



Duran-Struuck with Steve Gooseby at Smilow Center for Translational Research



NEW FACULTY
DR. KOTARO SASAKI
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Ralph Brinster to be Keynote Speaker at 50th Anniversary VMD/PhD Event PAGE 4



Carolina López
CAMINOS EN CIENCIA
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NEWSLETTER



Tolerance, Transplant Immunology

Dr. Raimon Duran-Struuck, DVM, PhD, Diplomate ACLAM, joined Penn as associate director of University Laboratory Animal Resources (ULAR) and assistant professor in the Pathobiology Department Division of Laboratory Animal Medicine. Raimon is a trained laboratory animal veterinarian and his research focuses on preventing graft rejection through development of therapies that increase immunological tolerance in recipients. As a comparative medicine veterinarian, Raimon aids scientific and clinical

Pre-Clinical
Large Animal
Models

investigators with animal modeling, and works to develop (and refine) preclinical animal models that can translate with high fidelity to the clinic.

Dedicated to the improvement of human and animal health—

Raimon received his veterinary degree from Tufts University School of Veterinary Medicine. Afterwards, he pursued a clinical and surgical internship at the Florida Veterinary Specialists and Cancer Treatment Center. Raimon’s strong interests in clinical immunology and transplantation led him to seek a four-year laboratory animal residency training program at the University of Michigan, where he joined the bone marrow transplant laboratories of Drs. Pavan Reddy and James Ferrara. During this time, Raimon was struck by the profound impact that graft vs. host disease (GVHD) has on pediatric patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT). Enabled by a K_or award, Raimon developed large animal transplantation models capable of enhancing translation from cage- to bed-side at the Transplantation Biology Research Center, Massachusetts General Hospital and Harvard University, under renowned transplant researchers Dr. David H. Sachs, MD and Christene Huang PhD. Specifically, he focused on the development of a miniature swine large animal tumor model and the development of hematopoietic cell transplantation protocols to achieve mixed hematopoietic chimerism as a platform for generating immunological tolerance (see below). During that time, Raimon also completed his PhD in Immunology (at the Universitat Autònoma de Barcelona) and was promoted to instructor in surgery at the Harvard Medical School and Assistant Immunologist at the Massachusetts General Hospital. In 2012, Raimon became an Assistant Professor in Surgical Sciences at the Columbia University Medical Center and Head of the Large Animal Pre-Clinical Transplant Laboratories. In collaboration with scientists and clinicians, he established a liver, kidney, bone marrow and pancreatic islet pre-clinical transplant program. Raimon came to Penn in late 2015 to join a well-respected laboratory animal medicine program and a top medical and veterinary research community to continue his exciting work, which he hopes can be translated to both human and veterinary patients. His current research focuses on cellular therapies exploiting the immunomodulatory roles of regulatory T cells and the use of genetically engineered cells for the treatment of rejection and autoimmunity in large animal models.

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Publications



S Kumar, RK Srivastav, DW Wilkes, T Ross, S Kim, J Kowalski,

S Chatla, Q Zhang, A Nayak, **M Guha, SY Fuchs, C Thomas, & R Chakrabarti** (2018) Estrogen-Dependent DLL1-mediated Notch signaling promotes luminal breast cancer Oncogene—ePub ahead of print.



LY Hung, D Sen, TK Oniskey, J Katzen, NA Cohen, **AE Vaughan**, W Nieves, A Urisman, MF Beers, MF

Krummel and **DR Herbert** (2019) Macrophages promote epithelial proliferation following infectious and non-infectious lung injury through a Trefoil factor 2-dependent mechanism. *Mucosal Immunol* 12(1): 64-76.



SE Gullbrand, BG Ashinsky, ED Bonnevie, DH Kim, **JB Engiles**, LJ Smith, DM Elliott, **TP Schaer**,

HE Smith, & RL Mauck (2018) Long-term mechanical function and integration of an implanted tissue-engineered intervertebral disc. *Sci Transl. Med*: 10(468), p.eaau0670.

Immunological tolerance and why it is important in transplantation and autoimmunity—

When a transplanted immunocompetent host recognizes a foreign (donor) graft, the consequent immune response can lead to graft rejection. The greater the degree of genetic disparity between donor and recipient, the more likely rejection is to occur. To control rejection, patients are required to take life-long immunosuppressive medications that are associated with infections and many comorbidities. Unfortunately, thousands of patients die worldwide waiting for a transplant because a suitable donor is never identified or because they are unable to withstand the toxic immunosuppressive protocols. Identifying protocols that promote immune tolerance to foreign grafts would greatly reduce this number by permitting the acceptance of genetically disparate grafts and avoiding the toxicity of immunosuppressants.

Immune recognition of foreign molecules is primarily driven by T cell recognition of major histocompatibility complex (MHC)-peptide complexes. While such recognition is beneficial for the control of a myriad of foreign pathogens; unfortunately 10-20% of T cells can also recognize antigens derived from a donor graft, leading to graft rejection or graft-vs-host disease (GVHD) in allo-HCT. In addition, a fraction of T cells can recognize self antigens. While central tolerance mechanisms eliminate the vast majority of self-reactive T cells, peripheral tolerance mechanisms are required to delete or functionally inactivate autoreactive T cells that have escaped. The importance of regulatory T cells (Tregs) in preventing activation of autoreactive T cells is also demonstrated by increases in autoimmune diseases (such as Type I diabetes, etc) in the absence of Tregs. The Duran-Struuck laboratory is interested in manipulating central and peripheral tolerance mechanisms to develop novel approaches to “re-set” the immune system so that donor cells or organs are recognized as “self”, thereby reducing the chance of graft rejection and GVHD.

Mixed chimerism and regulatory T cell therapy for tolerance induction and prevention of graft-versus-host disease and rejection—

Allo-HCT is a powerful therapy for the treatment of many malignant and non-malignant lymphohematopoietic disorders and is also important for the

Welcome



Drs. Ellen Puré and Ralph Brinster welcome **Dr. Kotaro Sasaki** to Penn Vet. In October, Dr. Sasaki, assistant professor joined the Department of Biomedical Sciences. Dr. Sasaki received his MD and PhD from Hokkaido University in 2005 and Kyoto University in 2017, respectively. He is a board certified anatomic pathologist, completed pathology residency at University of Pittsburgh in 2011 and renal pathology fellowship at University of Washington in 2012. Prior to joining Penn Vet, he completed a postdoc training at Mitinori Saitou Lab at Kyoto University, Japan. His major research interest involves the understanding the molecular mechanisms of human germline and gonadal development using single cell genomics and their *in vitro* reconstitution using pluripotent stem cells.



For **Carolina López**, an associate professor of microbiology and immunology in the Department of Pathobiology and the subject of the *Caminos en Ciencia* podcast’s first episode, personal drive was never an issue. She knew from an early age that she wanted to pursue research. And, although she was well prepared by her studies in Chile, she looked outside of her home country when it came to beginning her Ph.D., sensing that she would find more robust resources elsewhere. Despite being pregnant, and concerned about the language barrier,

Carolina and her husband chose to move to the United States. to begin their scientific careers. Carolina says the podcast offers “an opportunity for us to share facets of our careers that we normally don’t talk about and, through this, help those thinking ‘this is impossible’ see that if you love it you can do it.” Currently, she is communicating with her research group regularly from her work at the Pasteur Institute in Paris fulfilling her Fulbright US Scholar Award to study virus dynamics and evolution for six months. And hot off the press is her new publication in **PLOS Pathogens**. “Unexpected lessons from the neglected: How defective viral genomes became important again (2019) 15(1): e1007450. Podcast URL <https://www.caminosenencia.org/episodios/>

Stephen Cole, Lecturer in Microbiology in the Department of Pathobiology is now a Diplomate of the American College of Veterinary Microbiology and qualified in the specialty areas of Bacteriology/Mycology AND Immunology. DACVM (Bacteriology/Mycology, Immunology). He is the very **FIRST PennVet Board Certified Microbiologist** (and Immunologist) ever. He also achieved this recognition from a non-traditional Fellowship route rather than a Residency Training Program, which is another PennVet FIRST.



UPCOMING Student Research Day and the 50th Anniversary of Penn Vet’s Combined Degree Program—2019 marks the 50th anniversary of the Penn Vet VMD-PhD program. To celebrate this milestone, our Annual Student Research Day will combine with the VMD-PhD 50th Anniversary Symposium to form a two-day research event at Penn Vet. The event will be held in Penn Vet's Hill Pavilion, 131 Billhardt Auditorium, 380 University Ave., Philadelphia, PA

19104. All welcome—admission is free but registration is required. An outstanding program is slated with presentations by Penn Vet alumni from academia, industry and government.

Thursday, Marcy 21, 2019: Annual Student Research Day

Friday, March 22, 2019: VMD/PhD 50th Anniversary Symposium "Penn Vet: Advancing Research and Medical Synergies". Dr. Ralph Brinster will deliver a keynote address!

Registration Link:

<https://www.vet.upenn.edu/research/news-events-conferences/research-day-vmd-phd-symposium>

The event is free but registration is a requirement.

development of immunological tolerance for solid organ transplantation. Unfortunately, because donor T cells are introduced during this process, allo-HCT is often met with GVHD, a lethal side effect, whereby donor T cells attack all of the recipient’s tissues (mainly liver, gut, skin and the lymphohematopoietic organs). Dr. Duran-Struuck is interested in controlling GVHD (or rejection in the case of solid organ transplantation) by modulating allo-immune responses(1). As outlined below, the laboratory works closely with investigators within the University of Pennsylvania Perelman School of Medicine and Penn Vet clinicians and scientists.

Successful allo-HCT can establish a state of tolerance to tissues or organs from the same marrow donor due to the persistence of a small number of donor bone marrow-derived cells in the recipient, a state known as “mixed hematopoietic chimerism”. Unfortunately, the ideal mixed chimeric state is often difficult to maintain and imbalance or activation of donor or host lymphocytes can lead to GVHD or graft loss. Dr. Duran-Struuck studies how this mixed chimeric state can be manipulated (and enhanced) in miniature swine by using donor leukocyte infusions (a cellular therapy used for cancer treatment) to maintain beneficial graft-versus-host responses without GVHD(2, 3). In addition, the laboratory continues to focus on developing GVHD-free allo-HCT protocols across MHC barriers (where donor and recipient are genetically disparate). Recent work by Dr. Duran-Struuck demonstrated that co-infusion of bone marrow plus Tregs (4) led to robust engraftment (of the donor marrow) and immunological tolerance. The new marrow graft was long-lived and GVHD was never induced. Moreover, tolerance was robust as a donor kidney transplanted months after the original BMT survived without use of immunosuppressants (4). Dr. Duran-Struuck currently aims to further refine cellular therapies by developing more efficient protocols for expanding polyclonal Tregs and engineering antigen specific Tregs (CAR Tregs) for treatment of solid organ rejection, GVHD and autoimmune disorders. Indeed, in a project funded by the Helmsley Foundation, Dr. Duran-Struuck, working in collaboration with Dr. Jim Riley and Ali Naji and lab teammates Gavin Ellis PhD and Delaine Wynn BS at Perelman School of Medicine, aim to design donor-specific CAR Tregs to protect donor pancreatic islets grafts for the treatment of Type-I diabetes.

Development of miniature swine as a large animal tumor model of cellular immunotherapies—The lack of a large animal transplantable tumor model has limited the study of novel therapeutic strategies for the treatment of liquid cancers. Swine provide a natural option based on

Publications



A Kehl, K Heimberger, I Langbein-Detsch, S Boehmer, K Raj, E Mueller, **Urs Giger** (2018) Molecular characterization of blood type A, B, and C (AB) in domestic cats and a CMAH genotyping scheme *PLoS One* 13(9):e0204287, 1-13.



K Muta, ME Matsen, NK Acharya, **D Stefanovski**, RN Bergman, MW Schwartz, GJ Morton (2019) Glucoregulatory responses to hypothalamic preoptic area cooling. *Brain Res* 1710: 136-145



Syrett CM, Sindhava V, Sierra I, Dubin AH, **Atchison M and Anguera MC** (2019) Diversity of Epigenetic Features of the Inactive X-Chromosome in NK Cells, Dendritic Cells, and Macrophages. *Front. Immunol.* 9:3087.



A Safronova, A Araujo, ET Chamando, TJ Moon, MR Elliot, **DP**

Beiting, and F Yarovsky (2019) Alarmin S100A11 initiates a chemokine response to the human pathogen *Toxoplasma gondii*. *Nature Immunol* 20(1): 64-72.

their similarities to humans and their extensive use in biomedical research. Specifically, the Massachusetts General Hospital miniature swine herd retains unique genetic characteristics that facilitate the study of hematopoietic cell and solid organ transplantation. Spontaneously arising liquid cancers in these swine, specifically myeloid leukemias and B cell lymphomas, closely resemble human malignancies (5, 6). Raimon has characterized myeloid and lymphoid tumors in major histocompatibility characterized miniature swine and has established aggressive tumor cell lines in vitro. With the current availability of novel genetic technologies, he aims to develop the first reliable transplantable tumor model in collaboration with Dr. Christene Huang and David Sachs.

Bringing it all together – laboratory animal medicine and animal modeling

—Dr. Duran-Struuck's expertise in laboratory animal medicine has focused on fine-tuning protocols for the care of immunodeficient large and small animals(7-9) and characterizing additional animal models. As an example, he recently immunophenotyped the lymphohematopoietic organs of naïve cynomolgus macaques and determined that B cell levels were lower than previously thought and that CD4+CD8+ T cells were constitutively activated, informing transplant researchers that changes in these populations may have not been as significant as previously believed (10).

At ULAR, Dr. Duran-Struuck is part of a phenomenal team of specialized veterinarians that provides state of the art veterinary care for animals used in biomedical research and helps investigators to design, develop, and improve their animal models. In collaboration with the University of Michigan, Temple University and NOTA laboratories, Raimon received an SBIR-NIH award to test a novel therapy for chronic rhinosinusitis. Raimon's post-doctoral fellow Margaret Hull DVM, in collaboration with Dr. Noam Cohen (from Penn's Perelman School of Medicine), is developing a rhinosinusitis model in rabbits. To further illustrate how laboratory animal veterinarians synergize with investigators, Caroline Blevins DVM (ULAR resident) and Jim Marx, DVM PhD, ULAR veterinarian and Assistant Professor (Pathobiology) are studying novel safe anesthetic regimens in rabbits compromised by rhinosinusitis. Finally, in conjunction with Dr. Mason, Dr. Duran-Struuck is excited to have established a canine phoresis core at Penn Vet that utilizes phoresis protocols optimized from his published protocols in other species(8). Under the leadership of Dr. Mason, Dr. Duran-Struuck, Vicky Anderson (BA, LVT, LATG), ULAR laboratory animal residents and other ULAR and VHUP support staff, the core has begun leukaphoresis in patients at Ryan Hospital that will help move forward novel CAR T cell and Treg therapies for canine patients.

Dr. Duran-Struuck's office is located in 177 E Old Vet Quadrangle.

References

1. R. Duran-Struuck, P. Reddy, Biological advances in acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Transplantation* **85**, 303-308 (2008).
2. D.-S. R. Hanekamp J.H., Sachs D.H., in *The minipig in biomedical research*, D. A. McAnulty PA, Ganderup N-C, Hastings KL, Ed. (CRC Press, 2011), chap. 23.
3. R. Duran-Struuck *et al.*, Donor Lymphocyte Infusion-Mediated Graft-versus-Host Responses in a Preclinical Swine Model of Haploidentical Hematopoietic Cell Transplantation. *Biol Blood Marrow Transplant* **22**, 1953-1960 (2016).

Recent Awards (Direct Costs)

Nicola Mason

Abramson Cancer Center
Sarcoma TCE Project
\$134,189 11/1/18—10/31/20

James Perry

Companion Animal Research Fund
Feasibility of assessing drug response
to injection of anti-cancer drugs using
(CIVO device in cats with mammary
carcinoma \$58,301 1/1/19—12/31/20

Jennifer Lenz

Companion Animal Research Fund
Defining the efficacy and elucidating the
immunomodulatory role of alkylating
chemotherapeutics for canine T-cell lymphoma
\$74,303 1/1/19—12/31/20

Anna Gelzer

Companion Animal Research Fund
Determination of anti-arrhythmic efficacy
of sotalol and amiodarone in Boxers with
ARVC by electrophysiologic testing,
electroanatomic mapping and novel
ECG monitoring.
\$20,552 1/1/19—12/31/20

Dana Clarke

Companion Animal Research Fund
Incidence of Pharyngeal Collapse and
Effect of Corrective Upper Airway
Surgery in Symptomatic Brachycephalic
Dogs \$26,552 1/1/19—12/31/20

Christine Cain

Companion Animal Research Fund
Fosmidomycin for treatment of canine
otitis extern \$41,192 1/1/19—12/31/20

Deborah Silverstein

North Carolina St. Univ.
The Effect of Tranexamic Acid on
Hyperfibrinolysis in the Dog Following
Trauma \$38,548 1/1/18—5/23/19

Susan Volk

AKC Canine Health Foundation
Tumor-permissive collagen signatures
in canine mammary gland tumors:
development of prognostic markers
and targeted therapies for improved outcomes
\$150,648 3/1/18—2/29/20

Dan Beiting

PA Dept of Agriculture
Development of a rapid, stall-side diagnostic assay for equine
respiratory pathogens
\$74,682 1/1/18—6/30/19

Cindy Otto

Virox
Testing Nose Blindness associated with
cleaning compounds \$9,945 1/1/19—12/31/19

Oriol Sunyer

NIH
Unearthing phagocytic IgM+ plasma cells
and their previously unrecognized roles
in innate and adaptive immunity
\$275,000 12/1/18—11/30/20

Daljit Vudathala (Lisa Murphy Lab)

PA Dept Agriculture—Histopathology and analysis of anatoxin-a
using LCMS in channel catfish
\$34,700 1/1/18—6/30/19

Daljit Vudathala (Lisa Murphy Lab)

PA Dept Agriculture —Method development for
bromethalin analysis in biological samples
\$9,250 1/1/18—6/30/19

Daljit Vudathala (Lisa Murphy Lab)

PA Dept Agriculture—Method development for trace analysis
of avermectins and related animal drugs in
compost \$8,510 1/1/18—6/30/19

James Lok

NIH
Insulin-like signaling in parasitic nematode
development
\$1,250,000 11/9/18—10/31/23

Ellen Puré

NIH P01
Extending Chimeric Antigen (CAR)T
cell therapy to thoracic cancers
\$127,311 9/14/18—8/31/23

Ellen Puré

Boehringer Ingelheim Pharmaceuticals
Boehringer Collaborative Research Agreement 2018
\$1,449,836 1/1/19-12/31/21

Ellen Puré

Tmunity Therapeutics
Pre—Clinical Development of FAP CAR
\$925,925 12/1/18-11/30/21

Andrew Vaughan

Margaret Q. Landenberger Research Foundation
Angiogenesis and Vasculogenesis in Lung Regeneration
After Influenza
\$200,000 12/31/2018-12/31/2020

Karin Sorenmo & Sue Volk

GreaterGood Organization
High serum estrogen promotes restrictive
collagen signatures in the tumor micro-
environment in canine mammary carcinoma
\$9,737 1/1/19—1/31/20

Continued from page 6

4. R. Duran-Struuck *et al.*, Effect of Ex Vivo-Expanded Recipient Regulatory T Cells on Hematopoietic Chimerism and Kidney Allograft Tolerance Across MHC Barriers in Cynomolgus Macaques. *Transplantation* **101**, 274-283 (2017).
5. R. Duran-Struuck *et al.*, Myelogenous leukemia in adult inbred MHC-defined miniature swine: a model for human myeloid leukemias. *Vet.Immunol Immunopathol.* **135**, 243-256 (2010).
6. R. Duran-Struuck, A. J. Matar, C. A. Huang, Myeloid Leukemias and Virally Induced Lymphomas in Miniature Inbred Swine: Development of a Large Animal Tumor Model. *Front Genet* **6**, 332 (2015).
7. R. Duran-Struuck, R. C. Dysko, Principles of bone marrow transplantation (BMT): providing optimal veterinary and husbandry care to irradiated mice in BMT studies. *J Am Assoc.Lab Anim Sci* **48**, 11-22 (2009).
8. V. Pathiraja, A. J. Matar, A. Gusha, C. A. Huang, R. Duran-Struuck, Leukapheresis protocol for nonhuman primates weighing less than 10 kg. *J Am Assoc Lab Anim Sci* **52**, 70-77 (2013).
9. R. Duran-Struuck *et al.*, Miniature Swine as a Clinically Relevant Model of Graft-Versus-Host Disease. *Comp Med* **65**, 429-443 (2015).
10. J. S. Zitsman *et al.*, Distinctive Leukocyte Subpopulations According to Organ Type in Cynomolgus Macaques. *Comp Med* **66**, 308-323 (2016).

ELECTRONIC RESEARCH NOTEBOOK.....



The Vice Provost for Research with the Vice Provost for Education now provide the LabArchives **Electronic Research Notebook** for researchers, instructors, and students. LabArchives offers Penn Researchers free access to a modern, secure, cloud-based method of managing their lab data. It also offers Penn instructors a robust collaboration and instruction platform. To create your account, visit the [Getting Started page](https://researchnotebooks.upenn.edu/getting-started/): <https://researchnotebooks.upenn.edu/getting-started/>

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The **Penn Vet Research Newsletter** is distributed quarterly. Suggestions, requests, comments and story ideas should be directed to: resnews@vet.upenn.edu

Phillip Scott, Ph.D.
Vice Dean *for* Research and Academic Resources

Correction. In the October (2018) issue we incorrectly stated the name of student Kimmy Hildreth's mentor. During the Boehringer Ingelheim summer research program Kimmy Hildreth's mentor was Hannah Galantino-Homer, VMD, PhD, at New Bolton Center. She worked on protein chaperone expression resulting from endoplasmic reticulum stress in an HI model of laminitis pathogenesis.



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