Application to be sent to Christa Rachelle Joseph and Scarlett Weale:
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Deadline: February 27th, 2026

EUR CARe PhD program pre-proposal

PhD Director:
Prof. Laurence Nieto, Laurence.nieto@inserm.fr

PhD Director affiliation:
Université de Toulouse/centre de recherches en cancérologie de Toulouse (CRCT)

PhD co-Director:
Prof. Vijay Chudasama, v.chudasama@ucl.ac.uk

PhD co-Director affiliation:
Department of Organic Chemistry, University College London (UCL) https://chudasama-group.eu/

Research project title: Bispecific antibodies to treat melanoma: from antibody engineering using click chemistry to the evaluation of their pharmacodynamic impact in mice

Research program abstract:
Although immune checkpoint inhibitors (ICI) have revolutionized the treatment of advanced melanoma patients, many do not respond to the therapy or relapse. These drawbacks highlight the need to improve ICI therapies.
We have recently identified a new resistance pathway to ICI, involving and have shown that its blockade can improve the response to ICI in melanoma. Nevertheless, although blocking this pathway improved the efficacy of ICI, adverse events were observed. In this proposal, **we wish to develop bispecific antibodies (**BsAbs) to increase anti-tumor immunity, enhancing specificity and minimizing toxicities.
The objective of this transdisciplinary project will be:
i) To produce BsAbs (semester 1, Chudasama's lab, UK). To generate BsAbs that target two antigens simultaneously, we will use a unique click chemistry approach to couple 2 Fab fragments from 2 different monoclonal antibodies (Szijj *et al*, Nat Chem. 2023). Briefly, Fab moieties are isolated from the corresponding full antibodies, functionalized, re-associated by click-chemistry and purified by LC-MS. The high modularity of this technique allows for testing a large number of combinations. Indeed, this method is faster, reproducible and less expensive than the classical methods based on protein engineering, and will be applied using clinically available monoclonal antibodies.
ii) To characterize the BsAbs *in vitro* (semesters 2 to 4 in Ségui's lab) on immune cells (PBMC)
We will evaluate their specificity, affinity and biological activities *in vitro* using surface plasmon resonance, binding to cells that do, or do not, express the targeted antigens. Functional tests will be conducted on activated T cells as previously described Tocheva et al, Curr Protoc Immunol 2020).
iii) To evaluate the pharmacodynamic impact, tolerability profile and efficacy of BsAb in mice (year 3, Ségui's lab). To assess the pharmacodynamic impact of our BsAbs, we will use humanized mice grafted with melanoma cells. Biodistribution of Alexa680-labelled BsAbs will be evaluated using IVIS spectrum. Tolerability will be monitored through body weight, blood formula, plasma transaminases and cytokines analysis along therapy. Efficacy will be evaluated by tumorigenesis and immunophenotyping by spectral cytometry.

How this project fits the 3 defining criteria of the CARe graduate programme:

1) Relation to CARe topics of Cancer, Ageing and/or Rejuvenation

This project is focused on cancer, from basic findings to identify resistance mechanisms to ICI, to bispecific antibody engineering to overcome resistance to ICI.

2) Multidisciplinary aspect

Biotechnology, click chemistry and biochemistry (LC/MS) for BsAb engineering, Biophysic (Biacore), Cell Biology and Immunology (spectral cytometry) for antibody efficacy/specificity evaluation, Cancerology (mice breeding, grafts, spectral cytometry).

3) International and/or industrial aspect(s)

Thesis in collaboration between Toulouse University and University College London (UCL, UK).

5 keywords in line with EUR CARe

Cancer, Therapy, Resistance, Click chemistry, Bioengineering.

5 references of the teams, highlighting the co-signatory students:

(Last 5 years)

Segui/Andrieu's lab

Combining Nivolumab and Ipilimumab with Infliximab or Certolizumab in Patients with Advanced Melanoma: First Results of a Phase Ib Clinical Trial.
Montfort A, Filleron T, Virazels M, Dufau C, Milhès J, Pagès C, Olivier P, Ayyoub M, Mounier M, Lusque A, Brayer S, Delord JP, **Andrieu-Abadie N**, Levade T, Colacios C, **Ségui B**#, Meyer N#.
***Clin Cancer Res*.** 2021 Feb 15;27(4):1037-1047. doi: 10.1158/1078-0432.CCR-20-3449.
#co-last and co-corresponding authors.

Sphingolipid paracrine signaling impairs keratinocyte adhesion to promote melanoma invasion.
Noujarède J, Carrié L, Garcia V, Grimont M, Eberhardt A, Mucher E, Genais M, Schreuder A, Carpentier S, **Ségui B**, **Nieto L**, Levade T, Puig S, Torres T, Malvehy J, Harou O, Lopez J, Dalle S, Caramel J, Gibot L, Riond J, **Andrieu-Abadie N**.
Cell Rep. 2023 Dec 26;42(12):113586. doi: 10.1016/j.celrep.2023.113586.

TNF signature in advanced melanoma patients treated with immune checkpoint inhibitors: Results from the MELANFα clinical study.
Virazels M, Lusque A, Brayer S, Genais M, Dufau C, Milhès J, Filleron T, Pagès C, Sibaud V, Mortier L, Dereure O, Ayyoub M, Fabre A, **Andrieu-Abadie N**, Pancaldi V, Colacios C, Meyer N, **Ségui B**, Montfort A.
Int J Cancer. 2025 Aug 1;157(3):534-548. doi: 10.1002/ijc.35416.

Nieto L (previous lab – Muller's lab, IPBS, Toulouse)

Adipocyte Extracellular Vesicles Decrease p16INK4A in Melanoma: An Additional Link between Obesity and Cancer.
Lazar I, Clement E, Carrié L, Esteve D, Dauvillier S, Moutahir M, Dalle S, Delmas V, **Andrieu-Abadie N**, Larue L, Muller C, **Nieto L**.
J Invest Dermatol. 2022 Sep;142(9):2488-2498.e8. doi: 10.1016/j.jid.2022.01.026.

Chudasama's lab

Chemical generation of checkpoint inhibitory T cell engagers for the treatment of cancer.
Szijj PA, Gray MA, Ribi MK, Bahou C, Nogueira JCF, Bertozzi CR, **Chudasama V.**
Nat Chem. 2023 Nov;15(11):1636-1647. doi: 10.1038/s41557-023-01280-4.