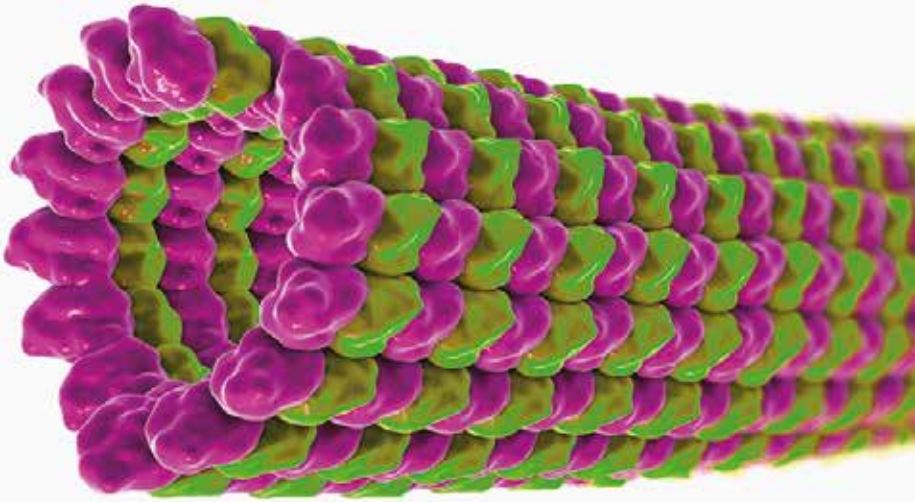
Tub in Train

European Joint Doctorate



PhD Projects

Marie-Skodowska Curie Innovative Training Network funded by the European Commission under the Horizon 2020 Programme

PHD PROJECT – ESR1

Computer aided molecular design and simulation of modulators of Tubulin-Tubulin and MAPs-Tubulin interactions

SUPERVISORS

Stefano Pieraccini, *University of Milan*

Alexandre Varnek, *University of Strasbourg*

OBJECTIVES

The aim of the project is the design and modelling of the action mechanism of peptides and molecules targeting either Tubulin-Tubulin or MAPs-Tubulin interactions.

DESCRIPTION OF THE PROJECT

The Early Stage Researcher (ESR) will model with molecular dynamics-based techniques the effects on Tubulin structure and dynamics of different Tubulin binding agents, both peptidic and non petidic. Then, the ESR will design modified peptides and small molecule ligands in order to tailor their effect on microtubules. Furthermore, Tubulin-MAPs interaction modulators will be also studied. The results obtained from ESR activity will support the work of chemoinformatics and chemical synthesis units operating within the network.
The ESR will be enrolled by the University of Milano (https://www.unimi.it/) under the supervision of Dr. Stefano Pieraccini and will be awarded a Double Doctorate degree in co-tutelle with the University of Strasbourg (https://en.unistra.fr/), under the supervision of Prof. Alexandre Varnek.
The research will involve secondments to the University of Strasbourg and to the company MindTheByte (https://www.mindthebyte.com/) in Barcelona, Spain.
The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

STEFANO PIERACCINI

Stefano Pieraccini is Assistant Professor of Physical Chemistry at the University of Milan, Department of Chemistry, Italy. In 2002, he graduated in Chemistry and in 2005 he obtained the Ph. D. in Chemistry from the University of Milan. His research interests are related to the use of molecular modelling techniques to study biomolecules. His activity has been focused on protein-protein interactions and protein stability modelling using molecular dynamics and free energy calculation techniques. He is author of 45 papers on peer reviewed journals and numerous communication in international conferences.

PHD PROJECT – ESR2

Molecular Modeling and Virtual Screening for Rational Design of Tubulin-Protein Interaction Modulators

SUPERVISORS
Alexandre Varnek, *University of Strasbourg*
Dragos Horvath, *University of Strasbourg*

OBJECTIVES

Design of novel, and adaptation of existing in-house modeling and virtual screening tools to the context of PPI (Protein-Protein interaction) modulator discovery, and their application to generate/prioritize new molecules for synthesis/purchase and test.

DESCRIPTION OF THE PROJECT

This multivalent PhD project is aimed at in Silico prioritization/focused library design of peptide based molecular probes able to modulate the Tubulin Tau and -Synuclein protein network. To this purpose, the protein-protein interaction interfaces will be analysed, in order to detect putative binding sites/binding pharmacophores for the putative ligands. In parallel, examples of any existing modulators will be mined from literature and public databases, in order to serve for ligand-based virtual screening strategies. The library of relevant polypeptides will be enumerated in Silico and prioritized by the above-developed virtual screening strategies. This can be extended to libraries of organic molecules, should an alternative to peptide modulators be proven of interest. Validity of candidates will be evaluated by docking. To this latter purpose, methodological developments of our in-house program S4MPLE. This tool was designed such as to allow the simulation of virtually any inter and intramolecular interaction scenarios. However, more development is currently needed, notably (1) the steady improvement of force field parameterization, by switching to a more realistic Generalized Born solvent model and (2) enabling S4MPLE to model protein-protein. Therefore, the candidate is expected to already possess a master-level

knowledge of chemoinformatics, be already acquainted with basic molecular structure handling, the concepts of similarity search, molecular structure encoding as descriptors, QSAR and pharmacophore models and the principles of docking (force field theory, solvent models) and programming skills.
The ESR will be enrolled by the University of Strasbourg (https://www.unistra.it/) under the supervision of Prof. Alexandre Varnek and Dr. Dragos Horvath.
The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

ALEXANDRE VARNEK

Alexandre Varnek got his PhD in physical chemistry from the Moscow Institute of Inorganic and General Chemistry of the Russian Academy of Sciences. In 1981-1995, he occupied positions of Assistant Professor then Associate Professor at the Mendeleyev University of Chemical Technology in Moscow. In 1995, Alexandre joined the University of Strasbourg, France, where he holds the position of a full professor in theoretical chemistry, head of the Laboratory of Chemoinformatics and the director of two MSc programs: master in chemoinformatics and master "In Silico Drug Design". Alexandre is (co)author of 7 books and more than 200 research articles and book chapters in the field of chemoinformatics and molecular modeling. He is the main organizer of the biannual Strasbourg Summer School in Chemoinformatics

DRAGOS HORVATH

Chemical engineer of the Cluj University, DH obtained his master's and Ph.D. (1997) in organic chemistry/molecular modelling within the framework of a joint European laboratory, associating the Pasteur Institute of Lille and the Free University of Brussels. He next joined the drug discovery company Cerep, where he lead the chemoinformatics team (Paris/Seattle). In 2003 he returned to academic research, as CNRS scientist, joining in 2007 Laboratory of Chemoinformatics of prof Varnek at the University of Strasbourg.
He is a CNRS research director since 2011. His expertise includes 2D chemoinformatics and 3D simulation methods, with focus on nature-inspired distributed computing.

PHD PROJECT – ESR3

Development of small molecules as MTs modulators acting on Tub-Tub interactions

SUPERVISORS
Daniele Passarella, *University of Milan*
Andrea Prota, *University of Basel*

OBJECTIVES

1. **Synthesis of analogs of maytansine, rhizoxine F and epothilone on the base of computational studies.**
2. **Evaluation of the stability of all the obtained compounds.**
3. **Biochemical evaluation of the activity of the obtained compounds on Tub polymerization.**

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will synthesize different compounds by functionalization of maytansine, maytansinol and rhizoxins with the aim to introduce a linker bearing a proper anchor point for the obtainment of conjugate compounds that could induce a double interaction with two different binding sites of tubulin. The target molecules will be designed according to the information received from the computational studies (ESR1). The stable obtained compounds will be studied in order to evidence their efficacy as binders of tubulin and modulators of tubulin/tubulin interaction.
The ESR will be enrolled by the University of Milano (https://www.unimi.it/) under the supervision of Prof. Daniele Passarella. A Double Doctorate degree will be awarded in co-tutelle with the University of Basel (https://www.unibas.ch/en.html), under the supervision of Dr. Andrea Prota (Paul Scherrer Institute https://www.psi.ch/en).
The research will involve secondments to the Paul Scherrer Institute (12 months, co-crystallization studies with the obtained and parent compounds) and LeadXpro (3 months, https://leadxpro.ch/)

The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

Daniele Passarella

Daniele Passarella is expert of organic synthesis, natural product chemistry and bioactive compounds. He leads a group of 10 researchers (post-doc, PhD students, master students). He is author of around 130 papers. He coordinated two COST Actions about Angiogenesis and Cancer Stem Cells. He acted as team leader in several national and international financed projects centered on Cancer and Neurodegeneration. He is the Italian Coordinator of an Italy-India Strategic Projects focused on tubulin targeting. He is involved in several collaborations about synthesis, biological evaluation, isolation of natural products, computational studies with academic Institutions, Research Centres and Pharmaceutical Companies.

PHD PROJECT ESR4

Development of small molecules to modulate MT stability

SUPERVISORS
Andrea Prota, *University of Basel*

OBJECTIVES

1. **Biochemical and biophysical characterization of Tubulin (Tub) interactions of the synthesized molecules using wave-guided interferometry and by thermal shift assays.**
2. **Characterization of ligand-mediated formation of higher Tub-aggregates by negative stained EM.**
3. **Crystallization of Tub-ligand complexes by co-crystallization and/or soaking.**
4. **Data collection at synchrotron and structure determination of the individual Tub-ligand complexes.**

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will be trained in the use of wave-guided interferometry, thermal shift assays, Crystallization of Tub-ligand complexes, co-crystallization and/or soaking and data collection at synchrotron. The evaluation of known tubulin binders will fix the reliability of the results. The ESR will be involved in the evaluation of the new compounds prepared by ESR3 in order to define their Tub binding kinetics and the activity on Tub aggregation.
The ESR will be enrolled by the Paul Scherrer Institut under the supervision of Dr. Andrea Prota and University of Basel. A Double Doctorate degree will be awarded in co-tutelle with the University of Milano (https://www.unimi.it), under the supervision of Prof. Stefano Pieraccini.
The research will involve secondments to the University of Milano (12 months, molecular modelling of compound derivatives) and Biorep (3 months, http://www.biorep.it/)
The selected candidate will participate in the network's training activities and

work placements in the laboratories of the participating academic and industrial partners.

Andrea Prota

Dr. Andrea E. Prota, PhD, is a Senior Scientist at the Paul Scherrer Institute, Villigen PSI, Switzerland (2004 – present; Laboratory of Biomolecular Research, Division of Biology and Chemistry).

- 2004 – 2010: Senior Scientist, Paul Scherrer Institute, Villigen PSI, Switzerland. Focus: structural analysis of VEGFs, Neuropilins and their cellular receptors and ligands involved in tumor angiogenesis.
- 2002 – 2004: Postdoctoral fellow, Paul Scherrer Institute, Villigen PSI, Switzerland. Focus: structural analysis of DNA mismatch repair proteins, VEGFs, Neuropilins and their cellular receptors and ligands involved in tumor angiogenesis.
- 2000 – 2002: Postdoctoral fellow, Beth Israel Deaconess Medical Center, Massachusetts General Hospital & Harvard Medical School, Boston, MA (USA). Focus: structural analysis of viral receptors and attachment proteins by X-ray crystallography.
- 1996 – 1999: PhD in pharmaceutical chemistry (Dr. sc. nat. ETH Zürich)
- 1989 – 1995: Graduate degree in pharmaceutical sciences (ETH Zürich)

Since early 2010 he is a tenured Senior Scientist in the Laboratory of Biomolecular Research at the Paul Scherrer Institute. His research interests include the use of X-ray crystallography and cryo-EM in combination with biochemical and biophysical methods to provide the molecular mechanisms of protein interactions implied in the regulation of microtubule cytoskeleton. His current research activity is devoted to the structural analysis of tubulin interactions with microtubule targeting agents. He has supervised 4 Ph.D. students and is author of 49 papers published in international journals.

PHD PROJECT – ESR 5

Development of molecular probes acting on Tau/Tubulin and -Synuclein/Tubulin interface

SUPERVISORS
Sara Pellegrino, *University of Milan*
Sandrine Ongeri, *University of Paris Sud*

OBJECTIVES

The aim of the project is the development of peptide based molecular probes able to modulate the Tubulin Tau and -Synuclein protein network.

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will first synthesize different protein domains of Tau and α-Synuclein involved in the interaction with tubulin that will be used for setting up the biochemical experiments (tubulin kinetics and binding). Then, the ESR will prepare a library of peptide molecular probes according to the information received from the computational design (ESR1). The obtained library will be evaluated in terms of conformation (CD, FT-IR and NMR experiments) and interaction with tubulin. Finally, starting from the most promising peptide sequences, peptidomimetics will be prepared by inserting non-natural AAs and secondary structure mimics.

The ESR will be enrolled by the University of Milano (https://www.unimi.it/) under the supervision of Prof. Sara Pellegrino and will be awarded a Double Doctorate degree in co-tutelle with the University of Paris Sud (https://www.u-psud.fr/en/index.html), under the supervision of Prof. Sandrine Ongeri.

The research will involve secondments to the University of Paris Sud (development of sugar based and fluorinated peptidomimetics) and AnkarPharma (http://ankarpharma.com/en/home2/), Spain.

The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

Sara Pellegrino

Sara Pellegrino is Associate Professor of Organic Chemistry at the University of Milan, Department of Pharmaceutical Sciences, Italy. In 2002, she graduated in Pharmaceutical Chemistry and Technology and in 2005 she gained the Ph. D in Medicinal Chemistry from the University of Milan. In 2005-2006 she has been visiting scientist (Vigoni fellowship) at the University of Regensburg (Germany). Her research interests are the synthesis of peptides and peptide mimics, and their application in Medicinal Chemistry, Biochemistry and Material Science. She is author of 66 papers in peer-reviewed journals, of three patents filed, and of more than 60 communications at international conferences.

Francesca Clerici

- Associate Professor, Organic Chemistry, Faculty of Pharmacy, University of Milan
- Responsible for internationalization of the Department of Pharmaceutical Sciences
- Erasmus Coordinator Department of Pharmaceutical Sciences.

More than 90 papers on peer-review journals, two patents, several communications, chapters of books. Research interests have been focused on a) design and development of new synthetic procedures for the preparation of organic compounds of biological interest b) stereo-controlled synthesis of non-natural constrained amino acids and their exploitation in different fields c) self-assembly.

Maria Luisa Gelmi

Maria Luisa Gelmi is a full professor in the Department of Pharmaceutical Sciences, University of Milano.

- Graduated in Chemistry, University of Milano
- Holds PhDs in Organic Chemistry and Pharmaceutical Sciences
- Worked as a full professor at the University of Milano

Current interests include i) diastereo- and enantioselective syntheses of non-coded amino acids characterized by poly-functionalization; ii) synthesis of peptide and peptidomimetics iii) conformational characterization of peptides (NMR, CD, IR); iv) use of peptide/peptidomimetics for biological applications (ID, Maf, PFKFB3 proteins, amyloid); v) use of short peptide sequences for the preparation of nanomaterials (nanotubes; nanoparticles; decorated gold-nanoparticles; fibers).

PHD PROJECT – ESR6

Development of inhibitors of Tau aggregation

SUPERVISORS
Sandrine Ongeri, *University of Paris*
Maria Luisa Gelmi, *University of Milan*

OBJECTIVES

Design, synthesis, biophysical and biochemical evaluation of peptides and peptidomimetics as ligands of Tau in order to modulate its aggregation.

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will synthesize mimics of β-strands and β-hairpins bearing specific sequences selected from Tau and involved in the aggregation. He/She will be involved in the synthesis of unnatural scaffolds, i.e. non-natural AAs and/or turn mimics from the library available at UMIL, or new scaffolds (fluorinated and or fluorescent), according to the results of the computational design. He/She will perform conformational studies using NMR techniques and will be involved in the biophysical and biochemical evaluations of the activity of compounds on Tau aggregation (ThT fluorescence spectroscopy, Microscopy, Capillary electrophoresis).

The ESR will be enrolled by the University of Paris Saclay (https://www.universite-paris-saclay.fr/en) under the supervision of Prof. Sandrine Ongeri and will be awarded a Double Doctorate degree in co-tutelle with the University of Milano (https://www.unimi.it/), Italy, under the supervision of Prof. Maria Luisa Gelmi.

The research will involve 12 months secondments at the University of Milano (synthesis of non-natural AAs and/or turn mimics) and 3 months secondments in cell microscopy and super-resolution, at San Raffaele Hospital (https://research.hsr.it/en/index.html, Cent. di Imaging Sperimentale,) under the supervision of Dr. Davide Mazza.

The selected candidate will participate in the network's training activities.

Sandrine Ongeri

Sandrine Ongeri is Full Professor in Medicinal Chemistry at the Faculty of Pharmacy, in the department BioCIS, a mixed unit CNRS/University Paris Sud, belonging to the University Paris Saclay, France. In 1995, she graduated in Pharmacy and in 1999 she gained the PhD in Organic Chemistry from the University of Paris Descartes (France). In the frame of her PhD, she worked for 12 months at the Dyson-Perrins Laboratory, Oxford (UK). In 1999, she got a two years post-doctoral position at the Univ Milan (Italy), funded by a European Network Grant. She became associated Professor at the Univ. Paris Sud in 2001 and Full Professor in this University in 2011. She has supervised 15 PhD students (7 in co-tutoring). She is co-author of 50 publications. She is Deputy director of the Doctoral School Therapeutic innovation (ITFA) that comprises 300 PhD students (40% of foreigners). She was involved in Marie Curie Host Fellowships for Early Stage Research project ("Foldamers" 2005-2009), and she is currently partner of a FET-OPEN (NoPest) in the frame of the European programme HORIZON 2020 (2019-2024)

The research interests of her team FLUOPEPIT "Molécules fluorées et peptides d'intérêt thérapeutique" are focused on the design, the synthesis and the biophysical evaluations of peptidomimetics as modulators of protein-protein interactions (PPIs) involving -sheet secondary structures. The team is particularly renowned in the field of PPIs involved in Alzheimer's disease and type 2 Diabetes. Her team is also well recognized in the design and the synthesis methodologies of non-natural fluorinated amino acids.

PHD PROJECT – ESR7

Development of inhibitors of α-Synuclein aggregation

SUPERVISORS
Sandrine Ongeri, *University of Paris*
Rolandt Brandt, *University of Osnabrück*

OBJECTIVES

Design, synthesis, biophysical and biochemical evaluation of peptides and peptidomimetics as ligands of α-Synuclein in order to modulate its aggregation.

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will synthesize mimics of β-strands and β-hairpins bearing specific sequences selected from α-Synuclein and involved in the aggregation. He/She will be involved in the synthesis of unnatural scaffolds, i.e. non-natural AAs and/or turn mimics from the library available at UMIL, or new scaffolds (fluorinated and or fluorescent), according to the results of the computational design. He/She will perform conformational studies using NMR techniques and will be involved in the biophysical and biochemical evaluations of the activity of compounds on Tau aggregation (ThT fluorescence spectroscopy, Microscopy, Capillary electrophoresis).
The ESR will be enrolled by the University of Paris Saclay (https://www.universite-paris-saclay.fr/en) under the supervision of Prof. Sandrine Ongeri and will be awarded a Double Doctorate degree in co-tutelle with the University of Milano (https://www.unimi.it/), Italy, under the supervision of Prof. Maria Luisa Gelmi.
The research will involve 12 months secondments at the University of Milano (synthesis of non-natural AAs and/or turn mimics) and 3 months secondments in cell microscopy and super-resolution, at San Raffaele Hospital (https://research.hsr.it/en/index.html, Cent. di Imaging Sperimentale,) under the supervision of Dr. Davide Mazza.
The selected candidate will participate in the network's training activities.

PHD PROJECT - ESR8

Dissecting the interaction of α-Synuclein with tubulin/microtubules

SUPERVISORS

Graziella Cappelletti, *University of Paris*

Rolandt Brandt, *University of Osnabrück*

OBJECTIVES

The aim of the project is to investigate in detail the interaction of -Synuclein with tubulin and microtubules and to disclose the role of such an interaction in molecular mechanisms of neurodegeneration.

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will first investigate the interaction of -Synuclein with tubulin and their aggregation properties in cell-free system. She/he will purify the proteins and carry out multiple experimental analyses including tubulin assembly kinetics, thermophoresis, NMR, cryo Electron Microscopy, and Real Time Quacking Induced Convertion (RT-QuIC). Then, the ESR will move to investigate i) microtubule assembly and dynamics, and ii) -Synuclein aggregation in neuronal cell cultures. She/he will perform biochemical and morphological studies in cultures overexpressing wild-type and pathological variants of -Synuclein including cell fractionation and Western blotting, confocal and super-resolution microscopy, and Proximity Ligation Assays. Finally, she/he will check in cell-free system and in neuronal cell cultures for the efficacy of those compounds and peptidomimetics that will be discovered by the TubinTrain network and will be indicated as the most promising in modulating -Synuclein/tubulin interaction and Synuclein aggregation.

The ESR will be enrolled by the University of Milano (https://www.unimi.it/) under the supervision of Prof. Graziella Cappelletti and will be awarded a Double Doctorate degree in co-tutelle with the University of Osnabrueck (https://www.uni-osnabrueck.de), under the supervision of Prof. Roland Brandt.

The research will involve 12 months secondment to the University of

Osnabrueck (analysis the impact of Synuclein on microtubules in neurons by using the quantitative live cell imaging approach developed by R. Brandt) and 3 months secondment to LeadXpro (http://leadxpro.ch), Switzerland.
The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

Graziella Cappelletti

Graziella Cappelletti is Associate Professor of Human Anatomy at the University of Milan, Department of Biosciences, Italy. She holds a degree in Biology from University of Milan and moved to the Neurological Institute "C. Besta", Milan, where she started her studies on molecular mechanisms in neurodegeneration. She spent a period in Eric Karsenti's lab at EMBL (Heidelberg, Germany) for acquiring expertise in the study of microtubule dynamics. Since 2001 she has a permanent position at the University of Milan. Her research interests are focused on cytoskeleton and its pivotal role in health and disease of the nervous system with the goal to identify key players in triggering neurodegeneration. Moving from purified proteins and cell cultures to mice models and human tissues, she has a long-lasting experience in studying the microtubule system, its organization and dynamics, in Parkinson's disease. To date, she is co-author of 60 papers in peer-reviewed journals and one patent. She is coordinator of the master-degree course in Biology Applied to Research in Biomedicine and member of the teaching committee of the PhD school in Molecular and Cellular Biology.

PHD PROJECT - ESR9

Evaluation of the interaction of MAPs and small molecules with Tub and MTs. in cells evaluation.

SUPERVISORS

Fernando Diaz

OBJECTIVES

1. **Structural characterization of the MAP/drug interaction with Tub and MTs using NMR, Cryo-EM**
2. **X-ray-crystallography of MAP, Tub complexes**
3. **Fiber diffraction of Tub polymers in the presence of MAPs and bifunctional compounds.**
4. **In cells toxicity evaluation of the compounds**

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will study the binding constants of the ligands and MAPs to Tub and MTs. The research activities will be based on the use of NMR for the mapping of the MAP/drug interaction of bifunctional compounds with the Tub and fiber diffraction to investigate the effects of compounds/MAPs in the Tub polymers. Furthermore the ESR will take care of the study of the effects of the compounds in tumoural cells sensitive and resistant to chemotherapy.

The ESR will be enrolled by the Centro de Investigaciones Biológicas (https://www.cib.csic.es) under the supervision of dr. Fernando Diaz and Universitad Internacional Menendez Pelayo (http://www.uimp.es/en/). A Double Doctorate degree will be awarded in co-tutelle with the Università degli Studi di Milano (https://www.unimi.it/en), under the supervision of Prof. Daniele Passarella.

The research will involve secondments to the Università degli Studi di Milano (12 months, Chemical synthesis of small molecules and target-assisted synthesis) and Indena (3 months, www.indena.com).

The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

Fernando Diaz

Fernando Diaz is Senior Staff Scientist at the Consejo Superior de Investigaciones Cientificas, Centro de Investigaciones Biol gicas, Madrid. In 1989, he graduated in Chemistry and in 1993 he gained the PhD in Chemistry from the Complutense University of Madrid. Tubulin and its assembly product, microtubules, are among the most successful targets in cancer chemotherapy. When he started his scientific career in 1988 only three binding sites had been discovered in tubulin, those of colchicine, taxane and vinca. Since then five new binding sites have been discovered, (eribulin, maytansine, pore site, laulimalide/peloruside and pironetin), from these five sites, four of them had been discovered and characterized by his group, either alone or in collaboration with other groups.

Furthermore, in coordination with a drug discovery group from Victoria University (New Zealand), a natural product synthesis group from the Swiss Institute of Technology and a crystallography group from the Paul Scherrer Institute (Switzerland), he provided with his group the biochemical techniques needed to optimize the formation of drug/protein complexes allowing the consortium to determine the structure of tubulin in complex with drugs and providing essential structural information about the interaction of these compounds with their binding site and the structural mechanism of activation of tubulin.

Another important problem that has occupied an important part of his scientific career is the search of methods that allow the in vitro evaluation of the potency of a drug in different tumoural cells. They have developed a method for the high throughput evaluation of the binding affinity of taxane binding site microtubule stabilizing agents which is now a standard for evaluating microtubule stabilizing agents. Later they have proof that the binding affinity of a given compound is a good predictive value for their toxicity, allowing the development of highly cytotoxic compounds using quick evaluations of the effect of chemical modifications in the drug structure.

Moreover, the development of a drug able to overcome resistance to chemotherapy is a final objective of his research. The technology developed to evaluate the binding affinity of paclitaxel site ligands have been employed to develop a super taxane, with more than 500 times the binding affinity of the parent compound paclitaxel, the compound is highly effective in all kind of tumoural cells resistant to paclitaxel chemotherapy. The same kind of approach has been used with the company Pharmamar S.A. to select a compound with high affinity targeting the newly discovered Maytansine site. The compound is effective in tumours resistant to chemotherapy and has entered clinical Phase II in Spain and USA. He is author of 165 publications and head of the Evaluation Panel for Biological Sciences of ALBA synchrotron.

PHD PROJECT - ESR10

Impact of small molecules on neuronal microtubule (MT) assembly and MT dynamics by quantitative live cell imaging of model neurons

SUPERVISORS
Rolandt Brandt, *University of Osnabrück*
Graziella Cappelletti, *University of Paris*

OBJECTIVES

1. Validation of the modelling and quantitative live cell imaging approach to determine MT-assembly and MT-dynamics in model neurons by using known compounds (epothilone, discodermolide, nocodazole), which interfere with MT polymerization.
2. Determination of the effect of novel cell-permeable compounds on MT dynamics using the validated approach from (1).
3. Analysis of the effect of potential modulating compounds as determined in (2) on MT-dependent spine loss, dendritic simplification and metabolic activities in ex vivo models of Alzheimer's and Parkinson's disease.

DESCRIPTION OF THE PROJECT

The Early Stage Researcher (ESR) will identify and characterize known and novel small molecules that affect neuronal MT assembly as potential lead structure for modulating MT dynamics in disease models and patients. The project will involve state-of-the-art single molecule tracking and live cell imaging approaches using model neurons and ex vivo models (for references see: Niewidok et al. (2018) J. Cell Biol. 217:1303–1318; Gauthier-Kemper et al. (2018) J. Biol. Chem. 293:8065-8076; Brandt and Bakota (2017) J. Neurochem. 143:409-417). The ESR will be enrolled at the University of Osnabrück (https://www.uni-osnabrueck.de/en/home/) under the supervision of Prof. Roland Brandt and will be awarded a Double Doctorate degree with the University of Milano (https://www.unimi.it/en/node/2) under the supervision of Prof. Graziella Cappelletti. The research will involve secondments to the University of Milano (to explore cellular neurodegeneration models of Parkinson's disease) and the company

IONOVATION GmbH (electrophysiological measurements and membrane biophysics (https://www.ionovation.com/), Germany. The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

Roland Brandt

Roland Brandt is Full Professor and Head of the Department of Neurobiology, School of Biology/Chemistry, and co-opted member of the Institute of Cognitive Science and the Center for Cellular Nanoanalytics (CellNanOs) at the University of Osnabrück, Germany. He studied Biochemistry and Philosophy at the Universities of Tübingen and Berlin (Germany). In 1990, he obtained his doctoral degree at the Max-Planck-Institute of Molecular Genetics, Berlin, and continued as a postdoctoral research fellow at the Center for Neurologic Diseases (CND), Harvard Medical School, Boston (USA). After returning to Germany in 1994, he became an independent research Group Leader at the Interdisciplinary Center for Neuroscience (IZN) at the University of Heidelberg, Germany, and moved 2002 to Osnabrück to become founding director of the Department of Neurobiology at the University. His research focuses on molecular mechanisms of neuronal development, aging and degeneration. He is author of more than 80 peer reviewed papers, which have been cited over 5,500 times. He serves as Deputy Chairperson of the Scientific Advisory Board of the "Alzheimer Forschung Initiative" (AFI), as Section Editor of the journal Brain Research Bulletin (Elsevier) and as Editorial Board Member of the journal Current Neuropharmacology (Bentham).

PHD PROJECT - ESR11

Impact of small molecules and peptides on Tau-MT interaction and tau aggregation in primary peripheral neurons and models of Alzheimer's and Parkinson's disease

SUPERVISORS

Rolandt Brandt, *University of Osnabrück*

Fernando Diaz, *Consejo Superior de Investigaciones Científicas (CSIC)*

OBJECTIVES

1. **Study of the efficacy of potential compounds modulating Tau/Tub interaction and Tau aggregation in vitro.**
2. **Establishing the use of primary cortical and peripheral neurons from Tau KO mice for the determination of Tau-MT interaction and Tau aggregation after virus-mediated expression of exogenous physiological and pathological Tau constructs by quantitative live cell imaging in authentic axons and dendrites.**
3. **Determination of the effect of novel cell-permeable compounds on the interaction between Tau and MTs in primary cortical and peripheral mouse neurons using the approach established in (2).**
4. **Analysis of the effect of potential modulating compounds as determined in (3) on MT-Tau interaction in ex vivo models of Alzheimer's and Parkinson's disease.**

DESCRIPTION OF THE PROJECT

The Early Stage Researcher (ESR) will identify and characterize small molecules and peptides that influence Tau-MT interaction and Tau aggregation as potential lead structure for modulating Tau-dependent toxicity in Alzheimer's and Parkinson's disease models and patients. The project will involve state-of-the-art single molecule tracking and live cell imaging approaches using model neurons and ex vivo models (for references see: Niewidok et al. (2018) J. Cell Biol. 217:1303–1318; Gauthier-Kemper et al. (2018) J. Biol. Chem. 293:8065-

8076; Penazzi et al. (2017) Neuropharmacology 113:434-444). The ESR will be enrolled at the University of Osnabrück (https://www.uni-osnabrueck.de/en/home/) under the supervision of Prof. Roland Brandt and will be awarded a Double Doctorate degree with the Consejo Superior de Investigaciones Científicas (CSIC) (https://www.csic.es/) under the supervision of Prof. Fernando Diaz. The research will involve secondments to the CSIC (Determination of the structural influence of Tau and small molecules on MTs using fibre diffraction and cryo-electron microscopy) and the company INDENA (quality assurance and management) (http://www.indena.com/), Italy. The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.

PHD PROJECT - ESR12

Systematic assessment of cell and metabolic impacts of Microtubule Targeting Agents (MTA) in neurodegeneration and neuron models

SUPERVISORS
Marta Cascante, *University of Barcelona*
Graziella Cappelletti, *University of Milan*

OBJECTIVES

The aim of the project is the characterization of the metabolic reprogramming associated with MTA therapy and neurodegeneration to minimize its metabolic side-effects.

DESCRIPTION OF THE PROJECT

The Early Stage Researcher (ESR) will study the impact of known MTA on the metabolic reprogramming associated with neurodegeneration and on transcriptional networks, with a special focus on metabolic networks at genome scale level. The experimental data will be integrated in Genome Scale Metabolic Models (GSMMs) generated by ESR13 to identify putative metabolic targets to reduce the side-effects of the MTA therapy. Then, the selected metabolic targets will be subjected to functional alteration (through gene silencing/overexpression or chemical inhibition) to assess their role in minimizing the metabolic side-effects of the MTA treatment. Finally, the ESR will test the effect of the combinations of MTA and selected metabolic adjuvants on the cell viability and metabolism in neurons.

The ESR will be enrolled by the Universitat de Barcelona (www.ub.edu) under the supervision of Prof. Marta Cascante and will be awarded with a Double Doctorate degree with the Università degli Studi di Milano (www.unimi.it) under the supervision of Prof. Graziella Cappelletti.

The research will involve secondments to the Università degli Studi di Milano to explore the effect of the selected drugs in cytoskeleton and cell physiology and to Biomax (www.biomax.co) to perform data integration and pathway analysis.

Marta Cascante

Marta Cascante is Full Professor at the Department of Biochemistry and Molecular Biomedicine at Universitat de Barcelona (UB). The research team "Integrative Systems Biology, Metabolomics and Cancer" that she leads has achieved outstanding international recognition for her pioneer work on developing and applying tools for the study of metabolic flux reprogramming in multifactorial diseases. She holds a degree in chemistry and a PhD in biochemistry from UB, where she was distinguished with the Outstanding Graduate and Thesis Awards. She has authored over 250 publications and supervised 30 PhD thesis. She is partner of European Translational Research Projects (H2020), including 3 Marie Curie Training Programs, in the field of systems medicine and metabolomics and member of the editorial advisory boards of Metabolomics and BMC Systems Biology. She also served in the scientific committee of numerous international conferences. She is member of the institute of Biomedicine of University of Barcelona (IBUB) and coordinator of the Spanish Network of Systems Medicine (SAF2015-70270-REDT). She leads a GC-MS platform for Stable-Isotope-Resolved Metabolomics at UB and she has also large experience in supporting biomedical community at national and international level in targeted metabolomics profiling for a wide range of sample types using the core LC-MS platform at CCiT at UB. She has been distinguished in 2010 and 2015 with ICREA Academia Prize and in 2015 with the Narcís Monturiol Medal of the Catalan Government for her scientific merits. She has large experience in collaborative projects with companies and clinical research centers to transfer the results of her research both at national and international level. Research interests are focused on metabolic alterations underlying multi-factorial diseases with the goal to identify key proteins to be used as biomarkers or drug targets. Furthermore, in the framework of H2020 project "PheNoMenal" her research group has contributed to develop and deploy an e-infrastructure to process, analyze and mine molecular phenotyping data, to facilitate large-scale data analysis.

PHD PROJECT - ESR13

Development of metabolic modelling tools to determine vulnerabilities associated with the metabolic reprogramming induced by MTA therapies on neurodegeneration models and in silico prediction of metabolic targets

SUPERVISORS

Marta Cascante, *University of Barcelona*

Alexandre Varnek, *University of Strasbourg*

OBJECTIVES

The aim of the project is to identify metabolic targets to improve the tolerance to MTA therapies using computational tools.

DESCRIPTION OF THE PROJECT

The Early Stage researcher (ESR) will first develop the Genome Scale Metabolic Model (GSMM) needed for modelling the metabolic phenotype of the neuron cell models used in the project. With this aim, the ESR will integrate in a generic GSMM the RNAseq data and the metabolomics and other experimental data generated by ESR12, in order to generate specific GSMMs of healthy and neurodegenerative neurons treated or untreated with MTA. These GSMMs will be used by ESR to identify transcriptional networks and metabolic pathways relevant in: i) the development of the neurodegenerative disorders, and in ii) the effect of MTA treatment in neurons. The most promising metabolic targets to be inhibited in combination with MTA will be validated experimentally by another ESR involved in the project (ESR12). Next, the ESR will design novel inhibitors against the identified metabolic targets using fragment based molecular design techniques.

The ESR will be enrolled by the Universitat de Barcelona (www.ub.edu) under the supervision of Prof. Marta Cascante and will be awarded a Double Doctorate degree with the Université de Strasbourg (www.unistra.fr), under the

supervision of Prof. Alexandre Varnek.
The research will involve secondments to the Université de Strasbourg to design the novel inhibitors using fragment based molecular design techniques, and LifeGlimmer (www.lifeglimmer.com), Germany, to learn new computational tools that will help in the analysis of data and in the development of GSMMs.
The selected candidate will participate in the network's training activities and work placements in the laboratories of the participating academic and industrial partners.