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Nitric Oxide from Room Air – The Development of the LungFit PH Technology

In this feature, Respiratory Therapy interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Dr Fred Montgomery, Inventor of LungFit and who has spent over 30 years developing and patenting nitric oxide delivery system technology that resulted in the commercialization of nitric oxide therapy.

Can you provide us with the history of your work in nitric oxide and designing technology to deliver nitric oxide to patients?

For the past three decades, I have devoted my career to developing nitric oxide delivery systems and making inhaled nitric oxide (iNO) more accessible for clinicians and patients. My involvement in nitric oxide began in 1993 at Ohmeda, the medical systems division of British Oxygen Company, an industrial gases company. We were one of the few businesses that had pharmaceutical and device development programs, as well as high quality, medical grade gas. We started iNO device development with a very basic delivery device that was being used in clinical trials. My development partner and co-inventor, Duncan Bathe, was on site in the UK when they put the first patient on iNO. The baby responded well and went home a few days later—it really was an exciting time for our team. After the clinical trial device, we started work on a commercial delivery system (INOvent) that could be taken to the bedside of a patient needing iNO treatment and be connected to any ICU ventilator. In January 2000, the FDA cleared the INOvent delivery system, making it the very first commercial system to be approved by the FDA.

Commercialization, along with the R&D program, shifted to INO Therapeutics, then Ikaria, followed by Mallinckrodt. We continued to develop delivery technology, focusing on ease of use, automation, and patient safety. In 2006 we received FDA clearance for the next-generation device, the INOmax DS. Additional next-gen system advancements quickly followed with the INOmax DSIR. These advancements and FDA clearances included adding a transport system for air and ground, increasing the geographic area and reach of iNO to treat and transport critically ill patients.

Our device development team also created the INOblender for bagging patients and the INOpulse for use in ambulatory patients with PPH. Duncan and I are on these patents as well and are proud of the work our team accomplished to innovate iNO delivery and make it easier for clinicians to access and treat with iNO.

However, the main challenge that we could not address at the time was how the iNO was supplied. The 45 lb pressurized iNO cylinders required for administration are big and bulky to transport. A sophisticated network and infrastructure are also required to manufacture and distribute the gas supply and then return the empty iNO cylinders. If you think about it, iNO cylinders might be the most inefficient drug packaging out there, with only 2 grams of actual iNO in a 45 lb package with 99.92% of the content being nitrogen. There was some promising research that provided evidence that we might be able to address this challenge, so Duncan and I decided to pursue development of an iNO system that took cylinders out of the equation.

What gave you the idea to create nitric oxide from air using electricity?

It's been known that lightning produces vast quantities of nitric oxide, and that it can also be produced in the lab by arc discharges. There was almost 20 years of published scientific research that demonstrated nitric oxide could be produced from electricity and room air. Various patents were filed, but the research did not progress to a level where you could produce the iNO in a controlled and continuous manner.

In 2011 Duncan and I left Ikaria to see if we could replicate what others had published and take it a step further to develop an alternative to iNO cylinders using electricity. The challenge was that if we wanted more iNO we had to use large spark discharges, and the bigger the spark, the more intense the current and the shorter time the electrodes lasted. The arcs only lasted a few micro-seconds and they could not generate the amounts of continuous nitric oxide we needed. While we were focusing on trying to control the quick, big spark, Duncan had an "aha" moment and asked a couple of crucial questions:

- What if we could inject current into the plasma and extend the time of the spark to produce more iNO?
- How do we control the current to a low level and maintain the spark for longer at a lower energy level?

Dr Fred Montgomery has spent over 30 years developing and patenting nitric oxide delivery system technology that resulted in the commercialization of nitric oxide therapy. He led the development of the INOvent delivery system for Datex-Ohmeda, which in 2000 was the first FDA 510(k) cleared nitric oxide delivery system that introduced inhaled nitric oxide therapy to the commercial market. He then established the Medical Device Group at INO Therapeutics, which developed the INOmax DS and INOmax DSIR products, the leading nitric oxide delivery systems in the United States to this day. Dr. Montgomery left Ikaria (formerly INO Therapeutics) in 2011 and cofounded NitricGen Inc. Since 2017 he has worked at Beyond Air, commercializing its LungFit PH family of products and further innovating delivery of iNO. He received his Doctor of Philosophy degree from the University of Salford, England and his Master of Business Administration from the University of Bradford, England.

Dr Fred Montgomery with the FDA-approved LungFit PH, the first and only 3-in-1 integrated system that generates and delivers inhaled nitric oxide from room air.

We brainstormed a few approaches and finally reached the stage where we could control the current at 70 mA in the plasma and extend the duration of the plasma from 10 µs to 20 ms, a range of 2,000:1. This change provided the flexibility to generate very small to very large quantities of NO from room air, a range of 0 ppm to 1500 ppm. We then developed a filter to remove the resulting impurities, O_3 and NO_2. In October 2011 we filed a patent.

In 2017 Duncan and I joined Beyond Air to commercialize this new technology, creating the LungFit family of products. At Beyond Air we have made significant investments in the technology with a robust product development team and research pipeline. Our current research focuses on a range of applications and therapeutic areas using high-concentration iNO (80 to 250 ppm) for antimicrobial treatment: Viral community-acquired pneumonia (VCAP), including COVID-19, bronchiolitis, and nontuberculous mycobacteria (NTM) lung infection, with additional research planned for the use of iNO to treat severe exacerbations due to lung infections in COPD patients.

What is the Ionizer™?

The Ionizer technology is the core of our LungFit platform and family of products. It is what generates the iNO from room air over a wide range of concentrations and at low electrical power. The LungFit product family includes the FDA (PMA) approved LungFit PH, which generates low concentration iNO (0-80 ppm) for use in the NICU to treat persistent pulmonary hypertension in newborns; as well as our LungFit PRO and LungFit GO, which generate high concentration iNO and are being studied for antimicrobial treatments in the hospital and home settings.

How does it work?

The Ionizer is a small chamber with two electrodes within each LungFit system that draws in room air and uses the power equivalent to a 60-watt light bulb to ionize the nitrogen and oxygen molecules. The molecules recombine as nitric oxide, and low levels of NO_2 are created as a by-product. The NO_2 Smart Filter then removes the NO_2 from the internal circuit. It's the Ionizer that gives us the flexibility to generate unlimited, on-demand iNO from room air.

We've come a long way since we first started testing this concept in 2011. With this simple, user-friendly technology, we can open access to iNO treatment at the global level in countries and on continents that don't have the infrastructure to support the use of cylinder-based iNO delivery systems. This is really exciting for me—removing barriers to care and empowering clinicians with this life-saving therapy.

Can you describe the LungFit Technology and how it fits into NICU operations?

We received US Food and Drug Administration approval for the LungFit PH on June 28, 2022. The LungFit PH generates iNO, a selective pulmonary vasodilator, and delivers it into the inspiratory limb of the patient breathing circuit of an ICU ventilator in a way that provides a constant concentration of nitric oxide, as set by the user. In the US, iNO is indicated to improve oxygenation in neonates with evidence of pulmonary hypertension. Outside of the US, including Europe, iNO has this same indication, and is also indicated for patients of all ages who are undergoing or have undergone heart surgery and develop pulmonary hypertension. We are currently working with the US FDA to expand our label to include this indication.

The LungFit PH is the first and only 3-in-1 integrated system for iNO generation, delivery, and monitoring. The system is fast, precise, and simple—power on and in seconds you can generate unlimited, on-demand iNO from room air, regardless of dose or flow. Because we generate iNO from air we are finally able to give clinicians in the NICU access to iNO at the bedside without pressurized 45-lb cylinders used by incumbent technology.

Given our involvement in the R&D that went into developing the first iNO system approved in the US and then subsequent systems, we had years of clinical, real-world feedback from users that helped inform the development of other key elements of the LungFit PH. It was also imperative to simplify the pre-use check and provide clinicians with immediate, on-demand access to iNO to treat their critically ill patients.

We kept the elements from our previous developments that worked well, such as the simple user interface, gas monitoring, and connections to the ventilator breathing circuit. At the same time, we eliminated the things that caused problems for users that came with using bulky 45 lb high-pressure cylinders. Examples are: no need to transfer heavy cylinders around in the NICU, no regulator connections to high pressure cylinders, no leak checking the connections, and no purging the gas lines of NO_2 before it is used on the patient. This all streamlines the workflow and reduces the setup time required to start iNO therapy.

How is the LungFit PH different than alternative nitric oxide delivery systems used in the NICU?

The incumbent iNO delivery systems in the NICU uses 45-pound

cylinders that deliver 800 ppm iNO and are pressurized to 2200 psi. The traditional cylinder-based iNO delivery system have worked well since their conception in 1999, but have various burdensome hurdles, specifically the iNO cylinders. These cylinders take up a large amount of storage space, must be returned to the manufacturer once used, require physical monitoring and cylinder emptying, pressure-testing, manual purging, and there is the potential for iNO leaks and wasted iNO before patient use.

The LungFit PH system generates iNO from room air, and consistently delivers and monitors iNO all in one compact system in under one minute. This system does not require reservoirs of iNO and automatically purges the delivery line with room air, eliminating the risk of unintended NO_2 bolus delivery to the patient. Additionally, the LungFit PH system includes a 2.5 oz NO_2 Smart Filter that removes NO_2 from the internal circuit, only takes a few seconds to replace, and can be stored at the point of care. The filters last 12 hours regardless of iNO dose or flow, creating predictability for the clinicians.

Nitric oxide has been researched and proposed as a therapeutic option to treat various cardiopulmonary conditions. What therapeutic areas are you currently focusing on as part of the research and development pipeline at Beyond Air?

Thanks to the Ionizer technology at the center of the LungFit family of products, Beyond Air is designing systems for a variety of clinical settings with the potential to treat across a broad spectrum of therapeutic areas. FDA approval currently includes PPHN, but we are not stopping there. We are researching treatments for viral and bacterial infections and NTM lung infections. Pending FDA review, we plan to conduct a pilot study to evaluate high concentration iNO to treat severe COPD exacerbations due to lung infections in hospitalized patients.

Beyond Air has conducted multiple pilot studies with the LungFit PRO system at 150 ppm of iNO to treat viral community-acquired pneumonia (VCAP), including COVID-19, resulting in promising safety and efficacy data. We are currently in discussion with the FDA on a US trial design for VCAP, including COVID-19.

This past fall, *The Annals of the American Thoracic Society* published a detailed review of our third pilot study of iNO in bronchiolitis patients. The study concluded that efficacy outcomes suggest intermittent administration of 150 ppm of iNO may be favorable, compared to the lower concentration, in shortening the time to improvement in clinically significant endpoints for hospitalized infants with moderate to severe bronchiolitis. The publication offers an overview of the study design and previously announced results, as well as the rationale for conducting a pivotal study.

We also released favorable safety, tolerability, and efficacy results from the at-home pilot study in patients with NTM lung infections treated with high concentration iNO using the portable LungFit GO System.

Beyond Air is the first bio-pharma company to prioritize investment in the research and development necessary to harness the power of nitric oxide. From hospital to home, our goal is to deliver global access to iNO and empower clinicians with more treatment options across a range of therapeutic areas.