treatment with recombinant IFNy was recommended, which improved the clinical condition of the patient and prevented further mycobacterial infections. Effectively, this cooperation has, to the patient benefit, brought together the expertise of four different clinics and departments. The paper adds to the expanding pool of patients who are diagnosed with inborn immunodeficiency in later adulthood and reports the first adult Czech patient diagnosed with penetrant MSMD.

Achieved key objectives = B, E

Year	Localization	Pathogen
1981	Inguinal and cervical lymph nodes	*M. kansasii*
1992	Lungs	Wrongly diagnosed as sarcoidosis
1993	Lymph nodes, Th-7, 8, 9, 11, 12, L1, 2, 5 left femur, maxilla, mandibula	*M. kansasii*
1995	Centre in the distal part of the left femur	*M. avium intracellulare* *M. gordonae*
1997	Granuloma in the right face	*M. lentiflavum*
1998	Left patella Distal part of the femur on the right Granuloma in the right face	*M. lentiflavum* *M. kansasii*
2001	Granuloma of the nasal septum	*M. avium intracellulare*
2002	Left knee	*M. flavescens*
2004	Sputum	*M. lentiflavum*
2007	Granuloma/nasal septum	*M. lentiflavum*
2009	Granuloma/nasal septum	*M. lentiflavum*
2013	Granuloma/nasal septum	*M. avium*
2014	TH 8, 11, L1, L5	*M. avium*
2016	Granuloma of the nasal septum	*M. lentiflavum*
2017	Colliquating granuloma in the nasal septum	*M. avium intracellulare*
2018	Granuloma of the nasal septum Colliquating granuloma in the right face	*M. avium* Start therapy rhIFN-γ
2020	Surgery of the nasal septum Granuloma of the right face healed	Microbiological investigation is negative

Representative figure: The sequence of infections with non-tuberculous mycobacteria in patient with autosomal dominant partial IFNyR1 deficiency

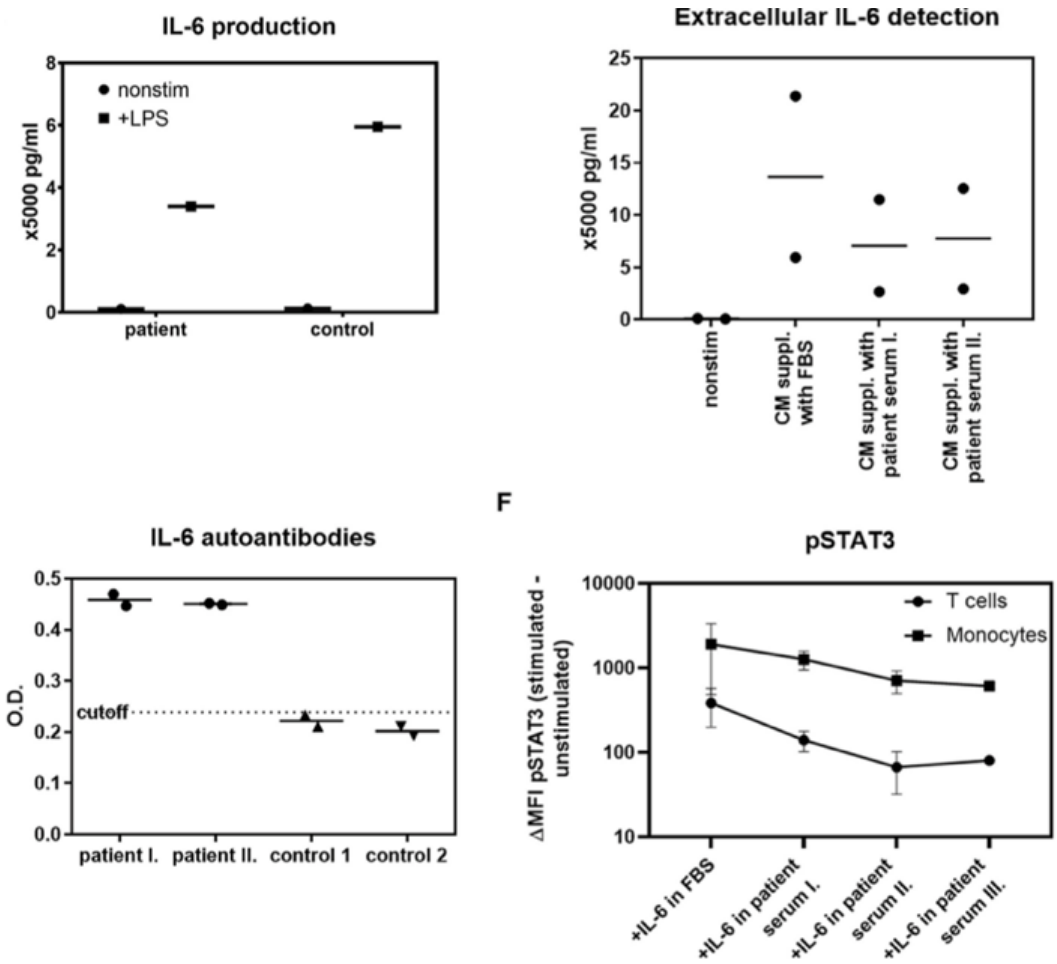
1.1.7 ANTI-IL6 AUTOANTIBODIES IN AN INFANT WITH CRP-LESS SEPTIC SHOCK

Bloomfield*, M., Z. Parackova*, T. Cabelova, I. Pospisilova, P. Kabicek, H. Houstkova, and A. Sediva. 2019. Anti-IL6 Autoantibodies in an Infant With CRP-Less Septic Shock. *Front. Immunol*. 10: 1–6. (IF 5.05, Q1)
*Authors contributed equally

Certain IEI are associated with skewed inflammatory acute phase response, as well as increased susceptibility to Staphylococcus aureus (e.g., STAT3 HyperIgE syndrome, IL6R deficiency, or gp130 mutation). Examining a child with staphylococcal sepsis, who failed to mount an adequate C-reactive protein (CRP) and IL-6 response, we tested the functional integrity of IL-6/gp130/IL6R/STAT3 pathway and established that the patient's cells were able to produce and secrete normal amounts of IL-6 and displayed normal STAT3 recruitment upon IL-6 stimulation. Surprisingly, the failed CRP induction was explained by the presence of autoantibodies against IL-6 in the patient's serum. Prior to this publication, only three patients with anti-IL6 autoantibodies had been reported to suffer localized bacterial infections. As such, this work provided a proof-of principle, that systemic Staphylococcal infection, too, may arise due to disturbed IL-6 signalling on the account of naturally occurring anti-IL6 autoantibodies. Since the monogenic defects of IL-6 signalling (other than STAT3 loss-of-function) have only been reported in a handful of patients, our findings indirectly affirmed the crucial role of IL6 signalling in the anti-staphylococcal immunity. Importantly, they also translated to a larger-scale clinical issue, i.e., the need for caution in patients receiving compounds interfering with IL-6 signalling, such as those currently used for several rheumatologic, immune dysregulation diseases and cancer.

Achieved key objectives = C, E

This work was received the best poster award in the 14th Paediatric congress in Olomouc in 2019.



Representative figure: IL-6/IL6R/STAT3 investigations in a patient with Staphylococcal sepsis and failed induction of C-reactive protein

1.1.8 NATIONWIDE OBSERVATIONAL STUDY OF PAEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME TEMPORALLY ASSOCIATED WITH SARS-COV-2 (PIMS-TS) IN THE CZECH REPUBLIC

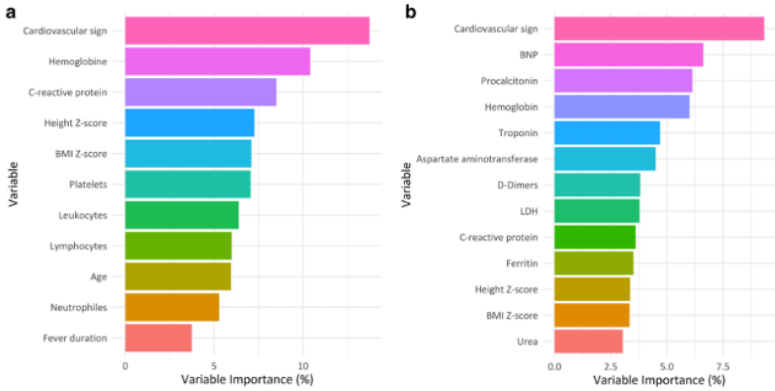
David J, Stara V, Hradsky O, Tuckova J, Slaba K, Jabandziev P, Sasek L, Huml M, Zidkova I, Pavlicek J, Palatova A, Klaskova E, Banszka K, Terifajova E, Vyhnanek R, **Bloomfield M,** Fingerhutova S, Dolezalova P, Prochazkova L, Chramostova G, Fencl F, Lebl J. Nationwide observational study of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the Czech Republic. *Eur J Pediatr.* 2022 Aug 20:1–10.
(IF 3.86, Q1)

PIMS-TS (MIS-C) is a novel life-threatening disease which emerged during the

COVID-19 pandemic. Its pathophysiology is unknown, yet, indisputably, the immune system dysregulation and genetic factors play the pivotal roles. As such, PIMS-TS represents another disease with predisposition to severe course of infection by a single pathogen, as all other infections seem to take on an uneventful course in these children. This retrospective nationwide observational study collected epidemiologic, clinical and laboratory data of 207 Czech children with PIMS-TS from nine university hospitals and eight regional hospitals, representing the largest cohort reported at the time of publishing. We established that the incidence of PIMS-TS out of all SARS-CoV-2-positivelly tested children was 0.9:1,000. The delay between PIMS-TS cases accumulation from the peak of the COVID-19 wave was 3 weeks. Beyond the epidemiological observations, several predictors of life-threatening myocardial dysfunction were identified. These included chiefly the clinical signs of cardiovascular involvement at the initial phases of the disease, decreased concentration of haemoglobin, thrombocytopenia, elevated concentration of CRP, procalcitonin B-type natriuretic peptide and troponin. Upon follow-up, majority of patients fully recovered and had normal cardiac function.

Achieved key objectives = D, E

Representative figure: Predictors of myocardial dysfunction in PIMS-TS stratified by the level of healthcare provider for the use of a) general practitioners b) hospital care providers

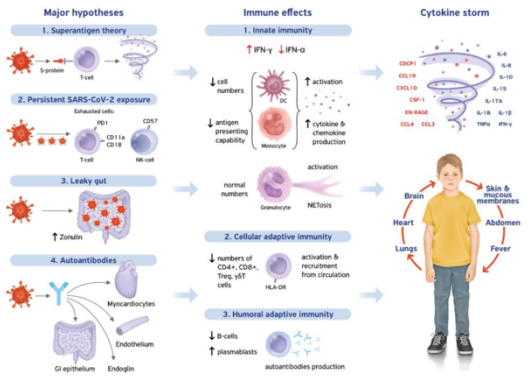


1.1.9 EAACI STATEMENT AND GUIDELINE ON THE PATHOGENESIS, IMMUNOLOGY, AND IMMUNE-TARGETED MANAGEMENT OF THE MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) OR PEDIATRIC INFLAMMATORY MULTISYSTEM SYNDROME (PIMS)

Feleszko W, Okarska-Napierała M, Pauline Buddingh E, **Bloomfield M,** Sediva A, Bautista-Rodriguez C, Brough HA, Eigenmann PA, Eiwegger T, Eljaszewicz A, Eyerich S, Gomez-Casado C, Fraisse A, Janda J, Jiméeneéz-Saiz R, Kallinich T, Krohn IK, Mortz CG, Riggioni C, Sastre J, Sokolowska M, Strzelczyk Z, Untersmayr E, Tramper-Stranders G. EAACI statement and guideline on the pathogenesis, immunology, and immune-targeted management of the Multisystem inflammatory syndrome in children (MIS-C) or Pediatric inflammatory multisystem syndrome (PIMS-TS). Under review in *Allergy in* 2022. (IF 14.71, Q1)

This multinational European collaborative endeavour reflected the need to address the multiple existing case definitions of MIS-C associated with SARS-CoV-2 infections and the lack of unified management guidelines. Members of European Academy of Allergology and Clinical Immunology formulated a joint statement regarding the immune aspects of MIS-C, as well as clinically practical management algorithms. Four main hypotheses of immune pathologic mechanisms were defined, involving both innate and adaptive components, i.e., the superantigen-driven hyperinflammation, persistent SARS-CoV-2 exposure, leaky gut theory allowing continuous exposure to the virus, and the presence of autoantibodies. The applicant directly contributed to this work, particularly to the section on Immunology of MIS-C, receiving the opportunity to familiarize herself with the proceedings of a Delphi-based consensus protocol.

Achieved key objectives = D, F



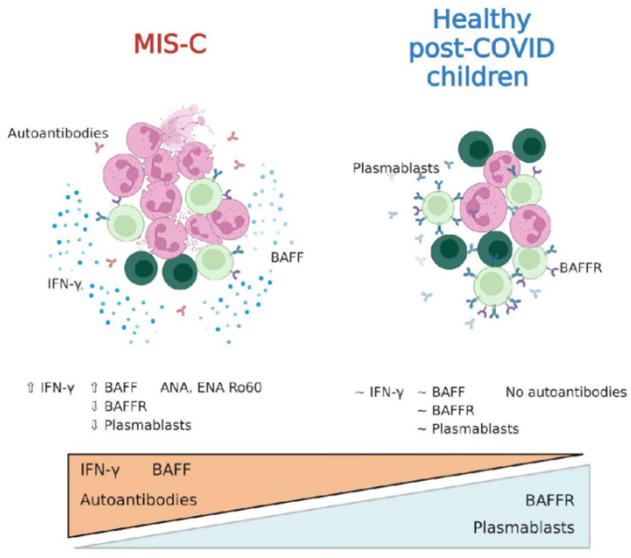
Representative figure: Overview of the hypothesized mechanisms of MIS-C (PIMS-TS) immunopathology

1.1.10 B CELLS, BAFF AND INTERFERONS IN MIS-C

Klocperk A*, **Bloomfield M*,** Parackova Z, Aillot L, Fremuth L, Sasek L, David J, Fencl F, Skotniova A, Rejlova K, Magner M, Hrusak O, Sediva A. B cells, BAFF and interferons in MIS-C. *MedRxiv preprint*, version posted May 21, 2022. doi: https://doi.org/10.1101/2022.05.18.22275245. (without IF)
*Authors contributed equally

This work was a hypothesis-driven exploration of the involvement of B cells in the pathogenesis of MIS-C associated with SARS-CoV-2 infections in children. Parallels with clinical and immune phenotype of a classic autoimmune disorder, systemic lupus erythematosus, such as the strong interferon-based proinflammatory bias and the presence of autoantibodies suggested a disorder of B cell maturation or survival. We found elevated serum levels of B-cell activating factor (BAFF) and a counter-regulative depression of its receptor (BAFFR) on MIS-C B cells, as well as decreased proportion of mature B cells, called plasmablasts. These findings implied that a polyclonal B cell activation may be an important driver of the self-reactive phenomena accompanying MIS-C. The project connected paediatric and immunology departments of three Czech university hospitals and colleagues from Academy of Sciences, Czech Republic.

Achieved key objectives = D, E



Ilustrative figure: The involvement of humoral immunity in PIMS-TS (MIS-C) with autoreactive B cells driven towards autoantibody production by elevated BAFF

1.2 SECONDARY ENDPOINTS

During the doctoral programme, the applicant also co-authored 9 peer-reviewed papers published in international journals with impact factors, which explored clinical and immunopathological features of other rare IEI predisposing to infections yet displaying a broader infectious phenotype. These are listed as Others in the List of publications

1.3 COVID-19 INTERMEZZO

During the outbreak of SARS-CoV-2 pandemic in 2019/2020, the applicant refocused on research of COVID-19-associated immune aspects and co-authored 5 peer-reviewed publications.

She also participated in a global effort led by Dr. Casanova and Dr. Shen-Ying to ellucidate the genetic background behind severe COVID-19 and MIS-C, as single pathogen-driven immunopathologies. These 5 publications are listed as Others in the List of publications

The applicant contributed to the HyperPed COVID Registry, a retrospective multinational observational study, and a global research consortium on MIS-C led by colleagues from Imperial Collage, London and Rockefeller University, New York. The results from these collaborations are pending.

1.4 SELECTED PRESENTATIONS AND POSTERS

The applicant actively participated in educational activities, i.e., oral presentations, poster presentations, webinars, in national and international events.

STAT1 gain-of-function dendritic cells have skewed autoinflammatory and tolerogenic functions and aberrant autophagy 13th International congress on Autoimmunity, Athens, Greece, 2022

STAT1 GOF vs. COVID-19 ESID School of Immunodeficiency, Kutná Hora, Czech Republic, 2021

Časné imunodeficience v dětském věku s dominantním plicním postižením, příklad kohorty s APDS (Activated Phosphoinositide 3-kinase δ syndrome) 15. Český pediatrický kongres, Hradec Králové, 2021

Covid-19 in children: managing MIS-C ESID Grand Rounds Webinar, online, June 2021

Jakinib for the treatment of inborn errors of immunity (IEI) with uncontrolled cytokine signalling: whom to treat? When and how? ESID meeting, online, 2021

Remise klinických komplikací STAT1 mutace při léčbě ruxolitinibem ČSAKI kongres, Česká republika, 2021

Chronická mukokutánní kandidoza jako primární imunodeficience ČSAKI pracovní schůze, Česká republika, 2020

CRP-less sepsis ESID Spring School, Kutná Hora, Czech Republic, 2019

Septický šok bez elevace CRP jako důsledek tvorby a-IL-6 autoprotilátek XIV. Pediatrický kongres, Olomouc, Česká republika, 2019

Funkční diagnostika IFNGR1 a NOD2 mutace II.BD Den, CSAC, Praha, Česká republika, 2018

To be or NOD2 be IFNGR1 deficient 14th International Conference on Innate Immunity, Crete, Greece, 2018

Chronická mukokutánní kandidóza na podkladě STAT1 GOF mutace u otce a syna 13. kongres českých pediatrů a sester, Praha, Česká republika, 2018

Management of CMC with JAK inhibitors EAACI Master Class of Primary Immunodeficiencies, Prague, Czech Republic, 2017

Management of STAT1 GOF CMC ESID Summer School, Calambrone, Italy, 2017

Ruxolitinib in management of novel STAT1 GOF chronic mucocutaneous candidiasis in 12 year old boy ESID meeting, Edinburgh, UK, 2017

DISCUSSION

The exploration of human genetic factors in the host-pathogen interactions and their defects offers unique opportunities to gain new insights into immune system composition and orchestration of its operational processes. This particularly resonates when clinically severe symptoms are not accompanied by any apparent abnormalities in routinely performed immunologic examinations, such as in the diseases addressed by the hereby presented research. Such patients, often initially reported in single-case studies, not seldomly unveil novel immune mechanisms and functionalities or confirm pre-existing hypotheses, which then drives multidisciplinary research. Given the interconnectivity of immune processes with each other, with other human biological systems and with the microbial biosphere, the translational potential of any new discovery is incontestable. However, it is a long route from the discovery of a novel gene, protein or mechanistic interaction to the verification of its causality and to the development and deployment of a new therapeutic strategy. In between, a long-term patient follow-up, disease course and treatment response monitoring provide additional data. If backed by multicentre collaborations, even the “rare” eventually becomes strong enough to build a thorough apprehension. In this thesis, the applicant hoped to participate in these efforts by some such insights.

CONCLUSIONS

This work contributed to the understanding of three rare IEI and one disease with presumed immunogenetic background, all with selective microbial susceptibility.

With the continuing emergence of new infectious diseases, as witnessed globally during the COVID-19 pandemic in 2019, and the alarmingly increasing resistance of pathogens to currently available antimicrobial compounds, the need for continuing investigations of the immune antimicrobial mechanisms is sorely evident and must receive major attention. In the future, the author hopes to continue to contribute to research activities concerning monogenic susceptibility to individual microbes and other rare diseases with antimicrobial immune failures.

SOUHRN (SUMMARY IN CZECH)

Výsledky předkládané v této dizertační práci přispívají k porozumění imunopatologie několika vrozených poruch imunity se zvýšenou náchylností ke konkrétnímu infekčnímu patogenu:

A) u **STAT1 gain-of-function chronické mukokutánní kandidózy** byly popsány nové mutace, imunoprofilace, klinické a buněčné odpovědi na novou efektivní terapii JAK inhibitorem, využití nově vyvinutého fosfoflow protokolu a imunogenicita a bezpečnost mRNA vakcíny proti COVID-19

B) u **Vrozené vnímavosti k mykobakteriálním onemocněním** byly popsány nové mutace, jejich klinické a imunopatologické aspekty a terapeutické využití IFNy

C) u sepse způsobené **Staphylococcus aureus** byly jako příčina selhání obranyschopnosti se systémovým projevem identifikovány **autoprotilátky proti IL-6**, jako první taková reference vůbec

D) u nového onemocnění **PIMS-TS** (**Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2)** byla publikována epidemiologická data, prediktory závažnosti průběhu onemocnění, popsány imunopatologické mechanismy týkající se autoreaktivních charakteristik B lymfocytů a navrženy doporučené postupy pro klinickou praxi

Autorka ustanovila pacientské kohorty a navázala národní a mezinárodní spolupráci. Výsledky se v řadě případů podařilo přenést přímo do klinické praxe; umožnily mimo jiné stratifikaci pacientů podle rizik, tvorbu individualizovaných léčebných plánů „na míru“ pacientovi, vč. konkrétních preventivních opatření, cílené terapeutické a profylaktické medikace, léčebných zákroků a možnosti poskytnutí genetického poradenství.

SUMMARY

The data presented in this dissertation thesis expanded the understanding of immunopathology underling several IEI with increased susceptibility to single infectious pathogens:

A) in **STAT1 gain-of-function chronic mucocutaneous candidiasis** novel mutations, corresponding immune profiles, clinical and cellular responses to novel, efficient therapy with JAK inhibitors, the utility of a newly developed phosphoflow protocol, and immunogenicity and safety of COVID-19 vaccination were reported

B) in **Mendelian susceptibility to mycobacterial diseases** novel mutation, clinical and immunopathological features, and the utility of IFNy were described

C) in **sepsis due to Staphylococcus aureus, IL-6 autoantibodies** were identified as the cause of immune failure with systemic consequence for the first time

D) in the novel **Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2** epidemiological observations, predictors of disease severity, management guidelines were established, and immune pathologic mechanisms, such as self-reactive B cell pathology, were identified

The applicant established patient cohorts and developed national and international cooperations. The findings were, in several cases, translated directly into the patients' clinical management. Our endeavours enabled risk stratifications, individualized management strategies, including avoidance behaviour, targeted therapeutic and prophylactic medications, procedures, and genetic counselling.

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LIST OF PUBLICATIONS

PUBLICATIONS SUPPORTING THE THESIS

Publications with impact factor, first or last authorship of the applicant:

1. **Bloomfield M**, Kanderová V, Paračková Z, Vrabcová P, Svatoň M, Froňková E, Fejtková M, Zachová R, Rataj M, Zentsová I, Milota T, Klocperk A, Kalina T, Šedivá A. Utility of Ruxolitinib in a Child with Chronic Mucocutaneous Candidiasis Caused by a Novel STAT1 Gain-of-Function Mutation. *J Clin Immunol.* 2018;38(5):589-601. (IF=4.85, Q1)

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