

RESEARCH SPOTLIGHT

TRANSLATING SCIENCE TO PRACTICE



“When you become sick, it doesn’t matter [whether] that came from the mouth or came from another part of the body. It will affect your systemic health sooner or later.”

— DR. GEORGE HAJISHENGALLIS

bad cascade of events,” Dr. Hajishengallis says. “Besides common risk factors, this is another mechanism that could explain why we have comorbidities.”

Dr. Hajishengallis and his collaborators theorize that, in certain contexts, inhibiting maladaptive trained innate immunity, particularly in vulnerable populations, such as elderly patients, could provide a therapeutic approach to combating chronic inflammation. Blocking that ongoing inflammation, he explains, could in turn prove beneficial against a host of chronic inflammatory diseases.

This work is of particular interest to the NIH, Dr. Hajishengallis notes, because there is a growing effort to better understand the association between oral diseases and systemic health. Why, for instance, do people with periodontitis have increased risk for arthritis, cardiovascular disease, diabetes, or Alzheimer’s? One way to illuminate these associations, Dr. Hajishengallis explains, is through the study of maladaptive trained innate immunity.

“When you become sick, it doesn’t matter [whether] that came from the mouth or came from another part of the body,” he said. “It will affect your systemic health sooner or later.”

Tracking the Downside of Immunity: An Oral-Systemic Health Connection

There’s a cliché in medicine that immunity is a double-edged sword. The same function that protects the body against viral or bacterial invaders can also cause harm when it goes into overdrive. “In immunity, nothing can be entirely beneficial,” said Dr. George Hajishengallis, the Thomas W. Evans Centennial Professor in the Department of Basic and Translational Sciences at Penn Dental Medicine. “Depending on context, you may want to inhibit or promote these processes.”

The downside of immunity — specifically, maladaptive trained innate immunity — took Dr. Hajishengallis to the National Institutes of Health earlier this year, when he was invited to be the keynote speaker at an NIH workshop. His talk was titled “Immunometabolic Crosstalk in Trained Immunity and Inflammation” and described a concept he’s working on with longtime collaborators in Germany that was also outlined this year in *Nature Reviews Immunology*. (Trained immunity is the property

of cells in the innate immune system — such as neutrophils and monocytes and their progenitors — to memorize an infectious or inflammatory event and respond much faster and stronger to a similar challenge in the future.)

In periodontitis, a key research focus of Dr. Hajishengallis’ laboratory, bacteria eventually move from the gums into the patient’s blood, causing the local inflammation to become systemic. When the patient’s bone marrow senses this inflammation, the immune system responds by producing more neutrophils and monocytes than a healthy patient would. This, explains Dr. Hajishengallis, is an example of maladaptive trained innate immunity, because instead of protecting the body, these hyperactive immune cells exacerbate inflammation. If left unchecked, this inflammation can worsen an existing condition, such as arthritis, or even instigate a new chronic inflammatory disease.

“When [a patient has] one inflammatory disease, it’s very easy to get another one. It’s a

continued on page 22

ACADEMICUPDATE

DEPARTMENT/FACULTY NEWS & SCHOLARSHIP

BASIC & TRANSLATIONAL SCIENCES

NEWS/ACHIEVEMENTS

Dr. Calga Akay-Espinoza was awarded a Penn Center for AIDS Research pilot grant for a project titled HIV viral dynamics and host-cell gene expression profiles in human-induced pluripotent stem cell-derived myeloid cells.



Dr. Marco Tizzano has joined the Department as an Associate Professor. His appointment to this tenure-track post was effective October 1.

SELECTED PUBLICATIONS

A selection of recently published work by department faculty (indicated in bold).

Alawi F. *Hidden clinicians.* Oral Surg Oral Med Oral Pathol Oral Radiol. 2021 Aug;132(2):123. PMID: 34148847

Ali H. *Revisiting the role of MRGPRX2 on hypersensitivity reactions to neuromuscular blocking drugs.* Curr Opin Immunol. 2021 Apr 12;72:65-71. PMID: 33857758

Amponnawarat A, Chompunud Na Ayudhya C, **Ali H.** *Murepavadin, a Small Molecule Host Defense Peptide Mimetic, Activates Mast Cells via MRGPRX2 and MrgrprB2.* Front Immunol. 2021;12:689410. PMID: PMC8261236

Chinipardaz Z, Liu M, **Graves D** (co-author Dept. of Periodontics), **Yang S.** *Diabetes Impairs Fracture Healing Through Disruption Of Cilia Formation In Osteoblasts.* Bone. 2021 Sep 8;116:176. PMID: 34508881

Chompunud Na Ayudhya C, Amponnawarat A, **Ali H.** *Substance P Serves as a Balanced Agonist for MRGPRX2 and a Single Tyrosine Residue Is Required for β -Arrestin Recruitment and Receptor Internalization.* Int J Mol Sci. 2021 May 18;22(10):5318. PMID: PMC8158387

Campagno KE, **Mitchell CH.** *The P2X7 Receptor in Microglial Cells Modulates the Endolysosomal Axis, Autophagy, and Phagocytosis.* Front Cell Neurosci. 2021;15:645244. PMID: PMC8005553

de Brito LCN, Doolittle-Hall J, Lee CT, Moss K, Bambirra Júnior W, Tavares WLF, Ribeiro Sobrinho AP, **Teles FR.** *The apical root canal system microbial communities determined by next-generation sequencing.* Sci Rep. 2020 Jul 2;10(1):10932. doi: 10.1038/s41598-020-67828-3. PMID: 32616783

Deepak V, Komarow HD, Alblaihees AA, Carter MC, Metcalfe DD, **Ali H.** *Expression of MRGPRX2 in skin mast cells of patients with maculopapular cutaneous mastocytosis.* J Allergy Clin Immunol Pract. 2021 Jun 25;S2213-2198(21)00697-8. PMID: 34182161

Dhingra A, Sharp RC, Kim T, Popov AV, Ying G-S, Pietrofesa RA, Park K, Christofidou-Solomidou M, **Boesze-Battaglia K.** *Assessment of a Small Molecule Synthetic Lignan in Enhancing Oxidative Balance and Decreasing Lipid Accumulation in Human Retinal Pigment Epithelia.* Int J Mol Sci. 2021 May 28;22(11):5764. PMID: PMC8198017

Ding Y, Chen W, Lu Z, Wang Y, **Yuan Y.** *Kaposi's sarcoma-associated herpesvirus promotes mesenchymal-to-endothelial transition by resolving the bivalent chromatin of PROX1 gene.* PLoS Pathog. 2021 Sep 7;17(9):e1009847. PMID: 34492084

Feres M, Retamal-Valdes B, Fermiano D, Faveri M, Figueiredo LC, Mayer MPA, Lee J-J, Bittinger K, **Teles F.** *Microbiome changes in young periodontitis patients treated with adjunctive metronidazole and amoxicillin.* J Periodontol. 2021 Apr;92(4):467-478. PMID: 32844406

Hajishengallis G, Lamont RJ. *Polymicrobial communities in periodontal disease: Their quasi-organismal nature and dialogue with the host.* Periodontol 2000. 2021 Jun;86(1):210-230. PMID: 33690950

Hajishengallis G, Chavakis T. *DEL-1: a potential therapeutic target in inflammatory and autoimmune disease?* Expert Rev Clin Immunol. 2021 Jun;17(6):549-552. PMID: PMC8405457

Hajishengallis G, Hasturk H, Lambris JD, Apatzidou DA, Belibasakis GN, Bostanci N, **Corby PM** (co-author Dept. of Oral Medicine), Cutler CW, D'Aiuto F, **Hajishengallis E,** Huber-Lang M, Ioannidou E, Kajikawa T, Kantarci A, **Korostoff JM** (co-author Dept. of Periodontics), Kotsakis GA, Maekawa T, Mastellos DC, Moutsopoulos NM, Myneni S, Nagelberg R, Nilsson B, Papapanou PN, Paphanasiou E, Potempa J, Risitano A, **Sahingur ES** (co-author Dept. of Periodontics), Saito A, Sculean A, Stavropoulos A, **Teles FR,** Tonetti M, Yancopoulos D. *C3-targeted therapy in periodontal disease: moving closer to the clinic.* Trends Immunol. 2021 Oct;42(10):856-864. doi: 10.1016/j.it.2021.08.001. Epub 2021 Sep 2. PMID: 34483038



BATTLING RHEUMATOID ARTHRITIS

A new study led by Dr. George Hajishengallis shows that the protein DEL-1 could reduce the painful inflammation of RA in an animal model. See the following article:

Wang, H., Li, X., Kajikawa, T., Shin, J., Lim, J.-H., Kourtzelis, I., Nagai, K., Korostoff, J., Grossklaus, S., Naumann, R., Chavakis, T. & **Hajishengallis, G.** *Stromal cell-derived DEL-1 inhibits Tfh cell activation and inflammatory arthritis.* J Clin Invest 131(19):e150578 (2021). PMID: 34403362

He W, Baysal C, Lobato Gómez M, Huang X, Alvarez D, Zhu C, Armario-Najera V, Blanco Perera A, Cerda Bennaser P, Saba-Mayoral A, Sobrino-Mengual G, Vargheese A, Abranches R, Alexandra Abreu I, Balamurugan S, Bock R, Buyel JF, da Cunha NB, **Daniell H**, Faller R, Folgado A, Gowtham I, Häkkinen ST, Kumar S, Sathish Kumar R, Lacorte C, Lomonossoff GP, Luis IM, K-C Ma J, McDonald KA, Murad A, Nandi S, O'Keef B, Parthiban S, Paul MJ, Ponnendorf D, Rech E, Rodrigues JCM, Ruf S, Schillberg S, Schwestka J, Shah PS, Singh R, Stoger E, Twyman RM, Vargheese IP, Vianna GR, Webster G, Wilbers RHP, Christou P, Oksman-Caldentey K-M, Capell T. *Contributions of the international plant science community to the fight against infectious diseases in humans-part 2: Affordable drugs in edible plants for endemic and re-emerging diseases.* Plant Biotechnol J. 2021 Jun 28; PMID: 34181810

Huang G, **Boesze-Battaglia K**, Walker LP, Zekavat A, Schaefer ZP, Blanke SR, **Shenker BJ**. *The Active Subunit of the Cytolethal Distending Toxin, CdtB, Derived From Both Haemophilus ducreyi and Campylobacter jejuni Exhibits Potent Phosphatidylinositol-3,4,5-Triphosphate Phosphatase Activity.* Front Cell Infect Microbiol. 2021;11:664221. PMID: PMC8039388

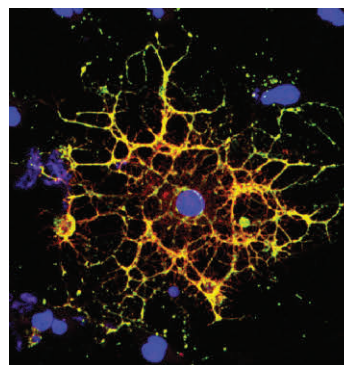
Jassim AH, Inman DM, **Mitchell CH**. *Crosstalk Between Dysfunctional Mitochondria and Inflammation in Glaucomatous Neurodegeneration.* Front Pharmacol. 2021;12:699623. PMID: PMC8334009

Jordan-Sciutto KL. *Effects of Antiretroviral Therapy in the Central Nervous System: Beyond Viral Suppression.* J Neuroimmune Pharmacol. Off J Soc Neuroimmune Pharmacol. 2021 Mar;16(1):71-73. PMID: PMC8118691

Khan I, **Daniell H**. Oral delivery of therapeutic proteins bioencapsulated in plant cells: preclinical and clinical advances. Curr Opin Colloid Interface Sci. 2021 Aug;54:101452. PMID: PMC8098715

Kumar Singh R, Pei Y, Bose D, Lamplugh ZL, Sun K, **Yuan Y**, Lieberman P, You J, Robertson ES. *KSHV-encoded vCyclin can modulate HIF1α levels to promote DNA replication in hypoxia.* eLife. 2021 Jul 19;10:e57436. PMID: PMC8315796

Li X, Yang S, Deepak V, Chinipardaz Z, **Yang S**. *Identification of Cilia in Different Mouse Tissues.* Cells. 2021 Jun 29;10(7):1623. PMID: PMC8307782



Roth LM, **Akay-Espinoza C**, Grinspan JB, **Jordan-Sciutto KL**. *HIV-induced neuroinflammation inhibits oligodendrocyte maturation via glutamate-dependent activation of the PERK arm of the integrated stress response.* Glia. 2021 Sep;69(9):2252-2271. PMID: 34058792

Li X, Yang S, Qin L, **Yang S**. *Type II collagen-positive embryonic progenitors are the major contributors to spine and intervertebral disc development and repair.* Stem Cells Transl Med. 2021 May 25; PMID: 34032373

Li Y, Liu M, Yang S, Fuller AM, Karin Eisinger-Mathason TS, **Yang S**. *RGSI2 is a novel tumor suppressor in osteosarcoma that inhibits YAP-TEAD1-Ezrin signaling.* Oncogene. 2021 Apr;40(14):2553-2566. PMID: 33686240

Li Y, Yang S, Qin L, **Yang S**. *TAZ is required for chondrogenesis and skeletal development.* Cell Discov. 2021 Apr 20;7(1):26. PMID: PMC8058044

Lobato Gómez M, Huang X, Alvarez D, He W, Baysal C, Zhu C, Armario-Najera V, Blanco Perera A, Cerda Bennaser P, Saba-Mayoral A, Sobrino-Mengual G, Vargheese A, Abranches R, Abreu IA, Balamurugan S, Bock R, Buyel JF, da Cunha NB, **Daniell H**, Faller R, Folgado A, Gowtham I, Häkkinen ST, Kumar S, Ramalingam SK, Lacorte C, Lomonossoff GP, Luis IM, Ma JK-C, McDonald KA, Murad A, Nandi S, O'Keefe B, Oksman-Caldentey K-M, Parthiban S, Paul MJ, Ponnendorf D, Rech E, Rodrigues JCM, Ruf S, Schillberg S, Schwestka J, Shah PS, Singh R, Stoger E, Twyman RM, Vargheese IP, Vianna GR, Webster G, Wilbers RHP, Capell T, Christou P. *Contributions of the international plant science community to the fight against human infectious diseases - part 1: epidemic and pandemic diseases.* Plant Biotechnol J. 2021 Jun 28; PMID: 34182608

HIV & THE BRAIN

A study from the lab of Dr. Kelly Jordan-Sciutto details the mechanism by which HIV infection blocks the maturation process of brain cells that produce myelin, a fatty substance that insulates neurons. See the following article:

Marchesan JT, Moss K, Morelli T, **Teles FR**, Divaris K, Styner M, Ribeiro AA, Webster-Cyriaque J, Beck J. *Distinct Microbial Signatures between Periodontal Profile Classes.* J Dent Res. 2021 Apr 27:220345211009767. doi: 10.1177/00220345211009767. Epub ahead of print. PMID: 33906500

Nguyen MN, Yeung JG, Randall Y, **Boesze-Battaglia K**, **Panchal N (Co-author dept. Oral Surgery & Pharmacology)**. *Oral and Maxillofacial Surgery Social Media Boom: Potential Concerns of Social Media Use for the Surgeon.* J Oral Maxillofac Surg Off J Am Assoc Oral Maxillofac Surg. 2021 May 26;S0278-2391(21)00522-X. PMID: 34174220

Singh R, Ren Z, Shi Y, Lin S, Kwon KC, Balamurugan S, Rai V, **Mante F (co-author Dept. of Preventive & Restorative Sciences)**, **Koo H (co-author Dept. of Orthodontics)**, **Daniell H**. *Affordable oral health care: dental biofilm disruption using chloroplast made enzymes with chewing gum delivery.* Plant Biotechnol J. 2021 Oct;19(10):2113-2125. doi: 10.1111/pbi.13643. Epub 2021 Jun 22. PMID: 34076337

Srinivasan A, Herzog RW, Khan I, Sherman A, Bertolini T, Wynn T, **Daniell H**. *Preclinical development of plant-based oral immune modulatory therapy for haemophilia B.* Plant Biotechnol J. 2021 May 5; PMID: 33949086

RESEARCH SPOTLIGHT CONT. FROM PAGE 20

Dr. Hajishengallis and his team have been working closely with the laboratory of Triantafyllos Chavakis, faculty at the Institute for Clinical Chemistry and Laboratory Medicine at Technische Universität in Dresden, Germany, on this research. The partnership has yielded dozens of journal articles and research papers. "It's a very prolific collaboration," Dr. Hajishengallis said. "We consider them our sister lab."

The earliest iteration of the collaboration, published in the journal *Cell*, showed that innate immune memory takes place in bone marrow progenitor cells, which give rise to lines of differentiated blood cells for months to come. The team later showed that trained neutrophils could actually kill tumor cells — in other words, that trained innate immunity could provide protection against cancer. Now, the partners have turned their sights on the unfortunate side effects of trained innate immunity.

The next step, Dr. Hajishengallis said, is to formally prove the connection between maladaptive trained innate immunity and chronic inflammation. To do this, the team will cause periodontitis in mice and monitor whether the infection makes the rodents more susceptible to other chronic inflammatory diseases. If a connection is found, he said, "then we can explain it by induction of maladaptive trained immunity in bone marrow progenitor cells."