A mathematical model of glucose metabolism

Dr. Darko Stefanovski is an assistant professor of Biostatistics (tenure-track) in the Department of Clinical Studies, New Bolton Center. Dr. Stefanovski received a B.A. in Computer and Information Sciences from Shepherd College, West Virginia in 1999, and subsequently worked as a research specialist at the New Bolton Center (NBC), University of Pennsylvania. At NBC he developed a new mathematical modeling program called MINMOD that is currently being used by diabetes investigators and pharmaceutical companies worldwide (1). After receiving his Ph.D. in physiology and biophysics

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from Keck School of Medicine of University of Southern California (USC) in 2009, he joined the faculty at the Department of Physiology and Biophysics, Keck School of Medicine of USC in 2010 as an assistant professor. Subsequently, Dr. Stefanovski moved to Cedars-Sinai Medical Center where he was one of the founding members of the Diabetes and Obesity Research Institute (DORI). Dr. Stefanovski joined the Department of Clinical Studies, New Bolton Center (NBC) in 2014, where his research focus is Obesity and Type 2 Diabetes. However, as a statistician and a mathematical modeler he often has to wear two hats. In collaboration with his colleagues from NBC and the University of Pennsylvania Veterinary School as a whole, he is working on developing novel statistical methodologies and mathematical models that significantly broaden the spectrum of scientific endeavors in which he is involved.

**The Force Within! Insulin Independent Glucose Disposal**—

The increasing prevalence of obesity is associated with many diet-related chronic diseases including diabetes mellitus type 2, cardiovascular disease, stroke, hypertension and certain cancers. Today, 210 million people around the world suffer from diabetes. The onset of Type 2 Diabetes is preceded by a state in which insulin is unable to regulate glucose metabolism, so called insulin resistance. To combat the onset of insulin resistance, our bodies increase insulin production/secretion, a process termed hyperinsulinemic compensation. While hyperinsulinemic compensation can be beneficial, it also has paradoxical harmful effects. Specifically, increased insulin production may lead to “beta cell exhaustion”, resulting in beta cell apoptosis/necrosis, decreased beta cell mass and, ultimately, the onset of frank diabetes. Therefore, early detection of insulin resistance is vital to the successful prevention of diabetes. To this end, Dr. Stefanovski helped develop the biomedical program called MINMOD, which in conjunction with the frequently sampled intravenous glucose tolerance test (FSIVGTT), is used worldwide by investigators and pharmaceutical companies for early detection of insulin resistance (1). The primary goal for developing MINMOD was to provide a user friendly mathematical model of glucose metabolism.

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A memorandum of understanding has been signed by the state government of Andhra Pradesh, India to implement an Elite Dairy Project. As a result of the MoU, the Center for Animal Health and Productivity (CAHP) has agreed to work with the government of Andhra Pradesh, India to implement the project. The overall goals are to improve the economic and environmental sustainability of the smallholder dairy producers through the implementation of emerging reproductive and genomic technologies as well as training to improve animal management practices (e.g. nutrition, milk quality, breeding). A series of grant opportunities from India as well as other sources will be sought to fund the overall project. CAHP was established in 1986 to implement teaching, research and service programs directed toward the improvement of health and productivity in food animal herds and flocks. Each year, Penn Vet students visit India on summer internships to gain experience on dairy practices. In support of such research activities by CAHP team and creation of model village for dairy in Andhra Pradesh, India, funding was received from Penn Global Engagement Fund.

Second year Penn Vet Student, Megan Clark, has been named as a medical research fellow by the Howard Hughes Medical Institute (HHMI). She was chosen to be one of 66 medical and veterinary students, out of 195 applicants, to spend a year in a laboratory working with a mentor on a research project proposed by the student. She will receive $41,000 in grant support from HHMI. Megan will be working in the laboratory of Dr. Phillip Scott, professor immunology, in the Department of Pathobiology. She will examine the role of skin-resident memory T cells and their migration into non-inflamed skin sites during infection with the parasite Leishmania, which causes a serious skin disease common in the tropics called Leishmaniasis.
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metabolism for clinicians who might not have expertise in mathematical modeling (2). Although not well known, the mathematical model underpinning MIMMOD serendipitously identified a novel mechanism of insulin-independent glucose disposal termed glucose effectiveness (GE). However, while MINMOD provided a way of quantifying GE, the mechanisms driving insulin-independent glucose disposal remained unclear. In 2012, more than 30 years after development of the mathematical model, Dr. Stefanovski used a novel model of lactate kinetics to identify a potential mechanism through which GE could arise (3). Specifically, Dr. Stefanovski’s work implicated glucokinase (GK), a liver-produced kinase that phosphorylates glucose in this process. Interestingly, GK has been previously implicated in diabetes, as more than 600 point mutations in the GCK gene can give rise to maturity-onset-diabetes-of-youth (MODY). Currently, Dr. Stefanovski’s laboratory is utilizing novel Molecular Dynamics (MD) simulation approaches to study the biophysical mechanisms through which these GK mutations affect the proper function of GK in the liver. MD is a new branch of biophysics where simulations are conducted in-silico and physical forces are calculated for every single atom in the system. Dedicated multi-node computing facilities, such as the High-Performance Computing Cluster, are needed to perform these in-silico experiments. Ultimately, results from these studies will aid in the development of novel, small-peptide mimetic compounds that will modulate GK activity, thus providing novel therapeutic treatments for diabetes that act independently of insulin.

One Health

Upon arrival at NBC, one of Dr. Stefanovski’s responsibilities was to assist faculty and staff with their statistical analysis. Through these collaborations, he met Dr. Hannah Galantino-Homer, Department of Clinical Studies NBC, and Dr. Julie Engiles, Department of Pathobiology, whose primary research focus is laminitis. Laminitis is an inflammatory illness of the laminar tissue in a horse’s hoof. Abnormalities, such as Equine Metabolic Syndrome (EMS), that give rise to laminitis are very similar in presentation to human metabolic syndrome. Previously, and in collaboration with Dr. Rhonda M. Hoffman, Department of Animal and Poultry Sciences at Virginia Polytechnic Institute, Dr. Stefanovski has shown that EMS is associated with insulin resistance and hyperinsulinemic compensation, as reflected in elevated plasma insulin levels (4). However, unlike in humans where beta cell exhaustion limits the increase in insulin levels, hyper-insulinemic compensation in the horse continues due to the high propensity of their beta cells to produce insulin. Ultimately, these hyperphysiologic levels of insulin result in the onset of laminitis. Dr. Stefanovski, in collaboration with Dr. Mary Robinson, director of the Penn Vet Equine Pharmacology Laboratory, and Dr. James Orsini, Department of Clinical Studies NBC, is investigating novel therapies that decrease insulin secretion in the horse, either by increasing GE or more directly by reducing insulin secretion, thereby preventing the subsequent onset of
Selected Publications


Awards (direct costs)

Christopher J. Lengner
NIH/NIDDK R01
Control of intestinal regeneration by a Msi-mTORC1 signaling axis
05/15/2016 – 04/30/2020
$900,000

Rumela Chakrabarti
NIH/NCI K22
Probing the role of tumor suppressive functions of Elf5 in breast cancer
6/01/16 to 5/31/2019
$520,713

Peijing Jeremy Wang
NIH/NIGMS R35-MIRA award
Regulation of meiosis in mice
5/05/2016-4/30/2021
$1,738,000

Hannah Galantino-Homer
Animal Health Foundation
Epidermal stress in the pathogenesis and diagnosis of endocrinopathy-associated laminitis
6/1/2016-5/31/2025
$1,761,275

Angelica Ortiz
NIH/NCI F32
IFNAR1 down regulation in melanoma cells and stromal cells promotes melanoma progression and pulmonary metastasis
4/1/16 to 3/31/18 $108,588.00

Eldin Jasarevic
NIH/NICHD F32-
Maternal stress and the gut microbiome: impact on neurodevelopment
12/17/16 to 11/30/18
$114,120

Mia Krlikoski
American Heart Association Pre-doctoral Fellowship
The Effect of Arterial Stiffness on Macrophage Polarization and Plasticity
7/11/16 -6/30/17
$25,950

Megan Clark
HHMI Fellowship
The role of skin-resident memory T cells in promoting immunity to Leishmaniasis
8/22/16-8/21/17 $43,000

Bruce Freedman
NIH S10 Equipment
Building Enhanced Capability for the PennVet Multiphoton Core
5/1/16-4/30/17
$600,000

Lisa Murphy
Dept. of Agriculture
Maintenance of membership laboratory requirements
5/1/16-4/30/17
$2,164,647

Karim Sorenmo
Petco—The PennVetShelter Canine Mammary Tumor Program
5/1/16-4/30/18
$525,000

Cindy Otto
Dept. of Homeland Security IAI CAMEL Phase II
5/3/16-3/1/18
$29,144

Erika Krick
Petco—Charitable Care Fund for Pet Cancer Treatment
5/1/16-4/30/19
$350,000

Urs Giger
AKC CHF
Genetic Predisposition to Avian Tuberculosis in Miniature Schnauzers and Bassets Hounds
5/1/16-4/30/17
$106,858
laminitis. Thus, the work of Dr. Stefanovski and his colleagues contributes to the One Health Initiative, translating their knowledge of glucose metabolism in humans to help prevent laminitis in the horse.

Dr. Stefanovski’s current research is supported by the NBC’s Equine Foundation and USDA Formula Grants. His office is located at the Center for Animal Health and Productivity (CAHP) at the New Bolton Center campus, Room 207.

References


Penn Vet’s 2016 Annual Faculty Research Retreat—On Friday, June 17, approximately 150 faculty, residents, postdoctoral fellows, students and staff gathered for the Annual Research Retreat at New Bolton Center. Phillip Scott, Vice Dean for Research and Academic Resources, convened the conference. William Murphy, PhD, professor from the Department of Veterinary Integrative Biosciences at Texas A&M University gave the Marshak Lecture entitled “The Promise and Future of Comparative Genomics in Mammals”. Dr. Ellen Puré introduced the session on Comparative Oncology featuring Susan Volk, PhD, VMD; Rumela Chakrabarti, PhD, MS; Amy Durham, MS, VMD; and Nicola Mason, PhD, BVetMed. Following a noontime poster session, the afternoon session included a talk on grantsmanship by Leslie King, PhD. Dan Morris, DVM, MPH; Ellen Puré, PhD, Gary Althouse, DVM, MS, PhD; and Christopher Hunter, PhD gave talks on their research programs. Barbara Dallap Schaer, VMD told of the new Robotics in clinical research at New Bolton Center. Dr. Althouse, chair of Clinical Studies NBC, presented the Zoetis Award for Veterinary Research Excellence to an unsuspecting recipient, Ashley Boyle, DVM. Dr. Scott invited the conference attendees to a brief demonstration at the new robotics facility before concluding the day with a reception for all.
MEET DE’BROSKI HERBERT
—Dr. Herbert has joined the Penn Vet faculty as an associate professor, in the Department of Pathobiology. Dr. Herbert received his BS in microbiology at Xavier University (1994) and his PhD in immunology from Thomas Jefferson University in 2000. The Herbert laboratory studies Type 2 immune responses in the context of host immunity against gastrointestinal nematode parasites. The overarching goal is to investigate the cross-talk between mucosal epithelia and tissue macrophages for gaining deeper insight to maintenance and restoration of mucosal barrier function under steady-state and infectious conditions. Currently, our main focus is to elucidate the biological role(s) of Trefoil factor proteins, a tripartite family of enigmatic mucosal cytokines, in the context of inflammation, immunity, and repair at the mucosal interface.

A 2017 ARVO Achievement Award (The Association for Research in Vision and Ophthalmology) goes to Penn Vet’s Gustavo Aguirre, VMD, PhD, FARVO. Dr. Aguirre has received the prestigious Proctor Medal that was established in 1949 memorializing Dr Francis Proctor, ophthalmologist. The Proctor award honors outstanding research in clinical or basic sciences as applied to ophthalmology. He is the first veterinarian to be granted the Medal in its 67-year history.

Center for Host-Microbial Interactions Pilot Awards Announced—

—Carolina López, Department of Pathobiology, project entitled “Identification of Defective Viral Species During a Natural Respiratory Viral Infection”

—Michael Povelones & Sara Cherry for their project entitled “Defining the Mechanisms by Which the Microbiota Primes Antiviral Immunity to Enteric Viral Infection in Insects”

—Marie-Eve Fecteau and Raymond Sweeney “Changes in the fecal microbiota of calves experimentally infected with Mycobacterium avium subsp. paratuberculosis”

Partial awards were given to Shelley Rankin and Stephen Cole—Bacterial Transcriptomics of Canine Urinary Tract Infections and Christine Cain, Charles Bradley, and Dan Morris for their project: The Cutaneous and Rectal Microbiome of Perianal Fistulas and the Effect of Cyclosporine Therapy. These pilot awards were made possible by generous gifts from Hope Sheft, Jay Goldman, and CHOP.