PERSONAL INFORMATION

Name (family, first): **Benitah, Salvador Aznar**
Researcher ORCID: http://orcid.org/0000-0002-9059-5049
Date of birth: 12 June, 1975 (Montreal, Canada)
Nationality: Spanish, Canadian
URL for web site: https://www.irbbarcelona.org/es/research/stem-cells-and-cancer

CURRENT POSITIONS

2023-present Director of Aging and Metabolism Program, IRB Barcelona
2014-present ICREA Professor at IRB Barcelona (Stem cells and Cancer Laboratory)
2019-present Founder and Scientific Advisor of *ONA Therapeutics*
2020-present Founder Pediatric Osteosarcoma Program for Metastasis, IRB/SJD Hospital, Barcelona

EDUCATION AND PREVIOUS POSITIONS

2007-2013 Junior ICREA Group Leader, Center for Genomic Regulation (Barcelona)
2003-2006 Postdoctoral fellow, London Research Institute, Cancer Research UK
1998-2003 PhD (*Magna cum laude*), Biomedical Research Institute (Madrid, Spain)
1997-1998 Masters in Biochemistry, McGill University, (Montreal, Canada)
1993-1998 Bsc Biochemistry **AND** Bsc Molecular Biology (*Honours degree*), McGill University (Canada)

AWARDS

2022 Foundation Lilly Award for Life Sciences
2022 Spanish Association for Cancer Research award (2022)
2021 EACR best publication of the year award in cancer in Europe
2020 ***i)*** Lilliane Bettencourt Award for Life Sciences; ***ii)*** Axa Award in Life Sciences; ***iii)*** Carmen and Severo Ochoa Award in Life Sciences; ***iv)*** Foundation Serra in Biomedicine Award
2018 ***i)*** Foundation Pfizer Award ; ***ii)*** **ERC Advanced Grant**
2017 ***i)*** Bank Caja Rural National Award for Life Sciences; ***ii)*** City of Barcelona Award for Life Sciences; ***iii)*** Catalan Society of Biology Award
2016 Spanish National Award in Biomedicine
2014-2015 ***i)*** Banc Sabadell Award in Biomedicine (2015); ***ii)*** Foundation Botín Award (2014)
2013 ***i)*** Beug Foundation Award; ***ii)*** **ERC Consolidator Grant**
2001-2012 ***i)*** Lancöme Award for Skin Research ***ii)*** Max Dellbruck Award for Stem Cell Research**;** ***iii)*** Marie Curie Intra-European Postdoctoral Fellowship**;** ***iv)*** Long-Term EMBO Postdoctoral Fellowship**;** ***v)*** Cancer Research UK Postdoctoral Prize**;** ***vi)*** Award for Best PhD Thesis of the Year, Spain**;** ***vii)*** EACR Young Investigator Award **2001** AND **2002**

ORGANIZATION OF MEETINGS

2024 *Forbeck Meeting* on Cancer and Metabolism
2023 *Keystone Meeting* on Aging AND *Gordon Research Conference* Epithelial Differentiation
2022-2023 Virtual monthly meetings for epithelial stem cell community (over 300 attendees monthly)
2022 Biomed Conference on Aging IRB meeting (Barcelona)
2021 *Skin Epigenetics Symposia*, International Society of Dermatology
2019 *Gordon Research Conference Epithelial Differentiation* (USA)
2018 *Metastasis Research Society*, Princeton University (USA)
2018 *Mechanisms of Metastasis* IRB meeting (Barcelona)
2017 *Epigenetics in Skin* Symposium (Salzburg)
2016 *Beyond the Cancer Genomes* meeting (Barcelona)

INSTITUTIONAL RESPONSIBILITIES/ ACTIVITIES

2023-now Director of the Aging and Metabolism Department, IRB Barcelona
2023-now Member of the EMBO Council (selection of EMBO members, EMBO YIP, etc)
2023-now Member of the ERC Consolidator Grant Evaluating Panel
2023-now Member of the AACR organizing committee
2021-now Director of the Cancer Node at the IRB Barcelona

2018-now EMBO Member
2009-2012 Executive Board member of the Spanish Association for Cancer Research
2014-now International Committee *International Society for Stem Cell Research* (ISSCR)
2014-now Scientific advisor for *L´Oreal* (Paris, France)
2014-now ***i)*** Lectures to the public at the Center for Contemporary Culture of Barcelona
ii) Lectures of the City Council of Barcelona on stem cells, cancer, and aging
2013-now Evaluating panel of the *Leo Pharma Award*
2012-2017 Board member of the *European Society for Dermatological Research*
Since 2011 Lectures for PhD students at Universitat de Barcelona AND at University Pompeu Fabra
2007-2012 Permanent member of the *Ethical Committee for Animal Research*

REVIEWER AND EDITORIAL BOARDS

Journals: *Nature, Science, Cell Stem Cell, Cell, Aging Cell, Cancer Discovery, Cell Reports, Cell Metabolism, Nat Cell Biol, Nat Med, Nature Cancer, Nat Genetics, Nature Aging, Elife, Journal of Cell Science, The EMBO Journal, EMBO rep, Oncogene, PloS Genetics, Development, and J Invest Dermat.*

Associate Editor: *Aging Cell, Science Advances,* AND *Stem Cell Reports*
Grant reviewer: France, Belgium, US, MRC/*Wellcome Trust*, WWCR), Italy, ERC Consolidator panel
2009-2015: Permanent evaluating committee for the *Spanish National Agency for Grant Reviewing*

RESEARCH HIGHLIGHTS

Daily timing of adult stem cell function and its impact on aging and cancer: Our group pioneered the finding that the timing of stem cell function is regulated by the circadian clock (***Nature*** 2011). We have shown that circadian rhythms control many stem cell functions which are essential to maximize functionality while minimizing potential damages and energy expenditure. Importantly, deregulation of this internal clock results in premature tissue ageing and a high predisposition to cancer (***Nature*** 2011; ***Cell Stem Cell*** 2013). We have recently also shown that stem cells unexpectedly remain rhythmic during aging, yet their circadian output becomes reprogrammed to cope with age-related stresses (***Cell*** 2017a; ***Cell*** 2017b). Importantly, this circadian reprogramming is prevented by caloric restriction (***Cell*** 2017a/b). It has been unclear how different tissues achieve a synchronized rhythmic physiology. We have recently shown that unexpectedly light entrains circadian clocks without any commitment of other clocks but other clocks help tissues "remember" time in the absence of external cues (***Cell*** 2019a; ***Cell*** 2019b; ***Sci Advances*** 2021; ***Sci Advances*** 2022). Excitingly, we have now dissected for the first time how the brain communicates with peripheral tissues, and identified a completely unforeseen gatekeeper function of peripheral tissues over the central clock (Mortimer et al., under 2nd review ***Cell***; and Kumar et al., under 2nd review ***Cell****;* and ***Cell Reports*** accepted 2023)

Regarding niche cells, we observed that the identity of aged fibroblasts becomes noisy and gains traits of adipogenic cells, reducing secretion of matrix proteins and increased inflammatory cytokines surrounding stem cells (***Cell*** 2018). In addition, we have found that increased IL17 in T-helper 17 cells orchestrates much of the inflammatory signals that take place in the aged skin (***Nature Aging***, accepted 2023).

Epigenetic control of adult stem cells, homeostasis and disease: Epigenetic mechanisms ensure that cell lineages are stably established during development. However, we were among the first to show that they are relatively dispensable for maintaining adult stem cell identity, yet ensure that SCs remain flexible towards stress (***Cell Stem Cell*** 2011; ***EMBO*** 2011; ***Nat Rev Mol Cell Biol*** 2016; ***Cell Stem Cell*** 2016; ***eLife*** 2017). We have also shown how chromatin accessibility influences the mutational landscape of tumors, establishing a link between epigenetic regulation and mutational load (***Nat Cell Biol*** 2018; ***Cell Stem Cell*** 2021).

Identification of metastasis-initiating cells and how they are influenced by metabolism: In 2017 we described the cells responsible for metastasis in several types of tumors (***Nature*** 2017; ***Nature*** 2021; ***Nature Metabolism*** 2021; ***Nature*** *2022*; ***Cell Metabolism*** 2022). These cells have intriguing characteristics in that they express the fatty acid channel CD36, are characterized by a unique lipid metabolic signature, and they are exquisitely sensitive to the levels of fat in circulation. Importantly, they are highly sensitive to CD36 inhibition. Interestingly, specific dietary lipids are selectively utilized in the mitochondria for energy, and exert a striking long-term effect over metastatic-initiating cells related to promoting tumor innervation, putting forward a novel concept of ¨metastatic epigenetic memory¨ elicited by our diet (***Nature*** 2021; ***Nature*** 2022a; under 2nd review in ***Nature Metabolism***). We have also recently shown that systemic inhibition of CD36 restores muscle regeneration in aged mice (***Nature*** 2023). Based on this, in 2019 I founded a company (***ONA Therapeutics***) to develop anti-metastatic therapies, with a Series A capital funding of 32M euros obtained with a syndicate of international investors.

TOP PUBLICATIONS

Smith JG, Koronoski, et al, **Benitah SA***, Sassone-Corsi P*. A Minimal Circadian Clock Network for Glucose Tolerance in Mice. ***Cell Reports*** (accepted) 2023 (*co-corresponding)

Sola P, Mereu E, et al, **Benitah SA**. Local IL17 orchestrates skin aging. ***Nature Aging*** (accepted) 2023

Moiseeva M, Cisneros A, et al, **Benitah SA**, et al, Muñoz-Cánoves P. A senescence blueprint defines an aged-like inflamed niche that inhibits muscle regeneration. ***Nature*** 2023

Delaunay S, Pascual G, Feng B, et al, **Benitah SA***, Frye M*. Mitochondrial RNA modifications shape metabolic plasticity in metastasis. ***Nature*** 2022 (*co-corresponding)

Petrus P, Smith JG, Koronowski KB, et al, **Benitah SA**. The central clock suffices to drive the majority of circulatory metabolic rhythms. ***Sci Adv*** 2022

Pascual G, Domínguez D, Elosúa-Bayes M, et al, **Benitah SA**. Dietary palmitic acid promotes a prometastatic memory via Schwann cells. ***Nature*** 2021

Welz PS, Zinna VM, Symeonidi A, et al, **Benitah SA**. BMAL1-Driven Tissue Clocks Respond Independently to Light to Maintain Homeostasis. ***Cell*** 2019

Koronowski KB, Kinouchi K, et al, **Benitah SA***, Sassone-Corsi P*. Defining the Independence of the Liver Circadian Clock. ***Cell*** 2019 (*co-corresponding)

Salzer MC, Lafzi A, Berenguer-Llergo A, et al, **Benitah SA**. Identity Noise and Adipogenic Traits Characterize Dermal Fibroblast Aging. ***Cell*** 2018

Solanas G, Peixoto FO, Perdiguero E, et al, **Benitah SA**. Aged Stem Cells Reprogram Their Daily Rhythmic Functions to Adapt to Stress. ***Cell*** 2017

Sato S, Solanas G, et al, **Benitah SA*,** Sassone-Corsi P*. Circadian Reprogramming in the Liver Identifies Metabolic Pathways of Aging. ***Cell*** 2017 (*co-corresponding)

Pascual G, Avgustinova A, Mejetta S, et al, **Benitah SA.** Targeting metastasis-initiating cells through the fatty acid receptor CD36. ***Nature*** 2017

Rinaldi L, Datta D, Serrat J, et al, **Benitah SA**. Dnmt3a and Dnmt3b Associate with Enhancers to Regulate Human Epidermal Stem Cell Homeostasis. ***Cell Stem Cell*** 2016

Uribesalgo I, Buschbeck M, Gutiérrez A, et al, **Benitah SA***, Di Croce L*. E-box-independent regulation of transcription and differentiation by MYC. ***Nat Cell Biol*** 2011 (*co-corresponding)

Luis NM, Morey L, et al, **Benitah SA**. Regulation of human epidermal stem cell proliferation and senescence requires polycomb- dependent and -independent functions of Cbx4. ***Cell Stem Cell*** 2011

Janich P, Pascual G, Merlos-Suárez A, et al, **Benitah SA**. The circadian molecular clock creates epidermal stem cell heterogeneity. ***Nature*** 2011

SELECTED REVIEWS

Martin-Perez M, Urdiroz U, **Benitah SA**. The role of lipids in cancer metastasis. ***Cell Metab*** 2022

Benitah SA, Welz PS. Circadian regulation of adult stem cell homeostasis and aging. ***Cell Stem Cell*** 2020

Avgustinova A, **Benitah SA**. Epigenetic control of adult stem cell function. ***Nat Rev Mol Cell Biol*** 2016

Solanas G, **Benitah SA**. Regenerating the skin: stem cells and their niche. ***Nat Rev Mol Cell Biol*** 2013

MEETINGS AS SPEAKER (selected from the last 10 years)
Metastasis Research Society (2018, 2020, 2022, 2023); *Nature:* Cancer and metastasis (2019, 2020); *Foundation Les Treilles* Stem Cells and Cancer (2018, 2019, 2023); *Cold Spring Harbor* Stem Cells (2011, 2012, 2017); *Keystone:* Metastasis (2023, 2021); Cancer Metabolism (2023, 2022, 2017); Ageing (2023, 2016); Epigenetics (2015, 2016, 2018, 2020); *Gordon Research Conference:* Epithelial Differentiation (2013, 2015, 2017, 2023); Ageing (2013); Chronobiology (2011, 2013, 2017); Stem Cells (2023, 2017, 2019); *International Society for Stem Cell Research* ISSCR (2012, 2014, 2016, 2017, 2019, 2024); *EMBO:* Aging (2020); Tumor Metabolism (2022, 2018); Stem Cells (2010, 2011); Cancer (2010, 2012); *Nature Medicine:*

Metastasis (2016); *Cell:* Epigenetics (2015); Chronobiology and aging (2018, 2021); EACR (2008, 2015, 2018, 2020, 2022; 2023); Universities*: Cambridge; Oxford; Heidelberg, Princeton, Weizmann, Harvard, Yale, MIT*.

CONTRACTS, TECHNOLOGICAL OR TRANSFER MERITS

2017-2019: Scientific Advisor *with L´Oreal* (France)

2016-present: **Patent granted**: *Targeting metastatic stem cells through a fatty acid receptor*. Number: 15382474.3-4303. Countries: Europe and USA.

2021-present: **Five more patents filed** in 2021 through *ONA Therapeutics*.

2019: Founder of ***ONA Therapeutics*** to develop Abs for metastasis therapies. 32M eur Series A funding.