DR. JOSEF STEINER KREBSFORSCHUNGSPREIS 2013

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Der Dr. Josef Steiner Krebsforschungspreis 2013
wird zu gleichen Teilen Herrn Prof. Dr. Eduard Batlle und
Herrn Prof. Dr. Joan Seoane verliehen.
Herr Batlle ist Leiter des Onkolgie-Programmes am Institut für
Biomedizinische Forschung in Barcelona, Spanien.
Herr Seoane ist Direktor des translationalen Forschungsprogrammes am Vall
d'Hebron Institut für Onkologie in Barcelona, Spanien.
Die Preissumme beträgt gesamthaft CHF 1'000'000.

Dr. Josef Steiner Krebsforschungspreis 2013

Doktor Josef Steiner, Inhaber der „Dr. Steiner Apotheke und Bahnhofdrogerie“ in Biel, hat bei seinem Tode im Jahre 1983 ein grosses Vermögen hinterlassen, welches entsprechend seinem letzten Willen die finanzielle Basis der Dr. Josef Steiner Krebsstiftung bildete. Ziel der Stiftung ist die Förderung der Krebsforschung und die Auszeichnung hochverdienter Wissenschafter auf allen Gebieten der Krebsforschung. Als erster Preisträger konnte 1986 ein Schweizer, Dr. Peter Cerrutti, geehrt werden. Seither konnten zahlreiche hervorragende Wissenschafter aus Europa, USA, Australien und der Schweiz mit dem Dr. Josef Steiner Preis ausgezeichnet werden.

Im Bestreben, die Krebsforschung im Sinne des Stifters effizient und nachhaltig zu fördern, wird seit 1998 ein hervorragendes Forschungsprojekt für die Periode von vier Jahren mit einem Betrag von 1’000’000 Schweizerfranken unterstützt. Der Forschungsgruppenleiter oder die Forschungsgruppenleiterin wird zusätzlich mit einem persönlichen Preis in der Höhe von 50'000 Schweizerfranken ausgezeichnet.

Die Auswahl des preisgekrönten Projektes erfolgte nach einem mehrstufigen strengen Auswahlverfahren. Der Dr. Josef Steiner Preis 2013 wurde in renommierten Wissenschafts-zeitschriften ausgeschrieben. Die eingereichten Projektskizzen wurden vom Stiftungsrat und einer aus Fachvertretern zusammengesetzten Preiskommission gesichtet und bewertet. Als Kriterien wurden die wissenschaftliche Qualität und die Originalität der Projektskizzen, die Qualifikation der Projektverfasser, sowie die Beurteilung der Machbarkeit der vorgeschlagenen Projekte in Betracht gezogen. Fünf hervorragende Projektskizzen wurden ausgewählt und die Verfasser aufgefordert, ein überarbeitetes und detailliertes Projekt einzureichen. Für jedes Projekt wurden mindestens drei externe Gutachten eingeholt.

Zusätzlich wurden die fünf Projektverfasser zu einem Symposium eingeladen, welches im Januar 2013 an der Universität Bern stattgefunden hat. Anlässlich dieses Symposiums konnten die Forscherinnen und Forscher ihre Projekte vorstellen. Aus diesem strengen Auswahlverfahren sind Herr Prof. Dr. Eduard Batlle und Herr Prof. Dr. Joan Seoane als Sieger hervorgegangen.

Laudatio für Herrn Prof. Dr. Eduard Batlle

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis an Herrn Prof. Dr. Eduard Batlle in Anerkennung seiner wegweisenden Forschungsergebnisse zur Zell-Zell-Interaktion von Krebszellen mit ihrer Umgebung. Seine originelle Kombination von molekularbiologischen, bioinformatischen und genetischen Techniken führte zu neuen Einsichten in die Entstehung, Diversifizierung und Ausbreitung insbesondere von Dickdarmkrebs. Diese Resultate lassen erwarten, dass eine gezielte Zerstörung von Krebsstammzellen eine erfolgversprechende zukünftige Therapieoption darstellt.
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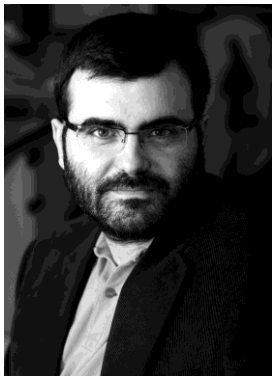
Curriculum Vitae Eduard Batlle



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Research Training

2000-2004	Postdoctoral Fellow. Prof. Hans Clevers Lab. Hubrecht Laboratorium, Utrecht, Netherlands.
1999-2000	Postdoctoral Fellow. Prof. Miguel Beato's Lab. Institut für Molekularbiologie und Tumorforschung (IMT). Marburg, Germany.
1994/1999	PhD Student. Prof. Antonio García de Herrero's Lab. Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain. Thesis title: "Role of PKC in the growth and differentiation of intestinal epithelial cells".

Academic Background

29/10/1999	**PhD in Biology**.	University of Barcelona (UB), Spain.
07/06/1993	**BSc in Biological Sciences**	University of Barcelona (UB), Spain

Awards and Distinctions

From 2011	Member of the Scientific Advisory Committee for the Association for International Cancer Research (AICR).
From 2011	Member of the jury for the Banc de Sabadell Award
2010	**Banc de Sabadell Award** for Research in Biomedicine (this is one of the most prestigious prizes awarded to biomedical researches in Spain).
2007	**ERC young investigator award (Starting Grant**). I qualified among the top 3% of 9167 applicants in all disciplines. This was the first ERC-StG call.
2006	**Debiopharm Life Sciences Award** for outstanding research in Oncology – École Polytechnique Fédérale de Lausanne (Lausanne, Switzerland).
From 2005	Head of the Oncology Program at IRB Barcelona.
2003	Senior Research Professor at ICREA (Institució Catalana de Recerca i Estudis Avançats).
2001:	Awarded a Marie Curie postdoctoral fellowship.
2001:	I was awarded an EMBO postdoctoral fellowship. I renounced in favor of Marie Curie position.

Patents and Industrial Innovation

1. **BATLLE E**; SANCHO E; ROSELL D; PALOMO S; ESPINET E; CALON A. *Methods and kits for the prognosis of colorectal cancer.* European Request **EP11382368** and worldwide **PCT/EP2012/072425**. Priority Date: 28-11-2011. And a second patent on the same subject**:** European Request **EP12192291**. Priority Date: 12-11-2012. Holder Entities for both: IRB Barcelona and ICREA.

2. **COLLAND F; BARKER N; CLEVERS JC; BATLLE E; VAN DE WETERING ML; SANCHO E.** *The use of specified TCF target genes to identify drugs for the treatment of cancer, in particular colorectal cancer, in which TCF/beta-catenin/WNT signaling plays a central role.* Request number: **WO2003EP07399** . Priority date: **08-07-02 .** Holder Entity: **Kylix, BV.**

Publications

- CALON A, ESPINET E, PALOMO-PONCE S, TAURIELLO DVF, IGLESIAS M, SEVILLANO M, NADAL C, JUNG P, ZHANG HFX, BYROM D, RIERA A, ROSSELL D, MANGUES R, MASSAGUE J, SANCHO E 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

- **BATLLE E** AND WILKINSON D.G. *Molecular Mechanisms of Cell Segregation and Boundary Formation in Development and Tumorigenesis.* **Cold Spring Harbor Perspectives in Biology**. 4 (1):doi:10.1101/cshperspect.a008227. 2012

- CAMPBELL K, WHISSELL G, FRANCH-MARRO X, **BATLLE E** and CASANOVA J. *Specific GATA factors act as conserved inducers of an endodermal-EMT*. **Developmental Cell.** 21 (6): 1051-1061. 2011.

- JANICH P, PASCUAL G, MERLOS-SUÁREZ A, **BATLLE E**, RIPPERGER J, ALBRECHT U, OBRIETAN K, DI CROCE L, BENITAH SA. *The circadian molecular clock creates epidermal stem cell heterogeneity.* **Nature**. 480 (7376): 209-214. 2011

- SOLANAS G, and **BATLLE E**. *Control of cell adhesion and compartmentalization in the intestinal epithelium.* **Experimental Cell Research**. 317 (19): 2695-2701. 2011

- JUNG P, SATO T, MERLOS-SUÁREZ A, BARRIGA FM, IGLESIAS M, ROSELL D, AUER H, GALLARDO MM, BLASCO MA, SANCHO E, CLEVERS H and **BATLLE E**. *Isolation and in vitro expansion of human colonic stem cells.* **Nature Medicine**. 17 (10): 1125 -1127. 2011

- 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 (9): 1100-1107. 2011

- MERLOS-SUÁREZ A, BARRIGA FM, JUNG P, IGLESIAS M, CÉSPEDES MV, ROSSELL D, SEVILLANO M, HERNANDO-MOMBLONA X, DA SILVA-DIZ V, MUÑOZ P, CLEVERS H, SANCHO E, MANGUES R 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

- CASAGOLDA D, DEL VALLE-PEREZ B, VALLS G, LUGILDE E, VINYOLES M, CASADO-VELA J, SOLANAS G, **BATLLE E**, REYNOLDS AB, CASAL J.I., GARCÍA DE HERREROS A, DUNACH M. *A p120-catenin-CK1 epsilon complex regulates Wnt signaling.* **Journal of cell science.** 123 (15): 2621-2631. 2010

- CASALI A and **BATLLE E**. *Intestinal Stem Cells in Mammals and Drosophila*. **Cell Stem Cell.** 4 (2): 124-127.

- **BATLLE E.** *A new identity for the elusive intestinal stem cell.* **Nature Genetics.** 40 (7): 818-819. 2008

- MERLOS-SUAREZ A and **BATLLE E**. *Eph/ephrin signaling in Adult tissues and Cancer*. **Current Opinion in Cell Biology.** 20 (2): 194-200. 2008

- CORTINA C, PALOMO-PONCE S, IGLESIAS M, FERNÁNDEZ-MASIP JL, VIVANCOS A, WHISSELL G, HUMÀ M, PEIRÓ N, DAVY A, LLORETA LL, SANCHO E and **BATLLE E**. *EphB-ephrin-B interactions suppress colorectal cancer by compartmentalizing tumor cells.* **Nature Genetics.** 39 (11): 1376-1383. 2007

- CLEVERS H and **BATLLE E**. *EphB/ephrinB receptors and Wnt signaling in Colorectal cancer.* **Cancer Research.** 66 (1): 2-5. 2006

- RIEDL J.A., BRANDT DT, **BATLLE E**, PRICE L.S., CLEVERS H, BOS J.L. *Down regulation of Rap1 activity is involved in ephrin-B1-induced contraction.***Biochemical Journal**. 389: 465-469. 2005

- **BATLLE E**, BACANI J, BEGHTEL H, JONKHEER S, GREGORIEFF A, van den BORN M, MALATS N, SANCHO E, BOON E, PAWSON T, GALLINGER S, PALS S, CLEVERS H. *EphB activity suppresses colorectal cancer progression.* **Nature.** 435 (7045): 1126-1130. 2005

- SANCHO E, **BATLLE E**, CLEVERS, H. *Signaling pathways in intestinal cancer and development.* **Annual Review in Cell and Developmental Biology**. 20: 695-723. 2004

- SANSOM OJ, REED KR, HAYES AJ, IRELAND H, BRINKMANN H, NEWTON IP, **BATLLE E**, SIMON-ASSMANN P., CLEVERS H, NATHKE I.S., CLARKE A.R., WINTON, D.J. *Loss of Apc in vivo immediately perturbs Wnt signaling, differentiation, and migration.* **Genes & Development**. 18 (12): 1385-1390. 2004

- BAAS A.F., KUIPERS J, VAN DER WEL N.N., **BATLLE E**, KOERTEN H.K., PETERS P.J., CLEVERS H.C. *Complete polarization of single intestinal epithelial cells upon activation of LKB1 by STRAD.* **Cell.** 116 (3): 457-466, 2004

- SANCHO E, **BATLLE E*** and CLEVERS H. [*first authorship shared]. *Live and Let die in the intestinal epithelium.* **Current Opinion in Cell Biology.** 15 (6). 763 – 770. 2003

- VAN DE WETERING M, SANCHO E, VERWEIJ C, DE LAU W, OVING I, HURLSTONE A, VAN DER HORN K, **BATLLE E**, COUDREUSE D, HARAMIS A.P., TJON-PON-FONG M, MOERER P, VAN DEN BORN M, SOETE G, PALS S, EILERS M, MEDEMA R, CLEVERS H. *The beta-Catenin/TCF-4 Complex Imposes a Crypt Progenitor Phenotype on Colorectal Cancer Cells.* **Cell.** 111 (2): 241 – 250. 2002

- **BATLLE E**, HENDERSON J.T., BEGHTEL H, VAN DEN BORN MM, SANCHO E, HULS G, MEELDIJK J, ROBERTSON J, VAN DE WETERING M, PAWSON T, CLEVERS H. *beta-Catenin and TCF Mediate Cell Positioning in the Intestinal Epithelium by Controlling the Expression of EphB/EphrinB.* **Cell.** 111 (2): 251- 263. 2002

- GUAITA S, PUIG I, FRANCI C, GARRIDO M, DOMÍNGUEZ D, **BATLLE E**, SANCHO E, DEDHAR S, DE HERREROS A.G., BAULIDA J. *Snail induction of epithelial to mesenchymal transition in tumor cells is accompanied by MUC1 repression and ZEB1 expression.* **The Journal of Biological Chemistry**. 277 (42): 39209 – 39216. 2002

- **BATLLE, E.**, SANCHO, E., FRANCÍ, C., DOMÍNGUEZ, D., MONFAR, M., BAULIDA, J., GARCÍA DE HERREROS, A. The transcription factor Snail is a repressor of E-cadherin gene expression in Epithelial tumour cells. **Nature Cell Biology.** 2:84-89, 2000

Dr. Eduard Batlle beschreibt sein preisgekröntes Projekt wie folgt:

Worldwide, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second most in females, with more than 1.2 million new cases every year. CRC is also one of the deadliest malignancies and is responsible for more than 600,000 deaths per year. The overall CRC survival rate is about 50% but this number drops to 5-10% when the cancer spreads to distant organs. My group investigates CRC with a pioneering emphasis on the relationship between the biology of stem cells and the development of these aggressive tumors.

The intestinal epithelium is a prime example of tissue regeneration by adult stem cells. While executing the processing and absorption of ingested micronutrients, intestinal epithelial cells face constant insults, including exposure to digestive enzymes, bile acids and constant mechanical erosion by intestinal contents. Maintaining the functionality of the tissue in this extremely harsh environment represents a phenomenal challenge. Evolution has thus procured an effective mechanism to ensure integrity of intestinal function throughout life: fast and incessant regeneration of the epithelial sheet. Mature cells only last for 3-5 days and are continuously replaced by new cells. Cell renewal is powered by a small number of multipotent cells, the intestinal stem cells (ISCs). ISCs live over lifespan, proliferate continuously and generate all cell types present in the gut epithelium. The progeny of ISCs, termed transient amplifying (TA) cells, is expanded through several rounds of mitosis while it migrates upwards along the crypt axis. Close to the intestinal lumen, TA cells undergo cell cycle arrest and terminal differentiation (figure 1).

The study of ISCs has provided new insights into the organization of colorectal cancer (CRC). CRC arise as benign lesions in the intestinal epithelium and progress over years through accumulation of hundreds of genetic and epigenetic alterations. Genetic evolution imposes distinct phenotypes and behaviors on tumor cells. As a result, advanced CRCs are amalgams of phenotypically distinct tumor cell populations. This phenomenon is the basis for the striking capacity of cancer to adapt to different environments, colonize foreign organs and resist therapy. In contrast, more than 30 years ago it was proposed that the phenotypic diversity in cancers could also arise from spontaneous differentiation of tumor cells. The concept, as originally developed by G. Barry Pierce (Univ. of Colorado, USA) in the 70-80s', states: "… carcinomas are composed of a mixture of malignant stem cells, which have a marked capacity for proliferation and a limited capacity for differentiation under normal homeostatic conditions, and of the differentiated, possibly benign, progeny of these malignant cells". This hypothesis was long ignored yet in the last few years, ours and other laboratories have put forward key

evidences supporting that Colorectal Cancer (CRC) complies the concept originally proposed by Pierce and colleagues. Our studies have revealed that tumor cells within CRCs adopt phenotypes that resemble either that of normal intestinal stem cells of the colon (colon stem cells or CoSCs) or of differentiated colonic cells. These two cell populations intermingle throughout the tumor mass and display striking differences in their tumorigenic potential; i.e. only CoSC-like cells have the capacity to propagate the disease with elevated efficiency when transplanted into immunodeficient mice whereas differentiated-like cells are poorly tumorigenic. Our experiments also indicate that xenografts generated by CoSC-like tumor cells reproduce the cell heterogeneity of the original CRC, including the ratio of stem *versus* differentiated-like cells. Hence, both tumor cell types are linked through a hierarchical relationship (i.e. differentiated tumor cells are essentially inert whereas CoSC-like tumor cells self-renew their own population and produce progeny that differentiates). These data extends the parallels between the organization of the normal mucosa and of CRC. CoSC-like cells correspond to the malignant stem cells of Pierce's original hypothesis.

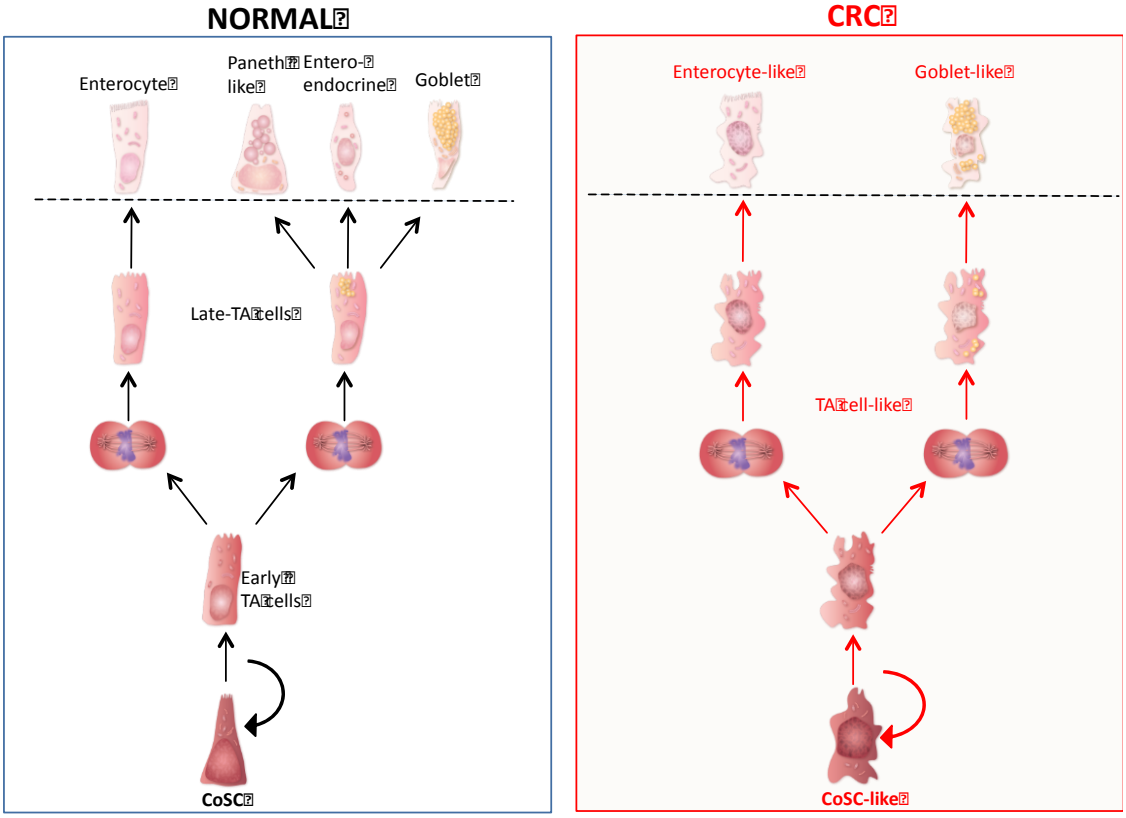

Fig 1. Working model displaying the parallels between the hierarchical organization of the normal colonic mucosa and of CRC.

Our interest is to study the relevance of such hierarchical organization for the growth and progression of CRC. Through the use of novel genetic tools, we aim to tackle several outstanding questions, including; would therapies directed towards CoSC-like tumor cell population cure CRC? Are CoSC-like tumor cells responsible for the regeneration of the disease after chemotherapeutic treatment? A particularly relevant aspect of our activity is to investigate the communication of CoSC-like cells with their environment. We have recently

discovered that TGF-beta signaling instructs tumor stromal cells to foster CoSC-like cells during the dissemination of the disease and that this phenomenon can be exploited to identify which CRC patients are at risk of developing metastasis upon treatment. We now propose to understand what additional dependencies may CoSC-like cells have during the propagation of the disease to distant sites. We are hopeful that this project will help improve the diagnosis and treatment of late stage CRC patients.

Laudatio für Herrn Prof. Dr. Joan Seoane

Die Dr. Josef Steiner Stiftung verleiht den Josef Steiner Krebsforschungspreis an Herrn Prof. Dr. Joan Seoane in Anerkennung seiner wegweisenden Forschungsergebnisse zur zellulären Signalübertragung in Krebszellen und deren Auswirkung auf die bösartige Krebsentstehung. In einer eindrücklichen Kombination aus molekularbiologischen und genetischen Experimenten hat er die molekularen Mechanismen beschrieben, wie bestimmte Signalwege die Bildung von Krebsstammzellen in Hirntumoren stimulieren und wie diese Signalwege als therapeutische Angriffspunkte genutzt werden können. Diese experimentellen Ergebnisse haben neuartige Möglichkeiten für die klinische Behandlung von bösartigen Hirntumoren in Patienten aufgezeigt.

Curriculum Vitae Joan Seoane

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Education

1989-1993. **B.S. Chemistry, program of Biochemistry,** University of Barcelona, Barcelona, Spain.

July-September, 1991. Student researcher, Boehringer Ingelheim, Malgrat, Spain. Director of the project: C. von Carsten, Ph.D.

July-November, 1993. Student researcher, Boehringer Ingeheim, Ingelheim, Germany. Director of the project: C. Naumann, Ph.D.

1994-1998. Ph. D. student in Biochemistry, Dept. Biochemistry and Molecular Biology, University of Barcelona, Barcelona, Spain. Dissertation work performed in the laboratory of Joan J. Guinovart, Ph.D.

July-September, 1997. Short stay in the laboratory of C.B. Newgard, Ph.D., Professor, Dept. of Biochemistry and Internal Medicine, University of Texas Southwestern Med. Center in Dallas, Texas.

17th April, 1998. **Ph. D. in Chemistry Program of Biochemistry**, University of Barcelona, Dept. Biochemistry and Molecular Biology. Barcelona, Spain.*1rst May- 5th June, 1998.* Short stay in the laboratory of Loranne Agius, Ph.D., Reader in Biochemistry, University of Newcastle upon Tyne, Dept. of Medicine at Newcastle, UK.

15th July, 1998- 15th July, 2001. **Research Fellow** position, Memorial Sloan-Kettering Cancer Center, New York.

15th July, 2001- December, 2003. **Research Associate** position, Memorial Sloan-Kettering Cancer Center, New York.

January, 2004-… . **ICREA Research Professor**, Group Leader, Medical Oncology Program, Vall d'Hebron University Hospital Research Institute, Barcelona, Spain.

September, 2006-… . Member of the Committee of Neuro-oncology. Vall d'Hebron Hospital. Barcelona, Spain.

October, 2007-… . **EMBO (European Molecular Biology Organization) Young Investigator.**

January, 2008-…. **Member of Executive Committee** "European Association for Cancer Research" (EACR).

April, 2008-…..: Group Leader, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain.

September, 2008-…. **Assistant Professor Universitat Autònoma de Barcelona**, Barcelona, Spain.

November, 2008-2011: Coordinator of the Cancer/Biomedicine area of the Spanish grant evaluation agency "Agencia Nacional de Evaluación y Prospectiva" (ANEP).
January, 2010-…. Member of Executive Committee, Vall d'Hebron Institute of Oncology, (VHIO), Barcelona, Spain.

June, 2011-…. **Director Translational Research Program**, Vall d'Hebron Institute of Oncology, (VHIO), Barcelona, Spain.

July, 2012. Local Chair organizer of the 22nd Biennal Congress of the European Association for Cancer Research, EACR22, Barcelona "From Basic Research to Personalised Cancer Treatment".

Awards

Grantor: Sociedad Española de Bioquímica y Biología Molecular
Beckman-Coulter award
September, 2009

Grantor: Banco Sabadell
Biomedical Research award
July, 2009

Grantor: European Research Council (ERC)
ERC Starting grant
August, 2008

Grantor: European Molecular Biology Organization (EMBO)
EMBO Young Investigator
October, 2007

Grantor: Societat Catalana de Biologia
Josep M. Sala Trepat Award
July, 2004

Grantor: Memorial Sloan-Kettering Cancer Center
MSKCC Research Fellow Award
April, 2003

Patents

- Title: Therapeutic agents for treatment of diseases associated with undesirable cell proliferation (Agentes terapéuticos para el tratamiento de enfermedades asociadas con una proliferación celular indeseable)
  Application No. P200900928
  Country priority: Spain
  Priority date: April 3, 2009
  Holder entity: Vall d'Hebron Institute of Oncology (VHIO)-Institució Catalana de Recerca i Estudis Avançats (ICREA)
  Extension: PCT/ EP 2010/054499

- Tittle: Antibody recognizing human leukaemia inhibitory factor (LIF) and use of anti-LIF antibodies in the treatment of diseases associated with unwanted cell proliferation.
  Application No.: EP1038049.6
  Country priority: Spain
  Priority date: April 5, 2010
  Holder entity: Vall d'Hebron Institute of Oncology (VHIO)- Institució Catalana de Recerca i Estudis Avançats (ICREA)

Publication List

Leticia De Mattos-Arruda, Javier Cortes, Libero Santarpia, Ana Vivancos, Josep Tabernero, Jorge S. Reis-Filho and **Joan Seoane**. Circulating Tumor Cells and Cell-Free DNA as Tools for Managing Breast Cancer. **Nature Reviews Clinical Oncology** 2013 (in press).

De Mattos-Arruda L, Tabernero J, **Seoane J**, Cortes J. "Circulating tumour cells in early breast cancer". **Lancet Oncol**. 2012 Sep; 13(9):e370. PMID: 22935235 [PubMed - in process].

Ros-Blanco L, Anido J, Bosser R, Este J, Clotet B, Kosoy A, Ruiz-Avila L, Teixido J, **Seoane J***, Borrell JI. "Non-Cyclam Tetraamines inhibit CXC Chemokine Receptor Type 4 and target Glioma-Initiating Cells". **J Med Chem.** 2012 Aug 21, 55 (17), pp 7560–7570. (*co-corresponding author).

P.J. Eichhorn, L. Rodón, A. Gonzàlez-Juncà, A. Dirac, M. Gili, E. Martínez-Sáez, C. Aura, I. Barba, V. Peg, A. Prat, I. Cuartas, J. Jimenez, D. García-Dorado, J. Sahuquillo, R. Bernards, J. Baselga, **J. Seoane.** "USP15 stabilizes TGF-β receptor I and promotes oncogenesis through the activation of TGF-β signaling in glioblastoma". **Nature Medicine**. 2012 Feb19;18(3):429-35. [see News and Views, Nat. Cell Biol. (2012) 14, 656-7].

J. Anido, A. Sáez-Borderías, A. Gonzàlez-Juncà, L. Rodón, G.d Folch, M. A. Carmona, R. M. Prieto-Sánchez, I. Barba, E. Martínez-Sáez, L. Prudkin, I. Cuartas, C. Raventós, F. Martínez-Ricarte, M.A.Poca, D.García-Dorado, M.Lahn, J.Yingling, J.Rodón, J.Sahuquillo, J.Baselga, **J. Seoane**. "TGF-beta receptor inhibitors target the CD44high/Id1high glioma-initiating cell population in human glioblastoma" **Cancer Cell** (2010) Dec. 18, 655-668 [see Preview, Cancer Cell (2010) 18, 543-4].

J. Seoane "No Signals from the Cancer Stem Cell Niche" **Cell Stem Cell** (2010) Feb, 5:6 (2) 97-98.

J. Seoane "TGF-beta and cancer initiating cells" **Cell Cycle** (2009) Apr. 23, 3787-8.

A. Santamaria-Martínez, J. Barquinero J, A. Barbosa-Desongles, A. Hurtado, T. Pinós, **J. Seoane,** MF. Poupon, J. Morote, J. Reventós, F. Munell. "Identification of multipotent mesenchymal stromal cells in the reactive stroma of a prostate cancer xenograft by side population analysis". **Exp Cell Res** (2009) Oct. 15, 3004-13.

S. Peñuelas, J. Anido, R. M. Prieto-Sánchez, G. Folch, I. Barba, I. Cuartas, D. García-Dorado, M. A. Poca, J. Sahuquillo, J. Baselga, **J. Seoane** "TGF-beta increases glioma-initiating cell self-renewal through the induction of LIF in human glioblastoma" **Cancer Cell** (2009) 15, 315-27[see Preview, Cancer Cell (2009) Apr. 7, 15, 247-8].

P.J. Eichhorn, M. Gili, M. Scaltriti, V. Serra, M. Guzman, W. Nijkamp, RL. Beijersbergen, V. Valero, **J. Seoane,** R. Bernards, J. Baselga."Phosphatidylinositol 3-kinase hyperactivation results in lapatinib resistance that is reversed by the mTOR/phosphatidylinositol 3- kinase inhibitor NVP-BEZ235."**Cancer Res**. (2008) Nov. 15, 68, 9221-30.

J. Seoane, "The TGF-beta pathway as a therapeutic target in cancer" **Clin. Transl. Oncol**. (2008) Jan, 10, 14-19.

J Baselga, M. L. Rothenberg, J. Tabernero, **J. Seoane**, T. Daly, A. Cleverly, B. Berry, S. K Rhoades, C. A. Ray, J. Fill, D. L. Farrington, L. Anne, J. M Yingling, M. Lahn, C. Arteaga, M. Carducci, "TGF-beta signaling related markers in cancer patients with bone metastasis" **Biomarkers** (2008), March 13, 217-36.

J. Seoane, "TGF-beta signaling in homeostasis and cancer" TGF-beta in Cancer Therapy, Vol. 1, pp 23-35 Humana Press (2008).

A. Bruna, R.S. Darken, F. Rojo, A. Ocaña, S. Peñuelas, A. Arias, R. Paris, A. Tortosa, J. Mora, J. Baselga, **J. Seoane**, "High TGF-beta-Smad activity confers poor prognosis in glioma patients and promotes cell proliferation depending on the methylation of the PDGF-B gene" **Cancer Cell** (2007) 11, 147-160 [see Preview, Dev. Cell (2007)Feb. 12, 324-5].

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Dr. Joan Seoane beschreibt seine Arbeit wie folgt:

After finishing my post-doctoral stage in 2004, I decided to establish my own group pursuing an independent research project. My objective was to study molecular oncology and, since I believed that a way to fight cancer is through the combined efforts of basic and clinical research, I decided to physically set up my laboratory as close as possible to a clinical research unit in order to fluently interchange my findings in basic research with the clinical ambit and hence do translational research. For this reason, I chose to join a research institute linked to a hospital. Since the Vall d'Hebron Institute of Oncology (VHIO) is integrated in the Vall d'Hebron Hospital - one of the biggest hospitals in Spain with a Medical Oncology Department that has an outstanding clinical trial program in solid tumors - it provided an optimal setting through which to deliver on my objectives.

In 2004, I was appointed Group Leader at VHIO and ICREA Research Professor. I decided to focus my research in glioblastoma since it is the most common brain tumor and one of the most deadliest of all human cancers. However, my objective was to discern the molecular mechanisms involved in glioblastoma and then extrapolate the identified mechanisms to other tumor types.

Specifically, I wanted to tackle one of the most important challenges in the treatment of cancer: tumor heterogeneity. Cancer is a disease with two levels of heterogeneity, an intertumor heterogeneity (each patient has a different tumor) and an intratumor heterogeneity (cells within

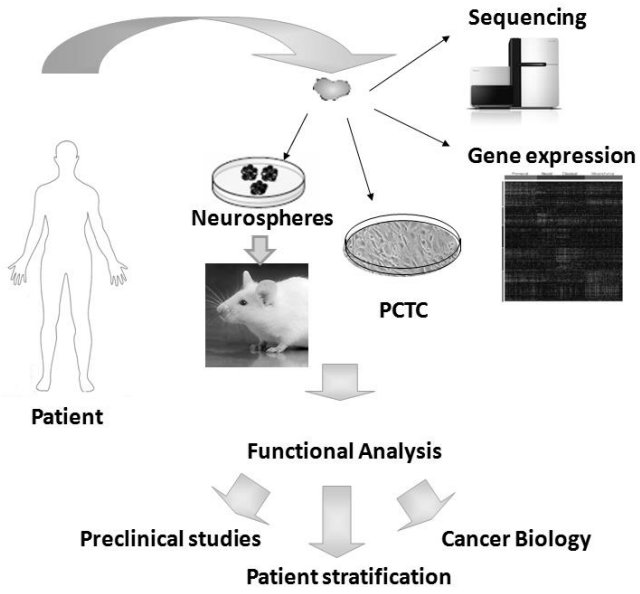
a tumor are different). Tumors from different patients are molecularly diverse and have different sensitivities to treatment. Hence, the molecular characteristics of a tumor determine the optimal treatment for each patient implying that anti-cancer treatments should be personalized. However, there is another level of complexity. Cells within a tumor are diverse because they present different genomic alterations or different states of differentiation. This has very important clinical implications since a therapeutic treatment might target one cell type but might not be effective against other cell entities within the same tumor being unable to cure the patient.

Linked to the intratumoral heterogeneity concept, a subpopulation of undifferentiated cells with stem cell-like characteristics has been identified within the tumor mass. This pool of cells, called cancer-initiating cells (CICs) or cancer stem cells, are considered to be responsible for the initiation, recurrence and chemo- and radio-resistance of tumors indicating that more effective therapies will result from approaches aimed at targeting CICs. These cells are characterized by their self-renewal capacity, their multilineage differentiation properties and their high oncogenic potential. CICs are therefore crucial therapeutic targets and better understanding of the molecular mechanisms involved in this type of cells is still needed.

In order to study tumor heterogeneity, cancer has to be studied as close as possible to the real tumor of the patient. Much of the research that is been developed in the field of molecular oncology is based on the study of established cell lines or genetically modified mice. Cells from established cell lines have undergone many passages and have been maintained in artificial conditions diverging from the original tumor cells and do not faithfully recapitulate the genotype and phenotype of tumor cells. On the other hand, tumors generated in genetically modified mice are very homogenous and cannot be used as models to study tumor heterogeneity.

In order to study patient-derived tumors, we generated a multidisciplinary team including oncologists, neurosurgeons and pathologits. I established a 'circuit' within the Vall d'Hebron Hospital through which to obtain human glioblastoma specimens from the neurosurgeons and pathologists to generate tumor models that recapitulate the characteristics of the human tumor of origin. We obtain tumor samples 15 minutes after surgery and we set up primary cultures and isolate cell populations from the tumor such as CICs. Moreover, CICs are orthotopically inoculated in the brain of mice to generate tumors that recapitulate the characteristics of the original human tumor. Figure 1.

Using these models, we generated relevant knowledge about brain tumors and cancer stem cells with important implications in the treatment of cancer. We have generated two patents and numerous publications. I would like to emphasize the following 4 articles in which I am the corresponding author: Bruna et al. Cancer Cell 2007, Peñuelas et al. Cancer Cell 2009, Anido et al. Cancer Cell 2010, and Eichhorn et al. Nature Medicine 2012. In them, we have identified markers of response to the treatment with anti-TGFβ compounds; we have identified therapeutic targets against glioblastoma, and since we are developing clinical trials in our hospital using anti-TGFβ compounds, our results have allowed the improvement of the design of the clinical trials providing markers to stratify the patients to be enrolled in the trial. Our work is considered an example of translational research.



The study of patient-derived tumors allow the rapid translation of our research into the clinic. Our patient-derived mouse models are very useful for the study of the molecular mechanisms involved in cancer and are optimal preclinical models for the evaluation of the efficacy of pharmacological compounds. Moreover, the patient that donated the tumour can benefit from our studies. While we are analyzing the response of our patient-derived tumor models to pharmacological compounds (the same compounds that are being developed in clinical trials in our hospital), the patient undergoes the standard of therapy (radiotherapy and temozolamide).

When the patient comes back with relapse and a clinical trial has to be offered, we can give advice about which clinical trial to select based on the results obtained with our model. Figure 1.

Since 2008, I am Associate Professor of the Universitat Autònoma de Barcelona and I am serving on the Executive Committee of the European Association for Cancer Research (EACR). Moreover, I am member of the neurooncology committee of the Vall d'Hebron University Hospital. My contributions to the field have been recognized through various awards and honors including the Memorial Sloan Kettering Cancer Center Research Fellow award and the Catalan Society of Biology award. In 2007, I became an EMBO Young Investigator and in 2009, I was awarded with the Bank Sabadell Award and the Sociedad Española de Bioquímica y Biología Molecular Award. In 2011, I became director of the Translational Research Program at VHIO.