



# GROWING A world-class faculty

**Penn Dental Medicine** does not operate by half-measures. “The dental school strives for excellence in clinical dentistry, in research, in service, and in teaching,” says Dr. Dana Graves, Professor in the Department of Periodontics and Associate Dean for Translational Research.

This year, the School has taken significant steps toward enhancing all of those areas of excellence, with the recruitment of three new talented and accomplished faculty members. Husband and wife Dr. George Hajishengallis and Dr. Betty Harokopakis-Hajishengallis joined Penn Dental Medicine in March, and Dr. Anh Le began her appointment in July. Each of them embodies the best of dental science and practice.

Their recruitment is the result of a renewed focus on augmenting innovative research enterprises and attracting field-leading researchers to join the faculty. Such a strategy promises to elevate the School for decades to come.

“It’s important that our new faculty complement the major research areas of the University to secure a strong place for Penn Dental in the future of the University as a whole,” says Dr. Kelly Jordan-Sciotto, Chair and Associate Professor in the Department of Pathology, who chaired the search committee for Dr. Hajishengallis.

Dr. Hajishengallis joins the Department of Microbiology as a Professor, Dr. Harokopakis-Hajishengallis was appointed Chief of the Division of Pediatric Dentistry and an Associate Professor of Pediatric Dentistry, and Dr. Le is now Chair and Norman Vine Endowed Professor of Oral Rehabilitation in the Department of Oral & Maxillofacial Surgery/Pharmacology.

“All three have dual degrees — dental degrees as well as a Ph.D. — so all of them have strong combinations of clinical training and research training,” says Dr. Graves, who led the recruitment committee for Dr. Le’s position. “By having strengths in these different areas, they’re particularly well-positioned and well-trained to fulfill the mission of the School.”

And the School is primed to provide these dental scientists what they require to actualize their potential. “Penn has a lot to offer high-profile researchers,” says Dr. Jordan-Sciotto. “We have a number of key research areas and leading researchers in each of those fields, colleagues who really complement one another. It’s a great place to do collaborative, interdisciplinary work.”

**GEORGE HAJISHENGALLIS, DDS, PHD**  
*Professor, Department of Microbiology*

### **Eye on Inflammation**

Trained as a dentist in Greece, Dr. George Hajishengallis was happy enough with the idea of practicing dentistry there. But something was missing. “As important as clinical treatment is — and I think it’s more important than research,” says Dr. Hajishengallis, “it can become routine.”

Realizing he would miss the stimulus of constant learning, he made the decision to continue his studies in the United States, enrolling in a doctoral program at the University of Alabama at Birmingham. His dissertation work focused on the development of a new platform for a vaccine that offers protection against tooth decay, a construct he has since patented.

After receiving his doctorate, he pursued postdoctoral studies at the University of Buffalo. There and in his subsequent faculty positions at Louisiana State University and University of Louisville his focus shifted to the bacterium *Porphyromonas gingivalis*, which is implicated in many cases of periodontitis.

Dr. Hajishengallis and other scientists had previously observed that, even in diseased animals, *P. gingivalis* was rare — far outnumbered by other kinds of bacteria. Through experiments with mice, he noticed that adding *P. gingivalis* to the mouth caused a jump in the numbers of other bacteria. The composition of the bacterial community also changed upon addition of *P. gingivalis*. And when mice raised in a germ-free environment were given *P. gingivalis*, they did not develop the bone loss associated with periodontitis.

“So we started to espouse this heretical view,” says Dr. Hajishengallis. “It’s not actually the *P. gingivalis* that causes the bone loss; it’s the other bacteria. But they need *P. gingivalis* to do it.”

Because of this, they dubbed *P. gingivalis* a “keystone pathogen.” In the September issue of *Nature Reviews Microbiology*, Dr. Hajishengallis and colleagues have supported the view

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that keystone pathogens may also underlie the pathogenesis of other diseases, such as inflammatory bowel disease, colon cancer, and obesity.

He and his colleagues discovered that *P. gingivalis* subverts the immune system response by “hijacking” a receptor on white blood cells, rendering them unable to clear infection. As a result, other bacteria increase and, along with *P. gingivalis*, feast off the nutrients released by the inflammatory response and destruction of gum tissue.

By blocking the hijacked white blood cell receptor, the researchers could stop the damaging inflammation catalyzed by *P. gingivalis*. They are now testing this technique of blocking access to the receptor in more advanced animal models, hoping to develop a new therapy for periodontitis.

Another line of Dr. Hajishengallis’s recent work, culminating in a publication that was featured on the cover of the journal *Nature Immunology* earlier this year, may also lead to a potential drug against gum disease, as well as other inflammatory diseases that strike in old age.

He arrived at this enticing molecule by searching mice for proteins that were expressed in the mouth and that also declined as the animals aged. Among those that turned up was a protein called Del-1.

Other scientists had found that Del-1 prevented immune cells like neutrophils from moving to and accumulating at the site of infection or inflammation. Dr. Hajishengallis hypothesized that older mice — and people — may be more likely to develop periodontitis because, as Del-1 levels drop, they are no longer able to prevent inflammatory cells from

moving to the gums. This overwhelming inflammation may then lead to not only periodontal disease but also systemic diseases such as diabetes and atherosclerosis.

Sure enough, Dr. Hajishengallis found that young mice bred to lack Del-1 developed gum disease, just as older mice did naturally. Injecting Del-1 into the mice’s gums protected them from this inflammation and bone loss. And interestingly, preliminary research indicates that humans with periodontal disease have low levels of Del-1 in their diseased gum tissues, but maintain higher levels of Del-1 in their healthy tissues.

Moving forward, Dr. Hajishengallis plans to examine whether Del-1 and associated molecules might be potential drugs or drug targets. He also hopes to collaborate with new Penn colleagues who can share their expertise in other inflammatory conditions.

“Penn has been historically a research intensive institution and is currently an international leader in the generation of new knowledge in both basic and translational biomedical sciences,” he says. “It’s an honor and privilege to be a part of this institution and have all the necessary support to develop treatments for oral diseases.”



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GEORGE HAJISHENGALLIS, DDS, PHD

## ANH LE, DDS, PHD

*Professor & Chair, Department of Oral & Maxillofacial Surgery/Pharmacology*

### Speaking Two Languages

Like Dr. Hajishengallis, Dr. Anh Le cares deeply about making an impact at the levels of basic science and clinical practice. So deeply, in fact, that she views it as her mission.

“That’s always been the guiding principle in my career. I don’t want to only speak the language of the basic scientist, because I can do lots of hard work and it will only stay in the lab,” says Dr. Le, who in her new role here will lead oral surgery at Penn Dental Medicine as well as within the Hospital of the University of Pennsylvania and

“At other institutions people always talk about collaboration, but here I can see it in the infrastructure, the culture, the history, and the leadership.”

ANH LE, DDS, PHD

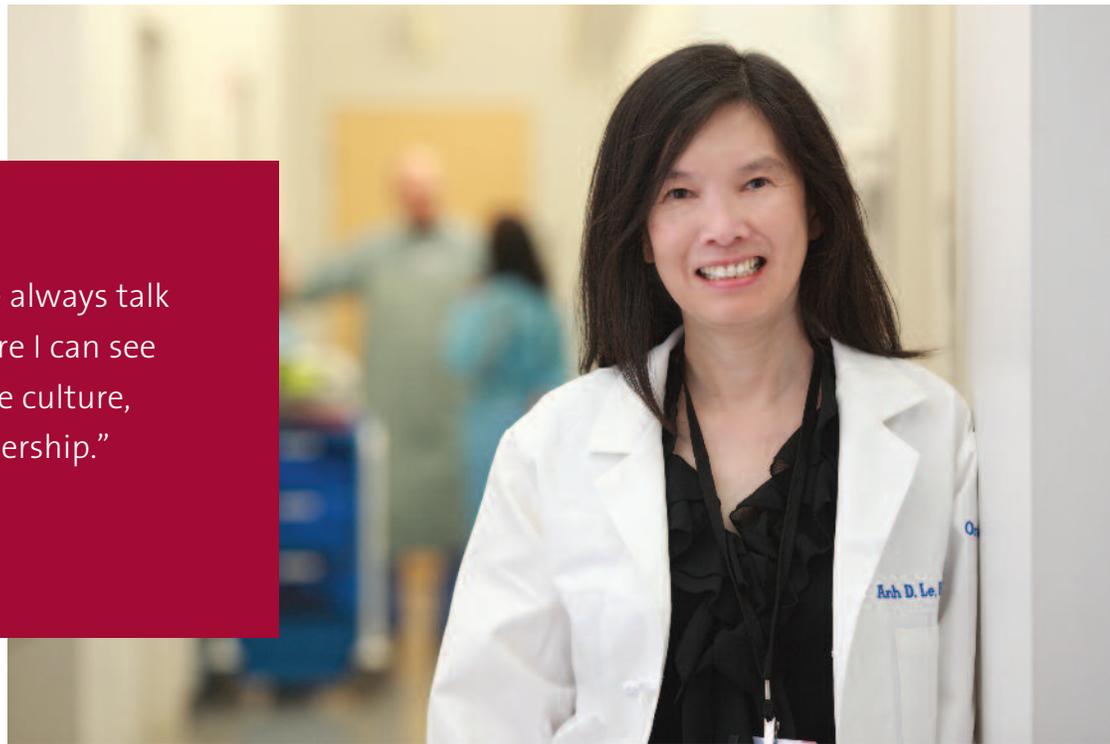
Children’s Hospital of Philadelphia. “I need the ability to also speak the language of the clinician to be a bridge between basic science and its clinical applications.”

This drive to generate translational scientific findings was planted in her during her undergraduate years at the University of California, San Diego.

“I started from a very strong basic science background,” says Dr. Le. “As an undergrad, I was engaged in some landmark research with Gordon Sato and John Mendelson.”

The work involved developing antibodies that target cellular growth factors. Though at the time Dr. Le was simply involved in the day-to-day bench science, the seeds of that work evolved into an FDA-approved chemotherapy called Erbitux, today used to curtail the growth of certain cancers.

Dr. Le went on to pursue her dental degree at the University of California, Los Angeles, and, encouraged by mentor Charles Bertolami, now dean of New York University’s College of Dentistry, followed that with a Ph.D. in oral biology in combination with residency training in oral and maxillofacial surgery. Her doctoral research examined wound healing on



the cellular and molecular level — an ideal complement to her concurrent clinical experiences, which included working with trauma patients in Los Angeles’ King Drew Medical Center.

Faculty appointments at Charles Drew University of Medicine and Science and UCLA followed. In 2004, Dr. Le was recruited to the University of Southern California’s School of Dentistry and began investigating mesenchymal stem cells from adult oral tissues. Together with collaborators, she isolated and characterized adult stem cells from gingival tissue — a discovery she patented while at USC. Studying those stem cells further, Dr. Le proposed a new mechanism by which they might aid in wound healing.

"Initially, the paradigm was that the role of stem cells is to arrive at the site of a wound and differentiate into different tissues to replace missing cells," she says. "That's a beautiful concept, but scientists have struggled to prove that an adequate number of cells actually arrive at the site of injury to fill in the missing tissue component. So we were proposing that maybe the stem cells perform other functions, like modifying the environment of the wound."

This new concept, that stem cells are the conductors rather than the musicians in the orchestra of wound repair, earned Dr. Le and her colleagues NIH funding and a wealth of new avenues of research to explore, all aimed at regenerating missing craniofacial tissue.

Those threads of research connect to another area of investigation for Dr. Le — the study of bisphosphonate-related osteonecrosis of the jaw, or BRONJ. It is a condition involving degeneration of the mandible that can arise after taking certain bisphosphonate-based drugs to treat cancer or prevent bone loss associated with osteoporosis.

Research by Dr. Le and collaborators in mice has identified biomarkers that put individuals at a higher risk of developing osteonecrosis of the jaw. They have found that an infusion of mesenchymal stem cells can cure the condition in mice — a promising breakthrough for patients with this debilitating and painful disease.

At USC, Dr. Le worked with colleagues at both the dental and medical schools to gather samples from 80 human patients to test them for a biomarker of vulnerability to osteonecrosis of the jaw. She plans to expand those studies into patients with multiple myeloma, likely collaborating with Penn researchers. And last year, she organized a symposium dedicated to antiresorptive-agents-induced osteonecrosis of the jaw — an event she would like to make an annual occurrence, working with her new Penn Dental Medicine colleagues in oral medicine and oral surgery.

Dr. Le's drive to apply lab-earned knowledge to medical practice permeates every aspect of her work. "Our field will only evolve if we face the challenges that science has been giving us," she says.

To accomplish such an evolution, she looks not only to her colleagues, but to the next generation of researchers. In her short time at Penn so far, Dr. Le made sure to reach out to the School's oral surgery residents to share her vision.

"I have had the benefit of being mentored by great role models and that's shaped my life and my career," says Dr. Le. "For the field to advance, we need to nurture and develop more clinician-scientists who share the same mission."

As she settles into her position, Dr. Le is eager to collaborate not only with other researchers at the dental school, but also with faculty at Penn Medicine, those who specialize in cancer, stem cells, and other fields.

"At other institutions people always talk about collaboration, but here I can see it in the infrastructure, the culture, the history, and the leadership," she says. "That's the reason I joined Penn."

### BETTY HAROKOPAKIS-HAJISHENGALLIS, DDS, MSC, PHD

*Associate Professor & Chief of the Division  
of Pediatric Dentistry*

#### **Focus on Young Patients**

In her new role, Dr. Betty Harokopakis-Hajishengallis will be deeply involved in such collaborations with fellow faculty members, students, and administrators from around Penn. She will spend half her time teaching, splitting the remaining time between administration and research. It is a multi-faceted appointment requiring the flexibility and versatility that have been characteristic of her career.

Dr. Harokopakis-Hajishengallis earned her dental degree at the University of Athens, where she also met her husband. When the two made the move to the University of Alabama at Birmingham (UAB) and, shortly after giving birth to the couple's twin daughters in 1991, Dr. Harokopakis-Hajishengallis began work on a master's in oral biology. "It was a challenge, having the twins, but I'm convinced that if you want something enough, you can do it," she says.

Finding a passion for research, she continued her training in a combined Ph.D./pediatric dentistry certificate program — one that she designed with the assistance of Dr. Marjorie Jeffcoat, former Dean of Penn Dental Medicine and current Professor in the Department of Periodontics, who was then an Assistant Dean at UAB. In 1997, Dr. Harokopakis-Hajishengallis was awarded a Dental Scientist Award from the National Institutes of Health for research focusing on designing new strategies for oral vaccination.

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After finishing her degree program in 1999, Dr. Harokopakis-Hajishengallis returned to Greece for a few years to work in private practice, while spending time with her family who still lived there. “I was the first pediatric dentist practicing in my province, so it was very busy from day one,” she says. “I enjoyed that time, enjoyed the interaction with other dentists, local dentists, and my community, but I missed the scientific interaction.”



She rejoined academia in 2003 with a position at Louisiana State University, when her husband also joined the faculty there, and later with an appointment at the University of Louisville. Throughout, she focused on clinical duties, while continuing her research part-time. A key element of her laboratory studies involved identifying a role for Toll-like receptors in the pathway leading to *P. gingivalis*-induced inflammation. At Louisville, Dr. Harokopakis-Hajishengallis was appointed Chief of the Division of Pediatric Dentistry, working with the predoctoral students as well as postgraduate residents, garnering experience that is serving her well now at Penn.

“Here, I feel very supported by Dean Kinane; I feel like the vision I have for pediatric dentistry can be accomplished, because he also wants the division to go forward.”

BETTY HAROKOPAKIS-HAJISHENGALLIS,  
DDS, MSC, PHD

“Being an administrator has a lot of challenges, but at the same time, I think it builds other skills in you, the persistence, the diplomacy,” she says. “Here, I feel very supported by Dean Kinane; I feel like the vision I have for pediatric dentistry can be accomplished, because he also wants the division to go forward.”

Together with Children’s Hospital of Philadelphia, Dr. Harokopakis-Hajishengallis is working to expand Penn Dental Medicine’s pediatric dentistry

residency program. Among her many goals for the Division, she also hopes to develop a sedation program by bringing a dental anesthesiologist on board, to introduce new rounds for the predoctoral students, and to continue her laboratory research in collaboration with Penn faculty.

“I’m going to be looking at a type of periodontal disease in monkeys,” she says, “trying to find different anti-inflammatory molecules to see if we can stop or prevent disease from emerging or progressing.”

Dr. Harokopakis-Hajishengallis notes she and her husband drew up a pro-con list to decide whether to make the move to Penn Dental Medicine; clearly, they felt the benefits were many. “It is a privilege to be here, no doubt,” she says. **PDJ**

—Katherine Unger Baillie