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Sylvie Waucquez, sylvie.waucquez@ulb.ac.be, n. réf : ACAD/4270/0911/YE-sw

Bruxelles, le 23 septembre 2011

Monsieur,

J'ai l'honneur de vous informer que la Commission Permanente de la Recherche a, à l'unanimité, retenu la candidature de

Mme **Alexandra KREINS**

à la bourse de perfectionnement de la Fondation Horlait-Dapsens.

Je vous prie d'agréer, Monsieur, l'expression de mes sentiments très distingués.

Le Doyen,

Y. ENGLERT.

Rapport de commission

Bourse de la Fondation Horlait-Dapsens

La commission a reçu 3 candidatures et a été consultée par voie électronique.

Monsieur Olivier DE HENAU a 35 ans. Il est diplômé docteur en Médecine de l'Université Libre de Bruxelles en 2002 avec grande distinction et a obtenu le DES en Médecine interne en 2008. Il est actuellement Aspirant FNRS au sein de l'IRIBHM où il réalise une thèse de doctorat su les effets anti-tumoraux de la chémérine et des ses récepteurs sous la supervision du Professeur Marc Parmentier. Il fait état d'une publication comme co-auteur dans le Journal of Immunology et d'une publication comme co-auteur en soumission, et est premier auteur de 2 abstracts. Il demande le soutien de la Fondation pour finaliser son travail de thèse dans le laboratoire du Professeur Parmentier et ne fait pas mention de séjour futur à l'étranger.

Madame Alexandra KREINS a 29 ans. Elle est diplômée docteur en Médecine de l'Université Libre de Bruxelles en 2007 avec grande distinction en ayant obtenu le Prix du meilleur mémoire de Recherche, et est en formation au sein du DES en Médecine Interne, ayant débuté au CHU Saint-Pierre. Elle est actuellement en formation dans le programme d'Immunologie et de Pathogénèse Microbienne à la " Well Cornell Graduate School of Medical Sciences " à New York depuis 2008 et réalise son projet de recherche au sein du "St Giles Laboratory of Human Genetics of Infectious Diseases" de la "Rockfeller University" sous la supervision du Professeur JL Casanova et du Dr. S Boisson-Dupuis. Elle fait état de 3 publications internationales à comité de lecture, dont 1 comme premier auteur dans le J. Exp Med (IF 14,8) et 2 comme co-auteur dans Diabetologia et Blood ainsi que de 3 abstracts. Elle demande le soutien de la Fondation pour poursuivre son travail de recherche et de thèse consacré à l'étude de nouvelles déficiences immunes primaires prédisposant aux pathologie mycobactériennes au sein du laboratoire où elle séjourne actuellement. Après finalisation de ce travail de thèse et de cette formation, la candidate envisage de poursuivre son activité clinique et de recherche en Belgique dans le domaine de l'Immunologie Pédiatrique.

Monsieur Benoit VOKAER a 31 ans. Il est diplômé docteur en Médecine de l'Université Libre de Bruxelles en 2004 avec la plus grande distinction en ayant obtenu le Prix Fleurice Mercier et est en formation au sein du DES en Médecine interne. Il est actuellement Aspirant FNRS au sein de l'Institut d'Immunlogie (IMI) où il réalise une thèse de doctorat su les mécanismes d'immunorégulation du rejet d'allogreffe par l'expansion des lymphocytes T régulateurs in vivo sous la supervision du Dr. Alain Le Moine. Il fait état de 6 publications internationales à comité de lecture, dont 1 comme premier auteur dans le Journal of Immunology (IF 5,8) et 5 comme co-auteur (PNAS, J. Immunol., Am J Transplant, ..). Il demande le soutien de la Fondation pour finaliser son travail de thèse dans le laboratoire du Dr . Le Moine et ne fait pas mention de séjour futur à l'étranger.

Les trois dossiers sont jugés recevables. Les trois candidats présentent des projets de recherche d'excellente qualité dans lesquels ils sont engagés depuis plusieurs années. Une candidate, A. Kreins, propose de poursuivre son séjour de recherche dans une très bonne équipe étrangère à la Rockefeller University; les deux autres ne mentionnent pas de séjour futur à l'étranger et sollicitent l'obtention de la bourse pour finaliser leurs travaux au sein d'excellents laboratoires de la Faculté. A. Kreins et B. Vokaer font chacun état d'une publication comme premier auteur dans des revues d'excellent et de très bon niveau, respectivement. Dans ce contexte, la commission propose de soutenir Alexandra Kreins, et recommande donc unanimement l'attribution de la bourse de la Fondation Horlait-Dapsens à Alexandra KREINS.

Pour la commission, composée de M. Allaoui, M. Sosnowski et S. Schiffmann ,

S. Schiffmann ,

9/9/2021

WAUCQUEZ Sylvie

De: Alexandra Kreins <akreins@ulb.ac.be>
Envoyé: jeudi 23 juin 2011 21:25
À: MEURIS Sylvain; WAUCQUEZ Sylvie
Objet: Fondation Medicale Horlait-Dapsens
Pièces jointes: HorlaitDapsens_Kreins Alexandra.pdf; Recommendation Letter_Kreins Alexandra.pdf

Prof. Meuris, Madame Waucquez,

Bonjour.

Veuillez trouver ci-joint les documents pour ma candidature au sein de la faculte de medecine pour une bourse de la Fondation Medicale Horlait-Dapsens.

Ceux-ci comprennent une description de mon projet de recherche avec les resultats preliminaires(New primary immune deficiencies predisposing to mycobacterial disease), mon curriculum vitae avec ma "lettre de motivation" (personal statement), ainsi qu'une lettre de recommandation de mon promoteur de recherche aux Etats-Unis, Jean-Laurent Casanova.

Je travaille sur un projet ambitieux et innovateur dans une equipe de renommee mondiale qui etudie la predisposition genetique aux infections mycobacteriennes. Je collabore egalement sur un projet qui etudie la predisposition genetique aux candidoses muco-cutanees chroniques et notre papier (pour lequel je partage la position de 1ere auteur) vient d'etre accepte pour publication dans le Journal of Experimental Medicine. Il sera en ligne d'ici quelques jours!

Le soutien de la faculte de medecine pour l'octroi de cette bourse me permettrait de poursuivre ma recherche l'annee prochaine et de cloturer mon projet dans les meilleures conditions possibles, avant mon retour sur Bruxelles pour reprendre ma formation clinique. Dans un futur proche, j'espere donc contribuer au dynamisme de notre faculte avec mes acquis en genetique humaine et en immunologie, tant sur le plan clinique qu'en recherche.

Merci de m'informer des criteres de selection ainsi que de me tenir au courant du statut de ma postulation.

Bien a vous,

Alexandra

Alexandra Kreins

New primary immune deficiencies predisposing to mycobacterial disease

1. Abstract:

Mendelian Susceptibility to Mycobacterial Disease (MSMD) is a primary immunodeficiency consisting of clinical disease caused by poorly virulent mycobacteria[1,2]. The genetic dissection of MSMD has led to the identification of eight morbid genes involved in IL-12-dependent IFN-γ-mediated immunity[3,4,5]. Affected individuals are also more vulnerable to *Mycobacterium tuberculosis*[6]. Our laboratory has further provided the first molecular proof-of-principle evidence that tuberculosis (TB) may result from genetic predisposition, following the identification of the first mutations in *IL12RB1*, which impair IFN-γ immunity and predispose to disseminated TB in children[6]. Since approximately half of the patients in our MSMD cohort still lack a genetic etiology, we hypothesize that children with MSMD who do not carry mutations in known MSMD-causing genes bear MSMD-causing mutations in other genes. **This project aims to identify and characterize novel disease-causing single-gene inborn errors of immunity to mycobacteria.** Using a genome-wide linkage (GWL) approach, we recently identified a second patient carrying a homozygous mutation in *TYK2* as well as two patients with homozygous mutations in *JAK2*. TYK2 and JAK2 are involved in several signaling cascades, including the IL-12/23 pathway. I started the complete functional characterization of various TYK2-dependent signaling pathways (IL-12, IL-23, IFN-α/β, IL-6, IL-27 and IL-10). I also intend to characterize the role of JAK2 in IL-12/IFN-γ-mediated immunity. Moreover, I would like to identify additional patients with mutations in *TYK2* and *JAK2*. This research will contribute to the elucidation of the molecular basis of mycobacterial disease, providing information with important genetic, immunological and clinical implications.

2. Specific aims:

Specific aim 1: To characterize the cellular responses of the TYK2-deficient patients. I intend to characterize the role of TYK2 in the IL-12/23-dependent IFN-γ signaling pathways, as well as its requirement following different stimuli (cytokines, viruses, bacteria) in a range of cell types (EBV-transformed B cells, T saimiri cells, SV40 fibroblasts and PBMCs) from healthy controls, the previously described TYK2-deficient patient as well as the newly identified TYK2-deficient patient.
Specific aim 2: To characterize the cellular responses of the JAK2-deficient patients. I intend to determine the impact of the mutated JAK2 alleles on IL-12/23-mediated IFN-γ signaling, as well as on the response to different stimuli (cytokines, bacteria) in a range of cell types (EBV-transformed B cells, T saimiri cells, SV40 fibroblasts and PBMCs).

3. Background:

(1) Introduction.

Mendelian susceptibility to mycobacterial disease (MSMD) is a primary immunodeficiency syndrome characterized by severe disease caused by weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria, in otherwise healthy children[1,2]. Patients with MSMD are also more vulnerable to tuberculosis, caused by the more virulent *Mycobacterium tuberculosis*[6]. Genetic dissection of MSMD over the last 15 years has resulted in the identification of eight morbid genes, including six autosomal (*IFNGR1*, *IFNGR2*, *STAT1*, *IL12B*, *IL12RB1*, *IRF8*) and two X-linked (*NEMO*, *CYBB*) genes[1,3,4,5]. The high level of allelic heterogeneity at these eight loci has led to the definition of up to 15 distinct disorders. The pathogenesis of MSMD in the majority of these patients involves impaired IL-12/IFN-γ immunity. However, only about half of the 500 children tested in our laboratory carried one of these genetic defects. We thus hypothesize that MSMD in the remaining patients results from other single-gene inborn errors of immunity, possibly but not necessarily involving the IL-12/IFN-γ circuit.

In order to identify new genes involved in mycobacterial disease, we performed GWL in patients for whom no disease-causing mutations had been found in previously identified genes[7]. One patient was found to be homozygous for a 9 basepair frameshift deletion resulting in a premature stop codon in *TYK2*. Using this approach, two additional patients were identified, each with a missense mutation in *JAK2*. TYK2 and JAK2

are non-receptor tyrosine kinases that belong to the Janus kinase (JAK) family. Two knockout mice for *Tyk2* have been generated[8,9]. One mouse showed reduced responses to IL-12 and IFN-α/β, while the other mouse had a normal response to IL-12, except for a reduced IFN-γ production. Both mice had normal responses to IL-6 and IL-10. Complete recessive TYK2 deficiency has been described in one Japanese patient suffering from Hyper IgE syndrome (HIES) associated with mycobacterial disease and very mild viral disease[10]. This patient presented abolished responses to IL-12 and IL-23, accounting for the susceptibility to bacterial infections, and abolished responses to IFN-α/β, underlying the mild susceptibility to viral infections. Impaired responses to IL-6 and IL-10 were also reported, which can explain the susceptibility to pyogenic infections in the context of HIES in this patient. The clinical phenotype of our patient differs, as he suffers from severe intracellular bacterial and mild cutaneous viral infections, but does not suffer from HIES[11]. In mice, complete JAK2 deficiency is lethal *in utero*[12,13], but a conditional *Jak2* knockout mouse was recently generated[14]. This mouse exhibited defects in dendritic cell development and effector function and interestingly, also presented a lower capacity to clear intracellular bacterial infections. In contrast, inherited JAK2 deficiency in humans has not yet been reported, although several patients with chronic myeloid leukemia have been described with somatic mutations in *JAK2*[15]. We have thus identified the first patients with inherited mutations in *JAK2*. One patient suffered from disseminated tuberculosis and the other from salmonellosis. Both TYK2 and JAK2 are involved in the IL-12 signaling pathway. TYK2 is also thought to be involved in the responses to IFN-α/β, IL-6 and IL-10 and JAK2 in the responses to type 2 IFN and IL-6[8,9,11,12,13]. From a basic biological standpoint, studying the involvement of TYK2 and JAK2 in these signaling pathways will contribute to a better understanding of host defense mechanisms against mycobacteria and other pathogens. From a clinical standpoint, further dissection of the pathogenesis of mycobacterial disease will make it possible to provide molecular diagnoses for patients and genetic counseling for families. It will also pave the way for the development of a new approach to the treatment of children with mycobacterial disease.

(2) Preliminary results:

I have begun to characterize the cellular phenotype of the newly identified TYK2-deficient patient. This patient presents a susceptibility to mycobacteria and other intracellular bacteria, as well as a mild susceptibility to viruses. The complex clinical manifestations of the patient may be explained by the observed defects in multiple cytokine signals *in vitro*. Consistent with the intracellular bacterial infections observed in the patient, TYK2-deficient T cells and NK cells display an impaired, but not abolished induction of IFN-γ in response to IL-12. Interestingly, in contrast to the Japanese TYK2-deficient patient, cells from our patient responded normally to IL-6 as shown by normal phosphorylation of STAT3. This finding suggests that impaired IL-6 responses in the Japanese patient underlie at least some features of the HIES.

4. Design and Methods:

Specific Aim 1: To characterize the cellular responses of the TYK2-deficient patients.

I am currently characterizing the cellular phenotype of the newly identified TYK2-deficient patient using EBV-B cells, T saimiri cells, SV40 fibroblasts, and PBMCs, as compared with equivalent cells from both healthy controls and the previously described Japanese TYK2-deficient patient. In particular I would like to investigate the integrity of the IL-6 responsive pathway in both TYK2-deficient patients to understand the discrepancy between the clinical presentations of the patients. To do so I will perform whole exome sequencing, in collaboration with our bioinformatics team, on genomic DNA from both patients and I will analyze the data initially by focusing on other components of the IL-6 signaling pathway (for example, *IL6R*, *gp130*, *JAK1* and *JAK2*). In parallel, I will also investigate the response to additional gp130 cytokine members (HHV-8 vIL-6, hyper-IL-6, LIF, IL-11 and IL-27) in different cell types from both patients using western blotting and electromobility shift assay (EMSA). For every cellular phenotype I identify, I will use a retroviral vector that expresses wild type TYK2, to attempt to restore normal function. Moreover, I intend to screen the laboratory's cohort of patients with mycobacterial disease to identify any additional patients with mutations in TYK2.

Specific Aim 2: To characterize the responses of the JAK2-deficient patients:

To investigate the cellular phenotype of the JAK2-deficient patients, I will develop a similar approach as described above for the characterization of the cellular responses of the TYK2-deficient patients. I will first focus on identifying any defects in the IL-12/23 –IFN-γ signaling pathways to explain the mycobacterial disease using western blotting, electromobility shift assay (EMSA), enzyme-linked immunosorbent assay (ELISA) and flow cytometry. I will also explore additional signaling pathways, as JAK2 is also thought to be involved in the responses to type 2 IFNs and IL-6. In addition, retroviral-based transduction of JAK2 mutants will be done to ascertain whether these mutations are hypomorphic or amorphic in function. Subsequently, I will once again complement any observed defects in cellular phenotypes by gene transfer of the wild type using retroviral vectors to confirm the deleterious role of the mutated molecule. Given the specific defect in dendritic cells in the conditional *Jak2* knockout mice, I will also investigate the development and the function of dendritic cells in these patients. Furthermore, I will also look for additional patients with mutated JAK2 alleles in the laboratory's cohort of patients.

5. References:

(1) Casanova et al. Annu.Rev.Immunol. 2002. 20:581-620
(2) Alcais et al. J Clin Invest. 2009. 119(9) :2506-2514
(3) Filipe-Santos et al. Semin Immunol. 2006. 18(6):347-61
(4) Bustamante et al. Nat. Immunol. 2011. 12(3):213-21
(5) Hambleton et al. N Engl J Med.2011
(6) Alcais et al. J.Exp.Med. 2005.202:1617-1621
(7) Grant et al. J Med Genet. 2011
(8) Karaghiosoff et al. Immunity. 2000. 13:549-560
(9) Shimoda et al. Immunity. 2000. 13:561-571
(10) Minegishi et al. Immunity. 2006. 25:745-755
(11) Sebnem et al. Submitted
(12) Parganas et al. Cell. 1998. 93(3):385-95
(13) Neubauer et al. Cell. 1998. 93(3):397-409
(14) Zhong et al. PlosOne. 2010. 5(3):e9593
(15) Ghoreshi et al. Immunol Rev. 2009. 228(1) :273-87

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Alexandra Yema KREINS	**Graduate Fellow**
DOB 04.10.1982	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Université Libre de Bruxelles, Brussels, Belgium	M.D.	2000-2007	Medicine
Université Libre de Bruxelles, Brussels, Belgium	Resident	2007-	Internal Medicine
Weill Cornell Graduate School of Medical Sciences, New York, NY, USA	Graduate Student	2008-	Immunology and Microbial Pathogenesis
The Rockefeller University, St. Giles Laboratory of Human Genetics of Infectious Diseases (Prof. Jean-Laurent Casanova), New York, NY, USA	Graduate Fellow	2009-	Pediatric Immunology

A. PERSONAL STATEMENT

In 2007 I graduated from the Medical School of the Université Libre de Bruxelles in Belgium. Because of my interest in infectious diseases, I started my clinical residency at the Centre Hospitalier Universitaire Saint-Pierre in Brussels, which is a major reference hospital in this area. Previously I had completed a research internship at the Laboratory of Experimental Medicine (directed by Prof. Decio Laks Eizirik), which has one of the best publication records at the Université Libre de Bruxelles' Medical School. I worked with a team studying apoptosis of insulin producing cells, in the context of immune-mediated beta cell death in type 1 diabetes. My Master's dissertation was based on this research, investigating the role of the cytokines IL-1β and TNF-α and role of the transcription factor NF-κB for the apoptosis of insulin producing cells. It was awarded the annual Prize for Research from the Medical Faculty. With the foundation I obtained from this first experience in research in Immunology, I decided to join the Immunology and Microbial Pathogenesis program at the Weill Cornell Graduate School of Medical Sciences in New York. In September 2009 I joined the St. Giles Laboratory of Human Genetics of Infectious Diseases (directed by Prof. Jean-Laurent Casanova) at The Rockefeller University. Prof. Casanova's group studies genetic predisposition to pediatric infectious diseases, particularly mycobacterial diseases, herpes simplex encephalitis and invasive pneumococcal diseases. I was drawn to join the group investigating Mendelian susceptibility to mycobacterial disease (MSMD), which confers a predisposition to infections caused by weakly virulent mycobacteria. To date, fifteen genetic defects affecting eight genes (*IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, IRF8, NEMO and CYBB*) and causing MSMD have been reported. Most of these genes encode proteins involved in IL-12/23-dependent IFN-γ-mediated immunity. Our group hypothesizes that MSMD patients for whom no mutation was identified in one of those known MSMD-causing genes, must have another, hitherto unknown, monogenic inborn error of immunity. With the mentorship of Prof. Casanova and Dr. Stephanie Boisson-Dupuis, I initiated a research project which aims to identify novel single-gene inborn errors of immunity to mycobacteria, with a particular focus on the IL-12 signaling pathway. I am currently completing a cellular and molecular characterization of TYK2-deficiency, a novel primary immunodeficiency. This research will provide new insights into the mechanisms of immunity to mycobacteria and other pathogens. I am also collaborating on a project characterizing *STAT1* mutations in patients with chronic mucocutaneous candidiasis. Upon completion of my doctoral research work, I intend to orient my residency towards Pediatric Immunology as I am committed to pursuing a career as a physician scientist in this area, with a focus on the clinical and scientific aspects of primary immunodeficiencies.

B. POSITIONS AND HONORS.

Professional experience:

2004-2006:
-Teaching Assistant to Prof. R. Naeije and Prof. S. Sohraby, Laboratory of Physiology and Physiopathology, Université Libre de Bruxelles, Brussels, Belgium

November 2006-June 2007:
-Research Internship, Laboratory of Experimental Medicine (Prof. D.L. Eizirik), Université Libre de Bruxelles, Brussels, Belgium

September 2007-September 2008:
-Resident in Internal Medicine (Prof. J-P. Praet, Prof. N. Clumeck), CHU St. Pierre, Université Libre de Bruxelles, Brussels, Belgium

August 2009-Present:
-Graduate Fellow, St. Giles Laboratory of Human Genetics of Infectious Diseases (Prof. J-L. Casanova), The Rockefeller University, New York, NY, USA

Advanced training:

July 2004:
-Summer University in Tropical Medicine, Tropeninstitut Berlin, Berlin, Germany

September 2010:
-2010 CIS School in Primary Immunodeficiency Diseases, Clinical Immunology Society, USA

International Placements:

October 2003-July 2004:
- ERASMUS exchange student at the Humboldt Universitaet zu Berlin, Berlin, Germany

August 2004-September 2004:
-Clinical Elective in Infectious Diseases, Department of Internal Medicine, Clinique Ngaliema, Kinshasa, Democratic Republic of the Congo

March 2005-April 2005:
-Clinical Elective in Pediatrics, Bukas Palad, Pasay City, Manila, Philippines

January 2006-February 2006:
-Clinical Elective in Plastic Surgery, Burns Unit, Royal North Shore Hospital, University of Sydney, Sydney, Australia

July 2006-August 2006:
-Clinical Elective in Pediatrics, Neonatal Intensive Care Unit, Tokyo Women Medical University Hospital, Tokyo, Japan

Awards and distinctions:

2003-2004	Recipient of European Union ERASMUS fellowship
2005	Fellowship from the Centre Universitaire pour le Développement (ULB) for academic merit
2006	Fellowship from the Fonds Génicot for academic merit
2007	TWMU Fellowship for academic merit
2007	University Prize for Scientific Research 07 (ULB) for Dissertation Defense: "Role of the cytokines IL-1β and TNF-α and role of the transcription factor NF-κB for the apoptosis of insulin producing cells"
2009-present	Member of the Alumni Committee of the Belgian-American Educational Foundation
2011-present	Member of the Belgian-American Educational Foundation

Oral Communications:

New Genetic Deficiencies Predisposing to Mendelian Susceptibility to Mycobacterial Disease: Cellular and Molecular Characterization of TYK2-deficiency, Oral presentation at 2010 First North American Primary Immune Deficiency National Conference, Philadelphia, PA, May 2010

Characterizing human TYK2 deficiency, Oral presentation at 2011 Vincent du Vignaud Symposium, New York, NY, April 2011

Poster Presentations:

1. F. Ortis, N. Naamane, **A.Y. Kreins**, P. Pirot, and D.L. Eizirik. *Characterization of the pattern of gene expression induced by IL-1β and TNF-α in insulin producing INS-1E cells,* Poster presented at the EASD (European Association for the Study of Diabetes), 43rd Annual Meeting of the EASD, Amsterdam, the Netherlands, September, 2007

C. PEER-REVIEWED PUBLICATIONS

1. F. Ortis, P. Pirot, N. Naamane, **A.Y. Kreins**, J. Rasschaert, F. Moore, E. Théâtre, C. Verhaeghe, N.E. Magnusson, A. Chariot, T.F. Ørntoft and D.L. Eizirik. *Induction of nuclear factor-kappaB and its downstream genes by TNF-alpha and IL-1beta has a pro-apoptotic role in pancreatic beta cells.* Diabetologia 2008; 51 1213-25
2. XF. Kong, M. Ciancanelli, S. Al-Hajjar, L.Alsinia, T. Zumwalt, J. Bustamente, J. Feinberg, M. Audry, C. Prando, V. Bryant, **A. Kreins**, D. Bogunovic, R. Halwani, X. Zhang, L. Abel, D. Chaussabel, S. Al-Muhsen, JL. Casanova, S. Boisson-Dupuis. *A novel form of human STAT1 deficiency impairing early but not late responses to interferons.* Blood 2010
3. **A.Y. Kreins***, L. Liu*, S. Okada*, XF. Kong*, S. Cypowyj* (* equal contribution) *et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis.* Journal of Experimental Medicine. In press.
4. SS. Kilic, M. Hacimustafaoglu, S. Boisson-Dupuis, **A. Kreins**, A. Grant, L. Abel, JL. Casanova, *A Tyk2-deficient patient without hyper-IgE syndrome.* Clinical case report. Submitted.

D. RESEARCH SUPPORT

2008-2009 Fellowship from the Belgian American Educational Foundation

The Rockefeller University
SCIENCE FOR THE BENEFIT OF HUMANITY

Jean-Laurent Casanova, MD, PhD
Professor/Head of Lab/Senior Attending Physician
St. Giles Laboratory of Human Genetics of Infectious Diseases
p: 212-327-7331
f: 212-327-7330

June 21, 2011

Dear Members of the Review Committee,

It is my pleasure to recommend **Alexandra Kreins**, MD, for the Fondation Medicale Mathilde E. Horlait-Dapsens Fellowship. Alexandra joined my lab in September of 2009. She is an exceptionally talented young researcher, who after graduating from medical school in Belgium in 2007, decided to complete her clinical residency in internal medicine at the Universite Libre de Bruxelles, and obtain a comprehensive research experience. She thus enrolled as a PhD student in the Immunology and Microbial Pathogenesis Program at Weill Cornell Medical College.

In the time that Alexandra has been a member of our team, she has exceeded my very high expectations, demonstrating her remarkable aptitude and her experimental and intellectual skills. I was impressed by the rapidity with which she learned and mastered the key concepts in the field of primary immunodeficiencies, and rapidly embarking her experimentation. She collaborates with ease, exchanging advice with fellow lab members, and she exudes confidence when voicing her opinion, which is always carefully thought out and insightful.

Alexandra is working on a very novel and ambitious project, to decipher novel genetic etiologies of Mendelian susceptibility to mycobacterial diseases (MSMD). She has already obtained very positive results and is currently preparing a manuscript for submission as a first author, detailing TYK-2 deficiency in two patients. Additionally, Alexandra was a key investigator in a multi-group project, where she combined her understanding of the MSMD pathways and applied this to further understand chronic mucocutaneous candidiasis disease. Her successful efforts resulted in a first co-authored manuscript that was recently accepted for publication in the high-profile *Journal of Experimental Medicine*. I have no doubt that she will make remarkable discoveries in this clinical research field.

The proposed research will benefit greatly from the scientific environment at Rockefeller University. Laboratories here conduct both basic and clinical research, and study a diverse range of biological and biomedical problems, including cutting edge research on infectious diseases. Our laboratory is fully equipped with all the necessary instrumentation to carry out Alexandra's experimentation, and she will have ample time to complete her work. Our collaboration with the Necker branch of the HGID Laboratory, directed by Laurent Abel in Paris, where I am a Visiting Professor, provides us with a unique supply of patient samples from Europe, Northern Africa and the Middle-East. The collection of consanguineous families from these areas, begun over 15 years ago, is a unique asset to her project. The genomic core facility of the Rockefeller University has all technical resources to conduct the initial steps of this project, in collaboration with Agilent.

This is my eleventh year as the Head of the HGID Laboratory, which was cofounded by myself and Laurent

Abel in Paris. In 2008, I was invited by the Rockefeller University to expand the lab to New York, where I am a Professor, Head of Lab, and Senior Attending Physician. The laboratory has internationally recognized expertise in the field of human genetics of infectious diseases, as attested by its previous achievements.

Alexandra is very smart, passionate, very meticulous, clever, scholarly, and has outstanding experimental abilities. She is highly involved in the lab, as well as in the community. I think Alexandra is an extraordinary asset in our lab. She is moving in a steadfast direction to becoming a successful independent physician scientist, and I strongly believe that she will benefit significantly from funding through the the Fondation Meditale Mathilde E. Horlait-Dapsens.

I therefore recommend her for the award wholeheartedly and unreservedly.

Sincerely,

Jean-Laurent Casanova, MD, PhD
Professor, The Rockefeller University
Head, St. Giles Laboratory of Human Genetics of Infectious Diseases
Senior Attending Physician, The Rockefeller University Hospital