Call for expression of interest to apply for a MSCA Postdoctoral Fellowship 2023

Project title	**The development of multimodular formulations adapted to the Cystic Fibrosis gene therapy.**
Call for expression of interest description	The Marie S. Curie Postdoctoral Fellowship (MSCA-PF) programme is a highly prestigious renowned EU-funded scheme. It offers talented scientists a unique chance to set up 2-year research and training projects with the support of a supervising team. Besides providing an attractive grant, it represents a major opportunity to boost the career of promising researchers. The Université de Bretagne Occidentale, UMR1078 "Genetics, Functional Genomics & Biotechnology" research unit, **is thus looking for excellent postdoctoral researchers** with an international profile to write a persuasive proposal to apply for a **Marie S. Curie Postdoctoral Fellowship grant in 2023** (deadline of the EU call set **on 13 September 2023).** The topic and research team presented below have been identified in this regard.
Main Research Field	• Life Sciences (LIF)
Research sub-field(s)	**Cellular and molecular biology, gene therapy, pharmacology, biochemistry**
Keywords	**Gene delivery, synthetic vectors, aerosol, antibacterial properties, Cystic Fibrosis**
Research project description	**Development of multimodular formulations for Cystic Fibrosis gene therapy.** Cystic fibrosis (CF) is a lethal genetic disease frequently reported among the Caucasian population. In patients, the mutations occurring in the sequence of the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene result in absence or malfunction of CFTR chloride channel. The natural defense mechanisms of the lung are thereby impaired and the resulting sticky mucus constitutes a favorable environment for bacterial colonization. Species found into the lungs of patients change throughout the lifetime: *S. aureus* and *H. influenza (*children and teenagers), *P. aeruginosa (in adults)*. The chronic *P. aeruginosa* infection is associated with a decline in lung function and can become life-threatening. Curing CF would consist in gene therapy by delivering a wild type CFTR gene. This strategy will require a gene transfer agent to efficiently deliver the transgene into the epithelial cells of the lungs. Although viral vectors can show efficient transfection, they also trigger immune responses. In comparison, synthetic compounds display many advantages, as the full-control of their manufacturing process and a-depth characterization of their chemical structures. Importantly, their low toxicity and non-immunogenicity make re-administration possible. For these reasons, several CF clinical trials using non-viral vectors were conducted, the last one by the UK CF Gene Therapy Consortium. Here, a CFTR-encoding plasmid complexed with GL67A was assayed to determine the clinical efficacy when delivered to the airways of CF patients every month during one year. The results demonstrated the safety and feasibility of repeated nebulization but, it also emphasized that higher expression of the therapeutic CFTR gene is still needed to obtain relevant clinical benefits, such as a reduction of bacterial infections. This may be achieved by further developments and optimizations of synthetic delivery systems and related formulations. During the past decade, we have synthetized and evaluated a list of cationic lipids inspired from phospholipids constituting the membrane of the eukaryotic cells. Besides their proven efficiency for nucleic acids delivery, we have shown that some lipophosphoramides are capable of antibacterial action (cf ref). We demonstrated that: (i) bacteria can negatively affect the transfection of eukaryotic cells; (ii) some specific cationic lipids possess potent antibacterial effects; and (iii) efficient

	transfection can be obtained using such cationic lipids in the presence of bacteria. Noticeably, the antibacterial activities were obtained against Gram(+) bacteria such as *S. aureus* but none towards the Gram(-) *P. aeruginosa*. Considering the CF context, we proposed that it would be useful to have synthetic vectors with antibacterial activity encompassing the bacterial diversity found in CF lungs. To enlarge their biocidal spectrum to Gram(-), we added N-heterocyclic carbene (NHC) silver compounds. Then, their antibacterial activity was demonstrated against diverse strains of Gram (-) bacteria and their toxicity towards eukaryotic cells was low (cf ref) after aerosolization. Within this frame, we propose to a fellow to present a project aiming at improving, characterizing and evaluating the nanocomplexes in CF context. Two ways should be explored: 1. **Additional improvements and further characterizations** of the formulations could be implemented, notably a better characterization of the supramolecular assemblies. A Polyethylene glycol lipid ou polyoxazoline could also be included into the formulation in order to increase the colloidal stability, especially at the highest concentration that need to be reached for aerosol delivery in patients. *2.* **Evaluation of the different formulations on relevant in vitro and in vivo models**, taking into account the hyperviscosity of the mucus and the presence of bacteria and their biofilms. The aim of this work is to further develop gene delivery systems dedicated to CF lung gene therapy, in order to face the infection burden while delivering pDNA to counteract the genetic defect. *LE GALL T., BERCHEL B., LE HIR S., FRAIX A., SALAÜN J-Y., FEREC C., LEHN P., JAFFRES P-A., **MONTIER T.*** *Arsonium-based Lipophosphoramides, Poly-functional Nano-carriers for Simultaneous Antibacterial Action and Eukaryotic Cell Transfection* *Advanced Heathcare Materials, 2013, 2: 1513-1524. (IF = 11.2)* *MOTTAIS A., BERCHEL M., LE GALL T., SIBIRIL Y., D'ARBONNEAU F., LAURENT V., JAFFRES PA., **MONTIER T.*** *Antimicrobial and transfection activities of nebulized formulations incorporating long n-alkyl silver N-heterocyclic carbene complexes. International Journal of Pharmaceutics, 2019, 567: 118500 (IF = 6.5)* *LE GALL T, BERCHEL M, DAVIES L, MOTTAIS A, GHANEM R, FAUTREL A, GILL D, HYDE S, LEHN P, LEHN JM, LEMIEGRE L, BENVEGNU T, JAFFRES PA, PITARD B, **MONTIER T.*** *Aerosol-Mediated Non-Viral Lung Gene Therapy: The Potential of Aminoglycoside-Based Cationic Liposomes.* *Pharmaceutics, 2021; 14(1):25. (IF = 6.5)* *GHANEM R., BERCHEL M, TANGUY H, BUIN X, LAURENT V., YOUF R., BOURAOUI A., LE GALL T., JAFFRES PA., **MONTIER T**.* *Gene transfection using branched cationic amphiphilic compounds for an aerosol administration in cystic fibrosis context International Journal of Pharmaceutics, 2023, 631:122491 (IF = 6.5)*
Supervisor(s)	**Pr Tristan Montier** (MD – PhD) is a full professor (UBO) and a hospital physician (CHU de Brest). He is the team leader of **"Gene Transfer & Combined therapeutic Approaches / GTCA" - UMR INSERM 1078** (UBO) – Medical Faculty at Brest. He is also the CEO of the national **platform"SynNanoVect**" labelled by IBiSA and certified ISO-9001. Under the supervision of Pr C. Férec, he defended his PhD thesis in 2003 at the University of Brest and moved to the MRC Institute of Genetics and Molecular Medicine (Edinburgh – UK) for a post-doctoral fellowship in Pr D. Porteous's team. In 2005, he was recruited as a lecturer in the Western Brittany University and became full professor in 2014. He received the scientific prize of the French Paediatric Society in 2015 and is member of numerous scientific committees. He is one of the permanent member of the scientific council of the AFM Téléthon. **146 peer-reviewed international (web of science reference), 5 patents, H-Index = 33;**

	Expertise: Cellular and molecular biology, human genetics, gene delivery, biotechnology, Chemistry for Biology, Cystic Fibrosis, aerosol. 4 of his most significant publications: Lindberg MF, Carmoy N, Le Gall T, Fraix A, Berchel M, Lorilleux C, Couthon-Gourvès H, Bellaud P, Fautrel A, Jaffrès PA, Lehn P, **Montier T.** The gene transfection properties of a lipophosphoramidate derivative with two phytanyl chains. *Biomaterials, 2012, 33(26):6240-53. (IF =15.3)* Lindberg MF, Le Gall T, Carmoy N, Berchel M, Hyde SC, Gill DR, Jaffrès PA, Lehn P, **Montier T.** Efficient in vivo transfection and safety profile of a CpG-free and codon optimized luciferase plasmid using a cationic lipophosphoramidate in a multiple intravenous administration procedure. *Biomaterials, 2015, 59:1-11. (IF =15.3)* Le Guen YT**,** Pichon C**,** Guégan P, Pluchon K**,** Haute T**,** Quemener S**,** Ropars J, Midoux P, Le Gall T**,** **Montier T**. DNA nuclear targeting sequences for enhanced non viral gene transfer: an in vitro and in vivo study. *Molecular Therapy - Nucleic Acids, 2021, 24:477-486 (IF = 10.2)* Ghanem R, Roquefort P, Ramel S, Laurent V, Haute T, Le Gall T, Aubry T, **Montier T.** Apparent Yield Stress of Sputum as a Relevant Biomarker in Cystic Fibrosis. *Cells, 2021 ; 10(11): 3107. (IF = 7,6)* https://www.researchgate.net/profile/Tristan_Montier/
Department/ Research	**The UMR1078 "Genetics, Functional Genomics & Biotechnology"** (Dir : Mme Emmanuelle Genin) is an Inserm research unit of about 110 people which is dedicated to the discovery of genes related to inherited genetic disorders, then to the determination of the functional consequences of the identified mutations and finally to the exploitation of this knowledge to develop chemobiological-based approaches to find therapeutic solutions for these disorders, including gene delivery. http://www.univ-brest.fr/umr1078/?languageId=1
Location	Brest
Suggestion for interdisciplinary / intersectoral secondments and placements	This project is performed in the frame of a close and long-term collaboration with the teams of chemists such as Pr Paul-Alain Jaffres (UMR CNRS - Brest) and Pr Philippe Guegan (UMR CNRS – Paris Sorbonne) and some teams of biologists such as Dr Patrick Midoux (UPR CNRS – CBM - Orléans). This network is founded by national and international grants (ANR, AFM strategic project and Vaincre La Mucoviscidose projects). In parallel, we established an international project (PROCOPE) with a group of chemists at the Siegen University (Germany). Now, this project entitled "TARGET THERAPY" is founded by an ANR FR-DE AMR which will start in april 2021. The fellow will have the opportunity to participate to the existing collaborations with all these teams as well as creating and developing new collaborations.
Skills Requirements	Solid knowledge in cellular & molecular biology Strong knowledge in biochemical methods and/or in formulations is expected Technical skills in using some common bacterial strains & of mammalian cells are required. Veterinary ability to handle the animals. Some regular publications in top journals rather than a lot (one per year or more) in more confidential or specialized journals. Junior postdocs are invited to candidate but an already performed first postdoc will be an asset.

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<tr><td>Eligibility criteria for applicants</td><td>Academic qualification: By 13 September 2023, applicants must be in possession of a doctoral degree, defined as a successfully defended doctoral thesis, even if the doctoral degree has yet to be awarded.

Research experience: Applicants must have a maximum of 8 years full-time equivalent experience in research, measured from the date applicants were in possession of a doctoral degree. Years of experience outside research and career breaks (e.g. due to parental leave), will not be taken into account.

Nationality & Mobility rules: Applicants can be of any nationality but must not have resided in France more than 12 months between 13/09/2020 and 13/09/2023</td></tr>
<tr><td>Application process</td><td>We encourage all motivated and eligible postdoctoral researchers to send their expressions of interest through the EU Survey application form (link here), before 1st of May 2023. Your application shall include:

• a CV specifying: (i) the exact dates for each position and its location (country) and (ii) a list of publications;

• a cover letter including a research outline (up to 2 pages) identifying the research synergies with the project supervisor(s) and proposed research topics described above.

Estimated timetable

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<tr><td>Deadline for sending an expression of interest</td><td>1st of May 2023</td></tr>
<tr><td>Selection of the most promising application(s)</td><td>May – June 2023</td></tr>
<tr><td>Writing the MSCA-PF proposal with the support of the above-mentioned supervisor(s)</td><td>June – September 2023</td></tr>
<tr><td>MSCA-PF 2023 call deadline</td><td>13 September 2023</td></tr>
<tr><td>Publication of the MSCA-PF evaluation results</td><td>February 2024</td></tr>
<tr><td>Start of the MSCA-PF project (if funded)</td><td>1st of May 2024 (at the earliest)</td></tr>
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