BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Juan Jose Marugan	Group Leader NIH Chemical Genomics Center
eRA COMMONS USER NAME (credential, e.g., agency login) MARUGANJ	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Universidad de Salamanca, Spain	B.S.	1991	Chemistry
Universidad Complutense de Madrid, Spain	Ph.D.	1995	Organic Chemistry

A. Personal Statement.

Since 2008 I have led one of the NCATS teams focused on preclinical innovation, with the aim of validating new therapeutic approaches in areas of medical need and to improve the translational process. Among others our team has a high interest in developing new therapeutic approaches in oncology. In this sense our team has carry out a number of high throughput screens and optimization studies looking for novel antitumoral approaches. Some of these projects have used phenotypic approaches, looking unique characteristics in cancer. Recently we optimized nontoxic molecules able to disassemble the perinucleolar compartment (PNC), a recognize biomarker of metastasis. Our first in class PNC modulator metarrestin, effectively suppressed metastasis in the three cancer xenograft models tested so far, without signs of toxicity and it is advancing toward preclinical development in the aim of filling IND and starting human clinical trials in the next few months. Other approaches are more target directed, like our collaboration looking for small molecules able to disrupt the interaction between the transcription factor Six1 and Eya2 phosphatase, or our CD206 modulators able to activate M2 macrophages and enhance autitumoral innate immunity. In addition to our line of research in oncology, I personally have more than twenty years of experience in the pharmaceutical industry (Pharmamar S.A, 3-Dimentional Pharmaceuticals, Johnson & Johnson, Mithridion Inc.) and NIH working in translational research, drug discovery and development. During this time, I have been personally involved in numerous aspects of the translational process, with emphasis in medicinal chemistry and preclinical research including assay development, library screening and hit selection, structure activity relationship optimization studies, in vivo pharmacological, tolerability and efficacy evaluation, preclinical development and IND filing. During the course of my career I held positions of increasing responsibility with extensive experience as a team leader of programs in preclinical lead optimization, many of them advancing toward late development or clinical trials. Since I accepted my current position at NCATS, eight of my projects, have been adopted, out licensing the corresponding patents, by pharmaceutical companies, many of them being the foundation for securing multi-million dollar investments in several startup companies. I am also actively collaborating with several of these pharmaceutical companies through CRADA agreements.

1. “Targeting of estrogen receptor signaling with fulvestrant enhances immune and chemotherapy-mediated cytotoxicity of human lung cancer”, Duane H. Hamilton, Lesley Matthews Griner, Jonathan M. Keller, Xin Hu, Noel Southall, Juan Marugan, Justin M. David, Marc Ferrer, Claudia Palena, Clinical Cancer Research, Accepted. PMID: 27267852.
2. “Metarrestin disrupts nucleolar and PNC structures in malignant cells and suppresses metastasis in vivo”, Kevin Frankowski, Chen Wang, Samarjit Patnaik, Frank Schoenen, Noel Southall, Yaroslav Teper, Wei Sun, Irawati Kandela, Deqing Hu, Christopher Dextras, John Norton, Steve, Titus, Marzena Lewandowska, Yiping Wen, Katherine I. Farley, Lesley Mathews Greiner, Jamey Sultan, Zhaojing Meng, Ming Zhou, Min Fang, Charles Long, Ojus Khanolkar, Warren Chen, Jinsol Kang, Helen Huang, Eric Chow, Esthermanya Goldberg, Coral, Feldman, Romi Xi, Humair Quadri, Hye Rim Kim, Gary Sahagian, Susan J. Baserga, Andrew Mazar, Marc Ferrer, Wei Zheng, Ali Shilatifard, Jeffrey Aubé, Udo Rudloffd, Juan Jose Marugan, Sui Huang, Sci. Transl. Med., 10(441), eaap8307, 2018

3. “High-throughput screening identified selective inhibitors of exosome biogenesis and secretion: A drug repurposing strategy for advanced cancer”, Amrita Datta, Hogyoung Kim, Lauren McGee, Adedoyin E. Johnson, Sudha Talwar, Juan Marugan, Noel Southall, Xin Hu, Madhu Lal, Debasis Mondal, Marc Ferrer, Asim B., Abdel-Mageed, , Sci. Reports, 8(1), 8161, 2018.
4. "Identification of 4-phenylquinolin-2(1H)-one as a specific allosteric inhibitor of Akt", Huang, Bill; Newcomer, Kenneth; Kevela, Karl; Barnaeva, Elena; Zheng, Wei; Patnaik, Samarjit; Southall, Noel; Marugan, Juan; Ferrer, Marc; Kim, Hee-Yong, Sci. Rep., 7(1), 11673, 2017.

B. Positions and Honors

Positions and Employment

1990-1991	Research Collaborator, Universidad de Salamanca, Department of Organic Chemisty, Salamanca, Spain
1991-1995	Research Assistance, Pharma Mar S.A, Department of Chemistry, Tres Cantos, Spain
1996-1997	Postdoctoral Fellow, Tufts University, Department of Microbiology, Boston, MA
1998-2000	Research Scientist, 3-Dimensional Pharmaceuticals, Inc., Exton, PA
2000-2002	Principal Research Scientist and Team Leader, 3-Dimensional Pharm., Inc., Exton, PA
2002-2006	Senior Scientist & Project Champion, Johnson & Johnson PRD, L.L.C., Exton, PA
2007	Head Preclinical Drug Research, Mithridion, Inc., Madison, WI
2008-present	Team Leader, NIH Chemical Genomic Center, NCATS, Rockville, MD
2016-2018	Acting Branch Chief, NIH Chemical Genomic Center, NCATS, Rockville, MD

Honors

1991-1995	Doctoral Research Grant, Spanish Education and Science Ministry
1990-1991	Collaboration Research Grant, Spanish Education and Science Ministry
1986-1990	Spanish Education and Science University Scholarship
2012	Federal Laboratory Consortium (FLC) Mid-Atlantic Regional Award for excellence in technology transfer. Entry titled “Treatment of Niemann Pick Disease Type-C (NPC) with 2-Hydroxypropyl-β-cyclodextrin (HPβCD).”
2013	NIH Director’s Award in the Scientific/Medical Achievement category to the team that brought HPβCD to NPC human clinical trials in recognition for their outstanding accomplishment in identifying and developing a therapeutic for Niemann-Pick disease, type C, that can be evaluated in Patients.
2015	NCATS Director’s Award in the Collaborator Category for outstanding collaboration and excellent team work that has advanced the Niemann Pick C Disease project to Vtesse, a biotech company for the next level of clinical trials.
2015	Federal Laboratory Consortium (FLC) Mid-Atlantic Regional Award for excellence in technology transfer. Entry titled “Novel Therapeutics to Treat Niemann-Pick C Disease and Other Lysosomal Disorders”.
2015	NIH Director’s Award to the Niemann-Pick type C Collaboration team for sustained contributions to a collaboration among government, academic, industry researches and patient groups, to develop a therapy for Niemann-Pick Disease type C.
2018	NCATS Director’s Award in the Administrative Achievement category for demonstrating exceptional initiative in creating the strategic vision and developing and implementing action plans to make it a reality.
2018	NIH Director’s Award in the Scientific/Medical Achievement category for extraordinary leadership in advancing scientific understanding of Gaucher and Parkinson's diseases through discovery and development of first-in-class molecules with potential for treating these diseases
2019	NIH Director’s Award in the Scientific/Medical Achievement category to the team that Discover and Develop Metarrestin.

C. Contribution to Science

During the course of my carrier I investigate new translational solutions in several areas of the biomedical field. Some of my contributions can be followed up by reading my public disclosures (113 peer-reviewed publications, 43 filled patents, and 93 scientific public presentations), most of them can be found in public and commercial databases (PubMed, SciFinder, Research Gate, etc).

1. Contributions to oncology. Oncology has been an area of research where I have been intensively involved, especially evaluating new therapeutic approaches and optimizing lead compounds to produce drug candidates. Some of these projects involved compounds able to modulate known oncogenes or targets upregulated in cancer and angiogenesis such as Ras FTase, HDM2, Eya2-Six1, CBFβ-RunX1, αvβ3/αvβ5 integrins. Recently my team has focus in investigating exosome function and in finding small molecules as adjuvants for cancer inmmunotherapy. Our most recent development is a new anti-metastatic approach through the disassembly of the perinucleolar compartment (PNC), which led us to discover a non-toxic series able to block invasion and migration (unpublished data) across cancer cell lines. Our optimized candidate, currently in preclinical development toward IND filing for treatment of pancreatic cancer, displays excellent in vivo activity in three human xenograft models of metastasis. Investigation of the mechanism of action revealed inhibition of a new biological pathway involved in the modulation RNA polymerase I, nucleolar and PNC assembly, ribosomal biogenesis and EMT.

a. "Small Molecule, NSC95397, Inhibits the CtBP1-Protein Partner Interaction and CtBP1-Mediated Transcriptional Repression", Melanie A. Blevins, Jennifer Kouznetsova, Aaron B. Krueger, Rebecca King, Lesley Mathews Griner, Xin Hu, Noel Southall, Juan J. Marugan, Qinghong Zhang, Marc Ferrer, Rui Zhao, J Biomol Screen., 20(5), 663-72, 2015.
b. "Allosteric Inhibitors of the Eya2 Phosphatase Are Selective and Inhibit Eya2-mediated Migration", Aaron B. Krueger, David J. Drasin, Wendy A. Lea, Aaron Patrick, Samarjit Patnaik, Donald, S. Backos, Christopher J. Matheson, Xin Hu, Elena Barnaeva, Mike Holliday, Melanie A., Blevins, Tyler Robin, Elan Z. Eisenmesser, Marc Ferrer, Anton Simeonov, Noel Southall, Philip Reigan, Juan Marugan, Heide Ford, and Rui Zhao, J.Bio.Chem., 289(23), 16349-61, 2014.
c. "Identification of a selective small molecule inhibitor series targeting the Eyes Absent 2 (Eya2) phosphatase activity", Aaron Krueger, Jean Dehdashti, Tyler Robin, Noel Southall, Juan Marugan, Marc Ferrer, Xueni Li, Wei Zheng, Heide Ford, and Rui Zhao, J Biomol Screen., 18(1), 85-96, 2013.
d. Identification of Novel Short Chain 4-Substituted Indoles as Potent αvβ3 Antagonists Using Structure-Based Drug Design", Pierre Raboisson, Renée L. DesJarlais, Rolanda Reed, Jennifer Lattanze, Margery Chaikin, Carl L. Manthey, Bruce E. Tomczuk, and Juan José Marugán, Euro. J. Med. Chem., 42(3), 334-343, 2007.

2. Contributions to neurology. Another area of intense investigation in my team is neurology, where I have been involved in developing new therapeutic approaches in multiple programs from the classical neurodegenerative disorders such as Alzheimer, Huntington, Parkinson or ALS, to more rare diseases such as Gaucher, Niemann Pick C (NPC), or Spinal Muscular Atrophy. Several approaches produced molecules with pharmacological activity across multiple disorders. For example our optimized allosteric modulators of cAbl kinase correct the accumulation of insult and promote recovery in several models, both in vitro and in vivo, including Alzheimer's and NPC. Particular high attention has received several of our approaches for Lysosomal Storage disorders (LSDs), such as the use of HPβCD for NPC and other LSDs, currently in phase II human clinical trials, or our development of non-inhibitory small molecule chaperones of glucocerebrosidase able to correct the phenotype in both Gaucher's and Parkinson's diseases. Recently, we have found and optimized the first small molecule activator of TRAP1, a protein chaperone involved among others in folding of mitochondrial proteins. Our molecules display excellent in vitro and in vivo activity of several LSD's, including NPC and Fabry's disease.

a. "Collaborative Development of 2-Hydroxypropyl-β-Cyclodextrin for the Treatment of Niemann-Pick Type C1 Disease", Elizabeth Ottinger, Mark L. Kao, Nuria Carrillo, Nicole Yanjanin, Roopa Kanakatti Shankar, Marjo Janssen, Marcus Brewster, Ilona Scott, Xin Xu, Jim Cradock, Pramod Terse, Seameen Dehdashti, Juan Marugan, Wei Zheng, Lili Portilla, Alan Hubbs, Bill Pavan, John Heiss, Charles Vite, Steven U. Walkley, Daniel S. Ory, Steven A. Silber, Forbes D. Porter, Chris Austin, and John C. McKew, Current Topics in Med Chem, 14(3), 330-9, 2014. PMCID: PMC4048128.
b. "Macrophage models of Gaucher disease for evaluating disease pathogenesis and candidate drugs", Elma Aflaki, Barbara K. Stubblefield, Emerson Maniwang, Grisel Lopez, Ehud Goldin, Wendy Westbroek, Juan Marugan, Noel Southall, Samarjit Patnaik, Wei Zheng, Nahid Tayebi, and Ellen Sidransky, Sci.Trans.Med, 6(240), 240ra73, 2014. PMCID: PMC4161206.

c. “Neuronal gene repression in Niemann-Pick type C models is mediated by the c-Abl/HDAC2 signaling pathway”, Pablo S. Contreras, Marcelo Gonzalez-Zuñiga, , Lila González-Hódar, María José Yáñez, Andrés Dulcey, , Juan Marugan, , Edward Seto, Alejandra R. Alvarez, Silvana Zanlungo, BBA - Gene Regulatory Mechanisms, 1859(2), 269-79, 2016. PMCID: PMC5014229.
d. “Benzenesulfonamide upregulators of NPC1 for Neimann-Pick disease and other lysosomal storage disorders”, Samarjit Patnaik, Mercedes K Taylor, Raul Calvo, Juan Jose Marugan, Noel Southall, Wei Zheng, Marc Ferrer, Fannie Chen, Seameen Dehdasthi, Patrica Dranchak, Yiannis Ioannou, U.S. Patent Application No. 62/114,566.

3. Contributions to muscular dystrophies. My team also has investigated new approaches for the treatment of several kind muscular dystrophies. For example we produced molecules able to disrupt protein-RNA interactions as an approach for the treatment of myotonic dystrophy type-1 and we identified compounds able to increase in vitro and in vivo levels of $\alpha 7\beta 1$ integrin for the treatment of Duchenne muscular dystrophy. We also have investigated therapeutic approaches for many other rare disorders of a diverse nature such as marfan syndrome, macular degeneration, hyperammonemia and aminoacidophaties, among others

a. “Noncanonical TGFβ signaling contributes to aortic aneurysm progression in marfan syndrome mice”, Tammy M. Holm, Jennifer P. Habashi, Jefferson J. Doyle, Djahida Bedja, YiChun Chen, Christel van Erp, Ronald D. Cohn, Bart L. Loeys, Craig Thomas, Samarjit Patnaik, Juan J. Marugan, Daniel P. Judge, Harry C. Dietz, Science, 332, 358, 2011. PMCID: PMC3111087.
b. “Induction and reversal of myotonic dystrophy type 1 pre-mRNA splicing defects by small molecules“, Jessica Childs-Disney, Tuan Tran, Ilyas Yildirim, HaJeung Park, Catherine Z. Chen, Jason Hoskins, Krzysztof, Sobczak, Noel Southall, Juan J. Marugan, Samarjit Patnaik, Wei Zheng, Chris P. Austin, George C. Shatz, Charles A. Thornton, and Matthew D Disney, Nature-Communications, 4, 2044, 2013. PMCID: PMC3710115.
c. “Lomofungin and dilomofungin: inhibitors of MBNL1-CUG RNA binding with distinct cellular effects”, Jason Hoskins, Leslie O. Ofori, Catherine Z. Chen, Amit Kumar, Krzysztof Sobczak, Masayuki Nakamori, Noel Southall, Samarjit Patnaik, Juan J. Marugan, Wei Zhang, Chris P. Austin, Matthew D. Disney, Benjamin L. Miller and Charles A. Thornton, Nucleic Acids Res., 42(10), 6591-602, 2014. PMCID: PMC4041448
d. “A multiplex High-Throughput gene expression assay to simultaneously detect disease and functional markers in induced pluripotent stem cell-derived retinal pigment epithelium”, Marc Ferrer, Barbara Corneo, Janine Davis, Qin Wan, Kiyoharu Joshua Miyagishima, Rebecca King, Arvydas Maminishkis, Juan Marugan, Ruchi Sharma, Michael Shure, Sally Temple, Sheldon Miller, Kapil Bharti, Stem Cells Trans Med; 3, 911-922, 2014. PMCID: PMC4116245.

4. Development of specific GPCR ligands. I also have been deeply involved in the production, investigation and development of specific GPCR’s ligands. All of the investigated targets were selected for being intrinsically difficult for obtaining the desired modulator and in every case we delivered a final molecule displaying in vivo activity in relevant biological models. For example my team produce the first small molecule agonist of relaxin receptor 1, a target highly validated for acute heart failure and fibrosis. We also produced the first TSH receptor antagonist able to inhibit stimulation of thyroid function in vivo. Several of our GPCR’s ligands are involved in mood and additional disorders, such as our truly selective D2R and NPS receptor antagonists. GPCR’s activated by lipids are also investigated in my team, where we recently deorphanized GRP110 as the receptor for synaptamide, highly promoting neurogenesis and synaptogenesis.

a. “Identification and optimization of small molecule agonists of the relaxin hormone receptor RXFP1”, Jingbo Xiao, Catherine Z. Chen, Zaohua Huang, Irina U. Agoulnik, Marc Ferrer, Noel Southall, Xin Hu, Wei Zheng, Alexander I. Agoulnik, and Juan J. Marugan, Nature-Communications, 4, 1953, 2013. PMID: 23764525.
b. “A selective TSH receptor antagonist inhibits stimulation of thyroid function in female mice”, Susanne Neumann, Eshel Nir, Elena Eliseeva, Wenwei Huang, Juan Marugan, Jingbo Xiao, Andrés E. Dulcey, and Marvin C. Gershengorn, Endocrinology, 155(1), 310-4, 2014. PMCID: PMC3868809.
c. “A novel brain penetrant NPS receptor antagonist, NCGC00185684, blocks alcohol-induced ERK-phosphorylation in the central amygdala and decreases operant alcohol self-administration in rats”, Thorsell A., Liu K., Zook M., Bell L., Patnaik S., Marugan J., Damadzic R., Tapocik J., Dehdashti S.J., Schwandt M.L., Southall N., Austin C.P., Eskay R., Ciccocioppo R., Zheng W. and Heilig M., Journal of Neuroscience, 33(24), 10132-10142, 2013. PMCID: PMC3682378

d. “Orphan GPR110 targeted by N-docosahexaenoylethanolamine in brain development”, Ji-Won Lee, Bill X. Huang, Md Abdur Rashid, Samarjit Patnaik, Juan Marugan and Hee-Yong Kim Nature Commun., Accepted.

5. New approaches to target pathogens. Several of approaches of my team are involved in finding new solutions for targeting pathogens, with particular emphasis in virus and parasites. Many of the approaches involved screening using replication assays looking for molecules targeting host-dependent mechanism. For example repurposed and brought to human clinical trials the antihistamine inhibitor Chlorcyclizine for the treatment of HCV, later on further optimizing and out licensing the series. We also out licensed our patent for giardia inhibitors and are investigating several molecules with activity for VEEV. Recently we disclosed the high efficacy of emetine against CMV. Currently we are trying to bring emetine to clinical trials for the treatment of organ transplanted immunosuppressed patients infected with CMV

a. “Efficacy and mechanism of action of low dose emetine against human cytomegalovirus”, Rupkatha Mukhopadhyay, Sujayita Roy, Rajkumar Venkatadri, Yu-Pin Su, Wenjuan Ye, Elena Barnaeva, Lesley Mathews Griner, Noel Southall, Xin Hu, Amy Q. Wang, Xin Xu, Andres Dulcey Garcia, Juan J Marugan, Marc Ferrer, Ravit Arav-Boger, PLoS Pathog.,12(6), e1005717, 2016. PMCID: PMC4919066
b. “High Throughput Giardia Lamblia Viability Assay Using Bioluminescent ATP Content Measurements”, Catherine Z. Chen, Liudmila Kulakova, Noel Southall, Juan J. Marugan, Andrey Galkin, Christopher P. Austin, Osnat Herzberg and Wei Zheng, Antimicrob Agents Chemother., 55(2), 667-75, 2011. PMCID: PMC3028786
c. “High-throughput Screening, Discovery and Optimization to Develop a Benzofuran Class of Hepatitis C Virus Inhibitors”, Shanshan He, Prashi Jain, Billy Lin, Marc Ferrer, Zongyi Hu, Noel Southall, Xin Hu, Wei Zheng, Benjamin Neuenswander, Chul-Hee Cho, Yu Chen, Shilpa A. Worlikar, Jeffrey Aubé, Richard C. Larock, Frank J. Schoenen, Juan J. Marugan, T. Jake Liang, Kevin J. Frankowski, ACS Combinatorial Science, 17(10), 641-652, 2015. PMID: 26332742
d. “Discovery, optimization, and characterization of novel chlorcyclizine derivatives for the treatment of hepatitis C virus infection”, Shanshan He, Jingbo Xiao, Andrés E Dulcey, Billy Lin, Adam Rolt, Zongyi Hu, Xin Hu, Amy Q. Wang, Xin Xu, Noel Southall, Marc Ferrer, Wei Zheng, T. Jake Liang, and Juan J. Marugan, J. Med. Chem., 59(3), 841-53, 2016. PMCID: PMC4753534.

In the last few years I have been investigating trying to understand the underlying cell impairments induced by aging, which exacerbate the effects of disease-specific defects and insults triggering the development of sickness. Many of these investigations involve the function of the lysosome and the role of autophagy.

D. Research Support

The NIH Chemical Genomics Center (NCGC) belongs to the National Center for Advancing Translational Sciences (NCATS). NCATS permits the scientific staff employed by NCGC to serve as co-investigators and collaborators on NIH-funded extramural grants.