BIOGRAPHICAL SKETCH

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NAME: Zdenek Hel, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): HZDENE

POSITION TITLE: Professor, tenured

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Charles University, Prague, Czech Republic	M.S.	1990	Biochemistry
McGill University, Montreal, Canada	Ph.D.	1997	Experimental Medicine
National Cancer Institute, NIH, Bethesda, USA	Postdoctoral Fellowship	1997 –2002	Immunology

A. Personal statement.

My research focuses on immunology, disease pathogenesis, immune metabolism, cardiovascular and liver diseases, mucosal immunology, cancer immunology, immunodefficiencies, autoimmune diseases, vaccine development, immune therapy, and the effect of hormonal contraception on the immune system. Our most recent program focuses on the analysis of altered myelopoiesis and immune metabolism in infection, cancer, and other inflammatory conditions. We currently have several R01-funded clinical studies focusing on the effect of altered neutrophil and other myeloid populations on the mechanisms of cardiovascular and liver disease development in HIV-1-infected individuals and the role of innate immune system in HIV-1-associated immune suppression (R01 “Neutrophil dysregulation as a driving mechanism of cardiovascular disease in HIV-1-infection”; R01 “The Guts of HIV: Innate Immune Dysregulation as a Central Mechanism of Gastrointestinal and Liver Disease in HIV-1-Infected Individuals”).

I obtained M.Sc. degree (honors) at Charles University, Prague, a Ph.D. degree in experimental medicine (honors) at McGill University in Montreal, Canada, followed by a postdoctoral fellowship at the National Institutes of Health in Bethesda in the laboratory of Dr. G. Franchini. I joined the UAB faculty in 2003 to take advantage of the UAB Center for AIDS Research and to develop relationships with scientists who were interested in developing translational research. Currently, I am tenured Professor at the Department of Pathology and Department of Microbiology at UAB. I am a senior researcher at the Center for AIDS Research, Comprehensive Cancer Center, and several other research centers. I have a long-standing interest in understanding the pathogenic and immunological mechanisms of HIV-1 infection and in the search for strategies that may help us to treat or prevent HIV-1/AIDS. I have been a PI or Project leader on > 10 NIH-funded grants (R21, R01, PO1), Howard Hughes Medical Institute Junior Faculty Award, and various other awards. As a result of these previous experiences, I am aware of the importance of frequent communication among project members, constructing a comprehensive timeline, and adhering to the planned project milestones. I have experience in leading several clinical trials focusing on HIV-1immunology and effect of hormonal contraception on immune system. I have published 35 publications in peer-reviewed including *Nature Medicine*, *PLOS Pathogens*, *JAIDS*, *J. Immunol*, *Endocrinology* and others. Four publications are currently submitted or in revision. I serve as an editor and ad hoc reviewer for multiple scientific journals including *Blood, JAIDS, PLOS Pathogens,* and *J. Immunol*. Nationally, I serve as ad hoc member on multiple National Institutes of Health (NIH) Study Sections and on the Research Evaluation and Decision Panel of the AIDS and Cancer Specimen Resource (ACSR). International service is demonstrated by serving on a Creative and Novel Ideas in HIV Research Committee of the International AIDS Society, as an evaluator for the Howard Hughes Medical Institute International Scholarship, consultant for World Health Organization (WHO), USAID, and Bill & Melinda Gates Foundation and as an ad hoc member of grant evaluation committees of the Ministry of Education of Czech Republic, Czech Science Foundation, and South African Medical Research Council. I have participated in the organization of multiple clinical trials in USA and Zambia.

B. Positions and Honors.

Positions and Employment

1991 – 1997 Graduate student, Center for the Study of Host Resistance, Research Institute of Montreal General Hospital, McGill University, Montreal, QUE, Canada.
1997 – 2002 Postdoctoral Fellow, Laboratory of Animal Models and Retroviral Vaccines, National Institutes of Health, NCI, laboratory of Dr. G. Franchini, Bethesda, MD, USA.
1999 – 2002 Lecturer, Foundation for Advanced Education in Sciences, National Institutes of Health, Bethesda, MD, USA.
2003 Associate Scientist, Center for AIDS Research, Mucosal HIV and Immunobiology Center, Center for Cancer Research, Gene Therapy Center, UAB, Birmingham, AL, USA.
2003 – 2011 Assistant Professor, Dept. of Pathology, Dept. of Microbiology, University of Alabama at Birmingham, Birmingham, AL, USA.
2011-2012 Associate Professor, Dept. of Pathology, Dept. of Microbiology, UAB, AL, USA.
2012- 2017 Tenured Associate Professor, Dept. of Pathology, Dept. of Microbiology, UAB, AL, USA.
2017- present Tenured Professor, Dept. of Pathology, Dept. of Microbiology, UAB, AL, USA.

Other Experience and Professional Memberships

2009 Challenge Grants Study Section, NIH, Bethesda.
2009 HIV/AIDS Vaccine Study Section, NIH, Bethesda.
2009 Challenge Grants Panel, AIDS Immunology and Pathogenesis, Ad Hoc, NIH (June 2009)
2010 Special Emphasis Panel, Oral Mucosal Vaccination against HIV Infection, NIDCR, NIH
2010 Infectious Diseases and Microbiology Integrated Review Group (IDM), ZRG1 IDM-C, NIH
2010 ZRG1 VACC-J (02), AIDS Molecular Biology and Opportunistic Infections, NIH
2010 Special Emphasis Panel ZRG1 AARR-J (02), HIV/AIDS Immunology and Pathogenesis, NIH
2011 ZRG1 AARR-J (02) M, HIV/AIDS Immunology and Pathogenesis, NIAID, NIH
2011 HIV Vaccine Research and Design (HIVRAD) Program Study Section, PAR-09-134, NIH.
2012 HIV Vaccine Research and Design (HIVRAD) Program, PAR-12-087, NIH.
2012 World Health Organization (WHO) Consultant. WHO and Partners Stakeholders' technical consultation on hormonal contraception and HIV: A review of the science, research developments, and their implications for service delivery and priority research; Geneva, Switzerland.
2012 Special Emphasis Panel, ZRG1 AARR-K(52), NIH.
2012 HIV Vaccine Research and Design (HIVRAD) Program, PAR-12-087: ZAI1-RRS-A-J1; NIH.
2013 South African Medical Research Council, South Africa. Ad hoc reviewer.
2014 HIV AIP Study section, NIH. Ad hoc reviewer.
2014 NCI Contract Review: Support for Research on Retroviral Pathogenesis, Treatment and Prevention.
2015 Integrative and Clinical Endocrinology and Reproduction Study Section (ICER).
2016 Special emphasis panel, HIV Pathogenesis, NIAID/NIH, ZRG1 AARR-J (91).
2016 Special emphasis panel, HIV/AIDS, Mentored Patient-Orientated Research, ZRG1 AARR-K(04).
2016 Special emphasis panel, HIV in Digestive Diseases - Gastrointestinal Mucosa and Liver, NIDDK/NIH.
2016 Integrative and Clinical Endocrinology and Reproduction Study Section (ICER), NIH.
2016 Special emphasis panel, AIDS Clinical Studies and Epidemiology, ZRG1, AARR (02).
2017 Special emphasis panel, AIDS Molecular and Cellular Biology (AMCB).
2017 Special emphasis panel, Scientific Review Group 2017/05 ZRG1 AARR-K (02) M.
2017-2018 AIDS Immunology and Pathogenesis Study Section (AIP), permanent member.
2018 Special emphasis panel, HIV Pathogenesis, NIAID/NIH, ZRG1 AARR-K(91).
2019 NIDA HIV/AIDS Aviner Award Review Panel.
2018-2019 HIV Immunopathogenesis and Vaccine Development Section (HIVD), permanent member.

Honors

1990 Dean's list of honor, School of Natural Sciences, Charles University, Prague, Czech Republic.
1993 1st Place, Annual student competition, Canadian Society for Immunology, CA.
1994 Travel fellowship, National Meeting of the Society for Leukocyte Biology, Tucson, AZ, USA.
1994 4th Place, Annual student competition, Canadian Society for Immunology, CA.
1996 McGill Major Fellowship for Graduate Studies, McGill University, Montreal, Canada.
1996 Travel fellowship, International Meeting of the Society for Leukocyte Biology, Verona, Italy.
1997 Dean's list of honor, Department of Experimental Medicine, McGill University, Montreal, CA.

1997 – 2002 Fogarty International Center Postdoctoral Fellowship, NIH, Bethesda, MD, USA.
2003 Howard Hughes Medical Institute Young Investigator Award.
2008 – 2015 Graduate students: Warren Denning: John R. Durant Award for Excellence in Cancer Research (2008); Hiromoto Travel Award (2008); CMB Training Grant (2009); Katherine Michel: Basic Mechanisms of AIDS Pathogenesis T32 fellowship (2013); Nathan Bowers: GBS retreat award (2012); Pathology Trainee award (2012); Keystone Conf. Travel grant (2013); Immunology Training grant T32 fellowship (2013). UAB/Keystone Conf. Travel grant (2014)
2015 – 2019 Graduate students: Ashley Connelly: Translational and Molecular Sciences (TMS) Fellowship (2016); Exceptional Student Award by International Society for Advancement of Cytometry (ISAC) (2018); Winner, Exceptional Student Competition, 33td Congress of the ISAC, Prague, (2018); Marcus Davis: Winner, Society for Leukocyte Biology Trainee Award at the Southeastern Immunology Symposium, Birmingham, AL (2018); Winner, Society for Leukocyte Biology Mentoring Diversity Travel Award to SLB annual meeting in Chandler, AR (2018).

C. Contribution to Science. Science thrives when we constantly challenge ourselves to consider new ideas and new approaches to research. Much of my work has involved introducing new ideas to the field of HIV-1 pathogenesis and prevention and immunotherapy of cancer and chronic viral diseases.

C.1 Design and Testing of HIV-1 Vaccine Candidates. With a team of collaborators, we showed that: 1) Antiretroviral treatment (ART) initiated in the acute phase of HIV infection results in a functional cure and control of viremia in absence of ART; 2) Therapeutic immunization against HIV and possibly other chronic viral infections is feasible and effective; and 3) Peptide-based vaccine delivered on mucosal surface protects against HIV. These breakthrough paradigm shift publications have initiated a series of clinical trials in humans and changes in the treatment of HIV-1 infected individuals. Furthermore, we demonstrated that a vaccine based on the induction of cytotoxic ($CD8^+$) and helper ($CD4^+$) T cells protects against HIV infection in an animal model; this has significantly contributed to HIV vaccine development. We have also demonstrated prevention of infection by intravaginal application of agents enhancing the protective properties of the genital mucosa.
a. **Hel, Z.,** Venzon, D., Poydyal, M., Tsai, W.P., Giuliani, L., Woodward, R., Chougnet, C., Shearer, G., Altman, J., Watkins, D., Bischofberger, N., Abimuku, A., Markham, P., Tattaglia, J., and Franchini, G. 2000. Viremia control following structured treatment interruption and therapeutic immunization of SIV_{251} –infected macaques. **Nature Med.** 6:1140-6. (IF: 24.3; Citations: >164).
b. Belyakov, I.M., **Hel, Z.,** Kelsall, B., Kuznetsov, V.A., Ahlers, J.D., Nacsa, J., Watkins, D.I., Allen, T.M., Sette, A., Altman, J., Woodward, R., Markham, P.D., Clements, J.D., Franchini, G., Strober, W., and J. A. Berzofsky. 2001. Mucosal AIDS vaccine reduces disease and viral load in gut reservoir and blood after mucosal infection of macaques. **Nature Med.** 7:1320-6. (IF: 24.3; Citations: >185).
c. **Hel, Z.**, Nacsa,J., Tryniszewska, E., Tsai, W.P., Washington-Parks, R., Montefiori, D.C., Felber, B.K., Pavlakis, G.N., Tartaglia, J., and G. Franchini. 2002. Containment of SIV infection in vaccinated macaques: Correlation with the magnitude of virus-specific pre- and post-challenge CD4+ and CD8+ T-cell responses. **J. Immunol.** 169:4778-4787. (IF: 5.4; Citations: >116).
d. **Hel, Z.**, Tsai, W.-P., Tryniszewska, E., Nasca, J., Merjham, P.D., Lewsi, M.G., Pavlakis, G.N., Felber, B.K., Tartaglia, J., and G. Franchini. 2006. Improved vaccine protection from simian AIDS by the addition of nonstructural SIV genes despite antigen competition. **J. Immunol.** 176: 85-96. (IF: 5.4; Citations: >47).

C.2 Mucosal Biology of HIV-1 and SIV Infections. We have performed multiple studies on the effect of HIV-1 and SIV infection on mucosal immune cell populations, effect of Fc receptor on HIV-1 transcytosis, and use of menstrual cells as a readily available source of endometrial immune cells.
a. **Hel, Z.**, Nacsa, J., Kelsall, B., Tsai, W.P., Letvin, N., Parks, R.W., Tryniszewska, E., Picker, L., Lewis, … and G. Franchini. 2001. Impairment of Gag-Specific $CD8^+$ T-Cell function in mucosal and systemic compartments of Simian immunodeficiency virus mac251- and Simian-human immunodeficiency virus KU2-infected macaques. **J. Virol.** 75:11483-95. (IF: 4.8; Citations: 54).
b. **Hel, Z.**, McGhee, J., Mestecky, J. 2006. HIV infection: First battle decides the war. **Trends Immunol.** 27:274. (IF: 10.4; Citations: 45).
c. Gupta, S., Gach, J.S., …, Moldt, B., **Hel, Z.**, Lanzavecchia, A., Ruprecht, R.M., Burton, D.R., Mestecky, J., Anderson, D.J, and Forthal, D.N. 2013. The neonatal Fc receptor (FcRn) enhances human immunodefiency virus type 1 (HIV-1) transcytosis across epithelial cells. **PLOS Pathogens**. 9:e1003776, PMCID: PMC 3836734. (IF: 8.5).

d. Hel, Z., Xu, J., Denning. W., Helton, S., Heath, S. L., Christmann, B.S., Elson, C.O., Goepfert, P., and Mestecky, J. 2016. Dysregulation of systemic and mucosal humoral responses to microbial and food antigens as a factor contributing to microbial translocation and chronic inflammation in HIV-1 infection. **PLOS Pathogens.** 13:e1006087.

C.3 Effect of Hormonal Contraception on HIV-1 Infection. Safe and effective methods of contraception represent a critical component of preventive health care reducing maternal and infant mortality. Several epidemiological studies have suggested a correlation between the use of hormonal contraception and increased risk of HIV-1 infection. We demonstrated that medroxyprogesterone acetate (MPA), one of the most commonly used contraceptives in sub-Saharan Africa, suppresses antigen-specific cellular immune function via direct and indirect mechanisms. In a clinical study, we showed that the use of MPA is associated with thinning of vaginal epithelial wall and decreased production of IFN-α by plasmacytoid dendritic cells. In a recently published study, we demonstrated that the use of DMPA or NuvaRing was associated with reduced pDCs production of IFNα and TNFα in response to TLR-9 stimulation. The density of CD207+ Langerhans cells in the vaginal epithelium was reduced in NuvaRing and COC users but not in DMPA users. The presented evidence suggests that the use of some types of hormonal contraception is associated with reduced functional capacity of circulating pDCs and altered immune environment in the female reproductive tract. In our most recent studies, we have performed RNA-Seq analysis of vaginal biopsies of hormonal users; the acquired data demonstrate severe suppression of HBD2, HBD3 and SLPI in epithelium of DMPA users (manuscript in preparation).

a. **Hel, Z.**, Stringer, E., Goepfert, P., and Mestecky, J. 2010. Sex steroid hormones, hormonal contraception and the immunobiology of HIV-1 infection. **Endocr. Rev.** 31:79-97. PMID: 19903932, PMCID: PMC 2852204. (IF: 19.4; Citations: >116).

b. Huijbregts, R., Helton, S., Michel, K., Richter, H., Goepfert, P., and **Z. Hel**. 2013. Hormonal contraception and HIV-1 infection: Medroxyprogesterone acetate suppresses the function of T cells and plasmocytoid dendritic cells. **Endocrinology**. 154:1282-1295. PMCID:PMC 3578997. Associated editorial: **Endocrinology** 2013;154:985. Commentary published in: **Nat. Rev. Endocrinol.** 2013; 9:187.

c. Huijbregts, R.P.H., Michel, G., and **Z. Hel.** 2014. Effect of progestins on immunity: medroxyprogesterone but not norethisterone or levonorgestrel suppresses the function of T cells and pDCs. **Contraception.** 90:123-129. PMID:PMC 24674041.

d. Michel, K.G., Huijbregts, R.P.H., Gleason, J.L., Richter, H., E., and **Z. Hel**. 2015. Effect of hormonal contraception on the function of plasmacytoid dendritic cells and distribution of immune cell populations in the female reproductive tract. **JAIDS**. 68:511-518. PMID: 25763784.

e. Hapgood, J.P., Kaushic, C., and **Z. Hel**. 2018. Hormonal Contraception and HIV-1 Acquisition: Biological Mechanisms. **Endocrine Reviews.** 39:36-78. Selected for Press Release by Endocrine Reviews and for posting to AAAS EurekAlert Science News.

C.4 Immunodeficiency diseases; Combined Variable Immunodeficiency Disease (CVID)

The primary reason for studying CVID was its relevance to HIV-1 infection. CVID, the most frequent symptomatic humoral primary immunodeficiency, is associated with chronic T cell activation and reduced frequency of $CD4^+$ T cells, and thus it resembles HIV-1 infection. The underlying cause of immune activation in CVID is unknown. We found that in CVID subjects the concentration of plasma sCD14 is significantly increased and correlates with the level of sCD25, C-reactive protein and the extent of T cell activation. Furthermore, elevated plasma sCD14 is associated with decreased frequencies of $CD4^+$ T, NK, and B cells. The obtained data suggests that chronic T cell activation in CVID is associated with elevated levels of sCD14 and sCD25 but not with the signs of microbial translocation.

a. Litzman, J., Nechvatalova, J., Xu, J., Ticha, O., Vlkova, M., and **Z. Hel**. 2012. Chronic immune activation in common variable immunodeficiency (CVID) is associated with elevated plasma levels of soluble CD14 and CD25 but not endotoxemia. **Clin. Exp. Immunol.** 170:321-32. PMCID: PMC3518892

b. **Hel, Z.**, Nechvatalova, J., Xu, J., Ticha, O., Vlkova, M., and J. Litzman. 2014. Altered serum cytokine signature in common variable immunodeficiency. **J. Clin. Immunol.** 34:971-8. PMID: 25246148. PMC in process

C.5 Role of Neutrophils in the Pathogenesis of HIV-1 infection. We have demonstrated that neutrophils in the blood of HIV-1-infected individuals express high levels of PD-L1 and produce augmented levels of reactive oxygen species (ROS). PD-L1 and ROS are induced by HIV-1 virions, TLR-7/8 ligand, bacterial lipopolysaccharide (LPS), and IFNα. Neutrophil PD-L1 levels correlate with the expression of PD-1 and CD57 on CD4+ and CD8+ T cells, elevated levels of neutrophil degranulation markers in plasma, and increased

frequency of low density neutrophils (LDNs) expressing the phenotype of granulocytic myeloid-derived suppressor cells (G-MDSCs). Neutrophils purified from the blood of HIV-1-infected patients suppress T cell function via several mechanisms including PD-L1/PD-1 interaction and production of ROS. Collectively, the accumulated data suggest that chronic HIV-1 infection results in an induction of immunosuppressive activity of neutrophils characterized by high expression of PD-L1, ROS, and an inhibitory effect on T cell function.
a. Bowers, N., Helton, S., Huijbregts, R.P.H., Goepfert, P., Heath, S., and **Z. Hel.** 2014. Neutrophils in HIV-1-infected individuals express high levels of PD-L1 and exert immunosuppressive activity. **PLOS Pathogens. 10:** e1003993, PMCID:PMC 3953441. (Selected by F1000 Prime).

D. Mentoring of Junior Investigators. I assist younger investigators to successfully navigate through the process from junior to independent investigators. I believe that fostering the success of junior investigators is critical to developing scientists to push the field of HIV into the future. One of the most important values I strive to convey to my mentees is research integrity, because I am deeply committed to ethical principles such as intellectual honesty and the personal responsibility to conduct science to the highest possible professional standards. Since joining UAB, I have served as a mentor of > 25 PhD students and 3 postdoctoral fellows.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1Lg8aiaqdH7/bibliography/40756139/public/?sort=date&direction=ascending

E. Research Support.

Ongoing Research Support

R01, DK108353 (Hel) 09/24/15-08/31/20
The Guts of HIV: Innate Immune Dysregulation as a Central Mechanism of Gastrointestinal and Liver Disease in HIV-1-Infected Individuals.
This project focuses on immune innate dysregulation in liver and GI tract in HIV-1-infected ART-treated individuals with a specific focus on liver disease. Some of the experimental approaches on the characterization of neutrophils activation in this project are similar to the current application; however, this project focuses on liver and does not address the effect of innate immune dysregulation on CVD in HIV-1-infected patients. Thus, there is no scientific overlap with the specific aims proposed in the current application.

R01 (Hel) 09/01/16-8/31/20
National Heart, Lung, and Blood Institute (NHLBI)/NIH/DHHS.
Neutrophil dysregulation as a driving mechanism of cardiovascular disease in HIV-1-infection.
This application focuses on the role of neutrophil activation in the mechanisms underlying increased risk of cardiovascular diseases in HIV-1-infected individuals.

R01, HD083026-01, NIH, NIDDK (Hel; Hapgood) 4/2015 – 3/2020
Combination treatment for protection against HIV-1 and pregnancy.
We propose a series of detailed mechanistic studies aiming at the identification of an optimal combination of progestin and antiretroviral providing maximal protection of young women from HIV-1 infection. No overlap.

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1 U01 AI103401-01 (Saag) 01/01/13-12/31/18
Role on this project: Co-Investigator
UAB-MISS Women's Interagency HIV Study (WIHS).
UAB participation the nationwide sites for the WIHS project. WIHS was established in August of 1993 to investigate the impact of HIV infection on women in the U.S. The core portion of the study includes a detailed and structured interview, physical and gynecologic examinations, and laboratory testing.
Administrative Supplement (Hel)
Human beta-defensins and anti-HIV activity in the female genital tract. Determine the anti-viral activity of human β-defensin-2 and 3 (HBD2 and 3) in the cervicovaginal fluid of HIV-1-infected and uninfected women volunteers.