CURRICULUM VITAE ABREVIADO (CVA)

***IMPORTANT** – The Curriculum Vitae cannot exceed 4 pages. Instructions to fill this document are available in the website.*

Part A. PERSONAL INFORMATION

First name	David		
Family name	Santamaría		
Gender (*)	Male	Birth date (dd/mm/yyyy)	19/08/1971
Social Security, Passport, ID number	05280554F		
e-mail	d.santamaria@usal.es	URL Web	
Open Researcher and Contributor ID (ORCID) (*)		0000-0002-4711-3569	

(*) Mandatory

A.1. Current position

Position	Investigador Científico CSIC		
Initial date	01/12/2021		
Institution	Consejo Superior de Investigaciones Científicas (CSIC), Instituto de Biología Molecular y Celular del Cáncer (IBMCC)		
Department/Center	CIC	Molecular mechanisms of cancer program	
Country	Spain	Teleph. number	923294810
Key words	Lung cancer, KRAS oncogene, signalling pathways, mouse models, therapeutic intervention		

A.2. Previous positions (research activity interuptions, indicate total months)

Period	Position/Institution/Country/Interruption cause
2024-today	Deputy Director of scientific affairs, CIC, Salamanca, Spain
2021-today	Investigador CSIC, CIC, Salamanca, Spain
2017-2021	DR2 INSERM, IECB, Bordeaux, France
2016-2017	Group Leader, IECB, Bordeaux, France
2003-2016	Staff Scientist, CNIO, Madrid, Spain
2001-2003	Postdoctoral, Hutchison MRC Centre, Cambridge, UK
1999-2001	Postoctoral, Wellcome CRC Institute, Cambridge, UK
1994-1999	PhD student, CIB (CSIC), Madrid, Spain

A.3. Education

PhD	Universidad Autónoma, Madrid	1999
Graduated (BSc)	Universidad Complutense, Madrid	1994

Part B. CV SUMMARY *(max. 5000 characters, including spaces)*

I carried out my PhD (group J.B. Schwartzman, CSIC) working on the stability of DNA replication forks. At that time, the control of the initiation of DNA replication and its connection with cell cycle regulation was emerging. I joined Ron Laskey's lab (Wellcome/CRC, Cambridge, UK) as a postdoctoral fellow to characterize these mechanisms in higher eukaryotes. In 2003 I joined Mariano Barbacid's group (CNIO) as a staff scientist to coordinate research on the Cyclin-dependent kinase (Cdk) family. To this end we generated mouse models to dissect Cdk functions and found all interphase Cdks (Cdk2, 3, 4 and 6) to be dispensable. Cdk1, due to functional redundancy, could on its own sustain the mammalian cell cycle and most of embryonic development[1]. We showed that interphase

Cdks display cell, tissue and importantly tumour-specific functions[2]. Based on our results several clinical trials are ongoing to evaluate the efficacy of Cdk4/6 inhibitors for the treatment of patients with KRAS-driven lung adenocarcinoma (LUAD). Following similar genetic approaches we demonstrated the therapeutic efficacy and low toxicity upon inhibition of c-Raf, a KRAS-downstream effector within the MAPK pathway[3]. We also showed the additive value of combining Cdk4 and c-Raf inactivation[4]. Other innovative treatments (co-inhibition of DDR1 and Notch) were equally identified with the help of mouse models[5].

In 2016 I was recruited at the IECB, (Bordeaux, France) to establish my own laboratory and obtained a permanent INSERM DR2 position in 2017. From the beginning, my independent research has focused on enhancing our mechanistic understanding of RAS oncogenic signalling with a primary focus on the MAPK pathway. In particular, we have focused on investigating what I believe to be an essential variable in LUAD: the dynamic quantitative control of MAPK signalling output. Soon after relocating to the IECB, we demonstrated that there is a narrow and cell type specific threshold by which KRAS signalling through the MAPK pathway triggers LUAD[6]. This demonstrated that MAPK intensity is a critical determinant not only in dictating the cancer-initiating cell and tumour phenotype. Elucidating the factors that shape and maintain this optimal threshold will greatly improve our understanding of oncogenic signalling and could identify new therapeutic targets. One potential way to implement such control could be by regulating the formation of dimers and higher order KRAS nanoclusters on the cell membrane. We showed that if oncogenic KRAS is forced to function as a monomer it fails to activate downstream signalling thereby loosing its oncogenic capacity[7]. In 2020 I obtained a CSIC position affiliated to CIC/Salamanca where we are currently conducting research aimed at functionally and biochemically characterizing KRAS membrane clustering as well as other vulnerabilities with therapeutic potential. During this period I have supervised six PhD students plus an additional one currently ongoing.
In this context, I have established various research agreements with pharmaceutical companies that are actively involved in the RAS field –Aelin Therapeutics (Belgium), Revolution Medicines (USA)–. As a consequence, we have had anticipated access to compounds exploiting innovative mode of actions that have been (and will continue to be) invaluable research tools. Our intention is to go beyond the mere characterization of their mode of action and the phenotypic consequences, instead using these drugs as research tools to address fundamental biological questions in the RAS field that remain to be resolved. We have recently followed this strategy using patient derived biopsies to both identify resistance mechanisms to the first generation of KRAS inhibitors and to validate novel compounds with high therapeutic value in this important clinical context[8]. We are also privileged to collaborate with various thoracic oncology departments in the country (Ernest Nadal –Idibell–, Luis Paz-Ares –12 de Octubre–, Javier de Castro –La Paz– and Edel del Barco –Hospital de Salamanca–) and abroad (Colin Lindsay –Manchester Hospital–). These interactions will provide clinically relevant material and generate new research models. More importantly, our interactions will help to identify biological questions with clear clinical implications that may help to guide future therapeutic interventions in the field of KRAS-driven malignancies.

Key references:
1. Santamaría, D. et al. (2007) ***Nature*** 448, 811-5.
2. Santamaría, D. & Ortega, S. (2006) ***Front Biosci.*** 11, 1164-88.
3. Blasco, R.B. *et al*. (2011). ***Cancer Cell*** 19, 652-63.
4. Esteban Burgos, L. *et al*. (2020). ***PNAS*** 117, 24415-26.
5. Ambrogio, C. *et al*. (2016). ***Nature Medicine*** 22, 270-7.
6. Nieto, P., et al. (2017) ***Nature*** 548, 239-43.
7. Ambrogio, C. *et al*. (2018). ***Cell*** 172, 857-68.
8. Holderfield, M. et al. ***Nature*** (in press)

Part C. RELEVANT MERITS *(sorted by typology)*

C.1. Publications *(see instructions)*

Total publications: 43. Selected publications during the last ten years (CA=corresponding or co-corresponding author):

1. Holderfield, M., Bianca, J.L., Jiang, J., /…/ and Singh, M. (2024) Concurrent inhibition of oncogenic and wild-type RAS-GTP for cancer therapy. ***Nature*** doi: 10.1038/s41586-024-07205-6. Position and total authors: 43/53.

2. Nokin, M.J., Mira, A., Patrucco, E., /…/ **Santamaría, D.** and Ambrogio, C. Novel RAS(ON) inhibitors overcome clinical resistance to KRASG12C covalent blockade. ***Nat Commun*** (**in press**). Position and total authors: 25/26 (CA).

3. Nokin, M.J., Darbo, E., Richard, E., /…/ and **Santamaría, D.** Sequential redox vulnerabilities with therapeutic potential during the acquisition of drug resistance in BRAFV600E lung adenocarcinoma. ***Cell Reports Medicine*** (**in press**). Position and total authors: 26/26 (CA).

4. Ricciuti, B., Son, J., Okoro, J.J., /…/ and Ambrogio, C. (2022) Comparative analysis and isoform-specific therapeutic vulnerabilities of KRAS mutations in non-small cell lung cancer. ***Clin Can Res.*** doi: 10.1158/1078-0432.CCR-21-2719. Position and total authors: 22/26.

5. Sanclemente, M., Nieto, P., Garcia-Alonso, S., /…/ and Barbacid, M. (2021) RAF1 kinase activity is dispensable for KRAS/p53 mutant lung tumor progression. ***Cancer Cell*** doi: 10.1016/j.ccell.2021.01.008. Position and total authors: 10/12.

6. Nokin, M.J., Ambrogio, C., Nadal, E. and **Santamaría, D.** (2020) Targeting Infrequent Driver Alterations in Non-Small Cell Lung Cancer. ***Trends Cancer*** doi: 10.1016/j.trecan.2020.11.005. Position and total authors: 4/4 (CA).

7. Esteban-Burgos, L., Wang, H., Nieto, P., /…/ and Barbacid, M. (2020) Tumor regression and resistance mechanisms upon CDK4 and RAF1 inactivation in KRAS/P53 mutant lung adenocarcinomas. **PNAS** doi/10.1073/pnas.2002520117. Position and total authors: 17/19.

8. Nokin, M.J., Darbo, E., Travert, C., /…/ **Santamaría, D.** and Ambrogio, C. (2020) Inhibition of DDR1 enhances in-vivo chemosensitivity in KRAS-mutant lung adenocarcinoma. **JCI Insight** doi: 10.1172/jci.insight.137869. Position and total authors: 20/21 (CA).

9. Ambrogio, C., Köhler, J., Zhou, Z., /…/ and **Santamaría, D.***, Westover, K.D.* and Jänne, P.A.* (2018) KRAS dimerization impairs sensitivity to MEK inhibitors and is essential for oncogenic activity of mutant KRAS. ***Cell*** 172(4), 857-68.e15. doi: 10.1016/j.cell.2017.12.020. * Co-senior authors. Position and total authors: 13/15.

10. Nieto, P., Ambrogio, C., De Esteban, L., /…/ and **Santamaría, D**. (2017) A B-Raf kinase inactive mutant induces lung adenocarcinoma. ***Nature*** 548, 239-43. Position and total authors: 12/12 (CA).

11. Ambrogio, C., Barbacid, M. and **Santamaría, D**. (2017) *In vivo* oncogenic conflict triggered by co-existing *KRAS* and *EGFR* activating mutations in lung adenocarcinoma. ***Oncogene*** 36(16), 2309-18. Position and total authors: 3/3 (CA).

12. Ambrogio, C., Gómez-López, G., Falcone M., /…/ and **Santamaría, D**. and Barbacid, M. (2016) Combined inhibition of DDR1 and Notch signaling is a therapeutic strategy for KRAS-driven LUAD. ***Nature Medicine*** 22(3), 270-7. Position and total authors: 14/15 (CA).

13. Ambrogio, C., Carmona, F.J.,/…/ **Santamaría D.** and Villanueva A. (2014) Modeling lung cancer evolution and pre-clinical response by orthotopic mouse allografts. ***Cancer Research*** 74, 5978-88. Position and total authors: 16/17 (CA).

14. Cerqueira, A., Martín, A., Odajima, J., Dubus, P., Barbacid, M and **Santamaría, D**. (2014) Genetic characterization of the role of the Cip/Kip family of proteins as Cdk inhibitors and assembly factors. ***Mol Cell Biol*** 34, 1452-9. Position and total authors: 6/6 (CA).

C.2. Congress, indicating the modality of their participation (invited conference, oral presentation, poster)

1. Targeting RAS Symposium, Salamanca (Spain), 13-15 September 2023 (https://targetingras.com/). David Santamaría: co-organizer.

2. First symposium Conexión Cáncer CSIC, Benidorm, 23-25 January 2023. David Santamaría: invited speaker, title: *Targeting KRAS/MAPK signalling in lung cancer*.

3. The Fourth RAS Initiative Symposium, Frederick (USA), 17-19 October 2022. David Santamaría: oral communication, title: *RAS(ON) inhibitors overcome clinical adaptive resistance to KRAS G12C covalent blockade*.

4. 17th GSO Canceropole Carcassonne (France), 17-19 November 2021. David Santamaría: invited speaker, title: *Novel mechanisms controlling KRAS oncogenic output: impact on tumour fitness and cancer vulnerabilities.*

5. 1st DDR international meeting, Bordeaux, (France) 22-24 May 2019. David Santamaría: co-organizer.

C.3. Research projects, indicating your personal contribution. In the case of young researchers, indicate lines of research for which they have been responsible.

As principal investigator (last five years):

2022 Combination of structural and functional studies to elucidate the biology of the KRAS signalosome. Funding Institution: FCAECC. Amount granted: 300k €.

2021 Functional characterization and therapeutic potential of membrane-associated KRAS complexes, Proyectos I+D+i, Ministerio de Ciencia e Innovación. Amount granted: 283k €.

2019 Targeting KRAS dimerization in advanced lung adenocarcinoma. Funding institution: INCa plbio (France). Biology and Cancer Research. Amount granted: 432k €.

As co-applicant:

2022-2026 STOP RAS CANCERS: Program on Early Diagnosis and Targeted Intervention for RAS-driven Cancers. Funding Institution: AECC Excellence. Amount granted: 2M €. Co-applicant with Eugenio Santos.

2020-2022 Modulating glycemia to improve chemoradiotherapy and immunotherapy in Non-Small Cell Lung Carcinoma. Fundació la Marató TV3. PI: Cristina Muñoz Pinedo (Idibell, Barcelona, Spain). Amount granted: 300k € (100k for Santamaría lab).