For reprint orders, please contact: reprints@future-science.com

Looking to the future of nasal drug delivery – an interview with Per Gisle Djupesland

Per G Djupesland^{*,1}

¹ Co-Founder & Chief Scientific Officer of OptiNose AS, Oslo, Norway

* Author for correspondence: Tel.: +47 4809 0610; per.djupesland@optinose.com

Per G Djupesland, MD, PhD speaks to Hannah Makin, Commissioning Editor: Dr Djupesland is the inventor of OptiNose[®]'s patented, bi-directional nasal drug-delivery technology and is a Co-Founder of OptiNose AS. Dr. Djupesland is a lead inventor on all 38 OptiNose patent families/patent applications, and serves as Chief Scientific Officer of OptiNose AS, with primary responsibility for device discovery and early development efforts. These early development efforts include identifying new product opportunities that use bi-directional technology, advancing the design of devices using the bi-directional technology to treat a variety of medical conditions and conducting Phase I and IIa trials with new 'nose-to-brain' applications for the technology.

Dr Djupesland is an otolaryngologist (ENT) with a specialization in rhinology and more than 25 years of clinical experience. Among other positions prior to OptiNose, he served as a Clinical Research Fellow at the Hospital for Sick Children and Toronto General in Toronto, Canada, primarily studying the role of nitric oxide in the upper airways. Dr Djupesland has authored more than 60 peer reviewed articles in international medical journals and has lectured at numerous international scientific conferences.

He earned medical and doctorate degrees in the field of nasal physiology and aerodynamics from the University of Oslo.

First draft submitted: 24 May 2017; Published online: 9 February 2018

Keywords: brain drug delivery • nasal aerodynamics • nasal drug delivery • respiratory • technology

First of all, can you tell us a little more about your current position & what led you to where you are today?

I am the Chief Scientific Officer of the biopharmaceutical company OptiNose AS here in Norway and have had this position from when the company was founded back in 2000. Before this role, I was an ear, nose and throat surgeon and obtained a PhD in nasal physiology. It was during my clinical work as a nasal and sinus surgeon, some 20 years back, that I realized that the traditional spray pumps were inadequate for reaching the target areas for treating chronic inflammatory diseases in the nose. There is mismatch between the narrow and slender anterior passage (the valve area), and the conical expanding spray plume. In a way, it was this discovery during my clinical experience that started everything. I saw the need and potential for improvements in nasal drug-delivery technologies. In my PhD I studied nasal aerodynamics, and it was this combination of clinical experience and an understanding of nasal aerodynamics that gave birth to the idea of using the patient's own exhaled breath to improve drug deposition in the nose.

I first discussed the idea of using a patient's own exhaled breath for nasal drug delivery with my wife, who has a law degree and an MBA. We talked about how we could potentially transform this idea into something of value, and decided that the first step was to file a patent application. We subsequently entered into a business plan competition called the Venture Cup, organised by McKinsey & Co, and ended up winning first prize for our business plan in 2000. Before this competition, I had never worked in business, but my wife had a lot of experience in business management, which was very important. Winning first prize kick-started everything; we received some prize money and received grant funding from the Research Council of Norway and with this we started our company, OptiNose AS!

You have had quite an eminent career in the field of nasal drug delivery, what would you say has been your greatest achievement to date?

For me personally, and also for my wife, it has been this amazing journey that began over 16 years ago. My wife is the co-CEO of OptiNose AS, which is our Norwegian company, and being able to work together has been a fantastic opportunity and experience. Seeing my idea actually move forward through all the necessary steps of innovation, patenting, funding, device development and testing, clinical trials, to finally a stage where there is actually an approved product on the market in the USA, that's the greatest achievement. We successfully completed product development for our first product, which is for acute migraine, and the commercialization rights in North America were licensed out to Avanir Pharmaceuticals (www.avanirpharma.com; the product is marketed as ONZETRA® Xsail®). In September 2017, the US FDA approved our product (XHANCE™) for the treatment of nasal polyps in adults, which is expected to be launched in the USA in the second quarter of 2018. The approval was followed by successful listing of our parent company OptiNose, Inc. on the Nasdaq Stock Market in October. So overall, seeing ideas develop into approved products, which will improve people's lives, has been a unique and very satisfying experience.

It has also been great to experience this journey with so many skillful and dedicated co-workers – people that we worked with here in Norway, in the UK, and in the USA. We have also been very fortunate to receive grant support from Norwegian, EU and USA research institutions and associations, and we have had the fortune to have committed investors with long-term horizons.

What inspired you to co-found OptiNose AS?

In the early stages in my career as a sinus surgeon, it was fascinating to learn the new endoscopic surgical techniques that in many ways revolutionized the surgical treatment of chronic rhinosinusitis. However, even if the results look good from the surgical point of view, chronic inflammation persists. Therefore you realize that surgery alone is rarely sufficient. Continuous saline irrigation and topical treatment with anti-inflammatory drugs (i.e., topical steroids) is almost always needed. However, inflammatory swelling, secretions and polyp formation in the already complex nasal labyrinth, further complicates topical delivery. I realized through my clinical experience that inadequate drug delivery was one of the main challenges in the treatment of chronic inflammatory nasal diseases. Coupled with an insight into the complex nasal aerodynamics gained as part of my PhD, this clinical experience and knowledge really inspired me to think about how delivery could be improved.

In your own opinion, what has been the most important milestone for OptiNose AS?

Well again, it is really to take an idea and start a company and eventually see the idea turn into a product that is successfully taken through all the steps required for marketing approval – that is huge and unique achievement! That's a very long journey. In pharma especially, it is a much longer and cumbersome journey than many other types of business. There are new apps and new mobile phones coming out every year, or even more frequently, but in pharma, the development journey takes much more time and is both risky and expensive.

XHANCE, our recently FDA-approved product, required a quite large global clinical research program to support registration, including more than 1500 patients, some of whom were treated for up to 12 months. We have presented scientific abstracts with the excellent results from these studies at multiple scientific meetings [1–4]. The positive outcomes and continuous improvement over time in patients, most of whom had previously tried surgery and/or other steroids, is very encouraging. Patients in these studies reported substantial improvement in not only objective and subjective disease measures, but also reported improvement in measures of aspects of quality of life. XHANCE was well-tolerated in these studies and had an adverse event profile similar to that observed in several comparably designed third party studies of nasal steroid sprays. These results suggest that the exhalation delivery system (EDS) technology actually works well, and that it gets the drug high and deep in the nose just as intended. Other interesting research during this time has suggested that carbon dioxide (which is present in the exhaled breath delivered into the nose through an EDS), removal of nitric oxide, change in pH, or positive pressure, which are all effects of an EDS, also influence inflammatory mediator activity and neuropeptide activity, which further increases our enthusiasm for the benefits of EDS products.

In 2017, the US FDA approved XHANCE, a product that uses an OptiNose EDS to deliver a steroid medication into the nose. Can you tell us more about why this technology is so unique?

The first thing I should mention is that the device technology is based on mechanical principles that exploit natural nasal aerodynamics. It is very easy to use and automatically adapts to the state of the nose.

Essential components of the EDS-device are the movable mouthpiece and the shaped sealing nosepiece that allows this device to adapt to people with a wide range of facial anatomies. When exhaling into the mouthpiece the soft palate elevates to separate the oral cavity from the nasal cavities. So the mechanism of delivery takes advantage of a patient's own exhaled breath! The patient inserts the nosepiece in one nostril, takes a deep breath, closes their lips around the mouthpiece and exhales (similarly to the inflation of a balloon). A closed valve inside the device prevents airflow until the bottle is pushed up to open the valve, at which point the drug spray and exhaled breath are released simultaneously into the patient's nose and, thanks to the sealing nosepiece, which is critical to the mechanism of action, drug is propelled high and deep beyond the anterior narrowing in the nose called the nasal valve. Although the technology sounds sophisticated, the device was designed to be easy to use for the patient. The internal valve reduces the need for coordination and 98% of the patients in our clinical trials (87% responded) stated the device was easy to use [3].

The nasal valve is the narrowest point of the respiratory tract, and is a slender triangular opening just a couple of centimetres into your nose. The shaped sealing nosepiece stents open the nasal valve, especially the upper part, and also transfers the positive exhalation pressure, which helps to further expand the narrow passages of the nasal labyrinth. In addition, and this is especially important, the proportional pressure transfer into the nostril balances the pressure across the elevated soft palate, which helps secure an open communication behind the nasal septum, allowing the air to escape through the other nostril. This 'bi-directional' airflow (in one side and out the other) produces a high and deep pattern of drug deposition and takes away the risk of lung inhalation, which is another unique feature of an EDS. As I mentioned before, we have preliminary data [5] suggesting that the positive pressure and deep penetration of the CO₂-containing exhaled air may have therapeutic effects alone or in synergy with the delivered drug.

As this technology uses the patient's exhaled breath, we are sometimes asked: *"how do you know that you get the same air flow and the same pressure every time?"* However, this is not the point; the beauty of the system is that it automatically and instantaneously adapts to the dimensions/resistance and the patient's nasal passages, which helps to optimize delivery. In an obstructed nose, the exhalation force is used primarily to expand the anterior nasal segments to allow drug delivery to the surface of the congested tissues. As congestion and resistance to airflow decrease, the airflow increases, allowing the drug particles to be carried to higher and deeper nasal regions. This automatic adaptation is yet another unique feature of EDS delivery.

The new OptiNose product XHANCE uses an exhalation delivery system to deliver a liquid drug formulation and is now approved for the treatment of nasal polyps [6]. How do you think this technology could overcome the current challenges facing nasal drug delivery methods?

The approved product for the treatment of acute migraines, Onzetra Xsail, which is marketed in the USA by Avanir Pharma, uses an EDS designed for delivery of a powder. XHANCE uses an EDS designed for delivery of a liquid drug formulation. In both cases, the alternatives for nasal delivery that are currently used are actuated during non-flow conditions or with inhalation, such as sniffing. The expanding conical plume of these current products will, to a large extent, impact in the vestibule region, anterior to the slender triangular-shaped nasal valve. This region has a skin-like lining and is not the best target for a drug that can act by absorption into the body, as with Onzetra Xsail, or for drug that acts topically, as with XHANCE. When inhaling during delivery, such as when a patient sniffs, the nasal valve progressively narrows due to the laws of physics (Bernoulli's forces). The valve serves an important function in nasal aerodynamics, as the nose needs to filter, humidify and warm the air to protect the lungs. But with traditional approaches, these protective functions impede efficient drug delivery. The drug is deposited mainly anteriorly [7–11]. To avoid this 'drip-out', people tend to wipe their noses or sniff the drug along the nasal floor and therefore a large fraction ultimately ends up being lost or swallowed instead of reaching the targeted areas higher up and farther back in the nose. In contrast, EDS delivery takes advantage of a patient's own exhalation mechanics and the product design to overcome anatomic and physiologic restrictions that severely limit the delivery efficiency of traditional devices. This has been documented in several deposition studies [7–9], and

opens up possibilities for finally achieving better topical activity in the nose, better absorption into the body, or even better penetration of drug into the central nervous system.

Your company is also conducting early development work on products for neurologic orphan diseases [12]. How important do you think it is that researchers investigate further the ‘nose-to-brain’ (N2B) drug delivery route?

This is a very interesting area of research. The brain is a sensitive organ and to avoid potentially hazardous substances from reaching the brain, only a few very important molecules can pass the blood–brain barrier (BBB). The BBB, located in the walls of the millions of cerebral capillaries supplying the brain tissue with oxygen and essential nutrients, is however, an important bottleneck in the development of new therapies for common neurological, psychiatric and neurodegenerative disorders. Researchers are investigating multiple approaches that may allow targeted penetration of the BBB, but it is very challenging to achieve selective delivery across this protective barrier. With N2B delivery, we aim to circumvent the BBB, as the nose is really the only place in the body that allows direct contact between the brain and the atmosphere. This is because the olfactory nerve is an extension of the brain that interacts directly with the external surface of the body in the uppermost segment of the nose. Direct N2B-transport has been demonstrated convincingly in animal studies and rapid drug transport occurs in channels along the olfactory nerve without having to pass the BBB [13]. Similarly, drugs can also be transported along another cranial nerve, the trigeminal nerve, but in contrast to the olfactory nerve, the molecules first need to penetrate the mucosa to reach the nerve filaments. These olfactory and trigeminal nerves innervate most of the nasal mucosal surfaces and are responsible for the sense of smell and mucosal sensitivity.

One of the biggest challenges for efficient N2B drug delivery is getting the drug to the higher parts of the nose, particularly the olfactory regions, where N2B-transport is most efficient.

How does OptiNose delivery technology hope to overcome the difficulties of drug delivery to the brain?

With our technology, which uses the exhaled breath and a specialized N2B nosepiece, we can direct and propel the drug to the higher parts of the nose to a much greater extent than traditional nasal sprays. We have shown in deposition studies that we get a much higher fraction of the substance to the targeted regions in the upper part of the nose than with a traditional delivery approach [13].

We have done some recent studies in humans that support the idea that it is possible to transport a drug directly from the nose into the brain. We delivered oxytocin via the intranasal and also the intravenous route as a comparison [14,15]. Despite similar levels in the blood, significant differences in cognitive tests and corresponding brain activation were observed. Of course, this was a very small study and all of these results need to be confirmed with further research, but these results suggest that there is direct transport of oxytocin from the N2B using our EDS-N2B technology. We also have other projects in the pipeline in the N2B-area. These take advantage of the same technology of getting the drugs to the areas in the nose innervated by the olfactory nerve in particular, but also to the areas broadly innervated by the trigeminal nerve.

Can you tell us more on the progress of OPN-300 as a potential novel treatment alternative for several brain disorders, including autism?

Yes, as I mentioned briefly earlier, we’ve published a study in healthy volunteers in Phase I studies, where we had an intravenous oxytocin comparison [14,15]. Here we had a placebo and two different doses of oxytocin delivered to the volunteers using our device. We verified these findings using cognitive measures. We also used functional MRI and saw activities in the brain that corresponded well with the cognitive changes, which further supports that there is N2B transport when using our technology.

Another of our papers was also published recently, where we studied 16 autistic patients and delivered the same drug with our device [16]. Although this was a small crossover study with 16 patients, and we used only one single dose, we saw changes in some of the end points, which is very encouraging. Of course, it’s only one single dose and it’s in a group of patients that are very difficult to treat and get compliance from and so on, but we are quite happy with the results. We still have to get the funding and decide on where to go when it comes to the next phases with this program.

We have another program in narcolepsy that is also in very early stages. Following the vaccination campaign against swine influenza in 2009/2010, there were quite a number of children that developed narcolepsy as a serious

side-effect of the vaccine. Most likely, vaccine-induced antibodies destroyed the cells in the brain that produce Orexin-A (a neuropeptide that regulates the sleep/wake cycle). We have started a project supported by the Research Council of Norway aiming to replace the missing Orexin-A by N2B delivery. This project is still in its very early stages, so we haven't entered into the clinical phases yet. This is the project that we are working on most closely right now.

Is there anything else we can expect from OptiNose in the near future?

OptiNose has just achieved two essential milestones; the approval of XHANCE and an Initial Public Offering that raised substantial operating funds. Now the most important milestone will be a successful market launch of XHANCE in the USA, making it available to the millions of patients who can benefit from it. This is our near term number one priority. We will also plan to continue to develop XHANCE for other chronic inflammatory diseases of the nose, such as chronic sinusitis without nasal polyps (CRSsNP). Antibiotics, topical steroids, and oral steroids are all used, but to my knowledge no drug has to date been approved for the treatment of CRSsNP anywhere in the world – so XHANCE could be the first!

Finally, how do you think the field of nasal drug delivery will change over the next 10–20 years?

10–20 years sounds like a very long time away, but I know from experience that things take a lot of time. In some areas, there are enormous changes in 10–20 years. In pharma, there are of course changes, but it takes around 10–15 years to develop a new product from scratch and to get it on the market. When I grew up I remember we were given nasal drops if we got a problem in the nose. After this, the next innovation was the spray pump. Spray delivery is a more convenient method of nasal drug delivery, and these are now used all the time. In our EDS liquid devices, we still use the spray pump as the dose metering mechanism, but our EDS-device uses our own exhaled breath and novel device features to facilitate things like expanding the narrow passages and for creating the mechanics that help drive the medication to the target sites, making delivery much more efficient and less susceptible to user variability and user error. We see multiple opportunities for making good and safe drugs better with this EDS technology. Numerous injectable biologics have been approved or are in development for chronic diseases, also for airway diseases like asthma and nasal polyposis. These drugs are very expensive. In the nose more efficient topical delivery with EDS may be a better alternative both in terms of outcomes and costs.

Efficient delivery of drugs to the nose is really about understanding the complex nasal geometry and aerodynamics. Our novel EDS technology has the potential to significantly enhance the clinical effects of drugs that are already delivered nasally, and to open up the path to new indications and new molecules for nasal drug delivery in future years to come.

Disclaimer

Dr. Per Gisle Djupesland participated in this interview in his personal capacity. The views expressed are his own and do not necessarily reflect the views of OptiNose, Inc. (or its subsidiaries) or Future Science Ltd.

Financial & competing interests disclosure

Per Gisle Djupesland is a named inventor of the nasal delivery technology described in this interview and is an employee (Chief Scientific Officer) of OptiNose® AS, Oslo, Norway and owns stock and stock options in OptiNose. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. Soteres DF, Messina J, Carothers J, Mahmoud R, Djupesland PG. NAVIGATE I: a randomized double-blind trial of a fluticasone propionate exhalation delivery system (FLU-EDS) for treatment of chronic rhinosinusitis with nasal polyps (CRSsNP). *J. Allergy Clin. Immunol.* 139, 2 (2017). AAAAI 2017
2. Leopold D, Elkayam D, Messina J, Kosik-Gonzalez C, Djupesland PG, Mahmoud R. NAVIGATE II: a randomized double-blind trial of OPN-375, a fluticasone exhalation delivery system (FLU-EDS) for treatment of chronic rhinosinusitis with nasal polyps (nasal polyposis). American Rhinologic Society, San Diego, CA, USA, 16–19 September 2016.

3. Sher MR, Mair EA, Messina J, Carothers J, Mahmoud Rm, Djupesland PG. EXHANCE-3: A Phase 3, three-month study of safety and efficacy of fluticasone propionate exhalation delivery system (FLU-EDS) in patients with chronic rhinosinusitis with (CRSwNP) and without nasal polyps (CRSsNP). *J. Allergy Clin. Immunol.* 139, 2 (2017). AAAAI 2017
4. Palmer J, Jacobson K, Messina J, Kosik-Gonzalez C, Djupesland PG, Mahmoud R. Exhance-12: A One Year Study of Safety and Efficacy of OPN-375, a Fluticasone Exhalation Delivery System (FLU-EDS), in Patients with Chronic Rhinosinusitis with and without Polyps (CRS c/s NP). American Rhinologic Society, San Diego, CA, USA, 16–19 September 2016; See poster at: www.optinose.com/scientific-communications/abstracts-and-posters
5. Djupesland PG, Messina J, Mahmoud R. Novel exhalation nasal delivery systems (EDS) may produce beneficial activity independent of delivered drug in inflammatory nasal diseases and migraine via exhaled CO₂ and mucosal pH. American Rhinologic Society, San Diego, CA, USA, 16–19 September 2016; See poster at: www.optinose.com/scientific-communications/abstracts-and-posters
6. OptiNose Announces FDA Acceptance for Filing of the New Drug Application for OPN-375. www.optinose.com/press-releases/optinose-announces-fda-acceptance-filing-new-drug-application-opn-375
7. Djupesland PG, Skretting A. Nasal deposition and clearance in man: comparison of a bidirectional powder device and a traditional liquid spray pump. *J. Aerosol Med. Pulm. Drug Deliv.* 25, 280–289 (2012).
8. Djupesland PG, Skretting A, Winderen M, Holand T. Breath actuated device improves delivery to target sites beyond the nasal valve. *Laryngoscope* 116, 466–472 (2006).
9. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective – a review. *Drug Deliv. Transl. Res.* 3, 42–62 (2013).
10. Leach CL, Kuehl PJ, Chand RC, McDonald JD. Nasal deposition of HFA-beclomethasone, aqueous fluticasone propionate and aqueous mometasone furoate in allergic rhinitis patients. *J. Aerosol Med. Pulm. Drug Deliv.* 28(5), 334–340 (2015).
11. Emanuel IA, Blaiss MS, Meltzer EO, Evans P, Connor A. Nasal deposition of ciclesonide nasal aerosol and mometasone aqueous nasal spray in allergic rhinitis patients. *Am. J. Rhinol. Allergy* 28, 117–121 (2014).
12. Research & Development. www.optinose.com/research-and-development/overview-chart
13. Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases: an anatomic, physiologic, and delivery technology overview. *Ther. Deliv.* 5, 709–733 (2014).
14. Quintana DS *et al.* Low-dose oxytocin delivered intranasally with breath powered device affects social-cognitive behavior: a randomized four-way crossover trial with nasal cavity dimension assessment. *Translational Psychiatry* 5, e602 (2015).
15. Quintana DS, Westlye LT, Alnæs D *et al.* Low dose intranasal oxytocin delivered with breath powered device dampens amygdala response to emotional stimuli: A peripheral effect-controlled within-subjects randomized dose-response fMRI trial. *Psychoneuroendocrinology* 69, 180–8 (2016).
16. Quintana DS, Westlye LT, Hope S *et al.* Dose-dependent social-cognitive effects of intranasal oxytocin delivered with novel Breath Powered device in adults with autism spectrum disorder: a randomized placebo-controlled double-blind crossover trial. *Translational Psychiatry* 7, 5 (2017).