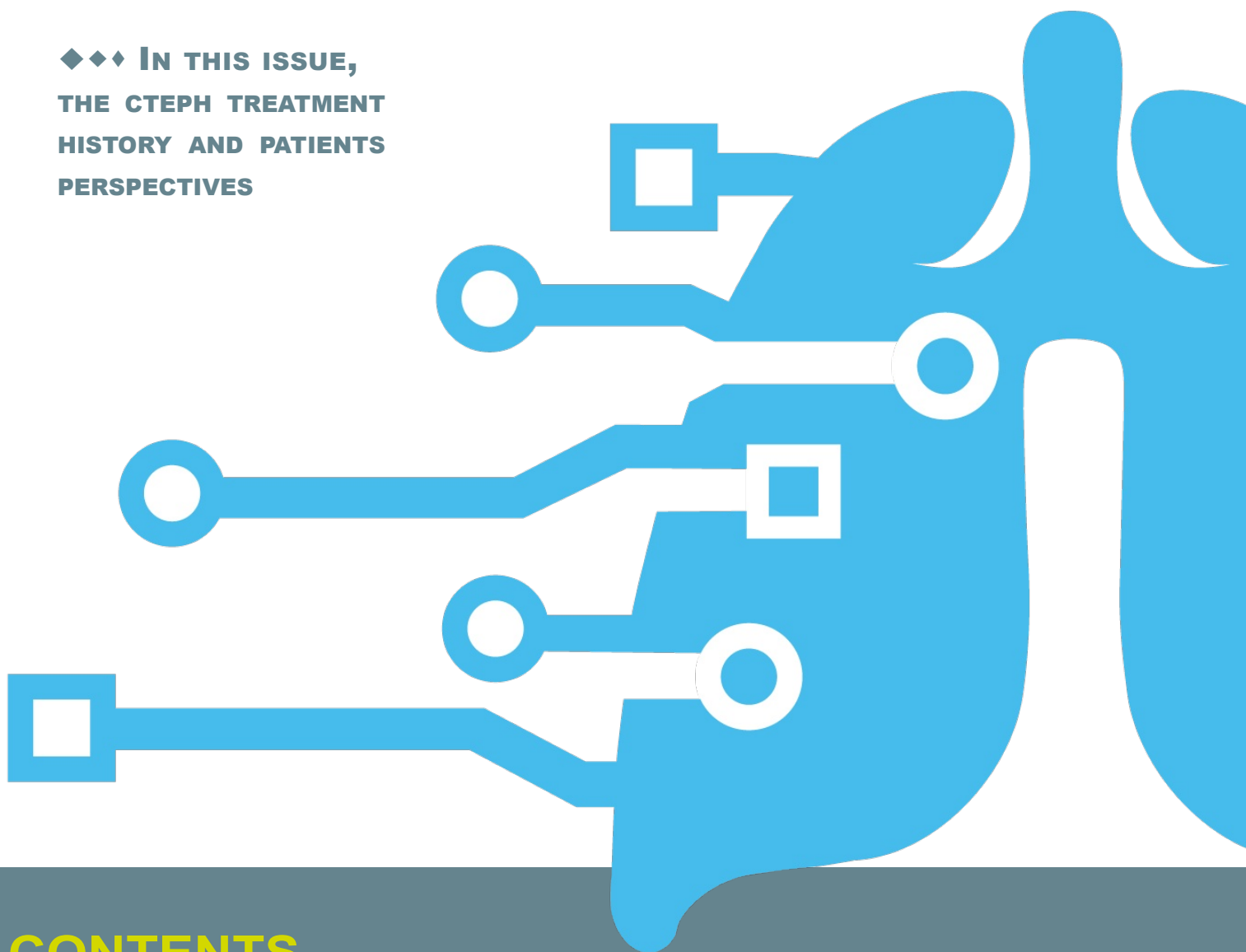


**DESTINATION 2024**

# **NEWSLETTER**

**2023 EDITION** 

◆◆◆ **IN THIS ISSUE,**  
**THE CTEPH TREATMENT**  
**HISTORY AND PATIENTS**  
**PERSPECTIVES**



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## A Brief History on Progress in CTEPH Treatment

*Nick Kim*

*Chief, Pulmonary Vascular Medicine  
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Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious but treatable cause of shortness of breath and right sided heart failure. CTEPH is believed to be a complication of pulmonary embolism – affecting roughly 2-3% of all patients following acute pulmonary embolism. Not all that long ago, CTEPH was a diagnosis unfortunately made at autopsy. Even now, patients frequently face considerable delays before diagnosis, often going beyond two years of symptoms before detection. Part of the challenge in early diagnosis stems from the fact that the symptoms are nonspecific, and up to 30% of patients never having prior history of venous thromboembolism. But thanks to the expansion of the field of pulmonary hypertension (PH) over the past two+ decades, there have been improved awareness and major advances also in the management of CTEPH.

Over a decade before the first reports of promising treatments for pulmonary arterial hypertension, Professor Kenneth Moser and his team reported successful outcomes in treating CTEPH with pulmonary thromboendarterectomy (now also referred in the literature as pulmonary endarterectomy or PEA) surgery. Unlike pulmonary embolectomy or thrombectomy, PEA surgery demands meticulous dissection of the pulmonary arterial wall as distally as possible and without vessel perforation, removing all accessible chronic scar tissue (remnants of chronic clot) blocking the pulmonary arterial circulation. The surgery also requires periods of complete circulatory arrest in order to optimize disease clearance, utilizing deep hypothermia while on cardiac bypass. In the early years, only

a few centers in the world had the capability of successfully performing this unique surgery. Much of the initial pioneering work was done at the University of California, San Diego (USA). Other prominent centers soon followed, including Duke (USA), Paris (France), Bad Nauheim (Germany), Cambridge (UK), and Vienna (Austria). But with only just select centers with such expertise, countless patients around the world with CTEPH faced a grim reality without access to this potentially life-saving surgery. Even now, the complexity and technical difficulty associated with PEA surgery have limited the availability of surgical centers. Furthermore, even for established surgical centers, nearly 40% of CTEPH patients were deemed ineligible for PEA surgery – and nearly half of all PEA cases undergoing surgery were found at risk with residual pulmonary hypertension during follow-up. Hence there was a major unmet need for finding alternative and complimentary treatment options in CTEPH.

The first report of percutaneous balloon pulmonary angioplasty (BPA) for the treatment of CTEPH was from the Netherlands in 1988. In this single case report, a 30-year-old man had CTEPH with mean pulmonary arterial pressure of 46 mmHg. After two sessions, his mean pressure dropped to 35 mmHg with improved perfusion scan in the area of treatment coinciding with improvement in symptoms. Despite this promising single case report, it wasn't until 2001 that a major case series of BPA was published out of Boston (USA). In this often-cited paper, 18 CTEPH patients deemed inoperable underwent series of BPA treatments. Although few cases benefited, the complication rates were alarming with one death (5.5%) and nearly 60% incidence of acute lung injury from the procedure, three requiring mechanical ventilation support. Perhaps undeterred from the complications reported in that seminal work, in 2012, three separate centers in Japan published their case-series of successful BPA employing refined strategies including pre-treatment with PH therapy and under-sizing the balloons depending on the severity of PH. These reports quickly triggered a global interest in BPA for the

treatment of inoperable CTEPH. Then one year later, in 2013, the first effective PH targeted therapy (soluble guanylate cyclase stimulator, riociguat) for the treatment of inoperable CTEPH received regulatory approval based on the positive randomized controlled CHEST-1 study. Therefore, within a span of one year, CTEPH went from being solely a surgical disease to one with multiple effective treatment options.

Currently, expert CTEPH centers utilize all three treatments in the management of CTEPH – often combining modalities to optimize safety and outcome. Drawing some parallels to cancer care, patients with CTEPH at expert centers now undergo multidisciplinary and comprehensive evaluations with both diagnostic and treatment input from all necessary stakeholders: chest radiologists, surgeons, BPA interventionalists, and PH specialists. Furthermore, a key concept now for managing CTEPH is the practice of systematic follow-up even after initial surgery or intervention. This is in recognition of the complimentary role across the three treatment options and the limitations of any single therapy.

## **Integrated Approach in CTEPH Patients: Pulmonary Endarterectomy & Balloon Pulmonary Angioplasty**

*Justin Issard and Elie Fadel  
Thoracic Surgeons  
(Marie-Lannelongue Hospital)*

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) treatment relies on the level of obstruction of the PA [pulmonary artery] and the patient's medical history. Pulmonary angiography CT [computed tomography] is broadly used to assess the level of PA

Lastly, there remain many unanswered questions in CTEPH in need of investigation. For example, are multiple PH targeted therapies superior to single medical therapy in inoperable CTEPH? What is the optimal choice and treatment sequence in cases borderline for either PEA or BPA? What defines successful treatment for each of the three modalities? What defines an expert CTEPH center? These and many other questions are being addressed currently by experts and through collaborative efforts.

In summary, the field of CTEPH has witnessed major advances in recent years – and promises to evolve even more to the benefit of our patients. Regardless of operable or inoperable status, our patients can be managed with improved prognosis across the board. In order to achieve optimal outcomes for any individual CTEPH case, providers are encouraged to consult and work with an expert CTEPH center capable of applying multidisciplinary approach and offering all treatment modalities.

obstruction. The CTEPH treatment algorithm includes a multimodal approach of combinaisons of pulmonary endarterectomy, balloon pulmonary angioplasty and medical therapies to target the mixed anatomical lesions: respectively proximal for PEA, distal for BPA and microvasculopathy for the medical therapies. All these treatments are available in our center and their indications are debated in the French national CTEPH staff once a week with the presence of a PEA expert surgeon, a BPA expert radiologist, PA imaging radiologist and CTEPH medical specialists. An integrated approach adapted to the anatomy of the lesions and the medical history of each patients are proposed. It can be PEA, BPA, medical therapy or a multimodal approach. CTEPH patient's follow-up can be carried out either in their regional center

or in the national referral center (Department of pneumology, Bicêtre Hospital AP-HP). In each case, if a complementary treatment is recommended, the case is presented at the national CTEPH Staff.

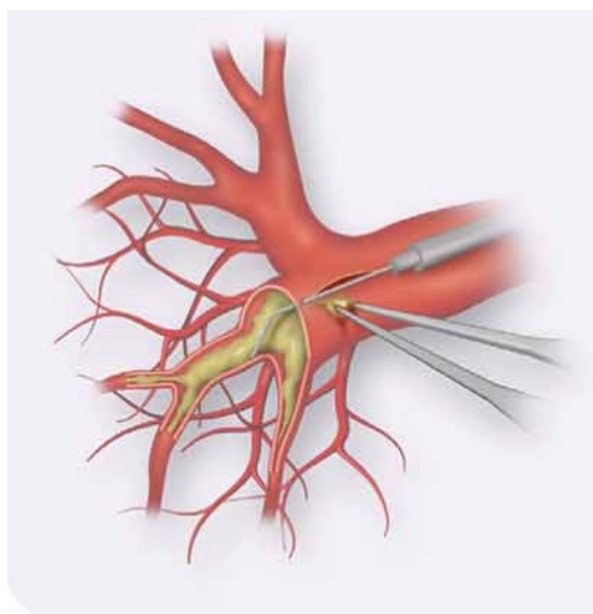
### **PULMONARY ENDARTERECTOMY (PEA)**

Pulmonary endarterectomy (PEA) is the surgical treatment of CTEPH. It is proposed to patients presenting surgically accessible PA lesions. The operability of the lesions is assessed by one of our three expert PEA surgeons during the national CTEPH staff. This surgical procedure is complex but well standardized since it has been performed since 1996 in our institution. Every year more than 100 patients underwent PEA in our hospital. It consists of a complete bilateral endarterectomy of the PA down to subsegmental levels (Fig 1.), which requires cardio-pulmonary bypass, aortic clamping and deep-hypothermia circulatory arrest. Despite these heavy means, surgical outcomes are favorable and we report a peri-operatively mortality rate <2,5%. Long term outcomes are also excellent, in term of survival (90% survival rate at 3 years) and quality of life. On the other hand, patients with proximal operable disease declining surgery have poorer

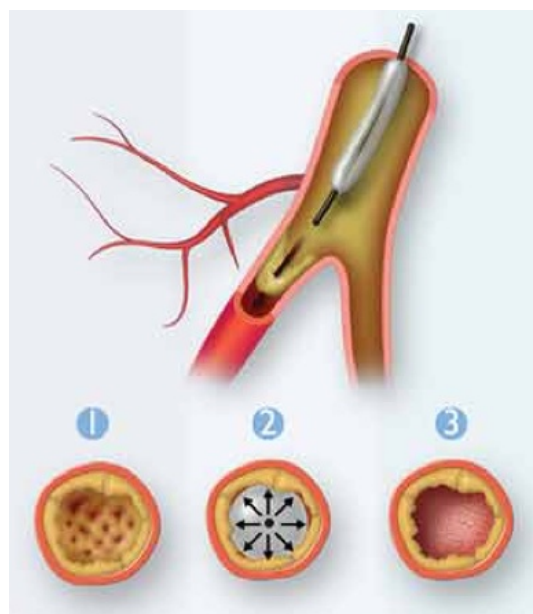
long-term outcome, with a 5-year survival of 53% compared with 83% in patients undergoing PEA. Therefore, PEA is offered to all operable patients with a favorable risk in our center. Emergency PEA and CTEPH patient with bad hemodynamics ( $PVR > 1000 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$  and/or cardiac index  $< 2 \text{ L/min/m}^2$ ) presents higher rate of peri-operative mortality. In our center, we used medical therapy in those patients in order to improved pulmonary hemodynamics before surgery, and lower peri-operative mortality rate. Yet commonly used in other center, this practice is controversial because it delays definitive treatment.

### **BALLOON PULMONARY ANGIOPLASTY (BPA)**

Since the last decade, BPA has become an established treatment for patients with inoperable CTEPH. Even if we lack a randomized prospective study, long-term outcomes are promising. Balloon pulmonary angioplasty improved PVR, right heart function and exercise capacity. It consists at of a dilatation of the PA lesions by endovascular access. A wire is place in the PA via the femoral vein, PA lesion are treated by dilatation of an endo-luminal balloon (Fig.2). Though BPA are effective, it can be associated with serious



*Figure 1: Pulmonary Endarterectomy  
(from Humbert et al, ERS, 2023.)*



*Figure 2: Balloon Pulmonary Angioplasty  
(from Humbert et al, ERS, 2023.)*



complications, which can be fatal. Per and post procedural complication such as wire perforation or lung injury may occur. To lower the rate of these complications and their consequences, a staged interventional procedure with a limited number of dilated PA segment in each session is preferred. As with all invasive procedure, a significant learning curve has been shown. In our hospital we started our BPA program in 2014, more than 800 patients later, our morbidity rate decreased significantly. In our center BPA is proposed to every patient presenting PA lesions non-accessible to PEA and patients with PA lesions accessible to PEA but with comorbidities contra-indicating PEA. As for surgery, the rates of interventional complications can be reduced by medical pre-treatment. If PVR are high, we proposed medical therapy before PEA.

### **MULTIMODAL APPROACH**

In some selected patients, multimodal therapy including surgery, BPA and/or medical therapy can be offered. In patients with high preoperative PVR, using medical therapy to improve pulmonary hemodynamics before surgery can lead to better outcomes. Some patients with CTEPH can present different

anatomical lesion on both sides. These patients can benefit from a combined therapy with BPA on one side and PEA on the other. This approach probably allows better outcomes because, BPA prior to surgery improve mPAP and PVR and one side PEA lower surgical time (less cardiopulmonary bypass time, less aorta clamping time and less circulatory arrest time). A significant proportion of patients present residual PH after PEA. Yet, not all patients are symptomatic. In order to correct, persistent or recurrent PH after PEA, additional session of BPA can be performed. It is a more challenging procedure because of the endarterectomy. This multimodal approach allows for a more personalized treatment to improve hemodynamics result and quality of life.

The multidisciplinary team involved and the heterogeneity of treatment available for CTEPH in our center offer each CTEPH patients the most accurate treatment according to the anatomy of their lesions and their medical history. The emergence of integrated multimodal procedure including medical therapy, BPA and PEA seems promising in the era of personalized treatment.

## **Navigating the Journey of Chronic Thromboembolic Pulmonary Hypertension: Insights, Challenges, and Aspirations**

*Pisana Ferrari*

*President of the Italian Pulmonary Hypertension Association (AIPI)*

The diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) profoundly impacts individuals facing this condition, extending well beyond the physical limitations it imposes. It introduces a range of challenges

that permeate various aspects of their lives. Many of these challenges are shared with other forms of pulmonary hypertension (PH). The imperative of ensuring access to support, information, and potentially life-saving treatments and interventions for all PH patients underscores the need for heightened awareness, advocacy, and expanded resources.

### **JOURNEY FROM SYMPTOMS TO DIAGNOSIS**

The rarity and non-specific symptoms of CTEPH may lead to misdiagnosis and/or diagnostic delays. Babacar, a Senegalese national living in Italy, endured a four-year journey to obtain a correct diagnosis. Alma\*, a 62-year-old Spanish woman, describes her

two-and-a-half-year journey from symptoms to diagnosis as "long and tortuous." Derek, a 57-year-old man from Canada, was initially misdiagnosed with pneumonia, and it took two years to have a correct diagnosis. Gabriele, a young semi-professional basketball player from Italy, was initially diagnosed with pulmonary arterial hypertension, and it took almost a year for his diagnosis. In the case of Rosa\*, a young woman from Spain, the diagnosis came swiftly, and within three months she was listed for pulmonary endarterectomy (PEA). The fact that many patients are unaware of the existence of this condition is an additional problem because they may not associate their symptoms with a potentially life-threatening disease. Maureen, a 48-year-old Canadian woman, initially attributed her breathing difficulties and racing heart to aging and being overweight. Rishabh, a 20-year-old student from Singapore, delayed seeking medical advice until a syncope incident.

## THE DIAGNOSIS

The diagnosis of CTEPH can be overwhelming, eliciting emotional responses such as shock, disbelief, and fear. Rosa says that it was a very traumatic moment for her, and that when she looked up CTEPH on the Internet and saw the expected life expectancy, she wanted to die. Gabriele, who had never experienced any health issues before, was in total disbelief and struggled to find information to help make sense of what was happening to him. Liliya, a 52-year-old woman from Kiev, wrestled with accepting her diagnosis for a long time and felt isolated, being the only patient in her part of Ukraine. Dario, a young man from Mexico diagnosed at the age of 20, initially only had mild symptoms so he chose to ignore the potential life-shortening effect of his diagnosis and go on living as normally as possible. His approach serves as a reminder that coping strategies can vary greatly among individuals. Derek says the hardest part for him was getting people to understand what CTEPH was. One employer told him that he did not look sick, and even he struggled to

fully grasp the severity of his condition. Alma had a similar experience, as people frequently commented on how well she looked. It is crucial to recognize that a diagnosis of CTEPH not only affects patients but can also have a significant emotional impact on families and caregivers. Rishabh's mother describes the moment of diagnosis as if a bolt of thunder had struck her.

## IMPACT ON DAILY LIFE

CTEPH imposes physical limitations that make daily tasks arduous and may require major lifestyle adjustments. Alma was exhausted with the slightest effort: "I wanted to do things, but my body would not let me." Rosa laments the devastating changes she experienced at the age of only 24 but found solace and support through the Spanish PH patient association HPE. Rishabh's condition deteriorated rapidly, impeding his ability to carry out everyday tasks and to pursue his academic endeavors. Recognizing the need for support, he turned to psychological counseling and therapy. Liliya says she has withdrawn from the outside world, secluding herself and cutting off communication. She shares, "Only my family is close to me now". Aykut, a 62-year-old patient from Turkey, is battling inoperable CTEPH. He shares his struggles with decreased mobility and the profound frustration of being unable to engage in activities he desires. Seeing friends succumb to the same disease adds to his distress, evoking concern for his children and family. "I am negatively affected both psychologically and physically", he says. Lifestyle adjustments may also be necessary for family members and caregivers. Derek's wife had to take time off work to help him as, at the time of diagnosis, he could barely walk a few meters.

## FINANCIAL IMPACT

The physical limitations of CTEPH may disrupt work and career paths, resulting in financial implications. Gabriele, fortunate to have a sedentary office job, managed to continue working, but the financial burden of some of

his treatments and the rehabilitation after his (successful) PEA was still significant. Babacar had to stop working, moved in with a cousin, and managed as best he could with support from friends and the Italian PH patient association AIPI. Liliya says that the severity of her breathlessness and fatigue forced her to resign from work. Derek also ended up losing his job. He had expenses going to and from the hospital, and, while the costs of his successful PEA surgery ten years ago were covered by the NHS, the drugs for his blood clots were hugely expensive, and the amount the insurance covered was capped. The government has a plan to help cover, he says, but it's not easy to get it.

### **THE CHALLENGES RELATED TO BPA AND PEA INTERVENTIONS**

Balloon pulmonary angioplasty (BPA) and PEA are vital procedures that can save lives but do not come without risks and consequences. Gabriela\*, a 65-year-old woman from Spain, is relatively stable on medication and, despite experiencing considerable side effects, dreads the thought of having to undergo surgery. Even after BPA or PEA, lifelong blood tests are necessary to monitor anticoagulant therapy, and patients with residual PH may require additional treatment. This is the case for Rosa, who underwent PEA surgery in 2015 but has residual PH and is being treated with riociguat. Maureen, who had PEA surgery five years ago, still has symptoms and is on medication for PH, as well as on oxygen. She has many plans and aspirations for the future and fervently hopes that her condition will not impede their realization. Gabriele, coming from a sports background, emphasizes the need for better support post-PEA to maximize recovery in terms of functional capacity and overall well-being. He says he had to rely on his own resources and knowledge, and that it was challenging.

### **ENSURING EQUAL ACCESS TO LIFE-SAVING OPPORTUNITIES**

It is disheartening that still today significant disparities exist in access to CTEPH treatments and to critical interventions such as BPA and

PEA. Katrina\*, a 58-year-old woman from the Ukraine, calls for treatments available in European hospitals to be made available in her country too. Faced with limited access, she chose to seek treatment abroad. Aykut has CTEPH with an underlying heart condition. The recommended course of treatment, a heart-lung transplant, is unavailable in Turkey. Babacar had no treatment options in his own country but was fortunate to undergo life-saving PEA surgery in Italy, 20 years ago, fully covered by the NHS, and reclaim an active life. Rishabh and his family decided to seek treatment in Japan, at the center led by world-renowned BPA expert Prof. Hiromi Matsubara. Following a few rounds of BPA, Rishabh is now back to a full and active life. Dario spent seven years believing that a cure was out of reach in Mexico due to his blood clots being distal. However, his fortunes changed last April when he underwent a successful PEA at UCSD, San Diego. Sadly, the financial constraints associated with seeking treatment abroad make this option inaccessible to many individuals.

These patient stories emphasize the importance of holistic care, addressing the physical and emotional aspects of CTEPH. Understanding, empathy, access to support and information are crucial in helping patients and their families navigate the multiple challenges they face. Addressing disparities in CTEPH care is vital in ensuring that all individuals with CTEPH have a fair chance at a better quality of life. Patient associations and networks can play a pivotal role in facilitating these processes.

(\*) Names modified.

*Many thanks to all the contributors to this article for their willingness to share their experiences and valuable insights.*

## WP2 Progress; the RHU DESTINATION 2024 Bliss

Marc Humbert,  
Scientific coordinator (AP-HP, UPSaclay)  
Stécy Jombert, Project manager (AP-HP)

*"Wanna go platinum? [Ludacris is] who you should get, get, get, get, get"*<sup>1</sup>

Wanna exceed targets? Christophe Guignabert is who you should get, get, get, get, get.

That sounds whimsical, but remarkably, Dr Guignabert's team has outperformed each of their specific indicator objectives ahead of schedule in RHU DESTINATION 2024.

Central to the WP2, his laboratory, Pulmonary Hypertension Pathophysiology & Novel Therapies (Inserm unit 999), studies endothelial cell dysfunction in various forms of human and experimental pulmonary hypertension, including CTEPH, with the ambition to better understand the key role of pulmonary endothelial cells in health and disease, and to identify novel therapeutic targets which could lead to decisive innovations for a better management of patients presenting with severe pulmonary vascular diseases. Dr Guignabert, who joined the laboratory in 2009 after a post-doctoral fellowship at Stanford University and a Ph.D. at University Paris-Est Créteil, focuses on the molecular and cellular mechanisms behind the process of vascular remodeling in pulmonary hypertension and on better understanding the role played by endothelial cells in pulmonary vascular remodeling. Serial author, he is credited with more than 100 original research papers, 50 review articles and 15 book chapters. Amongst those, *Tu, L. et al. Selective BMP-9 inhibition*

*partially protects against experimental pulmonary hypertension*, Circ. Res. 124, 846–855 (2019) and *Guignabert et al. Associations between serum activin a and FSTL3 levels and outcomes in pulmonary arterial hypertension*, Circulation 2023 (in press) are breakthroughs in the progress made for the understanding of the mechanisms involved in the remodeling of small pulmonary arteries which play a role in various causes of pulmonary vascular diseases such as CTEPH.

*"Christophe has reached an outstanding level of expertise in the understanding of endothelial cell dysfunction and pulmonary vascular remodeling in pulmonary hypertension. His active contribution as work package leader in the RHU DESTINATION 2024 project is a unique opportunity for the entire consortium. I have no doubt that his team will generate unique information supporting the project's key objectives to cure CTEPH"* Marc HUMBERT.

The work carried out by the WP2 team is of paramount importance in the project given that it will determine whether alterations are present in experimental and human CTEPH, by analyzing the endothelin-1 (ET-1), nitric oxide (NO), and prostacyclin (PGI<sub>2</sub>)-dependent pathways, and describe endothelial alterations resulting in imbalanced production of relaxing and contracting factors. This provides preclinical experimental information and serves as proof-of-concept that a restoration of the endothelium-dependent vasodilation should be an attractive treatment approach in CTEPH.

*"We are what we repeatedly do. Excellence, then, is not an act, but a habit."*  
Aristotle

1. Ciara and Ludacris. "Oh." Goodies, LaFace Records, 2004.



## Fostering the Potential of Teamwork to Uncover the Enigma of CTEPH in Science and Patient Care

*Raphaël Thuillet, Engineer (UPSaclay)*

*Mina Ottaviani, Bioengineer (Inserm)*

*Ly Tu, Research Associate (UPSaclay)*

*Christophe Guignabert, WP2 leader (Inserm)*

Biomedical research relies on collaborative efforts among diverse professionals to develop innovative solutions that can improve health outcomes for patients. Translational research is a crucial aspect of this process, as it involves translating scientific findings into clinical applications. One excellent example of such collaboration is the UMR\_S 999 "Pulmonary Hypertension: Physiopathology and Novel therapies" team, which comprises researchers from the Université of Paris-Saclay and the French National Institute of Health and Medical Research (INSERM) working to improve patient care.

Within **UMR\_S 999, Team 1 "Endothelial Dysfunction and Therapeutic Innovation"** focuses on studying the molecular and cellular mechanisms underlying vascular remodeling in Pulmonary Hypertension (PH), with a particular emphasis on the role of the pulmonary endothelium and its dysfunctions in this process. This team comprises various experts, including engineers, clinicians, students, researchers, and educators, who bring their unique perspectives and expertise to the group's collaborative efforts.

**The primary objective of Team 1 is to identify new targets for therapy that could help treat pulmonary hypertension and improve patient outcomes.** By collaborating and sharing their unique perspectives and

expertise, the team hopes to make significant advances in understanding disease mechanisms and developing effective treatments for patients with PH. Specifically, the team focuses on the pulmonary endothelial cell (EC), which is a crucial type of cell that regulates blood flow in the lungs. These cells can release substances like nitric oxide and prostacyclin in response to physical cues, which helps to relax blood vessels and prevent blood clots. However, they can also release endothelin-1, which causes blood vessels to constrict.

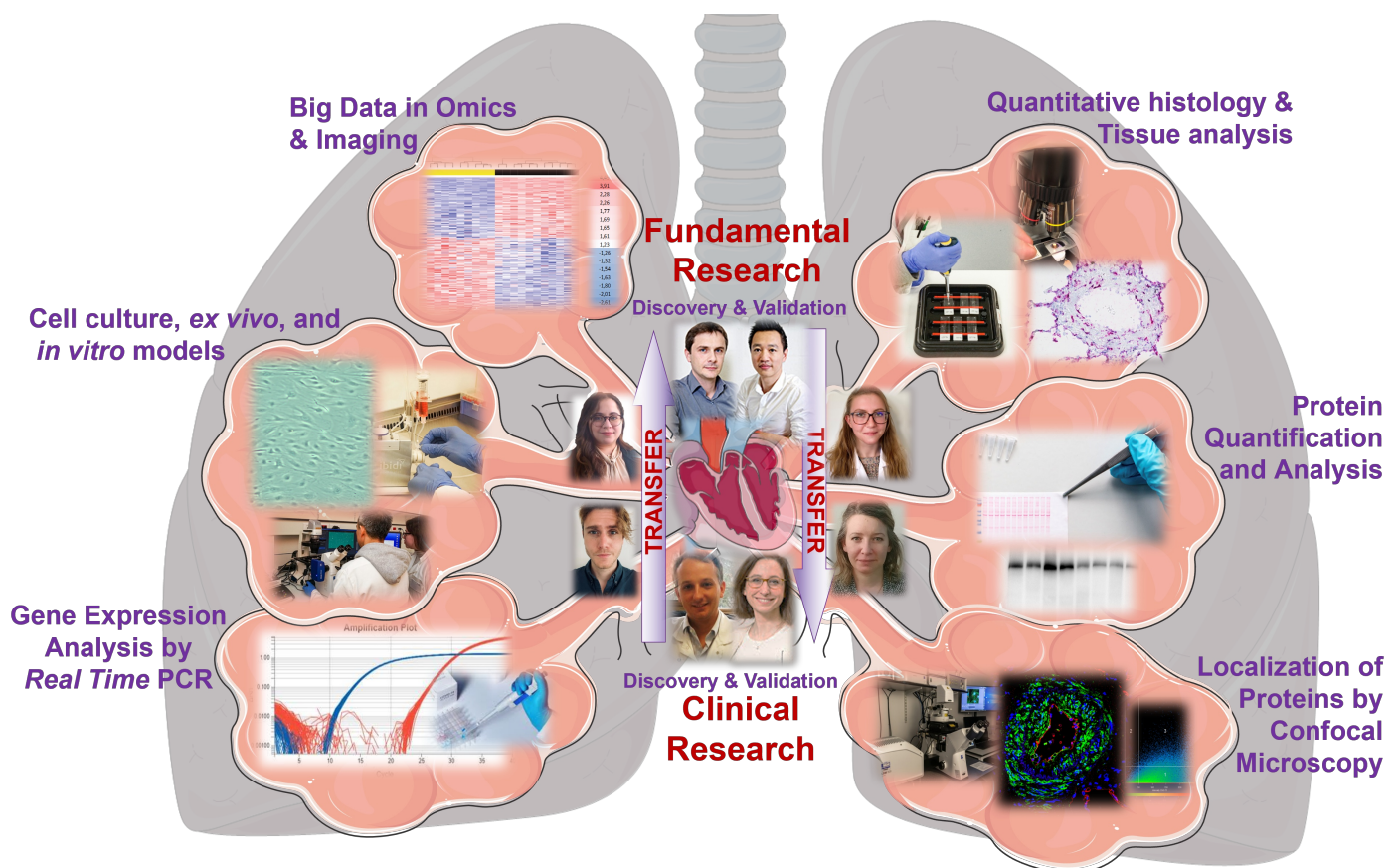
Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are two types of lung diseases that affect the blood vessels in the lungs, leading to an increase in resistance in the pulmonary arteries. CTEPH is a type of the disease where blockages caused by blood clots persist in the pulmonary arteries, while PAH can be caused by various conditions that affect the pulmonary blood vessels.

Currently, the treatment options for PAH mainly involve regulating the signaling pathways responsible for the contraction and relaxation of blood vessels. However, the same approach could also be applied to managing CTEPH in combination with existing treatments, such as drug therapies, balloon pulmonary angioplasty, and pulmonary endarterectomy. **As part of the RHU DESTINATION 2024 project, Team 1 aims to identify any potential defects in the molecular mechanisms responsible for vascular remodeling and contraction.** This includes the prostacyclin and nitric oxide systems, which are involved in regulating blood vessel dilation, as well as the endothelin system, which regulates blood vessel constriction. By pinpointing any abnormalities in these systems, the team hopes to gain a better understanding of the

underlying mechanisms contributing to CTEPH and potentially identify new targets for improving its management.

Team 1 is investigating why patients with CTEPH disease have blood vessels in their lungs that do not work properly. The team members are studying samples of lung tissues from patients to understand how certain genes and proteins affect blood flow.

This could help them develop new treatments for CTEPH. They are also using a pig model of CTEPH and human pulmonary endothelial cells to better understand the disease. The team has developed innovative techniques to simulate at a cellular level the stresses that occur when pulmonary arteries become blocked. Their goal is to find better treatments for patients with CTEPH.



***Team 1's success in investigating CTEPH lies not only in their individual expertise but also in their ability to work together and combine their knowledge. The team's collective experience in analyzing both human and animal lung tissues using specialized techniques, such as immunostaining, confocal microscopy, morphometry, and quantification, along with their extensive knowledge of endothelial cell analysis and culturing, allows them to gain a comprehensive understanding of the molecular and cellular processes involved in CTEPH. By working together and combining their expertise, Team 1 is well-positioned to identify new therapeutic targets and contribute to the management of CTEPH.***

## Principles of Cost-Effectiveness Studies and their Use in Pulmonary Hypertension

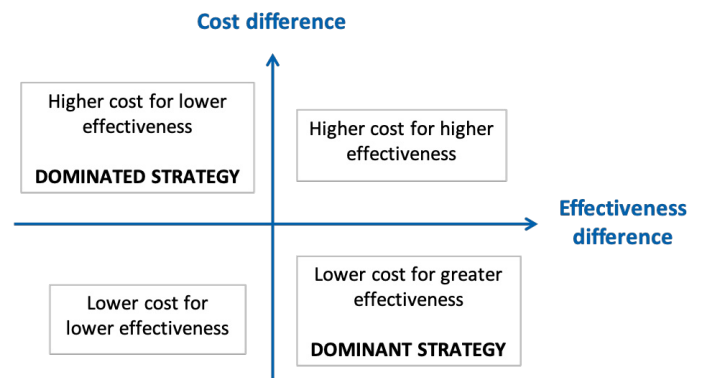
*Pr Isabelle Durand-Zaleski  
URCEco Director, WP3.2 leader (AP-HP)*

In developed countries, treatment decisions for patients were traditionally based on patients' needs and seldom on economic information. The high cost of new drugs, however, has led many health authorities to systematically include the economic aspects in their technology assessments.

Economic evaluations are necessary to ensure that resources are allocated where they produce the greatest health benefit. There are common misconceptions about economic evaluations. Firstly, their objective is not to reduce healthcare spending. Secondly, they are not a cost study or a business model. The usual term is 'health economic studies' or 'cost effectiveness studies', which indicates that there is always a health component in the result.

The general purpose of an economic evaluation is to relate the costs of a diagnostic or therapeutic strategy to its outcomes. Thus, the two components of the evaluation are a measure of effectiveness and an estimate of costs. Health economic studies are comparative, answering a question about change in the production of health for the population. The comparison of medical strategies (two or more) that use different resources and yield different outcomes requires a specific approach to ensure that the two dimensions, health outcomes and costs are combined and that a comparison across medical specialities is possible. The solution proposed by economists is to compare the costs and health outcomes of each alternative strategy using an

incremental cost-effectiveness ratio, the ICER. This ratio, calculated as the incremental change in costs divided by the incremental change in health outcomes, represents the cost for one additional unit of health outcome. The costs of each are expressed in monetary terms, while health outcomes are expressed 1) in a single medical unit, for example lives saved, or progression free survival and 2) quality-adjusted life-year (QALY) which is the single measure of health that allows comparisons across medical specialties. The lower the cost-effectiveness ratio, the more efficient the strategy (1-4).



*Figure 1: The cost effectiveness plane, adapted from Cost-Effectiveness Plane [online]. (2016).*

*York; York Health Economics Consortium; 2016.*

<https://yhec.co.uk/glossary/cost-effectiveness-plane/>

The endpoint for an economic evaluation is typically a ratio, the mean difference in costs divided by the mean difference in health (QALYs). It can be presented on a plane (figure1) the point estimate of the result has for coordinates the difference in costs (vertical axis) and the difference in QALYs (horizontal axis). The incremental cost effectiveness ratio can be represented visually as the slope of the line connecting this point to the origin.

In order to test the robustness of the results, deterministic sensitivity analyses vary each parameter with a predetermined range (e.g. 95% confidence interval when there is a distribution, negotiable price range for drugs or devices) and



recalculate the ICER. Results are presented on a ‘tornado’ diagram (named after its shape) (Figure 2). It is now common for economic evaluations of treatments to use the more sophisticated representation of uncertainty, which is based on bootstrap replications and show 1,000 results obtained by tacking one random cost outcome dividing it by one random effectiveness outcome. The set of these estimated ICERs is presented as a scatterplot of 1,000 points on a cost-effectiveness plane (Figures 3,4).

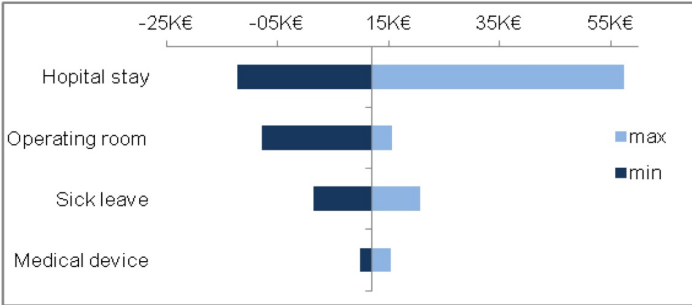
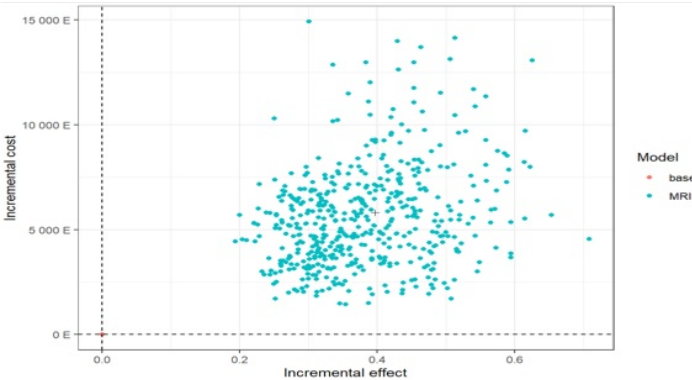


Figure 2: An example of a tornado diagram showing the results of a deterministic sensitivity analysis; the vertical line represents the point estimate of the incremental cost effectiveness ratio (mean difference in costs / mean difference in effectiveness).

Some countries have set an explicit threshold, others not. The World Health Organization (WHO) suggested that this threshold be based on the per capita national gross domestic product (GDP). An innovative strategy is considered cost-effective with a threshold of 3 times the GDP per capita, and very cost-effective with a threshold of one



Based upon 1,000 replications

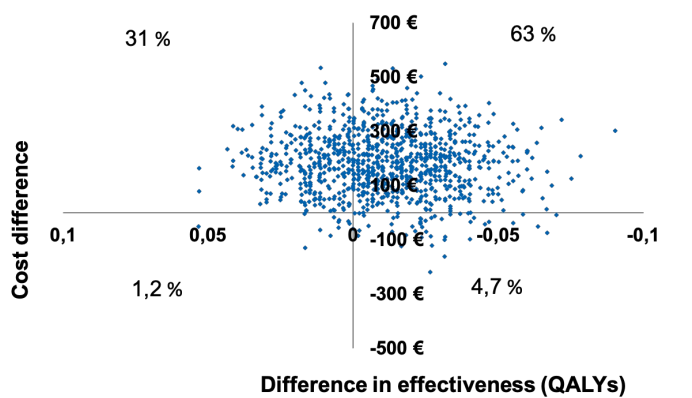
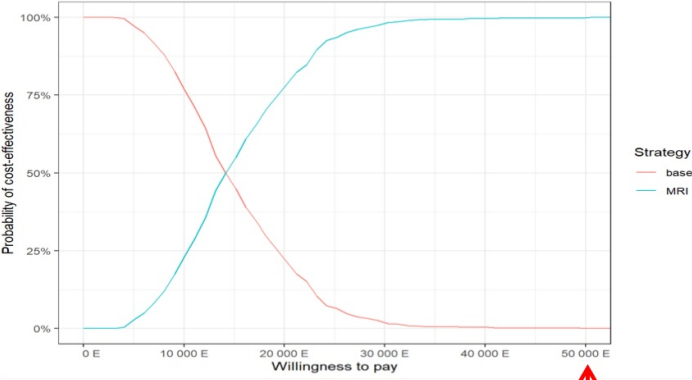


Figure 3: An example of a probabilistic sensitivity analysis; the percentages in each quadrant represents the % of the total replications.

time the GDP per capita. In France, the health authorities have not specified the WTP threshold and the decision to adopt an innovative strategy is taken on a case-by-case basis (5). These thresholds are usually fixed in cost per QALY.

Examples of cost effectiveness analyses for the management of pulmonary hypertension can be found in the medical literature and in the reports of the French national health authority (HAS), although this disease is far less subjected to economic evaluations than other lung disorders. Economic evaluations in pulmonary hypertension concern diagnosis, drug and non-drug interventions. The economic evaluation of Riociguat (Haute Autorité de santé (has-sante.fr)) compared three therapeutic options, 1) placebo, 2) bosentan and 3) riociguat. The incremental cost



At a willingness to pay (WTP) of €50,000/LY, MRI screening has a 100% probability of being cost effective

Figure 4: A probabilistic sensitivity analysis in the form of a scatterplot and the corresponding acceptability curve. This analysis compared the reference diagnostic workup to the use of magnetic resonance imaging (MRI). All replications are in the top right quadrant indicating that the use of MRI is always more effective and more effective than the standard workup.



effectiveness ratio of riociguat vs placebo was 239,145 €/QALY and 199,622 €/life year gained, and the incremental cost effectiveness ratio of riociguat vs bosentan was 108,876 €/QALY and 67,783 €/life year gained. These results were challenged in part because of the uncertainty on

the modelled gains in mortality and should therefore be taken cautiously, as an illustrative example. The relative scarcity of economic evaluations in hypertension reinforces the relevance of the IMPACT-CTEPH trial and of the cost effectiveness analysis attached to it.

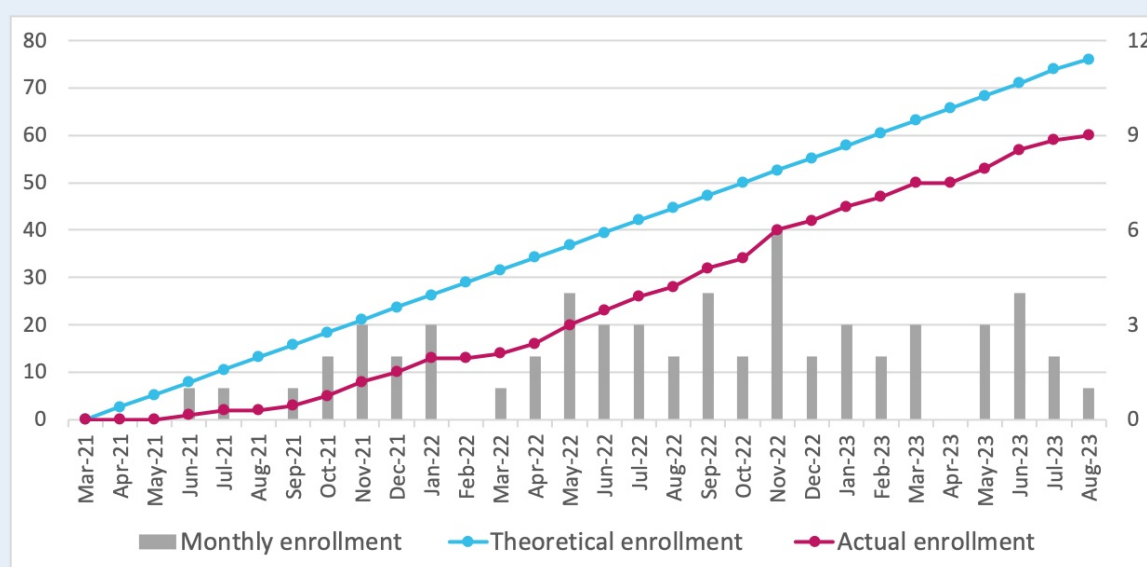
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## IMPACT-CTEPH STUDY PATIENT ENROLLMENT PROGRESS UPDATE



Data on August 11<sup>th</sup>, 2023

**Let's continue our efforts to reach  
96 enrollments.**

## A Magnificent Announcement

*Savvy Jocundity,  
Chief Steward of Methodical Jumble*

With great joy and fervor, we doth declare that the first RHU DESTINATION 2024 press release is shining as a bright beacon of the bountiful harvest that hath been brought forth

from our joint efforts and unwavering commitment to the task at hand. It doth serve as a true testament to the unflinching determination and steadfast devotion of our valiant team that hath vanquished countless obstacles and hurdles, each stride drawing us nearer to our common goal. We awaited it with bated breath for what seemed like an eternity. And lo and behold, the press release hath arrived, bringing so much excitement and anticipation to our lives that we felt like children on Christmas morn.



*The valiant team members celebrating the project first press release.*

*From left to right: S. Bourghes (GE HealthCare), M. Jevnikar (AP-HP), L. Dumont (GE HealthCare), H. Souchay (GE HealthCare), C. Chéron (AP-HP), M. Kohandani Tafresh (AP-HP), H. Pasquier (GE HealthCare), O. Meyrignac (AP-HP) and J. Hernandez Londono (GE HealthCare)*

Verily, time seemeth to have passed slowly as we eagerly awaited the release of this information. We hath heard tales of people pacing to and fro, anxiously awaiting the arrival of thee, dear press release. And some hath even reported hearing excited shrieks and hollers, like those of a pack of wild beasts! But 'tis all in good fun. With patience and perseverance, we hath finally been rewarded with this magnificent announcement.

Now that thou art here, we shall read thee with great fervor and enthusiasm, as though we art digging into the finest feast fit for a king. And we trust that readers everywhere shall relish thee and treasure thee in their hearts, like a precious gemstone. For thou art truly a thing of

beauty and a joy forever. May thy words bring awareness to all who readeth thee!

To the few remaining readers who still hath not had the chance to read it, we pray thee to click on the link below to access it.

<https://www.aphp.fr/contenu/lassistance-publique-hopitaux-de-paris-ap-hp-et-ge-healthcare-sassocient-pour-developper-des>

*"Many thanks to ChatGPT, a wise and knowledgeable interlocutor, who hath provided counsel and guidance in the writing of this text."*

# SHEDDING LIGHT ON PROJECT SUPPORT

## Behind the Scene: A Close-up Look on the Setting-up and the Management of DESTINATION 2024

*Antoine Campagne  
Grant writing project manager (AP-HP)*

The Grant Office of AP-HP Clinical Research & Innovation Department (DRCI) is a key player in the setting-up and the follow-up of collaborative projects, and as such has been fully involved in the different steps of the RHU DESTINATION 2024 project life cycle. With its main mission to support the AP-HP teams as well as the consortia they federate in responding to national and international calls for projects (IHU, RHU, Bioclusters, etc.), particularly with regard to administrative and financial aspects, the Grant Office team is the central point of contact for AP-HP scientific coordinators and links them to other DRCI teams likely to be involved in setting up the project in its various aspects (clinical study design and budget, intellectual property issues, administrative and legal aspects, etc.).

In the case of the RHU DESTINATION 2024 project, the Grant Office team provided support and advice regarding the specificities of the RHU call, and solicited the contribution of other expert departments within AP-HP DRCI in order to:

- build a budget coherent with the proposal,
- ensure that Intellectual Property aspects have been properly addressed with the help of the Collaborative Research and Partnerships team,
- check that the eligibility criteria regarding financial and administrative aspects have been respected,
- carry out the administrative requirements needed for the submission of the proposal.

For successful project applications, such as the RHU DESTINATION 2024, a rigorous monitoring is carried out by the Grant Office team, firstly, by acting as the point of contact for the funder, secondly, by appointing a project manager dedicated to the RHU project, whose mission is to manage the project's daily progress in close collaboration with the scientific coordinator. Along with this duo, the Grant Office monitoring and coordination team ensures the compliance with the consortium's contractual obligations towards the funder, for instance with the submission of periodic reports, the proper use of funds with regard to the initial budget, the management of amendment requests, etc.

Of note, the Grant Office team has recently decided to strengthen its support to project set-up by recruiting a team fully dedicated to this activity. This team of grant writing project managers assists project leaders in all matters related to the preparation of grant applications, in the manner of a consultant. With regard to the RHU projects specifically, the role of this new team covers numerous subjects, including precise knowledge of the call for projects as well as its eligibility and evaluation criteria; definition of a retroplanning and management of the progress of the application; coordination of the consortium partners; assistance in drafting non-scientific parts of the application; critical review of the project proposal; budget build-up and consolidation; as well as the collection of all the administrative information required for the submission of the application. As the single point of contact for the project leader, the project manager also further facilitates communication with all the DRCI teams involved in the project.

*To contact the team for a new project, please  
email: [drc-montage-projets@aphp.fr](mailto:drc-montage-projets@aphp.fr)*

## Innovation and Research Valorization

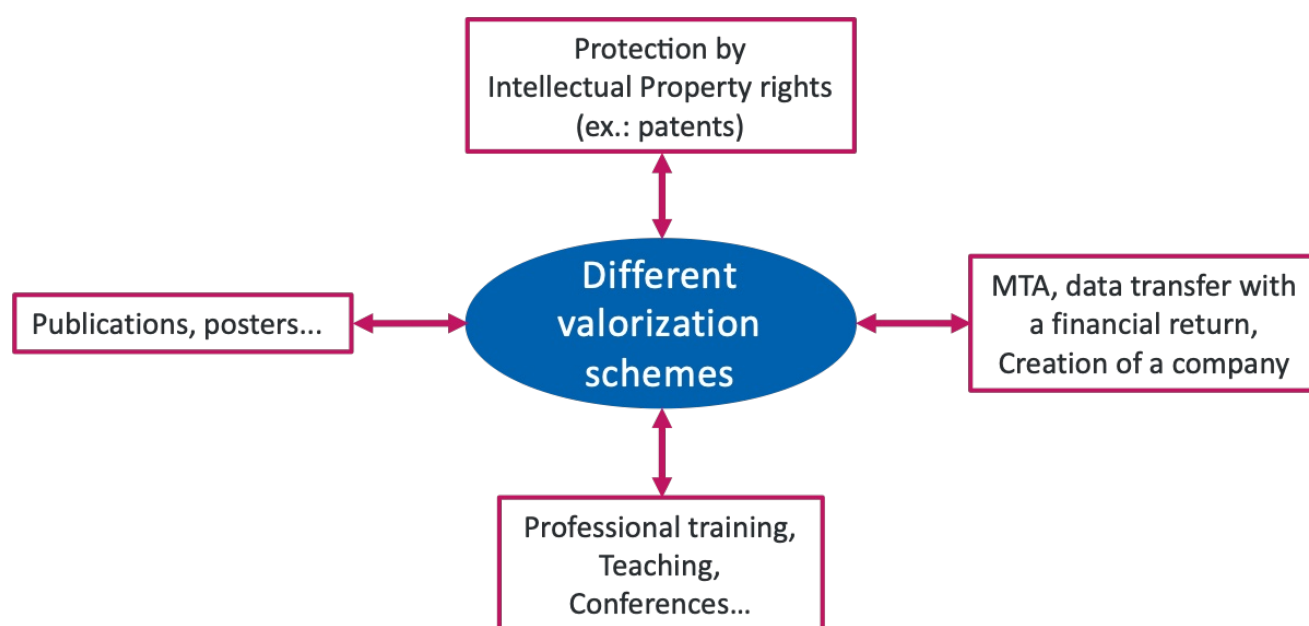
*Ouerdia Oumohand, Sourcing officer (AP-HP)*

The RHU call expects a large-scale research projects with strong potential for transfer to industry and/or to society. Precisely, it is stipulated that the projects must aim at a socio-economic impact, particularly by the improvement of medical practices, the performance of healthcare systems, or the optimization of health costs. Projects must include a research valorisation strategy as an objective and/or a technology transfer.

Obviously, RHU Destination 2024 project is all about these objectives. Thus, to deal with these situations and help meet valorization objectives, AP-HP, as coordinator, assigns a dedicated team to support involved researchers. This three-person team gathers one representative from the R&D partnership department in charge of collaboration R&D contracts (including consortium agreement), one from the technology transfer office (TTO) that is in charge of innovation detection, supporting the

innovation process for instance by liaising with licensing officers, and the project manager who coordinates the project work including the valorization aspects.

In addition to the resources provided by the coordinator, valorization committee is established to bring together valorization and technology transfer officers from all partners. In the case of the RHU DESTINATION 2024 project, this committee meeting has been organized to set up the *modus operandi* in terms of valorization of research results of the RHU. It was also the opportunity for the partners representatives to explain how the intellectual propriety rights (IPR) are managed within their respective departments from the innovation detection to the market access. This was the first step for clarifying the roles and duties of each partner in terms of intellectual property (IP) that is fully discussed and formalized in the consortium agreement. This meeting was essential to help maximize the chance for a successful technology transfer between the RHU partners and the socio-economic environment. Another important action carried out was the session dedicated to intellectual property management that was organized during the Steering Committees



*Figure 1: Different ways of spreading knowledge*



meetings with the aim to raise awareness on IPR whatever their typology. The different ways to protect knowledge and know-how were presented (cf. Figure 1). Patenting is the well-known despite being also the most expensive and very restrictive to some innovations such as biomarkers, tools of diagnostic, prognostics, etc.

Notwithstanding the three strict criteria as novelty, inventiveness and industrial application, it is expected from projects such as the RHU DESTINATION 2024 to reasonably file for one or two patents by the end of the project.

For non-patentable innovations with commercial/market potential, such as the annotation of medical images for artificial intelligence algorithms, useful/effective outcomes for clinicians could stem from the project work thanks to the close collaboration between industrial partners, hospitals and academic

partners. Therefore, we are eager to promote this type of valorization actions in order to set up valuable tools for clinicians and benefit patients. Now that the project valorization principles have been laid down in the consortium agreement, the following steps consist of discussions on specific results within the valorization committee to identify patentable innovations, valorization of items with commercial potential, and define an IP protection strategy. For any type of novelty from associate data transfer to know-how, this will be done following a typical process organized by the valorization committee (starting with inventors filling out the declaration of invention as schematized in figure 2). The project is expected to produce algorithms, software, patents, data and know-how transfer. All team members will be mobilized to foster and facilitate the valorization process.

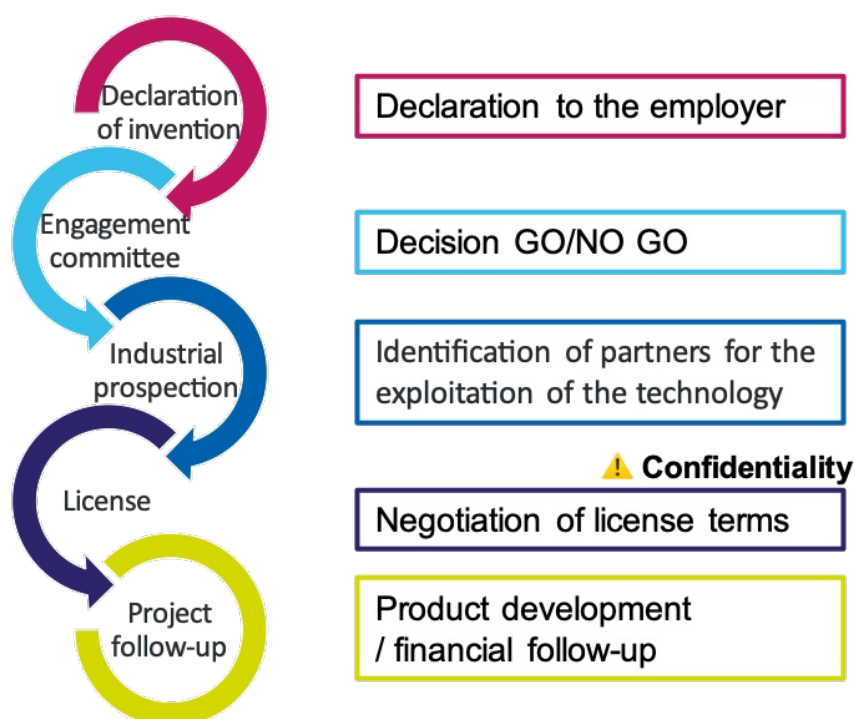


Figure 2: Administrative process of decision making of the invention declarations

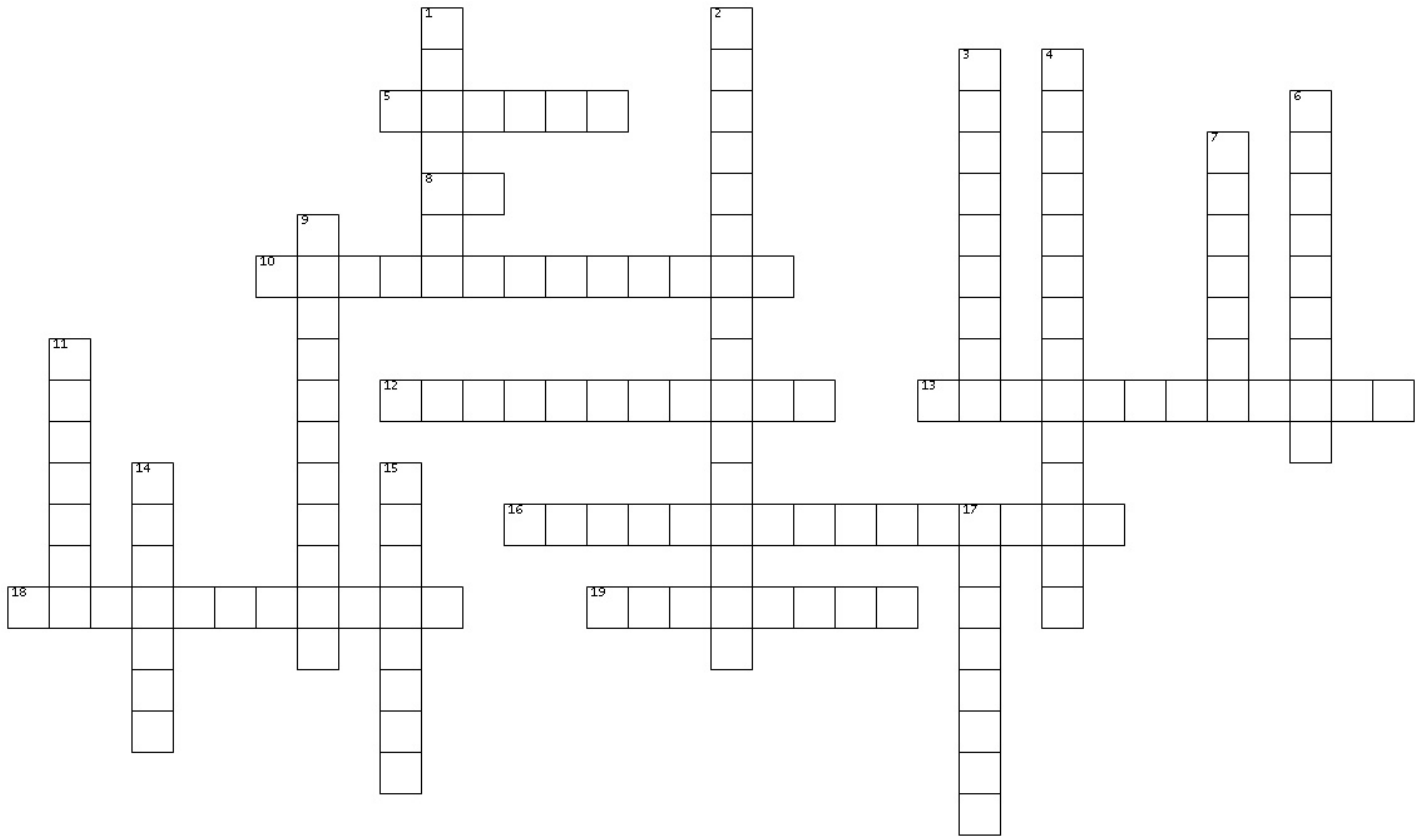
*This newsletter aims to communicate on the RHU DESTINATION 2024 project and related topics.  
If you wish to share information, please contact the project manager.*



# CTEPH CROSSWORD CHALLENGE



**WORD UP YOUR HEALTH GAME! NO PRESCRIPTIONS NEEDED FOR THIS CROSSWORD.**



Use the clues to fill in the words above. Words can go across or down. Letters are shared when the words intersect.

## ACROSS

5. Blood vessel that carries oxygenated blood away from the heart to the rest of the body
8. Gas that helps dilate blood vessels
10. Medication that prevents blood from clotting
12. X-ray image of the arteries after injection of a contrast material
13. High blood pressure
16. Insertion of a thin tube-like medical device (catheter) into a body cavity or blood vessel
18. Drug that causes blood vessels to relax and widen
19. Blockage of a blood vessel caused by a clot, air bubble, or other foreign substance

## DOWN

1. Persisting over a long period of time
2. The narrowing of blood vessels, which can increase blood pressure
3. Related to the lungs
4. Surgical procedure to remove a clot or other obstruction from an artery
6. Condition where there is a low level of oxygen in the blood
7. Medical device used to open up narrowed or blocked blood vessels
9. Relating to the cells that line the inside of blood vessels
11. Shortness of breath
14. Condition in which there is insufficient oxygen supply to the body's tissues
15. Obstruction of a blood vessel by a clot or other foreign material
17. Blood clot that forms inside a blood vessel and obstructs blood flow



## UPCOMING EVENTS



- ♦ **European Society of Cardiology Congress.** 25<sup>th</sup> – 28<sup>th</sup> August 2023, Amsterdam, Netherlands. <https://www.escardio.org/Congresses-Events/ESC-Congress>
- ♦ **European Respiratory Society International Congress.** 9<sup>th</sup> – 13<sup>th</sup> September 2023, MiCo in Milan, Italy. <https://www.ersnet.org/congress-and-events/congress/>
- ♦ **PH Professional Network Symposium.** 28<sup>th</sup> – 30<sup>th</sup> September 2023, Hyatt Regency Crystal City, Arlington, Virginia, USA. <https://symposium.phassociation.org>
- ♦ **International CTEPH Conference (ICC 2023).** 29<sup>th</sup> – 30<sup>th</sup> September 2023, InterContinental San Diego, USA. <https://cteph2023.us>
- ♦ **American Heart Association's Scientific Sessions (AHA 2023).** 11<sup>th</sup> - 13<sup>th</sup> November 2023, Philadelphia, Pennsylvania, USA. <https://professional.heart.org/en/meetings/scientific-sessions>
- ♦ **7<sup>th</sup> World Symposium on Pulmonary Hypertension.** 29<sup>th</sup> – 30<sup>th</sup> June/ 1<sup>st</sup> July 2024, Barcelona, Spain. <http://www.wsphassociation.org>
- ♦ **Annual Conference of the Saudi Association for Pulmonary Hypertension (SAPH2024).** <http://www.saphconference.com/index.php/welcome-message.html>
- ♦ **Pulmonary Hypertension Association conference.** 15<sup>th</sup> – 18<sup>th</sup> August 2024, JW Marriott in Indianapolis, USA. <https://phassociation.org/pha-conference/>



**DESTINATION 2024**

**DETECTION, ASSESSMENT AND TREATMENT OF  
CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION**

Contact us at [contact.destination2024@aphp.fr](mailto:contact.destination2024@aphp.fr)



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