SHORT CURRICULUM VITAE

Name: Eduard Batlle ***Birth Date:*** 24th July 1970 ***Nationality:*** Spanish

Current Position: Chair, Cancer Science Program. IRB Barcelona.
ICREA Research Professor
Principal Investigator, IRB Barcelona

Date of Start: 01/03/2004

URL for Website: http://www.irbbarcelona.org/ebatlle

Researcher identifiers: ORCID: 0000-0003-2422-0326, Research ID: K-8080-2014

Education & Training:

2000-2003 Postdoctoral Fellow. Prof. Hans Clevers Lab. Hubrecht Laboratorium, Utrecht, Netherlands.

1999-2000 Postdoctoral Fellow. Prof. Miguel Beato's Lab. IMT. Marburg, Germany.

1995/1999 PhD in Biology. University of Barcelona (UB), Spain. Prof. Antonio García de Herrero's Lab. Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain.

07/06/1993 BSc in Biological Sciences. University of Barcelona (UB), Spain

Institutional Responsibilities

2005-to date Head of the Cancer Science Program at IRB Barcelona: Activities include designing the strategic lines of the programme, the identification and recruitment of new group leaders, mentoring junior programme members, and organizing program activities.

2005-to date Member of the direction committee of IRB Barcelona: This is the maximum decision-making organ regarding strategic and scientific policies in the institute.

Representative publications as corresponding author since 2011

1. HERPES B et al. (36 AUTHORS), **BATLLE E** and THROSBY M. *Functional patient-derived organoid screenings identify MCLA-158 as a therapeutic EGFR x LGR5 bispecific antibody with efficacy in epithelial tumors.* **Nature Cancer.** 2022. *In press.*

2. TAURIELLO DVF, SANCHO E, AND **BATLLE E**. *Overcoming TGFβ-mediated immune evasion in cancer.* **Nature Reviews Cancer**. 2021. doi: 10.1038/s41568-021-00413-6

3. MORRAL C et al. (18 AUTHORS) and **BATLLE E**. *Zonation of ribosomal DNA transcription defines a stem cell hierarchy in colorectal cancer.* **Cell Stem Cell.** 26 (6): 845-861. 2020.

4. **BATLLE E** AND MASSAGUÉ J. *Transforming Growth Factor-β Signaling in Immunity and Cancer.* **Immunity**. 50 (4), 924-940. 2019. [Citations: 763]

5. TAURIELLO DVF, et al. (16 AUTHORS) and **BATLLE E**. *TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis*. **Nature**. 554:538-543. 2018. [Citations: 967]

→ *This study received 10 previews and editorial highlights: Trends in Cancer (10.1016/j.trecan.2018.03.005), Immunity (doi.org/10.1016/j.immuni.2018.03.037), British Journal of Cancer (doi.org/10.1038/s41416-018-0122-x), Cancer Discovery, Science Signaling, Nat Rev Gastroenterol Hepatol, Nat Rev Clin Oncol, Nat Rev Cancer, Nat Rev Immunol, Trends in Immunology. It is amongst the top 1% most cited articles of similar age in all journals.*

6. **BATLLE E** & CLEVERS H. *Cancer stem cells revisited.* **Nature Medicine.** 23 (10), 1124-1134. 2017. [Citations: 1492]

7. BARRIGA F, et al. (14 AUTHORS) and **BATLLE E**. *Mex3a marks a slowly dividing subpopulation of Lgr5+ Intestinal Stem Cells.* **Cell Stem Cell.** 20 (6): 801-816. 2017. [Citations: 122].

8. CALON A, et al. (17 AUTHORS) and **BATLLE E**. *Stromal gene expression defines poor-prognosis subtypes in CRC.* **Nature Genetics.** 47: 320-362. 2015. [Citations: 814]

→ *This study received **6** News & Views/Editorial Highlights: Nature Genetics, EMBO Molecular Medicine, Cancer Discovery, Nat Rev Clin Oncol, Nat Rev Cancer, Nat Rev Gastroenterol Hepatol*

9. WHISSELL G, et al. (16 AUTHORS) and **BATLLE E.** *The transcription factor GATA6 enables self-renewal of colon adenoma stem cells by repressing BMP gene expression*. **Nature Cell Biology**. 16: 695-707. 2014. [Citations: 121]

→ Cover page, News & Views in EMBO J and Cancer Discovery

10. CALON A, et al. (15 AUTHORS) and **BATLLE E.** *Dependency of Colorectal Cancer on a TGF-Beta-Driven Program in Stromal Cells for Metastasis Initiation*. **Cancer Cell.** 22: 571–584. 2012. [Citations: 885]

11. JUNG P, et al. (10 AUTHORS) and **BATLLE E.** *Isolation and in vitro expansion of human colonic stem cells*. **Nature Medicine.** 17**:** 1125**-**1127**. 2011.** [Citations: 628]

12. SOLANAS G, CORTINA C, SEVILLANO M and **BATLLE E**. *Cleavage of E-cadherin by ADAM10 mediates epithelial cell sorting downstream of EphB signaling*. **Nature Cell Biology**. 13**:** 1100-1107. **2011.** [Citations: 165]

13. MERLOS-SUÁREZ A, et al. (12 AUTHORS) and **BATLLE E.** *The intestinal stem cell signature identifies colorectal cancer stem cells and predicts disease relapse.* **Cell Stem Cell.** 8(5)**:** 511-524**. 2011.** [Citations: 897]

Awards and Distinctions

2021 **King Jaume-I Award in Medicine**
2019 **City of Barcelona Award in Life Sciences**
2018 **Medal from the International Foundation Olof Palme**
2017 **Francisco Cobos Foundation Award to Biomedical Research**
2016 **Carmen y Severo Foundation Ochoa Award**
2016 **Lilly Foundation Award** in Pre-clinical studies
2015 **Life Sciences National Award from Caja Rural de Granada Foundation**
2014 **The Pezcoller foundation-EACR Cancer Researcher Award**
2013 **Joseph Steiner Cancer Research Award (**Berna, Switzerland)
2013 **National Award in Cancer Research "Doctores Diz-Pintado"**
2010 **Banc de Sabadell Award** for Research in Biomedicine
2006 **Debiopharm Life Sciences Award** (Lausanne, Switzerland)

Main research projects granted (past 10 years)

2020 – 2025: ERC Advanced Grant. ERC-2019-AdG 884623; ResidualCRC.
2019 – 2024: CRUK /AECC. Accelerator Award: MACH3CANCER network.
2018 – 2023: CRUK/AECC. Accelerator Award: ACRClerate network.
2019 – 2022: La Caixa Foundation Health Research 2018. HR18-00359.
2019 – 2021: World Wide Cancer Research. 19-0005.
2018 – 2021: Spanish Association for Cancer Research (AECC).
2018 – 2020*:* Spanish Ministry of Education. SAF2017-86782-R.
2014 – 2019: ERC Advanced Grant. ERC-2013-AdG 340176; EditCRC.
2013 – 2017: Josef Steiner Cancer Research Award.

2013 – 2016: FP7-HEALTH-2013- 601876 SUPPRESSTEM consortium.
2008 – 2012: ERC Starting Grant. ERC-2007-StG 208488; CRC programme.

Invited Presentations (selection of more than 100 invited talks in the past 5 years)

Oct 2021	Cold Spring Harbor Biology of Cancer: "Microenvironment & Metastasis" (virtual).
Apr 2021	American Association for Cancer Research (AACR) Annual Meeting (virtual).
Oct 2020	European Society of Molecular Oncology (ESMO) Congress (virtual).
Oct 2020	EORTC-NCI-AACR Symposium on Cancer Therapeutics (virtual).
Nov 2019	Cell Symposia: Hallmarks of Cancer. Seattle. US.
Nov 2019	EACR Conference "Goodbye Flat Biology: Advancing 3D-based Models for Cancer Biology and Drug Discovery". Berlin. Germany.
Oct 2019	2nd joint EACR-MRS Conference on "Seed and Soil". Berlin. Germany.
Sep 2019	Cell Plasticity in Colorectal Carcinogenesis Symposium. Frankfurt. Germany.
Sep 2019	Oxford Stem Cell Institute Symposium 2019. UK
May 2019	International Society Stem Cell Research (ISSCR) Annual Meeting; Los Angeles.
May 2019	EMBO Workshop on "Mesenchymal cells in inflammation, immunity and cancer", Athens.
Mar 2019	American Association for Cancer Research, AACR 2019 Annual Meeting. Atlanta. US.
Sep 2018	AACR meeting Intestinal Stem Cells and Colon Cancer: Biology to Therapy. Washington. US.
Sep 2018	EMBO Workshop on Cellular signaling and cancer therapy. Cavtat. Croacia.
Sep 2018	ISREC-SCCL Symposia "Horizon in Cancer Biology and Therapy". Lausanne. Switzerland.
Aug 2018	Metastasis Research Society Bi-annual meeting, Princeton University. US.
May 2018	Ho-am Forum on Medicine. Seoul. Korea.
Apr 2018	Speaker and session Chair. AACR Annual Meeting. Chicago. US.
Sep 2017	Victorian Comprehensive Cancer Center Inaugural symposium. Melbourne. AUS.
Jun 2017	Sigrid Jusélius Symposium. Helsinki. Finland.
Apr 2016	AACR Annual Meeting. New Orleans. US.
Apr 2016	EMBO|EMBL Symposium: "Tumor microenvironment". Heidelberg. Germany

Organization of International Conferences

2007,-12,-21	Organizer of Barcelona Biomed Conference: "Stem Cells and Cancer" (with Hans Clevers).
2018	Member of the organization committee for the 2019 International Society for Stem Cell Research (ISSCR) symposia on Stem Cells & Organoids in Development and Disease.
2015-2016	Member of the organization committee for 2017 ISSCR Annual Meeting.
2016	Co-organizer of the 2016 Barcelona Conference on Epigenetics and Cancer.
2009	Organizer of CNIO Cancer Conference: Stem Cells and Cancer (with Maria A. Blasco, Elaine Fuchs, and Mirna Pérez-Moreno).

REVIEWING ACTIVITIES

2017-present	Member of the editorial advisory board of EMBO Molecular Medicine.
2013 / 2020	Member of the evaluating panel for ERC-Consolidator Grants.
2020	Evaluation panel of junior PIs for Francis Crick Institute (London. UK).
2018 / 2021	Member of selection committee of new group leaders at EMBL Barcelona.
2017	Member of the jury of the Fundación Lilly Award
2015	Member of the jury for the 2016 Pezcoller Foundation/AACR Award
2005-2012	External Advisor for group leader search and evaluation committees at the

	Center for Genomic Regulation (CRG-Barcelona)
2011- 2015	Member of the Scientific Advisory Committee for World Wide Cancer Research
2011-present	Member of the Jury for the Banc Sabadell Award.
2004-present	Peer-reviewer of research projects for the ERC, Spanish Agency of Evaluation (ANEP); Associazione Italiana per la Ricerca sul Cancro; Cancer research UK, MRC, Netherlands Organization for Health Research and Development (ZonMw TOP grants), KWF, WWCR; INSERM and more.

MAIN TECH-TRANSFER ACTIVITIES.

- Generation of a bi-specific LGR5 x EGFR therapeutic antibody MCLA-158. in collaboration with the pharmaceutical company MERUS (see details in the progress report section). A patent was granted: WO/2014/072517. MCLA-158 is currently in phase 1 clinical trials for metastatic CRC (see section below for for details).

-Development of companion diagnostic tests for TGF-β inhibitory therapies. Part of this program was funded by the Mind the Gap program of the Botin Foundation. A family of patents protect the biomarkers discovered (WO/2014/072517, PCT/EP2020/077270 and PCT/EP2020/077272). We are currently collaborating with several institutions and companies to implement the use of this test to stratify patients in an upcoming clinical trial based on treating cancer with TGF-β inhibitors.

- *mENVIRON* program in collaboration with pharmaceutical company MERUS. It is aimed at generating bi-specific antibodies to target distinct cell types of the tumor microenviroment. Several lead candidates are currently on an advanced preclinical development phase. Our contributions ranged from antibody screening to testing of therapeutic activies in propietary CRC model systems.

ORIGINAL DISCOVERIES & MAIN CONTRIBUTIONS TO CANCER RESEARCH

My laboratory at IRB Barcelona is a world reference for the study of colorectal cancer (CRC). We perform basic research using innovative model systems and technologies on topics that are clinically relevant. Our pioneering studies have help advance the state of the art in several important areas such the connection between stem cells and cancer, the role of the tumor microenvironment and the identification of mechanisms of metastasis and immune evasion. Some of our discoveries are considered key contributions and have inspired research of many groups worldwide. The impact is reflected in the high number of citations, editorial comments and awards that these studies have received over the past years. Furthermore, some our latest discoveries have inspired the development of new therapies that are currently being tested in patients through clinical trials. In brief:

1) During my doctoral thesis work I originally identified the transcription factor Snail as a suppressor of E-Cadherin expression in epithelial tumor cells. The Batlle et al. article in ***Nature Cell Biology, 2000*** (*3007 citations*) is - together with Cano et al. Nat Cell Biol. 2000 - one the founding papers of the field on epithelial-to-mesenchymal (EMT) transition in cancer.

2) A major and long-lasting contribution of my research has been linking the biology of intestinal stem cells (ISCs) to CRC development. During my postdoctoral training in the Clevers lab, we originally proposed that the first step towards malignancy in CRC consists in the acquisition of a crypt stem-like phenotype (Batlle et al. Cell. 2002; van de Wetering et al. Cell 2002). This discovery represented the first link between adult ISCs and CRC. Follow-up research carried out in my lab at IRB Barcelona crystallized in several additional important discoveries in this area: **1**- The first purification and "in vitro" expansion of human adult colon stem cells (Jung et al., ***Nature Medicine, 2011***). **2**- The characterization of the hierarchical organization of CRC and its relationship to that of the normal colonic mucosa (Merlos-Suárez et al., ***Cell Stem Cell, 2011;*** Whissell et al.***, Nature Cell Biology 2014;*** Cortina et al. ***EMBO Mol Med. 2017;*** *Morral et al.* ***Cell Stem Cell. 2020)***. **3** – The identification of a subpopulation of slow proliferating chemotherapy-resistant ISCs, which are marked by the expression of RNA binding protein Mex3a (Barriga et al. ***Cell Stem Cell, 2017***). **4-** The generation of a bi-specific antibody – **MCLA158** - that targets EGFR signaling in LGR5+ cancer stem cells (WO/2017/069628). A paper describing the generation of MCLA-158 has been recently accepted for publication (***Nature Cancer***. *In press*). This antibody is currently being tested in phase 1 clinical trials for advanced CRC (trial NCT03526835). The first results in patients demonstrated that the antibody is well tolerated. In a cohort of HNSCC patients, interim clinical data showed that the seven patients recruited obtained benefits from MCLA-158 treatment, including two showing partial responses and one achieving a complete remission (see https://merus.nl/wp-content/uploads/2021/10/P185_MCLA-158-HNSCC_virtual-poster_10Sep21_2.pdf). Given that these patients had previously progressed after multiple lines treatment, the responses triggered by MCLA-158 are very significant. Encouraged by these results, the clinical trial continues to recruit patients.

3) My lab pioneered the study of Eph/ephrin signaling in the compartmentalization of normal crypt cells and of CRC cells. The tyrosine kinase receptors Eph and their ligands, the ephrins, were first described as axon pathfinding molecules and their roles had been mainly studied during embryo development. We originally discovered that EphB receptors impose boundaries to the migration of epithelial cells in the intestine and also limit the expansion of colorectal cancers. Subsequently we worked out a downstream mechanism of cell repulsion and differential adhesion triggered by Eph/ephrin interactions in epithelial cells (Batlle et al. ***Cell 2002****;* Batlle et al. ***Nature 2005****;* Cortina et al. ***Nature Genetics 2007****;* Solanas et al. ***Nature Cell Biology 2011***). These works have inspired many laboratories worldwide to study the role of Eph/ephrin signalling in the physiology of other adult tissues and in the development of multiple cancer types.

4) We discovered that metastasis in CRC is a cancer cell non-autonomous process that depends on a TGF-beta-driven gene program expressed in stromal cells. This phenomenon is the central feature of poor prognosis CRC molecular subtypes (Calon et al. ***Cancer Cell,***

2012*;* Calon et al. ***Nature Genetics, 2015***). We recently developed a pre-clinical model of metastatic CRC that reproduces key features of poor prognosis CRC subtypes developed by patients (Tauriello et al. ***Nature 2018***). By exploiting this model, we discovered that elevated TGF-beta levels promote T cell exclusion and limit immune responses in metastatic CRC. Recent evidences suggest that this is a general mechanism of immune evasion co-opted by multiple tumor types. Importantly, we showed that therapies that combine TGF-beta inhibitors and immune checkpoint blockade eradicate metastatic disease in our CRC model systems. This combinatorial therapy is inspiring several clinical trials, some of which are already being implemented. In addition, my laboratory has developed a prognostic test – Colostage - that serves as Companion Diagnostics for the therapeutic use of TGF-beta signaling inhibitors (patent WO/2014/072517, PCT/EP2020/077270 and PCT/EP2020/077272). The lab is also involved in generating additional therapeutic tools to target the tumor microenvironment in collaboration with the pharmaceutical industry.