Challenges and hopes in treating interstitial lung disease in children

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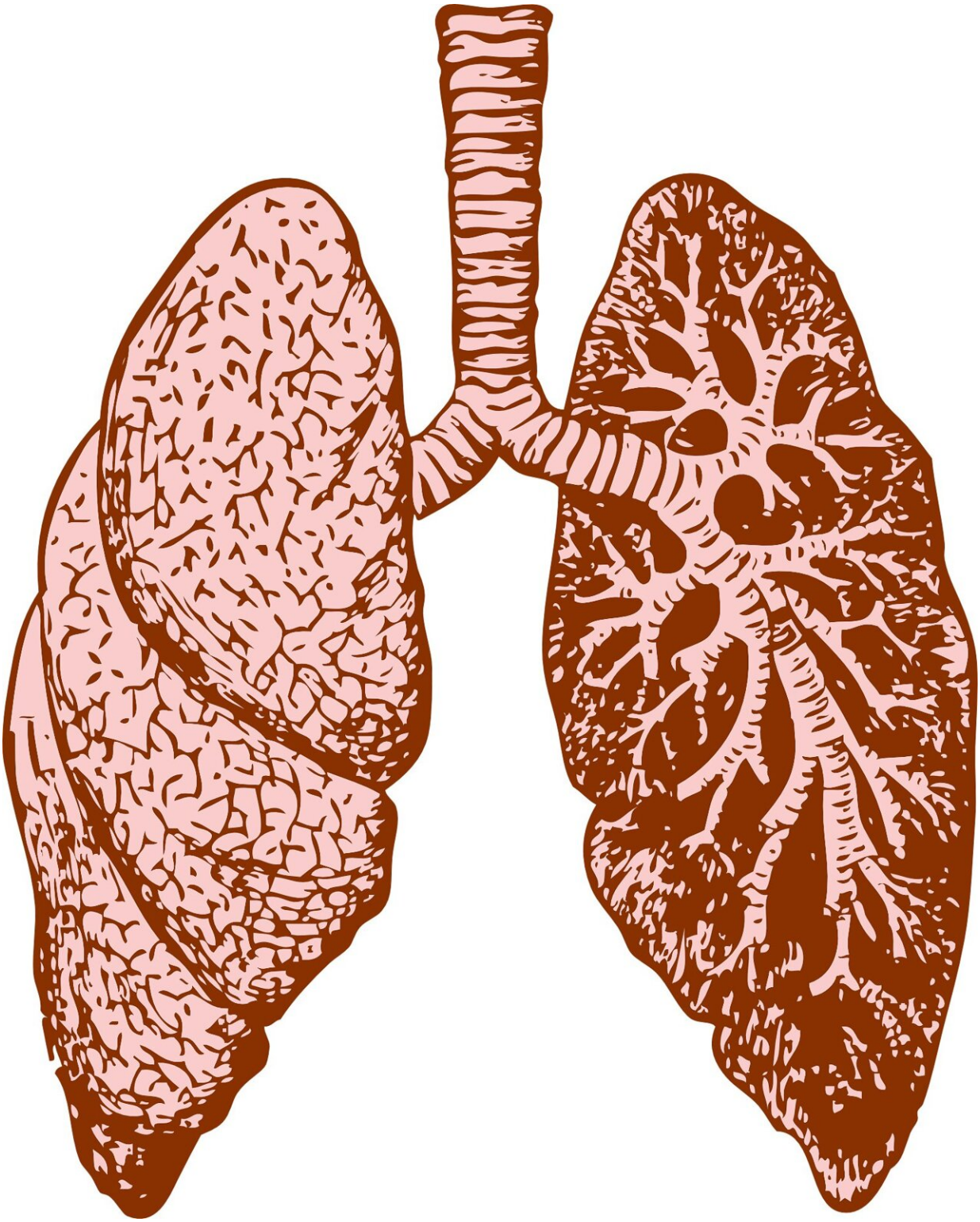

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Imagine a world where breathing is a luxury and a cough marks the sound of an inner battle. Interstitial lung disease (ILD), a condition characterized by inflammation and fibrosis, is a major cause of severe respiratory illness and can occur in children. While researchers have made progress in slowing the disease in adults, the situation for children remains grim: there are currently no effective treatments, and lung transplantation is their only hope for survival.

To enter the world of ILD is to enter a dark maze. Scientists are struggling to understand the natural history of the disease and its many forms, and the effectiveness of the treatments that have been discovered leaves much to be desired. ILD varies with age. Affected children often suffer from birth and can die within months if they do not receive a lung transplant. In adults, the progression of the disease is different, with symptoms starting subtly but worsening rapidly, typically resulting in death after just three to five years.

Not only when the disease strikes, but who is at risk of developing it varies widely, even within families, adding another twist to the search for a solution. Researchers know that genetic factors and mutations play an important role, but the rarity of these mutations makes it difficult to accumulate the kind of knowledge that could point the way to more effective strategies.

With so many layers of complexity to consider, scientists are forced to look for common factors that promise broader applicability. Prof. Killian Hurley, chair of Open-ILD at the Royal College of Physicians and Surgeons, sheds light on this complex issue.

The initiative Open-ILD (An Open Access Repository of Pluripotent Stem Cells from Children and Adults with Interstitial Lung Disease) took center stage following the completion of the COST Action ENTeR chILD (European Network for Translational Research in Children's and

Adult ILD). Working with organizations of patients and a network of clinicians and scientists, this project aimed to create a Europe-wide, open-access resource of patient-derived stem cells, intricately linked to patient data. The result was transformative, as Open-ILD helped to develop a robust preclinical model of ILD, leading to accelerated drug development pipelines and a reduction in toxic side effects.

Between transplants and drugs

For adults, there are currently only two drugs that slow the rate of decline in lung function, but they are unable to stop the disease from progressing, let alone offer a cure. And even this benefit is often accompanied by side effects, some of which, such as nausea or diarrhea, are very similar to the side effects of chemotherapy.

"Because of these severe side effects, many patients stop taking their medication," explains Prof. Hurley, "so we need better treatments for these patients."

For children, treatments include steroids and hydroxychloroquine, but there is much uncertainty about the best approach. While lung transplantation remains a viable option, it trades one set of challenges for another and offers an average life expectancy of only five years post-transplant.

According to Prof. Hurley, "Transplantation is a balance of benefits and risks. And so, it's a very personal, individual decision for each patient as to whether it's a good choice for them."

The financial burden is significant, with drug costs ranging from €20,000 to €30,000 per year per patient for adults, and intensive care and follow-up costs for children.

A standing ovation for resilience

The story of Open-ILD is intertwined with personal experience, where passion meets purpose. Prof. Hurley tells the powerful story of a patient with a rare form of genetic lung disease.

"This patient, not only a double lung transplant survivor but also a marathon runner, embodies resilience," he says. "He gave an amazing talk about his life, how his family was affected by the disease and how he overcame these challenges in his life. He went on to have a lung transplant and has run several marathons to raise money for research into better treatments. He is an inspirational person and at our meeting, there was a standing ovation for several minutes after he spoke. We continue to meet, and he has helped many other patients cope with their lung disease."

This patient's stem cells are now the focus of research to develop a targeted drug for him and his family. The standing ovation reflects the profound impact of these stories and inspires commitment to a collective effort.

ENTeR-chILD and Open-ILD: from vision to reality

The achievements of ENTeR-chILD and Open-ILD have gone beyond simply raising awareness, as important as that is, and have succeeded in driving research efforts worldwide. With over 300 participants, including doctors, scientists, and affected families, ENTeR-chILD has developed protocols for clinical trials and initiated two such trials in the last five years. A major achievement has been the creation of a web-based biobank, chILD-EU, for the secure storage of medical data, identification details, and biomaterials. It is freely accessible to all participants and prioritizes patient well-being by incorporating quality-of-

life questionnaires.

ENTeR-chILD evolved into Open-ILD. This follow-on project focused on genetic causes and building a model to unravel the complexities of genetic pulmonary fibrosis. This innovative testing platform, using patient-derived stem cells, accelerated drug discovery for interstitial lung disease. What's more, Open-ILD has fostered collaboration between scientists and physicians and helped to amplify the voices of patients.

Europe-wide collaboration in the design of better treatments

Prof. Hurley in 2022 seeks to identify new personalized treatments for patients with pulmonary fibrosis. His project will develop innovative stem cell models to test the effectiveness and understand the potential side effects of new treatments before administration to patients.

A new project led by Prof. Andreas Heise in the Royal College of Surgeons in Ireland aims to develop new testing platforms for interstitial lung disease and to design biocompatible materials that mimic the conditions inside a patient's body. Such materials would facilitate high-throughput screening (HTS), allowing researchers to test many drug candidates simultaneously.

Towards a future of hope: specific treatments on the horizon

In the dawning era of precision medicine, the focus is shifting to developing drugs tailored to individual patients or specific genetic mutations. Inspired by the success story of cystic fibrosis, where gene-targeted drugs have transformed outcomes, scientists are hoping for similar breakthroughs in interstitial lung disease.

As the journey continues, the vision is clear: within three to five years, says Prof. Hurley, the prospect of targeted treatments will usher in a new era of hope for patients with interstitial lung disease. Open-ILD remains at the forefront, not just as a research initiative, but as a testament to the power of collaboration, resilience, and the pursuit of transformative treatments.

Related research has been published in eBioMedicine and Stem Cell Research & Therapy.

More information: Killian Hurley et al, A roadmap to precision treatments for familial pulmonary fibrosis, *eBioMedicine* (2024). DOI: 10.1016/j.ebiom.2024.105135

Anja Schweikert et al, An evaluation of an open access iPSC training course: "How to model interstitial lung disease using patient-derived iPSCs", *Stem Cell Research & Therapy* (2023). DOI: 10.1186/s13287-023-03598-9

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