CAREERS

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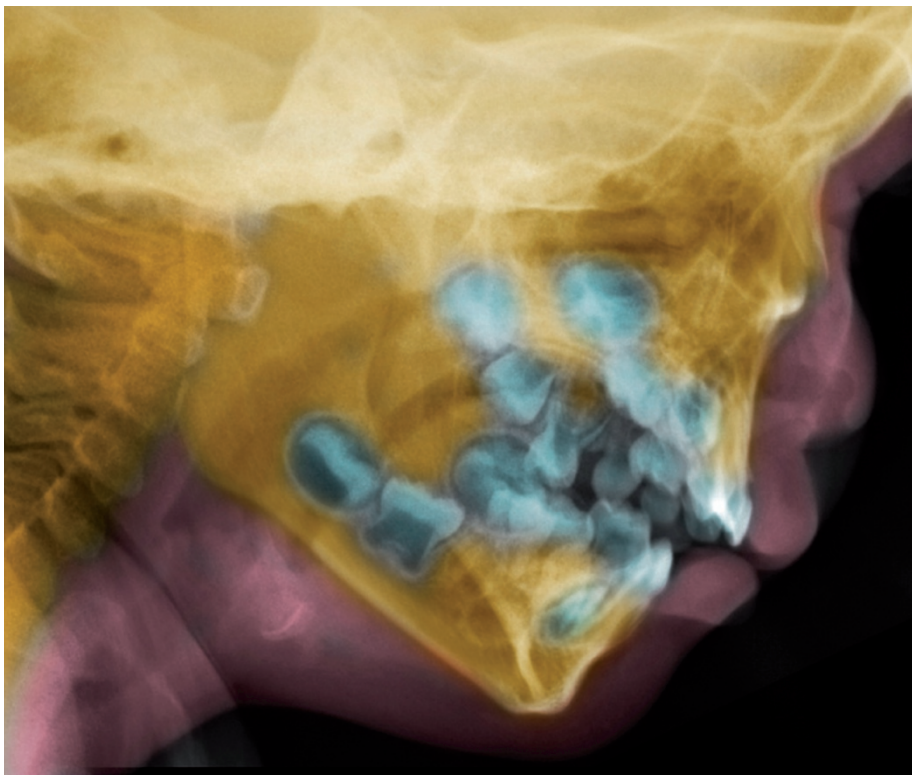


DENTAL SCIENCE

Oral observatory

Studying the mouth, including the diagnostic potential of saliva, is offering opportunities to explore overall health.

BY ROBERTA KWOK

In 2010, Michael Lau received an e-mail from a recruiter seeking candidates for a position at the University of California, Los Angeles (UCLA). Would he be interested, the recruiter asked, in applying for a postdoc related to salivary diagnostics? Lau, who was finishing his biochemistry and molecular biology PhD at the University of California, Riverside, and considering his career options, was intrigued and surprised. "I had no idea that you could actually detect systemic diseases, and oral diseases, using saliva," says Lau.

The opening was in the laboratory of David Wong, associate dean of research at the UCLA School of Dentistry. Wong's group had found in saliva potential biomarkers for oral cancer and the autoimmune disease Sjögren's syndrome, and was searching for others. With his interest piqued, and keen on the potential for practical diagnostic use, Lau successfully applied for the post.

Lau investigates how tumours in different parts of the body might affect the contents of saliva. In March, he co-authored a paper suggesting that tiny vesicles from breast-cancer cells can affect the protein and RNA contents of vesicles released by salivary-gland cells (C. S. Lau and D. T. W. Wong *PLoS ONE* **7,** e33037; 2012), and researching the possible mechanisms in a mouse model. Working in this field has offered Lau ample opportunities to break ground. At a time when most scientists are focused on other bodily fluids, such as blood and urine, this is "an untapped field," he says.

Many people assume that dental research is limited to teeth and gums. But dental researchers have long considered the mouth to be an indicator of conditions elsewhere in the body. Saliva contains many of the same molecules found in blood, albeit often at much lower levels, and might offer a non-invasive way to test for diseases in a dentist's office, in the field or even at home. Researchers have also uncovered possible links between gum disease and disorders such as diabetes and cardiovascular disease, creating the potential for research into whether improving oral health could help in the prevention or management of these conditions.

NON-INVASIVE DIAGNOSIS

Resources for scientists interested in the connections between oral and systemic health have grown over the past decade. The National Institute of Dental and Craniofacial Research (NIDCR) in Bethesda, Maryland, invested US$65.6 million into salivary diagnostics research between 2002 and 2011, and the human salivary proteome — an inventory of proteins secreted by salivary glands — was published in 2008 (P. Denny *et al. J. Proteome Res.* **7,** 1994–2006; 2008). The UK Biobank, a project to build a repository of health and lifestyle data and samples from half a million people, has collected about 130,000 saliva samples, and began accepting research proposals from the international scientific community in March. The Human Microbiome Project supported by the US National Institutes of Health (NIH) has sequenced the genomes of about 130 oral bacteria species. And in 2008, a collaboration between researchers in the United States and the United Kingdom launched the Human Oral Microbiome Database (HOMD), which currently contains the genome sequences of about 270 types of microbes that have been found — some of them only occasionally or during infection — in the oral cavity.

If a scientist were choosing a bodily fluid to investigate for disease biomarkers a decade ago, saliva wouldn't have made that list, says Wong. But technological advances and improved lab protocols have allowed researchers to conduct large-scale biomarker screens and detect, with more consistency, low concentrations of molecules such as proteins and RNA in saliva. Although job candidates ▶

may be cautious — some sceptics question how saliva could reflect systemic disease — other researchers say that now is a great time to enter this fledgling field. "You'll be a big fish in a small pond," says Daniel Malamud, who specializes in oral diagnosis of infectious diseases and is the director of the HIV/AIDS Research Program at New York University College of Dentistry.

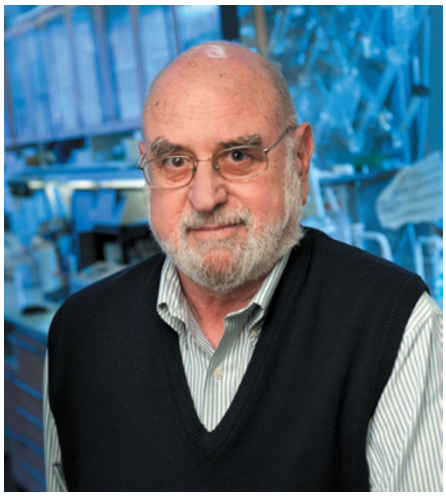
Tests on oral fluids already exist for hormones, illegal drugs and HIV. But the funding from the NIDCR over the past decade has kick-started the field, and teams are now investigating the use of salivary biomarkers for conditions ranging from Alzheimer's disease to heart attacks.

INTRIGUING LINKS

Researchers who work in salivary diagnostics are scattered across dental, medical, biology and engineering departments. PhD graduates in molecular biology, biochemistry, developmental biology and genetics are valued; and statisticians and bioinformaticians are also needed to distinguish significant biomarkers from noise in studies of tens of thousands of genes or proteins. Aims in basic research and device-development often entail technological tasks suited to biomedical engineers, who might develop assays for target molecules, and microfluidics experts, who work out how saliva will flow through a given device. People with experience in electrochemistry, nanotechnology, microfabrication and polymer science also have a role. For example, Fang Wei, a biosensor researcher at the UCLA School of Dentistry, is developing a platform for monitoring the contents of vesicles in saliva in real time. Dental training isn't necessary. Many of Wong's postdoctoral fellows have no dentistry skills at all when they first arrive at the lab, but pick up what they need on the job. Lau taught himself salivary biology, and was helped by lab members who did have dental training.

"I had no idea that you could actually detect systemic diseases, and oral diseases, using saliva."

Investigators should consider a wide range of agencies for funding options. The NIDCR is interested in salivary biomarkers for oral or head and neck cancers, and mechanisms to explain how an organ elsewhere in the body can affect the composition of saliva, says Penny Wung Burgoon, director of the NIDCR's salivary biology and immunology programme. But US researchers interested in systemic disease might have better luck seeking funding at the individual NIH institute that oversees their disease of interest. And last year, the US Defense Advanced Research Projects Agency (DARPA) in Arlington, Virginia, called for research proposals for diagnostic tests that can be easily used in the field to provide on-demand care, such as bioterror-pathogen testing for soldiers. Interest in salivary diagnostic research in Europe lags behind that in the United States, but investigators could apply for grants from funding bodies that cover specific diseases, says Gordon Proctor, a salivary biologist at King's College London Dental Institute.



Daniel Malamud says now is the perfect time to become a oral-diagnostics researcher.

Companies designing and developing tests value biochemists, immunologists or those with skills in molecular testing, says Stephen Lee, executive vice-president and chief science officer at OraSure Technologies in Bethlehem, Pennsylvania. Ronald McGlennen, medical director of OralDNA Labs in Brentwood, Tennessee, expects opportunities to arise for medical technologists — who would typically have a bachelor's degree in medical technology or have completed a relevant training programme — to refine protocols for handling and processing saliva samples. But jobs in this area may be limited because big pharmaceutical and diagnostic companies are waiting for further evidence that tests using saliva are comparable with those that use blood, and that they can meet regulatory standards, says Paul Slowey, chief executive of Oasis Diagnostics in Vancouver, Washington. "A lot of people are sitting on the fence," he says.

In addition to salivary diagnostics, scientists are investigating associations between gum disease and systemic disorders, raising questions about whether improving oral health could help in the prevention of these conditions. Researchers have long known that frequent gum abscesses can be an indicator of diabetes, and it has been suggested that there may be an association between a healthy mouth and improved control of diabetes. A link between poor oral health and cardiovascular disease and with pregnancy complications has also been suggested, but there is no clear evidence of whether gum disease actually contributes to these disorders.

Investigators seeking to establish associations with diseases need to avoid turning projects into fishing expeditions. "You can make a link with ingrown toenails if you want to," says Mark Bartold, director of the Colgate Australian Clinical Dental Research Centre at the University of Adelaide. Researchers need first to consider plausible reasons that a mouth infection or inflammation might affect another disease, he says.

Microbiologists, molecular geneticists and medical researchers could apply their expertise to this area. Researchers have found the DNA of oral bacteria in plaques that build up in blood vessels and in the synovial fluid of joints, raising the possibility that these microbes or their products may help to trigger heart attacks, stroke or prosthetic joint failure. Researchers at the Forsyth Institute in Cambridge, Massachusetts, plan to sequence another 100–200 microbe genomes in the next eight years. With genome data and good research tools, scientists can make connections between oral bacteria and disease more rapidly, says Floyd Dewhirst, an oral microbiologist at the Institute. Researchers can explore how these microbes interact with each other and with humans, including how they might affect systemic diseases.

DENTAL POTENTIAL

Yet Dwayne Lunsford, director of the NIDCR's microbiology programme, warns that because links between oral bacteria and systemic disease are still controversial, early-career investigators should be cautious. If peer-review groups are sceptical, they may score a grant application poorly, he says.

Although some research into salivary diagnostics and the links between oral health and systemic disease takes place in medical schools or conventional biology or engineering departments, biologists should not disregard dental-school faculty positions as a possible career destination. For example, the UCLA School of Dentistry has hired a proteomics researcher to work specifically in salivary diagnostics.

Many dental schools are looking for basic-research scientists, says Chris Overall, a proteomics researcher at the University of British Columbia Faculty of Dentistry in Vancouver, Canada. These institutions can give researchers access to patients, providing them with a better understanding of clinically relevant questions.

Researchers who apply for dental faculty positions may find job more easily than those who aim for basic biology departments. "It's challenging for dental institutions to find people of the calibre that we're looking for," says Laurie McCauley, a dentist and bone biologist at the University of Michigan School of Dentistry in Ann Arbor. For applicants with a track record in fields relevant to dentistry, McCauley calls dental faculty positions "a candidate's market". ■

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