OMB No. 0925-0001 and 0925-0002 (Rev. 12/2020 Approved Through 02/28/2023)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person.

NAME: Fernandez-Cuesta, Lynnette

eRA COMMONS USER NAME (credential, e.g., agency login): L.FERNANDEZ-CUESTA

POSITION TITLE: Staff scientist, Team leader

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University Lyon-1, France	Habilitation à diriger des recherches (HDR)	02/2017	Cancer Genomics
University Lyon 1, France	PhD	02/2010	Cell Biology
University of Oviedo, Spain	Master 2	09/2006	Molecular Biology
University of Turku, Finland	Master 1	09/2005	Biotechnology
University of Oviedo, Spain	Baccalaureate	04/2005	Biochemistry

OTHER TRAINING
Professional individual coaching by International Leadership & Culture Coaching (2023)
Research Leadership Training Course by Mobilize Strategy Consulting (2022)

A. Personal Statement

I have more than 10-year experience in the field of Cancer Genomics. My postdoctoral work in the Max-Planck Institute in Cologne, Germany, in the field of lung cancer functional genomics paved the way for creating the Rare Cancers Genomics initiative in my subsequent position as staff scientist in the International Agency for Research on Cancer (IARC-WHO) in Lyon, France. This initiative has been built around the multi-omic molecular characterization of two main thoracic rare cancers: lung neuroendocrine neoplasms (lungNENomics project) and malignant pleural mesothelioma (MESOMICS project). The success of this initiative gave rise to the Rare Cancers Genomics team that I am currently leading at IARC-WHO, and more recently to the Rare Cancers EPIC Working Group.

To translate our findings into the clinical setting, I work closely with pathologists (F Galateau-Salle, S Lantuejoul), clinicians (JY Blay, J Derks, N Girard, T Walter), surgeons (JM Maury) from the Centre Leon Berard (France), Hospices Civils de Lyon (France), the Maastricht University (The Netherlands), and Institute Curie (France), among others. To identify mutational signatures and mutational drivers, I collaborate with the worldwide experts in the field, L Alexandrov (UC San Diego, USA) and N Lopez-Bigas (Institute for Research in Biomedicine, Barcelona), respectively. To perform cancer evolution studies, I collaborate with J Kim (Cornell University, US) and NA Rosenberg (Stanford University, US). To apply deep learning to our data, I collaborate with L Chen (Ecole Central de Lyon, France) and D Samaras (State University of New York, USA). To do organoids-based mechanistic analyses, I collaborate with T Dayton, a former postdoc in the lab of the renowned expert H Clevers (University of Hubrecht) and currently group leader at the EMBL, Barcelona.

B. Supervision and funding

Over the past five years, I have supervised the work of seven Master students, four PhD students, five postdocs, and one staff scientist. Also, my work as Principal Investigator has been/is funded by several national and international funding bodies, as follows:

Agence National de la Recherche (ANR) FR - Tremplin – ERC Consolidator Grant (T-ERC CoG) 2023 – Fernandez-Cuesta (PI) 113,000 EUR 2023-2025 Aimed at helping to improve my unfunded A+ ERC CoG application for a future submission

Institute National du Cancer (INCa) FR - Integrated cancer research sites SIRIC designation – Fernandez-Cuesta (co-investigator and IRP3-WP1 leader) 6 million EUR 2023-2028 Acronym: LYriCAN+

NET Research Foundation – 2022 Investigator Award Fernandez-Cuesta (co-investigator) USD 270,000 2023-2025 Title: Reconciling lung carcinoids histopathological and molecular classifications

Department of Defense (DoD) – Concept Award Fernandez-Cuesta (co-PI) USD 100,000 2022-2023 Title: Intra-tumour heterogeneity of pleural mesothelioma at the single cell level

Worldwide Cancer Research – 2020 Grant Round Fernandez-Cuesta (PI) GBP 249,182 2021-2023 Title: Unveiling the evolutionary processes and molecular pathways underlying the development and progression of lung neuroendocrine neoplasms

Ligue Nationale contre le Cancer (LNCC) Fernandez-Cuesta (PI) 50,000 EUR 2021-2022 Title: Transcriptomic characterization of biphasic and sarcomatoid malignant pleural mesotheliomas

NET Research Foundation – 2019 Investigator Award Fernandez-Cuesta (PI) USD 300,000 2020-2022 Title: Comprehensive molecular characterization of lung supra-carcinoids

Dutch Cancer Society (DCS) Speel EJ (PI) 50,000 EUR 2018-2022 Title: The Orthopedia Homeobox transcription factor (OTP) in the diagnostics and tumorigenesis of lung carcinoids

Institute National du Cancer - INCa PRT-K-2017 Fernandez-Cuesta (PI) 687,052 EUR 2018-2022 Title: Genomic characterization of broncho-pulmonary carcinoids

Institute National du Cancer - INCa PRT-K-2015 Fernandez-Cuesta (PI) 600,993 EUR 2016-2020 Title: Molecular characterization of malignant pleural mesothelioma

Ligue Nationale contre le Cancer (LNCC) Fernandez-Cuesta (PI) 50,000 EUR 2018-2019 Title: Unveiling the intra-tumour heterogeneity of malignant mesothelioma

Ligue Nationale contre le Cancer (LNCC) Fernandez-Cuesta (PI) 50,000 EUR 2017-2018 Title: Epigenetic characterization of lung neuroendocrine tumors

National Institutes of Health - R03 PAR-14-007 McKay JD (PI) USD 100,000 2015-2017 Title: Genomic and transcriptomic characterization of atypical carcinoids of the lung

B. Positions, Scientific Appointments, and Honors

Positions

since 2021	Rare Cancers Genomics Team leader (RCG), Genomic Epidemiology Branch (GEM), International Agency for Research on Cancer (IARC-WHO), Lyons, France
2014-2021	Staff Scientist, Genetics Section (GEN), International Agency for Research on Cancer (IARC-WHO), Lyons, France
2010-2014	Postdoc in Cancer Genomics, Max-Planck Institute and Department of Translational Genomics, Cologne, Germany

Scientific Appointments

since 2023	Member of the International Conference of the International Mesothelioma Interest Group (iMig) Program Committee
since 2023	Member of IASLC Mesothelioma Committee

since 2022 Member of the IASLC World Conference of Lung Cancer (WCLC) Program Committee;
since 2023 Member of the European NEuroendocrine Tumors society (ENETS) Advisory Board
since 2022 Chair of the of the European Prospective Investigation into Cancer and Nutrition (EPIC) Rare Cancers Working Group
since 2021 European NEuroendocrine Tumors society (ENETs) - lung NET task force
since 2016 French MESOBANK Scientific Committee
2012 Scientific advisor for former NEO New Oncology GmbH, a company established by Prof. Thomas

Participation to workshops of experts

***Mesothelioma*:**
IASLC-EURACAN Multidisciplinary Workshop on Mesothelioma Classification 2018 (Lyon, France) resulting in a manuscript published in *J Thorac Oncol.* 2019 PMID: 31546041

(Lung) neuroendocrine neoplasms:
Co-author of the Neuroendocrine Tumors Chapter within the Thoracic Tumours WHO Classification of Tumours, 5th Edition, Volume 5
IARC-WHO expert consensus meeting to build a common classification framework for neuroendocrine neoplasms 2017 (Lyon, France) resulting in a manuscript published in *Mod Pathol.* 2018 PMID: 30140036

Peer reviewing activities
Grant funders: Worldwide Cancer Research UK
Scientific Journals: *Clinical Cancer Research, Journal of Thoracic Oncology, Lung Cancer, Nucleic Acids Research, New England Journal of Medicine, Annals of Oncology, Oncogene, Scientific Reports, British Journal of Cancer and Human Molecular Genetics*

Fellowships and Awards
2019 First-place Award Oral Abstract in the Basic Science Category (16th Annual ENETs Conference) 2015 Young Investigator Travel Award/Intl. Association for the Study of Lung Cancer/USA
2015 Fred R. Hirsch Lectureship Award for Translational Research (formerly Adi F Gazdar)/ Intl. Association for the Study of Lung Cancer/USA
2010 Max-PlanckpostdoctoralfellowMax-PlanckInstituteforNeurologicalResearch/Germany
2005 SOCRATES ERAMUS Scholarship/European Commission

European patents
"Novel NRG1 fusion genes in lung cancer" Filed in 2013 with the number 13 179 596.5
Lynnette Fernandez-Cuesta, Roman K Thomas, Julie George, Dennis Plenker

Teaching activities
2023 Invited as lecturer for the Visiting Professor Program at the University of Pavia
since 2019 Lecturer in the Central and East European School of Oncology (CEESO)
since 2014 Lecturer in the Master 2 "Omics technologies and big data in oncology" – Cancer Genomics/University of Lyon-1/France
2015 Lecturer – Cancer Genomics/IARC Summer School/IARC-WHO/France

Providing training in Cancers Genomics: beyond teaching, my team has become over the past years a reference for Rare Cancers Genomics studies as proven by the increase in the number of collaborators sending their students to get trained for a short period of time in my team. Jules Derks and Laura Moonen were both PhD students of our collaborator EJ Speel (University of Maastricht, The Netherlands) who came for a 3-month internship in 2016 and 2018, respectively. Ricardo Blazquez Encinas Rey, is a PhD student of our collaborator J Castano (IMIBIC in Spain), who joined us for a 3-month internship in 2021. In 2022, Dr Giovanni Centonze working with our collaborator in Milan, Massimo Milione, has joined us for a 2-month training. We are currently hosting a 6-month trainee (Eleonora Lauricella) from Mauro Cives lab (Policlinico di Bari, IT). Maike Morrison from Rosenberg's lab in Stanford University, will join us for the second time this year for a month internship, and we will also host for 3 months this year Lipika Lipika, from our collaborator Luka Brcic (Med Uni Graz).

C. Leading Contributions to Science

As shown in my Google Scholar profile, my contribution to science includes 44 publications in international peer-reviewed scientific journals as follows: 30 original research papers and 10 reviews; 10 as first/co-first author and 11 as corresponding author. I also co-authored three book chapters, one as leading author and the other two as co-author. Overall, I have 7,166 total citations and a h-index of 28. This initiative would have never seen the light without the large multidisciplinary network that I have built up over the past 10 years.

Identification of NRG1 fusion genes. I started my postdoc in the early years of next-generation sequencing technologies. At that time the amount of data generated was already pointing to the need of developing appropriate pipelines for sequencing data analyses. After leading the development of a computational approach for the identification of chimeric transcripts in cancer specimens (Fernandez-Cuesta *et al. Genome Biol.* 2015), I applied this bioinformatic tool to a series of lung adenocarcinomas of never smokers and identified recurrent *CD74-NRG1* fusions (Fernandez-Cuesta *et al. Cancer Discov. 2014*). This discovery led to an invited review (Fernandez-Cuesta *et al. Clin Cancer Res.* 2014), an oral presentation in the **15th World Conference on Lung Cancer (WCLC)** (2013), and a **European Patent** entitled *"Novel NRG1 fusion genes in lung cancer"* filed in 2014 under the number 13 179 596.5. *NRG1* fusions have since then been identified in 10-30% of invasive mucinous lung adenocarcinomas and in 1% of all solid tumors, representing an important therapeutic opportunity for these patients.

Genomic characterization of lung neuroendocrine neoplasms (NENs). During my postdoc I also participated in the genomic characterization of understudied lung NENs. I co-led a study in which we initially found in 29 cases (***1***) and further confirmed in 110 cases (George *et al. Nature* 2015) that small-cell lung cancer (SCLC) is a disease driven by *TP53* and *RB1* inactivation. This led me to evaluate afterwards, in my subsequent position at IARC-WHO, to what extent mutations in *TP53* could be used to detect circulating tumor DNA for the early detection of SCLC (Fernandez-Cuesta *et al. EBioMedicine* 2016). I was selected for an oral presentation at the **17th WCLC** (2016) to present this work. SCLC is a high-grade tumor that belongs to the group of lung NENs, which also includes the low-grade typical carcinoids, intermediate-grade atypical carcinoids, and high-grade large-cell neuroendocrine carcinoma (LCNEC). In a large study of more than 1000 tumors aiming at establishing a genomics-based classification of lung cancer, I contributed to the finding that LCNEC share mutational and expression patterns with SCLC (CLCGP and NGM *Sci Transl Med.* 2013). Considering these results, I got very interested in these understudied entities and decided to explore more in detail their molecular characteristics. In this context, I led the genomic characterization of 45 pulmonary carcinoids (***2***), as well as co-led a project aimed at the comprehensive genomic characterization of 60 LCNEC (***3***). As result of the LCNEC work, I got an oral presentation in the **16th WCLC** (2015) and the **Fred R. Hirsch Lectureship Award** for Translational Research by the IASLC.

1. Peifer M, **Fernández-Cuesta L (co-first)**, *et al.* Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. ***Nat Genet.*** **2012** PMID: 22941188

2. **Fernandez-Cuesta L** *et al.* Frequent mutations in chromatin-remodeling genes in pulmonary carcinoids. ***Nat Commun.*** **2014** PMID: 24670920

3. J. George, (…), **L. Fernandez-Cuesta (co-first)**, R.K. Thomas. Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. **2018.** ***Nat Commun.*** PMID: 29535388

In the beginning of my position as staff scientist and PI in the IARC-WHO I decided to further explore the molecular characteristics of these rare lung NENs by setting up the ***lungNENomics project***. Within this project, I have led the studies unveiling the existence of new molecular subtypes of pulmonary carcinoids, including, the discovery of a new entity that I named, supra-carcinoids (***4***). This ground-breaking discovery has disproved the general belief that low-grade and high-grade lung NENs are distinct well separated diseases. This important finding has been included in the Neuroendocrine Tumors chapter of the **WHO Classification of Thoracic Tumors, 5thEd, in which I participated as expert co-author**. These WHO books are the worldwide reference for pathologist to establish the right diagnosis of tumors. I also got an oral talk to present this work at the **16th Annual European Neuroendocrine Tumor Society (ENETS) Conference** (2019), for which I obtained the **first-place Award Oral Abstract** in the Basic Science category. I was also invited speaker to present this finding at the **11th Joint Meeting of the British Division of the IAP and the Pathological Society** (2018), **XV Int Symp GETNE** (2019), **20th WCLC** (2019), and **2020 Neuroendocrine Tumor Research Foundation (NETRF) Research Symp** (Boston). I have also co-led studies resulting in: (*i*) finding that the distinct molecular subtypes of LCNEC appear to be predictive of clinical response (***5***); (*ii*) generating the first molecular map of lung NENs

(Gabriel *et al. GigaSci.* 2020); (*iii*), establishing organoid systems for lung NENs to study evolutionary processes (***6***), and (*iv*) explore the use of deep-learning computer vision algorithms to improve the differential diagnosis of lung NETs (***7***). Thanks to my expertise in the field of NENs, I was invited to participate to the **IARC-WHO expert consensus proposal for a common classification framework for NENs** (Rindi *et al. Mod Pathol.* 2019). More recently, I have been invited to give an Educational Lecture in the upcoming **2023 American Society of Clinical Oncology (ASCO) meeting** in Chicago and to contribute to the ASCO Educational Book. I was also invited to give a talk in the upcoming **1st ENETS Basic and Translational NET Research** in Vienna, and to participate as member of the Program Committee for the SCLC and NETs session in the upcoming **2023 WCLC** taking place in Singapore.

4. Alcala N, (…), **Fernandez-Cuesta L (corresponding)**. Integrative and comparative genomic analyses identify clinically relevant groups of pulmonary carcinoids and unveil the supra-carcinoids. ***Nat Commun.*** **2019** PMID: 31431620

5. Derks JL, (…), **Fernandez-Cuesta L* (co-corresponding)**, Speel EM*, Dingemans AC*. Molecular subtypes of pulmonary large-cell neuroendocrine carcinoma predict chemotherapy treatment outcome. ***Clin Cancer Res.*** **2018** PMID: 29066508

6. Dayton T*, (…), **Fernandez-Cuesta L* (co-corresponding)**, Clevers H*. Druggable Growth Dependencies and Tumor Evolution Analysis in Patient-Derived Organoids of Neuroendocrine Cancer. bioRxiv preprint ***Cancer Cell*** In Press

7. Mathian E, (…), **Fernandez-Cuesta L**, Samaras D, Foll M, Chen L. HaloAE: A Local Transformer Auto-Encoder for Anomaly Detection and Localization Based On HaloNet. *Proceedings of the 18th International Joint Conference on Computer Vision, Imaging and Computer Graphics Theory and Applications (**VISIGRAPP 2023**)* – Volume 5: VISAPP; ISBN 978-989-758-634-7; ISSN 2184-4321, SciTePress, pages 325-337. DOI: 10.5220/0011865900003417

In parallel, I also started the ***MESOMICS project,*** a total new axis of research aimed at the molecular characterization of malignant pleural mesothelioma (MPM). I led the studies: (*i*) identifying *BAP1* as the key altered gene in malignant peritoneal mesothelioma (***8***); (*ii*) redefining MPM types as a continuum, uncovering immune–vascular interactions with clinical implications (***9***); (*iii*), revealing novel axes of molecular variation and specialized tumor profiles in this disease (***10***); and (iv) generating the first phenotypic molecular nmap of this disease (Di Genova *et al. GigaSci.* 2023). The published findings were also included in the **WHO Classification of Thoracic Tumors, 5thEd,** within the Mesothelial Tumors chapter, and allowed me to participate as **expert in the EURACAN/IASLC proposal for updating the histologic classification of pleural mesothelioma (**Nicholson *et al. J Thorac Oncol.* 2020**).** I was invited speaker at the **14th Int. Conference of the Int. Mesothelioma Interest Group (iMig)** (2018) and at the **20th WCLC** (2019) to present this work. More recently I have been invited as speaker to the upcoming **16th iMig** taking place in Lille, and to the **2023 EMBL Conference on Cancer Genomics**.

8. Leblay N, (…), **Fernandez-Cuesta L (corresponding)**, Brevet M. *BAP1* Is Altered by Copy Number Loss, Mutation, and/or Loss of Protein Expression in More Than 70% of Malignant Peritoneal Mesotheliomas. ***J Thorac Oncol.*** **2017** PMID: 28034829

9. Alcala N, (…), **Fernandez-Cuesta L (corresponding)**. Redefining Malignant Pleural Mesothelioma types as a continuum uncovers immune-vascular interactions. ***EBioMedicine*****. 2019** PMID: 31648983

10. Mangiante L, (…) **Fernandez-Cuesta L (corresponding)**. Multiomic analysis of malignant pleural mesothelioma identifies molecular axes and specialized tumor profiles driving intertumor heterogeneity. ***Nat Genet.*** **2023** PMID: 36928603 (Highlighted in a Research Briefing)