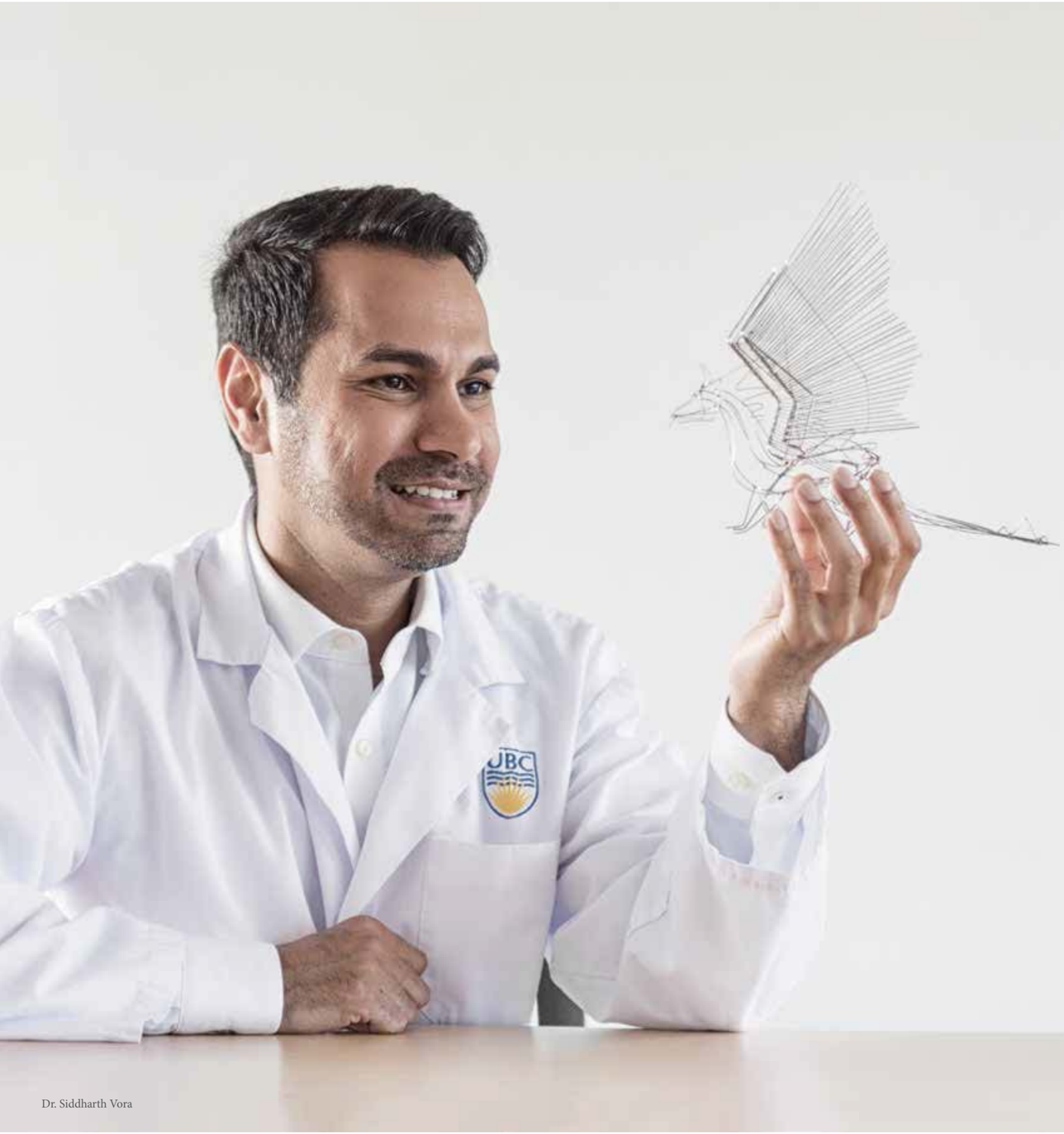

Dr. Siddharth Vora

Dentistry as Science and Art— And a Quest to Decipher Genetic Influences on Craniofacial Conditions

BY MARK WITTEN

What could be more central to a child's or an adult's identity than the distinctive features and contours of his or her face?

Dr. Siddharth (Sid) Vora wants to know more about what happens when the middle of a child's face develops and grows more slowly than the rest of the face. The condition is known as midface hypoplasia and can have potentially long-lasting effects on the health and visual appearance of an individual. The upper jaw and cheekbones do not grow at pace with the rest of the face, giving the face a concave appearance. The upper teeth don't meet the lower teeth correctly, resulting in an underbite, making the lower jaw protrude or stick out more than usual. In severe cases, chewing, speech and even breathing can be impaired.

As a clinician-scientist, Vora is also interested in how human genetics allows for infinite variations in facial construction. He would like to learn how genes play a critical role in craniofacial growth and an individual's response to craniofacial orthopaedic treatments. Such knowledge could potentially help to improve the timing and effectiveness of corrective treatments for midface underdevelopment in patients. "The genetic aspects of craniofacial conditions, like midface hypoplasia, are as yet poorly understood, and it's time to fill in the blanks," says Vora, who joined UBC Dentistry's Department of Oral Health Sciences as an assistant professor in the Division of Orthodontics in the fall of 2016.

His current research at UBC and previous research at the University of Washington (UW) in Seattle aims to build a comprehensive understanding of craniofacial growth and development, with a focus on understanding the genetic, epigenetic, morphological and molecular factors that control midface growth. He uses advanced genetic analysis techniques and high-resolution 3D micro-CT scanning, along with geometric morphometric techniques, to provide new insights and information about the underlying processes that contribute to midface growth underdevelopment.

Vora was attracted to UBC Dentistry because of its research-intensive environment and the presence of senior faculty members with similar research interests. Dr. Virginia Diewert and Dr. Joy Richman are world-leading scientists in the fields of craniofacial development and Dr. Ed Yen is a leading researcher in the area of bone physiology. "Virginia Diewert has done extensive work to increase our understanding of prenatal and postnatal growth of the human cranium. Any good textbook in the field of embryology has her images in it. The complementary nature of Joy's research makes for a good collaboration, and she has already been a mentor in sharing her in-depth knowledge and expertise," he says. Vora also looks forward to potential collaborations with colleagues Dr. Fernanda Almeida and Dr. Ben Pliska, who study many aspects of sleep apnea, including craniofacial features of affected patients.

Another drawing card is the university's major investment in leading-edge research facilities, such as the $9.4-million UBC Centre for High-Throughput Phenogenomics (CHTP) headed by Dr. Nancy Ford. This advanced imaging facility is open to UBC Dentistry researchers and others from a variety of fields for interdisciplinary research projects. "The CHTP is where I hope to develop and execute my projects, as it offers state-of-the art facilities, equipment and expertise. You can't find that everywhere and access to such a centre is very valuable," he says.

PHOTO BY MARTIN DEE

Schematics of the human craniofacial skeleton—(A) intact and (B, C) disarticulated—showing sites of bone apposition (+) and resorption (–). Apposition (growth) is found at sutures (lines of junction or an immovable joint between two bones) bordering the facial bones (B, C) as well as the cranial base (C). The arrow indicates the resultant downward direction of growth of the midfacial region.

Growing up in Mumbai, India, Vora wanted to be either an architect or a dentist. His mother was a science teacher; and in high school biology courses, he was fascinated by basic questions like: how do small heart cells know what to do to keep blood pumping through the heart? Dentistry ultimately appealed because "many patients are driven by a desire to have a better aesthetic appearance, so when you step back from it, dentistry really is a combination of an art form and a science aimed at delivering what is best for the patient."

Vora graduated from the Nair Hospital Dental College, University of Mumbai, in 2002. "It was old-school, regimented training and things had to be done a certain way. We'd sit for hours and carve out teeth from wax. If you didn't do it perfectly, they'd toss the teeth out and you'd have to start again. The school's approach was, 'know your stuff and be prepared for the real world,'" recalls Vora, who enjoyed treating dental patients during his internship but wanted more advanced, in-depth biology training.

From 2003 to 2009, while completing his PhD at Boston University, Vora learned how to do hard-core, basic science in the research lab of Dr. Philip Trackman, a professor of Periodontology and Oral Biology, and professor in the Department of Molecular and Cell Biology. Vora's research focused on investigating the role of the molecule lysyl oxidase propeptide (LOX-PP). While revealing the molecule's role in proliferating and differentiating osteoblasts (bone-forming cells), the researchers found that LOX-PP helps prevent tumour growth and metastasis. "Our team showed that the molecule's anti-cancer properties were effective against prostate cancer and breast cancer cells," says Vora, who earned the SDM (School of Dental Medicine) Dean's Award for his work on the molecule's role in regulating bone formation.

The five-plus years Vora spent investigating the different properties of a single molecule in Trackman's lab was a bench-science boot camp, which prepared him to become a clinician-scientist. "It was a completely different world that gave me focused, in-depth training in genetics and in molecular and cell biology. Trackman's approach to scientific problems was very methodical. From him, I learned how systematic and meticulous one has to be when trying to answer scientific questions."

Vora missed interacting with dental patients, however, and chose to pursue orthodontics at the University of Washington, earning an MSc in Dentistry and a Certificate in Orthodontics in 2013. "I wanted to get back into dentistry, where you are interacting with patients and making real-time changes in their daily life. And orthodontists rely on wire-bending, which I love, to move teeth within bone—a biological system. So it's a perfect fit."

At UW School of Dentistry, which has one of the oldest and most prestigious orthodontics programs in the US, Vora was able to pursue his specialty clinical training and related research at the same time. For his master's thesis project, he developed a new model for orthodontic tooth movement in mice. "One of the biggest challenges was the small size of the mouse and the delicate handling required. I was able to create a tiny stainless steel appliance for moving teeth. The method had the sensitivity to accurately measure small differences in tooth movement in genetically distinct strains of mice," he explains. Vora believes that knowing more about how specific genes and proteins affect tooth movement will help explain how individuals vary in their response to orthodontic forces, which will enable tailoring of treatment in the future. This type of preclinical tooth movement model could also be applied to test the effectiveness of certain promising drugs to reduce orthodontic relapse.

As an orthodontic resident, Vora also displayed his artistic flair and technical proficiency by winning the UW dental school's annual Orthodontics Wire Sculpture contest. Using orthodontic materials such as wires, elastic chains and headgears, he created a dazzling sculpture of a dragon whose wings ripple when they are fanned. "I was playing with headgear, an orthodontic appliance made of heavy wire. I bent two headgears and interlinked them together, and as I worked on it through the night, it morphed into a dragon."

Before coming to UBC Dentistry in 2016, Vora was a senior fellow at the Seattle Children's Hospital Research Institute, while also lecturing at UW and practising part-time as an orthodontist. With a fellowship from the American Association of Orthodontists Foundation, he worked in the lab of craniofacial researcher Dr. Timothy Cox, investigating genes potentially involved in midface deficiencies in mice and humans. His research uncovered strong associations between deficits in the cranial base and midface growth. (The cranial base is the floor of the cranial cavity that separates the brain from facial structures.) "I found that the cranial base deficits are influencing the growth of the middle of the face, and these findings support the central role of the cranial base and its integration with facial growth," he explains.

At UBC Dentistry, Vora hopes to build on these findings by studying different genetic strains of mice with mild and severe forms of midface hypoplasia. He's also investigating the relationship of the midface to the cranial base in pediatric patients, using CBCT (cone beam computed tomography) scans as a measurement tool. (Dental cone beam CT is a special type of X-ray equipment that produces 3D images of a dental patient's teeth and bone in a single scan.) "Our preliminary data suggest that children with early cessation of cranial base development show a retracted upper jaw."

While current treatments are effective for a majority of patients with midface hypoplasia, Vora points out that many patients fail to respond to treatment: "When a nine-year-old child wears headgear for 12 hours at night for a year and it doesn't work, that sticks in your mind. Research can give us more knowledge about treatment effects and how to improve treatments so all patients benefit." Vora wants to do studies to compare and evaluate the effectiveness of different treatment protocols for midface hypoplasia in both humans and animal models, with the goal of learning which treatments work best for which groups of patients. "Given the vast number of patients who undergo or need these orthopaedic procedures, the evidence in the current literature for the effectiveness of these procedures is poor," he says.

No two human faces are exactly the same (even those of identical twins) and each person's face develops in its own way. Vora aims to help personalize the diagnosis and treatment of craniofacial conditions for dental patients through his ambitious, cutting-edge research. "I see a future where orthodontists will use a combination of genetic profiling and 3D imaging for diagnosis and planning treatments that are more personalized and evidence-based. Such tools and knowledge will help us decide when to start treatment, what appliances to use and how to predict the outcome in a more accurate way."

Curriculum Rx: Teaching Dental Students to Adapt and Be Critical Thinkers

Sid Vora is enthusiastic about participating in the Faculty of Dentistry's ongoing curriculum renewal initiative. As a new Faculty member in the early stages of his career as a clinician-scientist, he is eager to contribute fresh ideas and innovative approaches for both undergraduate and graduate orthodontic education, to better integrate current and future clinical practice with biological paradigms. "It's exciting to be part of curriculum change. I recently made the transition from receiving knowledge to imparting knowledge. This gives me an interesting perspective," he says.

As a research-intensive school, UBC Dentistry gives students ample opportunities to be interested and involved in research. Vora believes the ability to apply new knowledge from research into clinical practice will be vital for future dentists and orthodontists. "In the field of orthodontics and craniofacial orthopaedics, we can now access and apply advances in robotics-assisted treatment methods, 3D imaging, molecular diagnosis and genetics in our daily practises. Future clinicians will have to adapt to changing technologies, something our students need to focus on during their training here at UBC."

Dental education should prepare students to evaluate new tools and techniques with an open yet critical mind. "Students need to be well trained in the fundamentals of orthodontics. Beyond that, education should be about trying to guide self-learning. There's so much information on the Internet now. As educators, helping to make students critical thinkers, to help them navigate this information, is the way to go," he says.

Such skills will be essential for clinicians in making the best decisions about whether and when to adapt a new technique or treatment. "The way that you do things as a clinician changes over time. If you're not trained to adapt, you might be missing out on more relevant techniques and treatments. Or, you might adopt a new technique too quickly, without understanding its implications. You have to be able to evaluate," Vora says. "Critical analysis is more important for today's and tomorrow's clinicians than memorization or following instructions. That's an aspect I would like to promote in the new curriculum."