Job Title	We propose to a Senior Postdoc in Chemical Biology to develop a project that aims at defining new and relevant therapeutic target(s) to unveil EBV-related cancers to the immune system.
Main Research Field	Life Sciences (LIF)
Sub Research Field:	Chemical Biology
Key words	Cell Biology, Cancer, Chemical Biology, Budding Yeast, Drug Screening, G-quadruplexes, translation regulation, immune evasion, FRET-based single molecule analysis
Job Description	**Deciphering the role of nucleolin (NCL) in immune evasion of the Esptein-Barr oncovirus** The Epstein-Barr virus (EBV) is the first oncogenic virus discovered in human and would be responsible for about 2 to 3% of human cancers, including Hodgkin lymphoma and 10% of gastric cancers. EBV evades the immune system but, fortunately, has an Achilles heel: its genome maintenance protein EBNA1. Indeed, EBNA1 is essential for viral genome replication and maintenance but also highly antigenic and T cells directed towards EBNA1 epitopes exist in all infected individuals. Hence, EBV evolved a system in which EBNA1 selflimits the translation of its own mRNA at a minimal level to ensure its essential function thereby, at the same time, minimizing immune recognition. Defining intervention points where to interfere with EBNA1 immune evasion is an important step to trigger an immune response against EBV-carrying cancers. Thanks to a yeast-based assay that recapitulates all the aspects of EBNA1 self-limitation of expression that we setup in the lab (Voisset et al 2014 & Lista et al 2015), we have recently uncovered the role of the host cell nucleolin (NCL) in this process via a direct interaction of this protein with G-quadruplexes (G4) formed in EBNA1 mRNA (Lista et al 2017). In addition, the G4 ligand PhenDC3 prevents NCL binding on EBNA1 mRNA and translation and antigen presentation (Lista et al 2017). This shows that the NCL-EBNA1 mRNA interaction is a relevant and druggable therapeutic target to unveil EBV-carrying cancers to the immune system. Within this frame, we propose to a postdoctoral fellow to present a project that aims at explaining and dissecting the precise role of NCL in EBNA1 stealthiness as well as defining new actors of this mechanism. Ideally, two aspects of NCL biology should be explored: 1- the way it interacts with G4s of the EBNA1 mRNA, and thus potentially modify their structure. This part of the project will imply the use of biophysical methods like FRET-based single molecule structure dynamic analysis. reverses its ability to selflimit its 2- the biological functions of NCL itself: NCL is a RGG motif protein and several members of this family have been implicated in

	translation regulation through interaction with various translation initiation factors mediated by their RGG motifs. We will make profit of yeast where there is a limited number of RGG domain proteins to determine the implication of these different host cell factors in self-limitation of translation. Once this network will be established in yeast, as all these proteins are conserved from yeast to Human, we will assess in various human cells (EBNA1-transfected or naturally infected by EBV) the implication of these factors in GAr-based self-limitation of translation in Human. References - Voisset C, Daskalogianni C, Contesse MA, Mazars A, Arbach H, Le Cann M, Soubigou F, Apcher S, Fåhraeus R, Blondel M (**2014**) A yeast-based assay identifies drugs that interfere with Epstein-Barr virus immune evasion. ***Disease Models & Mechanisms*** 7: 435-444 - Lista MJ, Voisset C, Contesse MA, Friocourt G, Daskalogianni C, Bihel F, Fåhraeus R, Blondel M (**2015**) The long-lasting love affair between the budding yeast Saccharomyces cerevisiae and the Epstein-Barr virus. ***Biotechnology Journal*** 10: 1670-1681 - Lista MJ, Prado Martins R, Billant O, Contesse MA, Findakly S, Pochard P, Daskalogianni C, Beauvineau C, Guetta C, Jamin C, Teulade-Fichou MP, Fahraeus R, Voisset C, Blondel M (**2017**) Nucleolin directly mediates Epstein-Barr virus immune evasion through binding to G-quadruplexes of EBNA1 mRNA. ***Nature Communications*** 8: 16043
Supervisor	Marc Blondel got his PhD in 1996 at Paris 11 University and then moved for a four years-postdoc at the Swiss Institute for Cancer Research (ISREC) in Epalinges (Switzerland). In 2000 he got a tenure research position (CR) at CNRS in Roscoff (France) before to get a full Professor position in 2006 at the University of Brest where he's currently leading a research team and is the deputy director of the Inserm UMR1078 unit. He's Senior Editor for Biotechnology Journal (Wiley-VCH) since its creation in 2005 & Editor for Microbial Cell since 2013. He received the CNRS Bronze Medal in 2004 and is member of numerous scientific committees, including CSS1 Inserm, La Ligue contre le Cancer & INCa. 3 of his most significant publications: - Bach, S., Talarek, N., Andrieu, T., Vierfond, J.M., Mettey, Y., Galons, H., Dormont, D., Meijer, L., Cullin, C. & **Blondel, M.** (2003) ***Nature Biotechnology***, 21, 1075-1081. - Couplan E, Aiyar RS, Kucharczyk R, Kabala A, Ezkurdia N, Gagneur J, St Onge RP, Salin B, Soubigou F, Le Cann M, Steinmetz LM, di Rago JP & **Blondel M** (2011) ***Proc Natl Acad Sci U S A*** 108: 11989-11994 - Lista MJ, Prado Martins R, Billant O, Contesse MA, Findakly S, Pochard P, Daskalogianni C, Beauvineau C, Guetta C, Jamin C, Teulade-Fichou MP, Fahraeus R, Voisset C & **Blondel M** (2017) ***Nature Communications*** 8: 16043 https://www.researchgate.net/profile/Marc_Blondel

Department/Research	The UMR1078 "Genetics, Functional Genomics &Biotechnology" is an Inserm unit of about 100 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. *http://www.univ-brest.fr/umr1078/?languageId=1*
Suggestion for interdisciplinary / intersectoral secondments	This project is performed in the frame of a close and long-term collaboration with the teams of Robin Fåhraeus (Inserm St Louis Hospital, Paris, France), Marie-Paule Teulade-Fichou (Curie Institute, Orsay, France) and Victoria Birkedal (Aarhus University, Denmark). The fellow will have the opportunity to develop the existing collaborations with these teams as well as creating and developing new collaborations.
Skills Requirements (optional) :	- Basic knowledge in cellular & molecular biology - Strong knowledge in biophysical methods for single molecule analysis (like FRET) and/or in chemical biology is expected - Technical skills in using the budding yeast *Saccharomyces cerevisiae* & of mammalian cells will represent a clear advantage - Some regular publications in top journals rather than a lot (one per year or more) in more confidential or specialized journals - Senior postdocs are expected so candidates that already performed one or two postdoc(s) will be privileged