

NASAL DRUG DEPOSITION

Controlled Particle Dispersion™: Applying Vortical Flow to Optimize Nasal Drug Deposition

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INTRODUCTION

Nasal delivery of local and systemic medical therapies is rapidly becoming a preferred treatment method for many medical conditions. Current technologies have significant challenges in being effective for many of these conditions. Local treatments would be more effective if the drug reaches and covers a greater area of the affected nasal mucosa and enters into the paranasal sinuses. For systemic applications, utilization of the entire mucosa significantly increases efficacy and onset-of-action rate. Current technologies were unable to reach the affected areas or to saturate the available mucosa until the introduction of Controlled Particle Dispersion (CPD™). Many treatments, such as those for chronic rhinosinusitis, have been unavailable to physicians due to ineffective drug delivery. CPD, developed by Kurve Technology, provides the opportunity to change drug

delivery as it is known today, creating a paradigm shift in the industry and enabling treatments for many medical conditions.

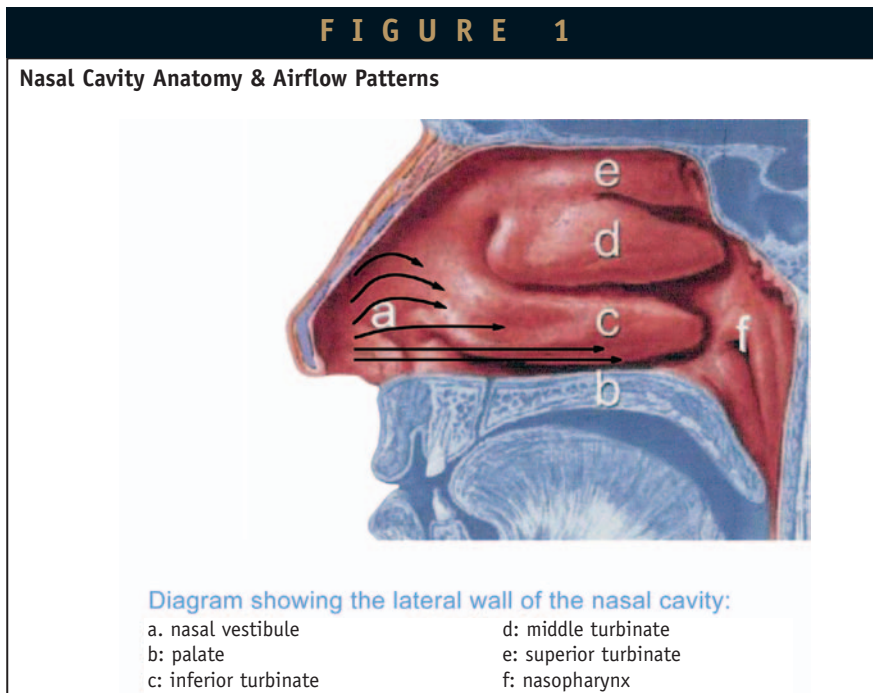
Although literature exists exploring the distribution pattern of topically applied medications to the nasal cavity, only a few studies have described the distribution of topically applied nebulized aerosols to the nasal cavity and paranasal sinuses.^{1,2} This paper discusses the four factors that influence drug deposition patterns: existing airflow patterns in the nasal cavity; and the size, velocity, and trajectories of delivered droplets. In addition, results of clinical studies comparing intranasal drug distribution of traditional nebulizers and nasal spray pumps with the ViaNase™ electronic atomizer using CPD technology are discussed.

NASAL CAVITY AIRFLOW PATTERNS

Transportation and deposition of droplets from a nebulizer within the nasal cavity are dependent on the existing airflow patterns. Figure 1 illustrates the inspired air profile, which is the dominant airflow pattern in the cavity. Inspired air patterns largely determine where and how drug deposition in the nasal cavity occurs.

Relatively low flow amounts are observed in the olfactory region (<10% of the inspired air) and in the nasal meatuses. This is predominately due to the small cross-sectional area of these regions, relative to the total cross-sectional area of the entire nasal cavity. These factors make it difficult to deliver drugs to these regions.

In a recent study examining airflow patterns in the nasal cavity, the greatest airflow velocities were observed between the top of the palate and under the inferior turbinate.³ Velocities and flows decrease in the upper regions of the nasal cavity. The inferior airway has a relatively small cross-sectional area, compared to the anterior portion of the cavity, which increases the velocity of the inspired air. The acceleration of the air through the inferior airway forces the inhaled airflow to become more



streamlined such that the airflow itself (and any particles carried by the flow) will also tend to move in a predominantly streamwise direction, ie, a direction aligned with the primary flow direction along the axis of the

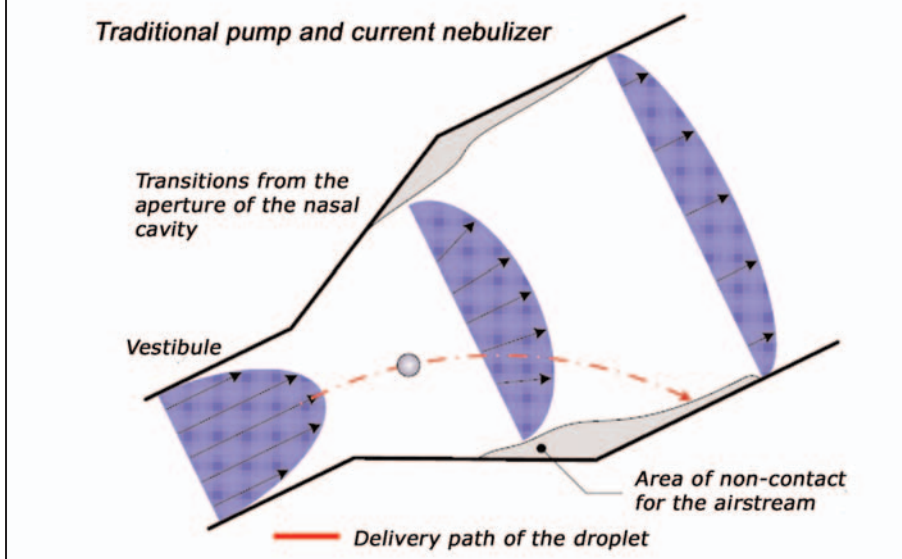
inferior airway. It is desirable to disrupt the axial streamlined trajectories of inhaled particles flowing along the inferior airway.

An effective delivery method has to create an environment in which the spatial

NASAL DRUG DEPOSITION

FIGURE 2

Linear Flow Pattern of Traditional Passive Nebulizers



TRADITIONAL NEBULIZERS LIMITED BY AIRFLOW PATTERNS

Nebulizers were originally designed to deliver small droplets into the lungs; pharmaceutical companies are now testing these devices for nasal deposition. Passive nebulizers deliver droplets to the nasal cavity through a hollow tube with perforations at one end producing a linear droplet flow as shown in Figure 2.

When passive nebulizers deliver drugs to the nasal cavity, the inspired air travels through the device and mixes with air used to generate the droplets. The droplets are then completely entrained in the inspired air and directly subjected to the airflow patterns produced in the nasal cavity. A recent study showed passive nebulizers deliver the majority of the drug in the anterior chamber and/or along the floor of the nasal cavity (Figure 3).⁴ The airflow transports the droplets through the inferior region of the nasal cavity, allowing deposition to occur specifically in the anterior portion of the cavity and in an area bounded by the inferior turbinate and the floor of the nasal cavity. In fact, it is well known that droplets in the range of 0.1 to 1 micron penetrate most efficiently to the deep lung due to their ability to follow the airflow streamlines with great fidelity.

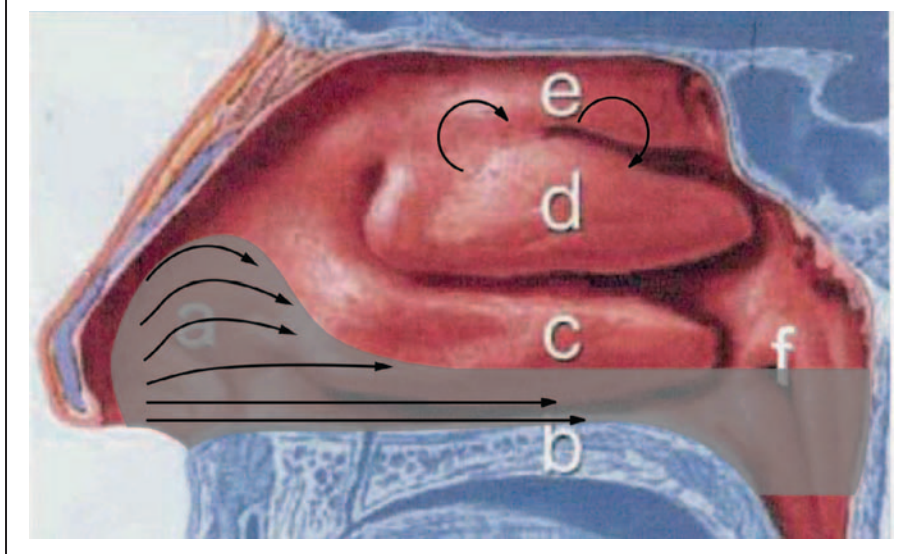
In addition, droplets generated from a passive nebulizer have a small mass and low velocity. After these droplets enter the inferior airway, only a small amount of deposition occurs. This is due in part to the extremely aerodynamic nature of the small droplets that allow them to follow the airstream without deposition.

DROPLET SIZE

In addition to airflow patterns, deposition is dependant on the diameter of the droplet delivered to the nasal cavity. Large droplets found in spray pumps have a tendency to fall out of the airstream immediately because the liquid comprising the droplets has a density approximately 1000 times larger than the airflow on which the droplets ride. Consequently, large droplets fall out of the airflow either due to gravitational settling or because they possess far too much inertia to negotiate the bends within the nasal passage and are removed from the flow by inertial impaction.

FIGURE 3

Deposition Pattern Produced by Passive Nebulizers



extent is capable of altering the airstream created by the inspired air, so droplets deposit beyond this stream. This airflow stream is the greatest obstacle to the delivery of medications into the upper posterior of the nasal cavity, which allows access to the olfactory region and paranasal sinuses.

Disrupting this airstream must occur in order to attain the desired result of effective nasal drug delivery. If a delivery technology is not disrupting the airflow streams, it will not deliver any more effectively than current technologies.

NASAL DRUG DEPOSITION

FIGURE 4

Vortical Droplet Flow Created by Controlled Particle Dispersion

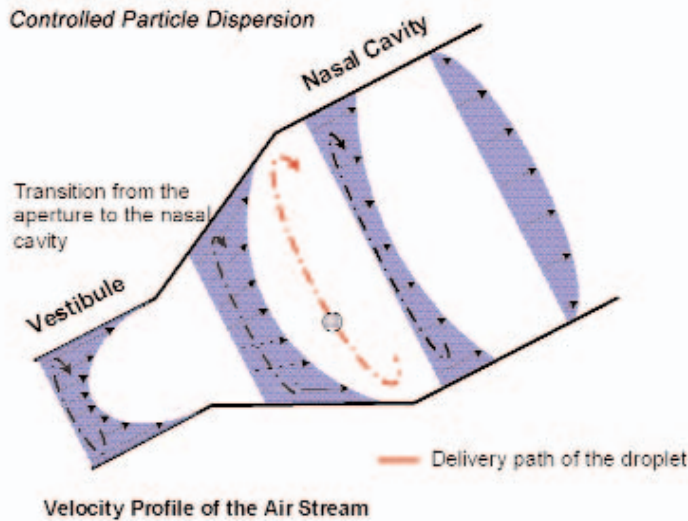
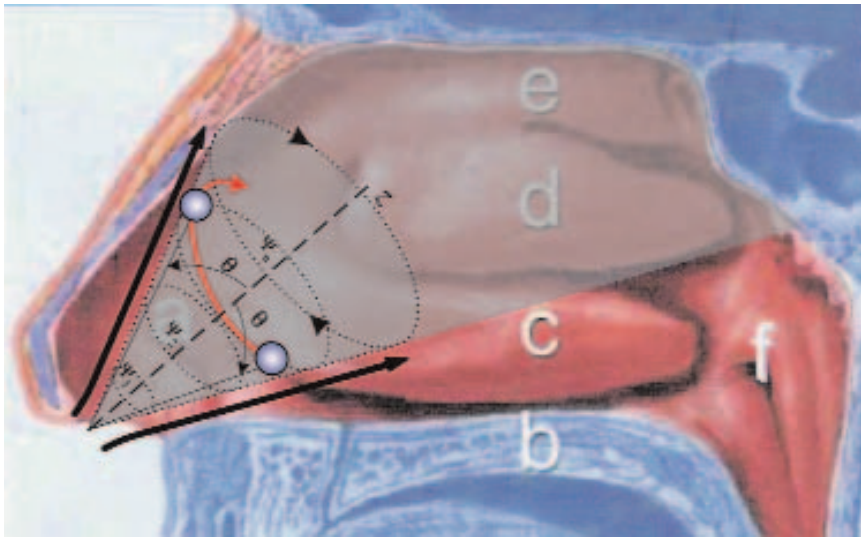


FIGURE 5

Deposition Pattern Produced by Controlled Particle Dispersion



Smaller droplets produced by nebulizers remain airborne. These ultrafine particles have high diffusional deposition efficiency, and given the narrow geometry of the nasal airway, will predominantly deposit in the lower airway or will be convected downstream to the extranasal regions.

The droplet size must be carefully controlled to avoid these extremes. The ideal droplet size would be somewhere in between the passive nebulizer and the spray pump.

The CPD technology platform is capable of producing droplet ranges from 10 to 50 microns in less than 5-micron increments with a perceived ideal of 15 to 20 microns.

Another advantage of 10- to 20-micron particles is the larger amount of medication contained by each droplet. For example, the amount of drug contained within a 10-micron droplet is 1000 times larger than that contained within a 1-micron droplet. Therefore, the deposition efficiency of

nebulizer particles needs to be proportionally larger to ensure comparable amounts of drug delivery.

DROPLET VELOCITY

The droplet velocity is inversely proportional to its residence time within the nasal passage. All factors being equal, a particle with a smaller velocity has a higher probability of remaining in the airway longer but must follow the trajectory and pathway of the airstream.

DROPLET DELIVERY TRAJECTORIES

If the flow is primarily in the axial direction of the inferior airway, the droplets simply will ride along the flow streamlines and quickly exit the intranasal passages. The ability to disrupt the primary streamwise flow and impart a significant flow component in the cross-stream direction (ie, a direction perpendicular to the primary or axial direction) is critical to dispersing droplets over the greatest possible area within the nasal passages. If particles are redirected along cross-stream trajectories, it greatly improves their residence time and penetration within the intranasal passages.

CONTROLLED PARTICLE DISPERSION

CPD technology addresses the limitations associated with passive nebulizers by controlling droplet size and delivery trajectories. Two limits define droplet size. The aerodynamic properties of the droplet set the upper limit of size (mean diameter). The lower limit is established to minimize lung deposition. The correct droplet size ensures the droplets are delivered to the nasal cavity.

CPD affects the delivery path by generating a vortical flow, giving droplets the environment needed to disrupt the inherent airflow streams and penetrate into the entire nasal cavity (Figure 4). Consequently, the airflow acquires two components: the primary flow, which is still directed along the axial direction, and a secondary component, which imparts a circular spin. The net result is the flow streamlines trace spiral or helical paths as they navigate the nasal passage. The vortex accelerates droplets in an upward direction at the same time centrifuging the droplets to the outer edge of the vortex, ie, to the walls of the nasal cavity. The centrifugal acceleration imparted to the droplets is proportional to the radial location of the droplet from the center

NASAL DRUG DEPOSITION

FIGURE 6A

Scintigraphy Results Comparing Nasal Deposition in One Patient
Results using: ViaNase

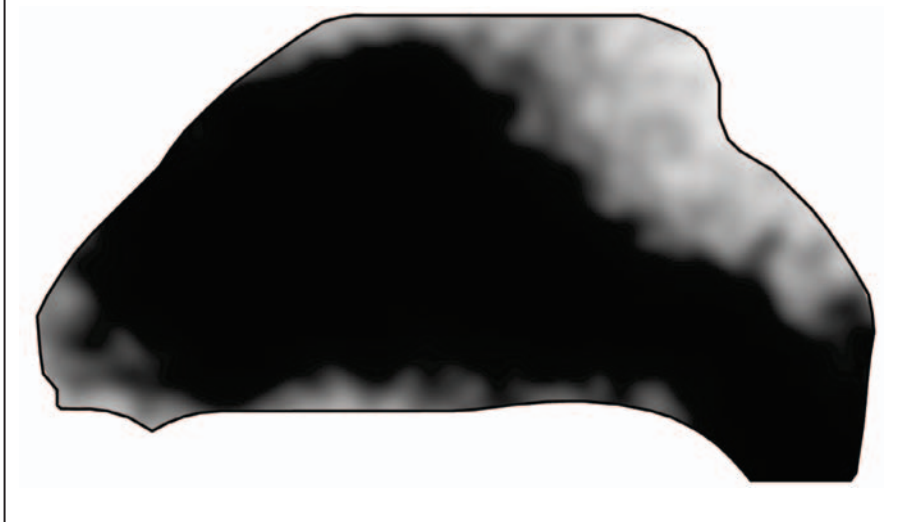
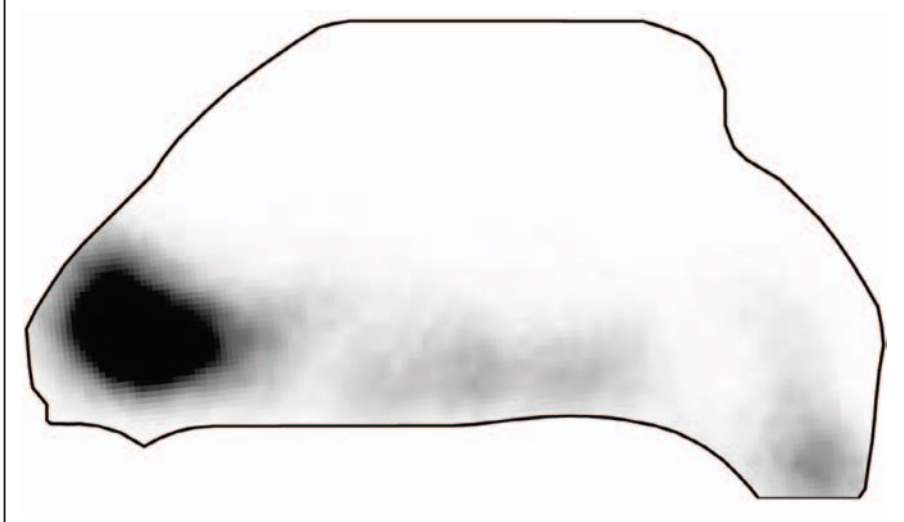


FIGURE 6B

Scintigraphy Results Comparing Nasal Deposition in One Patient
Results using: Passive Nebulizer



CPD is to reach these upper regions, taking advantage of these existing air patterns that prolong droplet residence time in the cavity.

CPD also uses the inspired airstream to enhance deposition. The inspired airstream enters the device through the nosepiece. The airstream is aligned with the vortex axis, and the flow acceleration along the nasal passage will cause a stretching of the vortex. Stretching the vortex increases its strength because vorticity is inversely proportional to its cross-sectional area. Incorporation of inspired air into the device design becomes a useful variable in the performance of the device as it can alter the air pattern in the nasal cavity and enhance the centrifugal forces generated by the vortex. The deposition pattern produced by CPD is shown in Figure 5.

CLINICAL STUDY METHODS

Scintigraphy studies were conducted at the Oregon Sinus Center at Oregon Health & Science University. For each study, a total of 10mCi^{99m} technetium-DTPA (^{99m}Tc) was delivered transnasally in saline. Each patient was instructed to hold the device securely to the nose and breathe comfortably, inhaling through the nose and exhaling through the mouth into a surgical mask.

Three devices were tested. The first was a commercially available, metered dose spray pump, which produced particle sizes of approximately 79 microns. The second device was a passive-diffusion nebulizer, which produced small droplets (mean diameter ~2 to 5 microns), a passive exit velocity, and a linear droplet flow. The third system was the ViaNase electronic atomizer, which produced larger droplets (9 to 14 microns), a faster exit velocity, and the ability to centrifuge the particles by generation of a vortical flow. Radiolabeled saline was subsequently imaged in the nose, lungs, and stomach. Images were scored by four blinded reviewers for degree of penetration at nine anatomic subsites.

NASAL DEPOSITION STUDY RESULTS

Delivery modality affected the dispersion of topical administered saline. In healthy individuals with no previous sinus surgery, ViaNase appeared to hold the greatest promise for sinus penetration of topical therapies.⁴

ViaNase showed a greater tendency for sinus penetration, with 60% of subjects

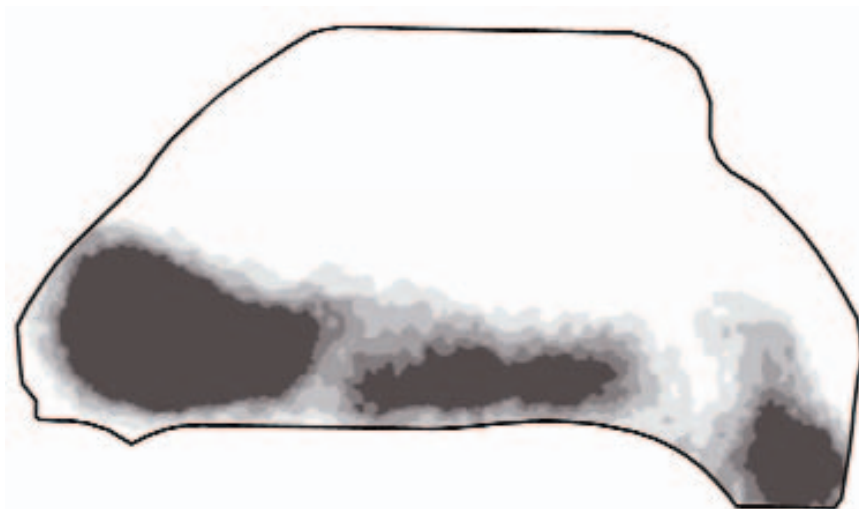
of the vortex and the square of the angular velocity (speed with which it is being spun about the vortex axis). Because the droplets are typically 1000 times denser than air, they are ejected outward (ie, they are centrifuged away from the vortex core). The vortex sorts the droplets by size. The larger droplets will move to the outer wall first, allowing the

smaller droplets to move upward. This disrupts the existing airflow patterns in the nasal cavity. When the airflow patterns in the nasal cavity have been disrupted, the smaller droplets move upward and into the middle and superior airways. In studies of air patterns in the nasal cavity, standing eddies have been noted in the superior airway.³ The objective of

NASAL DRUG DEPOSITION

FIGURE 6 C

Scintigraphy Results Comparing Nasal Deposition in One Patient
Results using: Nasal Spray Pump



showing some degree of sphenoid penetration, and 20% of subjects showing slight maxillary penetration. In contrast, no sinus penetration was observed with the passive nebulizer or the spray pump. Scintigraphy results of one subject are shown in Figure 6. ViaNase demonstrated more focal intranasal distribution with reduced nasopharyngeal, pharyngeal, and gastric penetration in normal subjects. In a separate study, ViaNase demonstrated probable frontal sinus penetration in 60% of the test cases. By comparison, there was no evidence of sinus penetration by the passive nebulizer or the spray pump.

CONCLUSION

For local or systemic treatment, CPD holds great promise for complete nasal cavity, olfactory region, and sinus penetration compared to passive-diffusion nebulizers or nasal spray pumps. In studies comparing the ViaNase device to the passive nebulizer, ViaNase consistently provided greater nasal cavity penetration and reached the paranasal sinuses in many subjects. In contrast, no upper nasal cavity or sinus penetration was observed with the passive nebulizer or nasal spray pump.

Complex conditions and airflow patterns are at the core of obtaining a better understanding how the nasal cavity works and the effects on intranasal drug delivery.

This knowledge translates into delivery modalities that have greater efficacy, lower dosages, fewer side effects, and are less invasive. These factors also have important implications for critical assessment of current treatment modalities and the development of future devices.

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BIOGRAPHIES



Marc Giroux is the CEO and Founder of Kurve Technology, Inc. He is also the inventor and lead designer of CPD Technology. A lifelong sinusitis and

allergy sufferer, Mr. Giroux applied 20 years of high-tech experience and engineering principles to nasal drug delivery in order to develop the next generation of nasal drug delivery devices. A veteran entrepreneur, he has also developed and invented new technology products and designed efficiency equipment for production manufacturing.



Dr. Peter Hwang established the Oregon Sinus Center, a comprehensive nasal and sinus care center at OHSU in Portland, Oregon, where he

joined the faculty in September 1997, bringing with him clinical and research expertise in the treatment of sinusitis and other nasal disorders. Dr. Hwang is the Principal Investigator of the CPD technology and is in no way compensated or affiliated with Kurve Technology, Inc.



Dr. Ajay Prasad is a Professor of Mechanical Engineering at the University of Delaware. He has more than 20 years of experience in

developing flow diagnostic tools using non-intrusive, imaging-based methods. He has applied these tools to measure the flow within anatomically accurate *in vitro* models of the human nasal passage, and the upper respiratory airways composed of bronchi. His research is aimed at characterizing the primary and secondary flows within the airways and their resulting impact on particle dispersion and deposition.