# H2020-ITN THERACAT (765497)

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| **Work Package Number** | WP7 | **Task Number** | T7.2 | **Deliverable Number** | D7.8 | **Lead Beneficiary** | IBEC |
| **Deliverable Title** | Updated Personal Career Development Plans (M24) | | | | | | |
| **Contractual Delivery Date** | 29/02/2020 | **Nature** | Report | | | **Dissemination Level** | CO |
| **Actual Delivery Date** | 15/05/2020 | **Contributors** | IBEC and All Beneficiaries | | | | |

**Overview/Abstract**

Personal Career Development Plans updated by all ESRs at Month 24.

**Explanation for large delay in submitting deliverable**

We have been waiting to receive all PCDPs updated by ESRs under guidance of their supervisors to submit this deliverable, which has been delayed due to difficulties caused by the COVID-19 outbreak.

**Led by**

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| **Name** | Rosa Miralles | **Partner** | IBEC | **Date** | 13/05/2020 |

**Reviewed by**

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|---|---|---|---|---|---|
| **Name** | Lorenzo Albertazzi | **Partner** | IBEC | **Date** | 15/05/2020 |

**Document Control**

| Issue # | Date | Changed Pages | Cause of Change | Implemented by |
|---|---|---|---|---|
| N/A | N/A | N/A | N/A | N/A |

# 1. Updated Personal Career Development Plans (M24)

A valuable tool in the implementation of the training of the ESRs are the individual **Personal Career Development Plan** (PCDP). The PCDPs contain the ensemble of research objectives and training actions to be undertaken by each researcher of the Network, both at short (1-2 years) and long term (over 5 years). Template and guidelines to prepare the PCDPs were already sent to all partners by the Coordinator (D7.1).

PCDPs are a dynamic document and should be continuously revised by the ESRs under guidance of their supervisors. In the framework of the THERACAT project, PCDPs are required to be updated at least every 12 months.

In this deliverable, updated PCDPs of all THERACAT ESRs are provided, which were revised by ESRs and supervisors after the feedback received in the last THERACAT Consortium Meeting (Meeting 2, February 3rd 2020, University of Edinburgh, UK), during fellows' presentations and Assessment Commissions.

## 2. References

N/A

# 3. Annex: THERACAT PCDPs (updated at M24)

Please find in the following pages the PCDPs of all THERACAT Early Stage Researchers duly updated.

# CAREER DEVELOPMENT PLAN

Name of fellow: Michela Vargiu (ESR1)

Department and Host Institution: Biomolecular Chemistry & Catalysis, Stratingh Institute for Chemistry, Rijksuniversiteit Groningen

Name of Supervisor: Prof. Dr. Gerard Roelfes

Date: 14-04-2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:**

Bioorthogonal catalysis is a powerful method for selective chemical reactions in a biological environment without involving endogenous functionalities of the cells. The main goal of my project is to design new anti-cancer drugs, composed of a catalytic system that includes a biologically inactive pro-drug (that differs from active drug due to a functionality that could be easily removed from the molecule) and a bioorthogonal organometallic catalyst that is capable uncaging the drug. In this way we hope to be able to free the active drug in situ, in order to limit unwanted side effects. To achieve these results, I will synthesize different pro-drugs (both with different scaffolds and different caging groups) and also various transition metal complexes. In this way I will carry out screenings in order to find the best combination substrate-catalyst, both from a chemical and biological point of view. The catalytic system we envision provides the action of the metal complex on a prodrug previously synthetized in order to obtain the release of the active drug in a physiological environment. After this step, the catalytic system will be tested against cancer cells in collaboration with other Theracat partners. A large number of drugs can be used as starting substrate; we focus on those that present an amino group.
The catalysts we have elected for this scope are organometallic complexes of Iridium and Ruthenium. Also a strategy that involves the use of light irradiation in combination with transition metal catalyst has been developed.
The features we hope to investigate during my PhD are: synthetic/mechanistic aspects, bioorthogonality studies, prodrug activation studies and target engagement studies.

**INDIVIDUAL SECONDMENT PLAN(S):**

1. Institution and sector (academic/non-academic): The University of Edinburgh (academic)

2. Duration: 3 months

3. Main research objectives:
   The main objective that I aim for these months is the study of my catalytic systems against human cancer cells.

4. New knowledge and competences expected to be acquired during the secondment:

I aspire to acquire skills in the biochemical/biomedical field, becoming able to perform reactions in cellular environments and study their biological effects.

5. Institution: TEVA Pharmaceutical Industries Ltd. (non-academic)

6. Duration: 3 months

7. Main research objectives:
   Formulation of a drug.

8. New knowledge and competences expected to be acquired during the secondment:
   I aspire to acquire skills in the pharmaceutical field, to become able to formulate a potentially marketable drug.

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals:
   After the end of my PhD I would like to continue my career in research, either in an academic environment or in a company. The goals I aspire to reach at the end of this path, for my personal growth as a scientist, are: increase my initiative, adaptability, communication skills, teamwork skills, decision-making skills, strategic-organization skills, innovative and creative skills, foreign language skills.

2. What further research activity or other training is needed to attain these goals?
   Increase my experience in research in general and in organic/medicinal chemistry and catalysis fields in particular.
   The University of Groningen, aims to allow its PhD candidates with the best possible development opportunities in preparation for their future careers, providing a personal budget for attending conferences and courses. PhD students are expected to follow an educational program of 30-36 ECTS credits, consisting of a variety of training elements. I will take 6 ECTS of formation related to transferable skills (such as project management, scientific writing, presentation skills etc.) as part of my PhD program, including Dutch courses as well as other courses related to my career development. Credits can be given for courses but also for other activities, for instance an internship at another lab or participation in a master class or summer schools.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications:

     All the results obtained in this project are expected to be published in international peer-reviewed journals. We hope to publish both about the synthetic strategy and the biological/medicinal application.

- Anticipated conference, workshop attendance, courses, and/or seminar presentations:

  All the workshop organized by the Theracat network, national yearly chemistry conferences in the Netherlands (CHAINS and NCCC), any suitable/applicable international conference, such as Bioorthogonal & Bioresponsive 2021 (Edinburgh, UK). I already attended four meeting/workshop organized by Theracat consortium (Eindhoven 2019, Edinburgh 2019, Basel 2019, Edimburgh 2020), an international conference (Bioorthogonal & Bioresponsive, Edinburgh 2019) and a national conference (NCCC 2020) in which I presented a poster titled "Novel Approaches to Ruthenium Catalysed Bioorthogonal Uncaging Reactions".

2. Research skills and techniques:

   - Local training:

     The University of Groningen offers a large number of specialist able to help PhD candidates to learn or improve a lot of different techniques, it is of fundamental importance for me to become an expert in organic synthesis and catalysis and to use analytical techniques such as NMR spectroscopy, HPLC techniques, GC techniques, Mass spectroscopy techniques, UV-visible and IR spectroscopy techniques. The head of my group has also encouraged me to follow any course that can be useful for built up my knowledge, for example in December 2019 I attended a mass spectroscopy course organized by the Interfaculty Mass Spectroscopy Center in Groningen.

   - THERACAT training:

     In the context of Theracat project, I hope to acquire, maybe visiting other institute involved in this network, expertise that are not part of my background. In particular I would like to increase my knowledge in biochemistry field. Training meetings already attended are: "How to Plan and Start a PhD" (University of Eindhoven, 2019) "Chemical Synthesis & Catalysis" (University of Basel, 2019), "Drug Delivery & Microscopy (University of Edinburgh, 2019)". Training meetings already planned are: "Going in Vivo, Chemistry and Cancer Biology" (University of Tel Aviv, 2020), "Getting Ready for the Next Career Step" (Institute for Bioengineering of Catalonia, Barcelona, 2021).

3. Research management:
   No other grant options are planned at this point.

4. Communication skills:
   During the following years I intend to reach a good level of communication, both oral and written. I would like to obtain good skills in communication with other professionals in the sector and also a good level in dissemination in order to promoting public comprehension of the researcher's work. Weekly group and sub-group meetings, both about our research progress and scientific literature updates, and presentations to whole institute (approximately every 1.5 years) are a very good training to reach good skills in communication.

5. Other professional training (course work, teaching activity):
   The University of Groningen gives every PhD student the opportunity to use until 10% of working time for teaching activities. I already taught one practical course titled "Synthesis and Analysis I".

6. Anticipated networking opportunities:
   All the meeting of Theracat project, conferences organized by other beneficiaries.

7. Other activities (community, etc.) with professional relevance:
   The University of Groningen organizes a lot of events which can help to increase my skills. For example, many lectures are organized, in which professors from all over the world present their scientific achievements.

Date & Signature of fellow
14-04-2020

Date & Signature of supervisor
14-02-2020

# CAREER DEVELOPMENT PLAN

Name of fellow: Shreyas Wagle

Department and Host Institution: School of Chemistry, Tel Aviv University.

Name of Supervisor: Prof. Roey J. Amir

Date: 10/04/2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:**

We intend to develop amphiphilic block-copolymers based on PEG-dendron hybrids which will contain binding sites based on 1,2-dimercaptoethers. These can act as complexing ligands due to their geometry formed during the thiol-yne reaction used to synthesize the dendritic end groups of the amphiphiles. Thus, they can form complexes with transition metals -such as Ru and Pd- to serve as catalytic centers where they will contain high local concentration of catalytic entities in the hydrophobic domains.

We want to systematically study the effect of hydrophobicity of the amphiphiles forming the micelles on their ability to carry out the depropargylation reaction in an aqueous environment. We tune the hydrophobicity of amphiphiles by changing the type of thiol used for forming it in the last step where the dendron is formed. This allows us to have a precise way of tuning the hydrophobicity and maintaining the narrow polydispersity of the synthesized polymer.

We will evaluate the catalytic performance of the micelles by comparing their rate of depropargylating 4-nitropheyl propargyl ether as well as testing these micelles to depropargylate substrates with varying hydrophobicities. This will help us to understand the structure property relationship with respect to the hydrophobicities of the micelles as well as the substrate.

**INDIVIDUAL SECONDMENT PLAN(S):**

- **Rijksuniversiteit Groningen**

1. Institution and sector (academic/non-academic): Stratingh Institute for Chemistry
2. Duration: The secondment duration was planned to be 3 months but currently, cut short to 1 month due to COVID-19 outbreak, which forced the university to shut down the labs.
3. Main research objectives: Ruthenium Catalyst Synthesis and combining it with micellar catalysis
4. New knowledge and competences expected to be acquired during the secondment: Organometallic Chemistry, Catalyst Synthesis, structure characterization, catalysis performance and profile.

- **Tagworks Pharmaceuticals BV**

1. Institution & sector: Tagworks Pharmaceuticals BV (Non-academic)
2. Duration: 4 months
3. Main research objectives: In-vivo micelle imaging
4. New knowledge and competences expected to be acquired during the secondment:
   In vivo chemistry, Radioimmunoimaging, PET imaging, Start-up development

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: Conduct research with different types of self-assembled systems for catalysis and for drug-delivery applications by undertaking post-doctoral positions

2. What further research activity or other training is needed to attain these goals?
   I would like to conduct further research in different polymer & supramolecular stimuli-responsive systems by collaborating with researchers and research groups having expertise in this domain.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications:

     We intend to publish papers on proof of concept of micellar catalysis, as well as on the structure property relationship effects to optimize the system, and on in vivo prodrug delivery and activation.

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations:

     Israeli Chapter of the Controlled Release Society (ICRS), Polymer Therapeutics (Valencia), NanoBioMed Conference (IBEC), NCCC (Noordwijkerhout).

2. Research skills and techniques:
   - Local training: PEG-dendron hybrid synthesis and self-assembly characteristics, studying and characterizing metal complexation and micellar catalysts

   - THERACAT training: designing in vivo models, prodrug design and synthesis, basics of high-resolution microscopy techniques

3. Research management:
   I intend to apply for external travel awards during my PhD studies and in the future to Marie Curie post-doctoral opportunities e.g. Postdoc COFUND Programmes in the future to support myself during my next stage of training.

4. Communication skills:
   PowerPoint and poster presentations, skills in report writing and preparing academic papers and books. Trying to undertake more public opportunities within the University and outside of it.

5. Other professional training (course work, teaching activity):
   Undertaking teaching assistantships by supervising laboratory courses and seminars during my time as a PhD student.

6. Anticipated networking opportunities:
   Conducting collaborative research with my peers by consulting them for my difficulties while also contributing to their research, attending national and international conferences along with the THERACAT meets for understanding newer developments for redesigning and evaluating my research

7. Other activities (community, etc.) with professional relevance:
   Career workshops for opportunities in industry and interview simulations, entrepreneurship strategies, searching for postdoc opportunities.

12/04/2020
Date & Signature of fellow

12/04/2020
Date & Signature of supervisor

European Training Network
THERACAT

# CAREER DEVELOPMENT PLAN

Name of fellow: Krishna Kanth Reddy Vippala

Department and Host Institution: TEVA Pharmaceutical Industries Ltd. (TEVA)

Name of Supervisor: Bianca Avramovitch

Date: 13-04-2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:** *half page should be enough*

The project will be focused on synthesizing self-assembling amphiphilic polymers and developing formulation to work as a Nano medicine. These nano particles will be characterized In-vivo and In-vitro to understand the systems physicochemical properties. These parameters will help us in designing the best formulation, which will exhibit improved pharmacokinetic profile and reduced toxicity.

**INDIVIDUAL SECONDMENT PLAN(S):**

**Institute for Bioengineering of Catalonia (IBEC)**

1. Institution and sector (academic/non-academic): IBEC, Academic
2. Duration: 4 months
3. Main research objectives: NP imaging
4. New knowledge and competences expected to be acquired during the secondment: Nano Particle imaging with super resolution imaging

**Technische Universiteit Eindhoven (TUE)**

1. Institution and sector (academic/non-academic): TUE, Academic
2. Duration: 3 months
3. Main research objectives: SAXS characterization of NP
4. New knowledge and competences expected to be acquired during the secondment: experience in using SAXS and using SAXS to characterize Nano particles

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: To acquire the skills and knowledge acquired during the life time of THERACAT PhD programme and apply to solve real world problems by developing new research tools and collaborations with academia and industry.

2. What further research activity or other training is needed to attain these goals?

Apart from in THERACAT's secondments, attending and participating department seminars in universities and TEVA. Soft skills and writing research grants and reports.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications: potential publication on characterization of Nano particles using Analytical tools.

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations: attended Italy-Israel Conference on Nanoscience and Nanotechnology for Medical Applications in sep 2019, TAU

2. Research skills and techniques:
   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

   - Local training: synthesizing and characterization of nanoparticles (TEVA and TAU), Learning about formulation design regulatory requirements in Teva. Furthermore attending the following courses in TAU: New Horizons in drug delivery system, carbohydrate chemistry, Design of smarty polymers, introduction to supramolecular chemistry, Methods and Applications in Mass spectrometry, and attending organic chemistry seminars every week in TAU. Attending relevant classes in Teva.

   - THERACAT training: events on Chemical synthesis and catalysis- hosted by BAS, drug delivery and microscopy (M18)- hosted by EDI (M24), Going in vivo, chemistry and cancer biology-hosted by TAU (M30).

3. Research management:
   *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*
   N/A

4. Communication skills: Honing oral communication skills by participating and presenting in weekly meetings in Tel Aviv University and bi weekly in Teva. Moreover, scientific communication skills by potential publication of research papers in scientific journals.

5. Other professional training (course work, teaching activity): N/A

6. Anticipated networking opportunities: THERACAT training events and TAU Faculty of Exact Sciences seminars, Teva global analytical and technological forums.

7. Other activities (community, etc.) with professional relevance: N/A

13.04.2020

Date & Signature of fellow

13.04.2020

Date & Signature of supervisor

# CAREER DEVELOPMENT PLAN

Name of fellow: Anjana Sathyan

Department and Host Institution: Eindhoven University of Technology

Name of Supervisor: Anja Palmans

Date: 16-04-2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:**

Nature has a unique way of catalyzing reactions in cells with the help of macromolecular biological catalysts called enzymes. Their catalytic activity has remarkable efficiency and specificity considering the very complex internal and external environment of the cell. Recent developments in bio-orthogonal catalysis have made mimicking the activity of such enzymes possible to a limited extent. This will be helpful for various therapeutic applications like pro-drug activation, drug delivery and imaging of cells. It is a challenging task to develop a synthetic catalytic system that can work efficiently inside the cells. Complex biological environment has different functional groups like nucleophiles, electrophiles, oxidants and reductants that can affect the stability of catalysts. Moreover, the catalysis should be feasible in water. To achieve this, single chain polymeric nanoparticles can be used as a catalytic system when they are modified to bear catalysts inside them. They can fold in water to form structured nanoparticles due to the optimal balance of hydrophobic and hydrophilic groups in the polymer backbone.[2] They have hydrophobic reaction spaces inside them that help to catalyze reactions in water with further scope of using them in complex biological media. Our aim is to develop a synthetic catalytic system using SCPNs that can function efficiently in cells to perform pro-drug activation for cancer therapy.

Liu et al. have shown the ability of Cu (I) and palladium (II) based SCPNs to act as catalysts in biological media.[1] They have studied carbamate cleavage reactions of rhodamine-based substrates in cellular environments which can be useful in catalysis based cancer therapy by uncaging bioactive compounds such as cytotoxic drugs. But efficiency of the these SCPNs in catalysis is greatly reduced from in vitro to in vivo due to the influence of biomolecules. The efficiency of these SCPNs to function in complex biological media has to be improved. In this project, we aim to study the catalytic activity of SCPNs in palladium mediated depropargylation reactions which will be tested in water, PBS buffer, serum and cells. The catalytic activity will be initially tested on different propargyl protected substrates which after depropargylation can be monitored using UV-vis or fluorescence spectroscopy. The best performing system in complex media will be used for the activation of cytotoxic pro-drugs.

References :


(1) Liu, Y.; Pujals, S.; Stals, P. J. M.; Paulöhrl, T.; Presolski, S. I.; Meijer, E. W.; Albertazzi, L.; Palmans, A. R. A. Catalytically Active Single-Chain Polymeric Nanoparticles: Exploring Their Functions in Complex Biological Media. *J. Am. Chem. Soc.* **2018**, *140* (9), 3423–3433.

(2) ter Huurne, G. M.; de Windt, L. N. J.; Liu, Y.; Meijer, E. W.; Voets, I. K.; Palmans, A. R. A. Improving the Folding of Supramolecular Copolymers by Controlling the Assembly Pathway Complexity. *Macromolecules* **2017**, *50* (21), 8562–8569.

**INDIVIDUAL SECONDMENT PLAN(S):**

**I$^{st}$**

1. Institution and sector (academic/non-academic): Universitat Basel

2. Duration: 3 months

3. Main research objectives: Study the catalytic activity of SCPNs loaded with new catalysts in cells

4. New knowledge and competences expected to be acquired during the secondment: I expect to gain more knowledge and acquire experience in the synthesis of catalysts and their characterization. I would also like to explore the possibility of incorporating these catalysts to SCPNs and study their activity in cells.

**II$^{nd}$**

1. Institution and sector (academic/non-academic): TEVA Pharmaceutical industries Ltd.

2. Duration: 3 months

3. Main research objectives: gain experience in management and skills needed for industrial research

4. New knowledge and competences expected to be acquired during the secondment: I expect to gain experience in industrial research focusing on management skills, regulatory requirements, preclinical and clinical demands.

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: I look forward to pursue academic research in the field of medicinal chemistry. After four years, I plan to continue my research in the form of Post doc and gain more knowledge in this field. Alternatively, I am also interested to have a future as research scientist in cancer research institutes.

2. What further research activity or other training is needed to attain these goals?
   Training to work in interdisciplinary field of organic chemistry and biology. Training in teaching and writing proposals. Training in mentoring students.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications: Journal of American Chemical Society, Macromolecules

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations:
     Courses – RPK polymer chemistry
     Presentation – MST colloquia, Dutch polymer institute days, CHAINS
     Conference – none at the moment

2. Research skills and techniques:

   - Local training: Training for research skills include courses offered by TU/e like Taking charge of PhD project, Writing articles and abstracts, Career Consult and Scientific Skills. In addition, I will receive training to mentor students.
   - THERACAT training: I will acquire skills to work in interdisciplinary field in collaboration with partners, improve team working skills, and develop scientific communication skills.

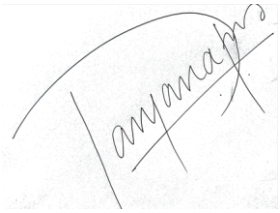
3. Research management: TU/e offers courses on Research data management, Introduction to exploitation of research results and knowledge transfer, Competing for a research grant, etc. These short and intense courses will be followed and will help me to improve my research management skills.

4. Communication skills: I plan to improve my presentation skills to larger community by continue doing poster presentations at Dutch polymer days, CHAINS etc. Presentations are to be done twice in a month in the group which will help me to improve my skills. MST quarterly report has to be submitted every three months and it will help me improve my report writing skills.

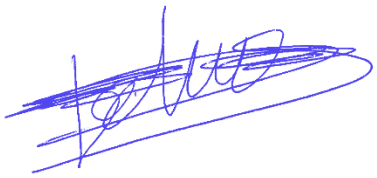
5. Other professional training (course work, teaching activity): I will be involved in teaching activity and will probably be done every year.

6. Anticipated networking opportunities: Successful completion of project requires close collaboration with other groups within the institution and within ITN network. Further networking opportunities will be evolved during the research depending on the results obtained.

7. Other activities (community, etc.) with professional relevance: N/A



16-04-2020
Date & Signature of fellow



16-4-2020
Date & Signature of supervisor

# CAREER DEVELOPMENT PLAN

Name of fellow: Stephen Croke

Department and Host Institution: University of Edinburgh

Name of Supervisor: Prof Asier Unciti-Broceta

Date: 17/04/2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:** *half page should be enough*

The overall aim of this research project is the investigation into novel therapies that incorporate bio-orthogonal catalysts. Specifically, this project will consist of two individual sub-projects.
The first sub-project will focus on the development of strategies for the biorthogonal assembly of proteolysis targeting chimeras (PROTACs) at specific locations using metal-catalysed ligations. PROTACs are emerging tools in drug discovery consisting of two covalently linked protein-binding molecules, one of which targets a disease-associated protein and the other one an E3 ligase, resulting in ubiquitination and subsequent proteolysis of the disease-associated protein. The project will involve installing azide moieties onto inhibitors of protein kinases and functionalizing E3 ligase recruiting ligands with an alkyne moiety. When these two molecules come in close proximity to each other in the presence of implants functionalized with Cu nanoparticles, this will allow a Cu(I)-catalyzed azide-alkyne cycloaddition reaction to occur, assembling the PROTAC *in vivo* at the location of the catalyst. This project aims to demonstrate the activation of said PROTACs using western blots and proteomic analysis.
The second objective of this project will involve the development of inactive PROTAC prodrugs that contain a moiety which is cleaved in the presence of Cu nanoparticles releasing the active PROTAC *in vivo.* My contribution to this project will be the design and synthesis of these prodrugs. This will involve the development of synthetic pathways to install metal labile protection group onto the E3 ligase ligand and the warhead ligand. This will employ organic synthesis methodology in addition to analytical techniques to synthesize said prodrugs. Demonstrate using *in vivo* assays that prodrugs have a >100-fold reduction in activity and activation in the presence of Cu nanoparticles.

**INDIVIDUAL SECONDMENT PLAN(S):**

1. Institution and sector (academic/non-academic): Tagworks Pharmaceuticals (Currently paused and under review due to COVID-19).

2. Duration: 4 months

3. Main research objectives: Imaging studies, protein functionalization and in vivo studies

4. New knowledge and competences expected to be acquired during the secondment: protein chemistry, animal models, in vivo imaging, industrial R&D experience

1. Institution and sector (academic/non-academic): Tel Aviv University

2. Duration: 3 months

3. Main research objectives: Test novel catalyst in vitro and in vivo.

4. New knowledge and competences expected to be acquired during the secondment: Polymer chemistry, kinetic studies, in vivo studies.

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: To be a competent scientist that is actively working in drug discovery research.

2. What further research activity or other training is needed to attain these goals?

Obtain PhD, successful management of projects, publications, networking, accredited courses, literary review, industrial experiences, incorporate methodologies/techniques that expand my knowledge of drug discovery i.e. metabolism and toxicity studies, computational modeling, animal trials etc. Take advantage of multi-disciplinary aspects of project i.e. nanoparticles emerging field for pharma (nanocarriers), learn more about each discipline. Demonstrate that I can work part of a multi-disciplinary team and can work together to achieve common goals.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications: A paper focusing on the activation of PROTACs *in vitro*.
   - Anticipated conference, workshop attendance, courses, and/or seminar presentations.

     Workshops: Scientific writing/communication, instruments workshops i.e. LC-MS and NMR, drug discovery related workshops i.e. computational modeling (Schodinger), research planning and management workshops.

     Conferences: Conferences that are focused on biorthogonal chemistry, chemical biology, drug discovery, cancer therapies, catalysis i.e. Bioorthogonal & Bioresponsive 2019

     Seminars: Attend university organized seminars focusing on organic synthesis, drug discovery, cancer therapies, catalysis, bio-orthogonal reactions.

2. Research skills and techniques:

   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

- Local training: Organic synthesis, advanced material chemistry i.e. synthesis of nanoparticles, characterization, design and development of assays and animal models, western-blots and proteomics analysis, critical thinking, literary reviews.

- THERACAT training: Incorporating techniques/methodologies that I as a chemist am not familiar with into my research i.e. *in vivo* studies; translational and outreach activities; industry experience.

3. Research management:

   *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*

   Organise meetings with supervisor and team to regularly discuss findings, troubleshooting etc. Determine deadlines for the project and deliver on said deadlines. Budget for cost of materials and any tests that may need to be conducted by external parties. Apply for funding opportunities to continue as a post doc.

4. Communication skills: Scientific writing/communication workshops, lab meeting presentations, poster presentations at conferences, paper writing, grant applications, lab notebook management.

5. Other professional training (course work, teaching activity): Undergrad research project supervisor, supervisor of undergrad labs.

6. Anticipated networking opportunities: RSC events, Seminars, Conferences, Marie Curie workshops, Post-Grad events.

7. Other activities (community, etc.) with professional relevance: PubhD, Pint of science, CRUK public engagement events.

17-04-2020
Date & Signature of fellow

17-04-2020
Date & Signature of supervisor

# CAREER DEVELOPMENT PLAN

Name of fellow: ESR06 - Emmanouil Archontakis

Department and Host Institution: TU/e - ICMS

Name of Supervisor: Lorenzo Albertazzi

Date: 15/04/20

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:**

Overview: ESR6 will develop a super resolution method to test at the single molecule level the catalytic efficiency, as well as, the properties of the nanomaterials proposed in THERACAT. Catalytically - activable prodyes will be synthesized to probe the efficiency of the catalyst developed in WP3. We anticipate that measuring catalytic activity and the single molecule level is crucial for synthetic structures due to the heterogeneity induced by the polydispersity in the synthesis. Individual catalyst will be anchored on a glass surface and a prodye substrate added to the solution. Single fluorescence events will be observed at any catalytic conversion using a TIRF microscope. The time profile of such events will provide information of the catalytic efficiency, turnover and stability of the catalyst and the distribution of such properties among a large population of nanostructures.

Methodology: Single-chain polymeric nanoparticles (SCPN) are nano-sized structures, which can mimic the activity of enzymes. SCPNs are heterogeneous due to the polydispersity of their synthesis, and in order to study them, is needed to go at the single-molecule level by using single-molecule localization microscopy (SMLM). In this project, SCPNs bearing a catalytic unit, will be used for pro-drug and pro-dye activation. The method workflow is divided into two parts; the structure characterization (size, polarity of the pocket), and the catalytic characterization (turnover frequency, stability, efficiency), of the catalytic nanomaterials, by combining spectroscopy and super resolution microscopy.

Major accomplishments:

- ESR06 implemented a multidimensional super resolution setup, which can reveal simultaneously spatial and functional information from individual catalytic nanoparticles.
- SCPNs immobilization for long time single molecule imaging (needs improvement, but results are encouraging).

**INDIVIDUAL SECONDMENT PLAN(S):**

1. Institution and sector (academic/non-academic): University of Groningen/ CRUK
2. Duration: 3 months
3. Main research objectives: characterization of SCPNs / training in outreach
4. New knowledge and competences expected to be acquired during the secondment: Synthesis and preparation of SCPN for super resolution imaging / experience in outreach and divulgation

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: Being a specialist in microscopy with a broad knowledge in the field of nanomedicine

2. What further research activity or other training is needed to attain these goals?

   More sample preparation research training (preparing SCPNs before imaging, labeling etc.), as well as, some software training (Matlab)

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications:
     Methods for DNA-PAINT quantification
     Structure and catalytic characterization of SCPNs at the single molecule level

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations:
     ICMS annual symposium (cancelled due to corona virus)
     Microscopy conference in 2021

2. Research skills and techniques:
   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

   - Local training: super resolution microscopy & methods (Microscopes: Nikon, ONI), sample preparation, optics, data analysis, chemical synthesis, prodyes basics

   - THERACAT training:

     - How to start and plan a phd (March 2019), Eindhoven
     - Chemical synthesis and catalysis (September 2019), Basel
     - Drug delivery and microscopy (February 2020), Edinburgh
     - Next training event: Going in-vivo- chemistry and cancer biology (September 2020), Telaviv

3. Research management:

   Nothing

4. Communication skills:

   Training on giving presentations

5. Other professional training (course work, teaching activity):

   Scientific integrity, supervising master students, microscopy webinars

6. Anticipated networking opportunities:

   - Collaboration with the university of Gronigen during first secondment
   - Looking forward to work at the Cancer research institute UK regarding outreach

7. Other activities (community, etc.) with professional relevance:

   Not yet

Date & Signature of fellow

16-04-20

Date & Signature of supervisor

16-04-20

# CAREER DEVELOPMENT PLAN

Name of fellow: **Rodica Alis Olea**

Department and Host Institution: **Nanoscopy for nanomedicine Group, Institute of Bioengineering of Catalonia**

Name of Supervisor: **Lorenzo Albertazzi**

Date: **21-04-2020**

## BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:

The project will be focused on tracking the delivery of the nanocatalyst, as well as assessing the catalytic activity in different cellular models or tissues. Three microscopy techniques will be used: stochastic optical reconstruction microscopy (STORM), single particle tracking (SPT) and fluorescence recovery after photobleaching (FRAP). The dynamics, uptake and localization of the nanocatalyst will be assessed at different time points in i) culture of cancer cells; ii) 3D models of tissue organization. STORM is a super-resolution microscopy technique capable of reaching 20 nm resolution. Therefore STORM is expected to provide valuable information on the localization and amount of nanocatalyst present in different cellular compartments or cell types. SPT and FRAP are techniques with higher time resolution, thus will provide insight on the capacity of different nanocatalysts to penetrate 3D tissue models. Furthermore, by using an analogous procedure relying on STORM-compatible and SPT-compatible pro-dyes, the localization and catalytic activity will be quantified in tissue samples and biological models.

**Accomplishments Expected:** Protocol for nanocatalyst super-resolution imaging; Data on nanocatalyst localization and dynamics in 2D and 3D cell cultures; Map of catalytic activity in cells and tissues.

## INDIVIDUAL SECONDMENT PLAN(S):

**First secondment:**

1. Institution and sector (academic/non-academic): Biogelx Limited (BGX), non-academic

2. Duration: 3 months, starting from M21

3. Main research objectives: Imaging gel models

4. New knowledge and competences expected to be acquired during the secondment: knowledge on manufacture of gels, ways of imaging porous structures in high resolution, information on the localization of the catalyst in 2D and 3D cell cultures

**Second secondment:**

1. Institution and sector (academic/non-academic): Tel Aviv University (TAU), academic

2. Duration: 4 months, starting from M30

3. Main research objectives: *In vivo* and *ex-vivo* imaging of catalysis

4. New knowledge and competences expected to be acquired during the secondment: tissue sample preparation for high resolution imaging, knowledge on the localization and function of the catalyst inside living organisms

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: Determine which future career path is more suitable, taking into consideration the present and future skills and interests. The considered possibilities include an academic path, with or without teaching, an industry path and the possibility of scientific communication, in particular scientific illustration and animation. The trainings within THERACAT are very well suited for giving a wider perspective on the considered future paths and are very likely going to help in taking an informed decision later on.

2. What further research activity or other training is needed to attain these goals?
   As part of the THERACAT training, the secondments in industry and academia, as well as the participation in training events and conferences should prove very useful in ultimately choosing a suitable career path.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications: Methods paper on super-resolution imaging of nanocatalysts; Research article on intracellular localization of nanocatalysts analysed using super-resolution microscopy; Research article on dynamics of nanocatalysts in 3D tissue model

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations: GRS (Gordon Research Seminar) and GRC (Gordon Research Conference) on Cancer Nanotechnology, IBEC Symposium, BIST Symposium, advanced microscopy seminars held in Barcelona area (ICFO, CRG, ICN2, IRB), Single Molecule Localization Microscopy Symposium (SMLMS)

2. Research skills and techniques:

   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

- Local training: provided by IBEC – workshops to train presentation skills, statistics, scientific writing, data analysis and visualization

- THERACAT training: "Going *in vivo*, chemistry and cancer biology" (Tel Aviv, month 30); "Getting ready for the next career step" (Barcelona, month 36).

3. Research management:

   *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*

   Apply to travelling fellowships for participating in conferences or for visiting research groups abroad; possibly an application for a Marie Curie PostDoctoral grant at the end of the ITN.

4. Communication skills: at least two poster or flash presentations in symposiums or events; monthly presentations in group meetings.

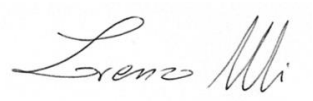
5. Other professional training (course work, teaching activity): supervising a bachelor or master student internship

6. Anticipated networking opportunities: THERACAT networking meetings; weekly seminars at IBEC; biweekly group meetings; participation in symposiums.

7. Other activities (community, etc.) with professional relevance: working on the THERACAT presentation movie.

Date & Signature of fellow
21.04.2020

Date & Signature of supervisor
24-4-2020



# CAREER DEVELOPMENT PLAN

Name of fellow: Linlin Deng

Department and Host Institution: Eindhoven University of Technology

Name of Supervisor: Anja Palmans

Date: 16th April, 2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:** *half page should be enough*

The ability to activate toxic drugs by inducing a decaging reaction of the non-toxic prodrug in the vicinity of diseased cells is one of the aims of the THERACAT network. In this context, dynamically folded single chain polymeric nanoparticles (SCPNs) were recently found to show promising catalytic behavior in the presence of cells. Although the activity and biocompatibility of the SCPNs is encouraging, a number of issues remain elusive such as the stability of the folded polymer, the stability of the catalyst, and interactions of the catalytically active SCPNs with the components of the complex mixture. This research aims to follow a bottom-up approach to elucidate the behavior of SCPNs in complex media, so that they ultimately can efficiently be applied for in vivo prodrug activation.

In this work, we studied the stability of single-chain polymeric nanoparticles in complex media by mixing Nile Red and its derivative with these nanoparticles and monitoring the change of emission spectra in different media. To this end, the amphiphilic polymer comprising a polyacrylamide-based backbone, hydrophilic side chains Jeffamine@M-1000, hydrophobic graft dodecyl, and supramolecular recognition motif benzene-1,3,5-tricarboxamide (BTA) was synthesized to prepare SCPNs in aqueous solution. Three Nile Red-related systems were developed to investigate the stability of these SCPNs in different media. The first system we designed is to mix commercially available Nile Red with SCPNs. However, the localization of Nile Red may not be exactly in the hydrophobic core of SCPNs. To improve the encapsulation efficacy, we therefore designed the second system by covalently attaching de-symmetrized BTA moiety to Nile Red and mixing the new dye BTA-Nile Red with SCPNs. In addition, we synthesized a Nile Red derivative with an amine linker which can be covalently attached to the polymer backbone and thus fulfills our third system. With the three systems, a combination of fluorescent spectroscopy, circular dichroism (CD) spectroscopy and dynamic light scattering (DLS) was applied to study the stability of SCPNs in four different media increasing complexity: (1) water, (2) Phosphate buffer, (3) Dulbecco's Modified Eagle Medium (DMEM), (4) 10% Fetal Bovine Serum in DMEM.

Using three Nile Red-based approaches as an indicator for the polarity change of the interior of nanoparticles, we gained a good understanding of the thermodynamic stability of single-chain polymeric nanoparticles prepared by post-polymerization of pPFPA in biologically relevant solutions. Experimental results show that the amphiphilic polymer can self-assemble in water, PBS buffer and DMEM solution with similar nanoparticle sizes, and the formed nanoparticles are stable in physiological media, suggesting their potential for biological application.

**INDIVIDUAL SECONDMENT PLAN(S):**

1. Institution and sector (non-academic): BGX combined with EDI (academic)
2. Duration: 3 months
3. Main research objectives: test catalytic activities in gel cancer models
4. New knowledge and competences expected to be acquired during the secondment:
   (1) Study how efficiently prodrugs can be cleaved by catalysts nanocarriers
   (2) Acquire skills in designing and synthesizing hydrogels
   (3) Learn how to develop 3D cancer model using peptide hydrogels

1. Institution and sector (academic): IBEC
2. Duration: 4 months
3. Main research objectives: STORM imaging of SCPN delivery
4. New knowledge and competences expected to be acquired during the secondment:
   (1) Acquire skills in targeted delivery strategies
   (2) Acquire skills in super resolution imaging to track the SCPN delivery.
   (3) Study the interactions of nanostructured materials with living matter via STORM

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: To find a teaching position in university

2. What further research activity or other training is needed to attain these goals?
   Research activities: to assist in teaching and guiding students at TU/e, like guiding OGO projects or giving tutorials. To attend seminars related to the research field. To attend different research-related lectures. To attend conference and communicate with researchers.

   Training: how to design, prepare and deliver lectures. How to facilitate small group seminars. How to provide feedback and assessment.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications: 1 or more

   - Anticipated conference: International Conference on Molecular Systems Engineering ICMSE; FMS Annual Meeting; Chains; Dutch Polymer Institute days
   - Workshop attendance: ITN training event
   - Courses: Academic writing course; RPK Polymer Chemistry
   - Seminar presentations: MST Colloquium

2. Research skills and techniques:

   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

   - Local training: Brush up Your Academic Writing: Academic Style; Analytic Storytelling; Competing for a Research Grant: Your Presentation, Giving an Audience-Focused Presentation; Information Literacy and Reference Management

   - THERACAT training: Transferable skills including scientific communication and dissemination; Project management; Entrepreneurship; Intellectual property; Ethics and gender awareness.

3. Research management:

   *None*

4. Communication skills:
   Oral communication skills, to talk confidently in front of large audiences. To express ideas clearly. To prepare well-organized posters and presentations.

5. Other professional training (course work, teaching activity):
   To attend literature reviewing course for finding, reading and analyzing complex documents. To attend writing course for conference papers, progress reports, articles and thesis.

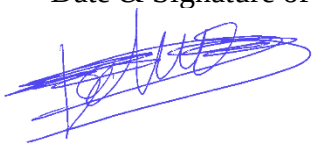
6. Anticipated networking opportunities:
   To attend events like seminars. To join professional organizations such as the Association for Women in Science. To meet scientists who make great progress in their research area.

7. Other activities (community, etc.) with professional relevance:
   To join community organization like service club. To create a profile on LinkedIn and join relevant LinkedIn groups. To serve on committee.

Date & Signature of fellow

15th April, 2020
Linlin Deng

Date & Signature of supervisor



16-4-2020

# CAREER DEVELOPMENT PLAN

Name of fellow: Maria de Africa Galvez-Flores

Department and Host Institution: Biogelx Limited

Name of Supervisor: Dr Chris Allan

Date: 2 APRIL 2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:** *half page should be enough*

**Development of Biogelx Synthetic Peptide-Hydrogels for Use in Anti-Cancer Strategies**

**Overview:**

*Background*

Biogelx designs and manufactures a range of tuneable synthetic peptide hydrogels capable of mimicking the properties of a variety of tissue types. Biogelx hydrogels are utilized across a range of cell culture applications, including 3D cell-based assays. *In vitro* 3D platforms are used in cancer research, bridging the gap between unrealistic *in vitro* 2D models and complex animal models. In particular, 2D *in vitro* models don't provide a platform where cells maintain full contact with their extracellular microenvironment (i.e. extracellular matrix and stromal cells). These contacts are important, since they participate in modulating cell behaviour through both physical and chemical signals, such as stiffness and key extracellular matrix proteins (e.g. fibronectin). It is known that cancer tissues have different, much more stiffer microenvironments compared to those of normal tissues, and different matrix-associated protein composition. These features affect cell differentiation, proliferation and migration, as well as response to anticancer drugs. 3D *In vitro* cell culture platforms provide cells with an extracellular microenvironment, offering a better alternative to 2D cultures and replicating morphology, function and behaviour of cells in their natural matrix *in vivo*. However, adoption of *in vitro* 3D systems in the drug discovery industry presents challenges in standardisation and analysis. Biogelx hydrogels are synthetic, and therefore provide an *in vitro* 3D matrix that is simple, reproducible and can be tailored to mimic the requirements of any cell type.

*Objectives*

The aim of this study is to design and optimise Biogelx hydrogels to aid in the development of the proposed bio-orthogonal catalysis anti-cancer strategy. Our specific objectives are:

1. Design, synthesis and characterisation of hydrogels with defined chemical compositions and tuned mechanical properties, capable of mimicking both healthy and cancerous tissue.
2. Development of realistic 3D *in vitro* cancer model using Biogelx hydrogels.
3. Assessment of the effectiveness of the new-developed bio-orthogonal chemotherapies in Biogelx 3D *in vitro* cancer model.
4. Generation of insight into the ability of Biogelx hydrogels to act as nanoparticle carriers.

*Methodology*

The methods applied to achieve these objectives involve assembly and characterization of peptide nanostructures using a range of spectroscopy and microscopy techniques, as well as analysis of mechanical properties using rheology. 3D cell culture is carried with tumorigenic (e.g. MCF-7 and MDA-MB-231) and non-tumorigenic (e.g. MCF10A) cell lines, upon standard and bio-functionalised hydrogels at specific stiffness to mimic cancerous and healthy tissues. Multicellular cancer spheroids are being created. Evidence for biocompatibility, cellular morphology and functionality, and therapy effectiveness in our models is being provided. This is being done through molecular biology techniques, as well as widefield, confocal/multiphoton and super-resolution microscopy.

*Major accomplishments expected*

1. Peptide hydrogel formulations tuned to mimic both cancerous and healthy tissues.
2. *In vitro* model for testing anti-cancer drug delivery.
3. Peptide hydrogel formulations for therapeutic delivery of catalytic nanoparticles.

**INDIVIDUAL SECONDMENT PLAN(S):**

**TUE**

1. Institution and sector (academic/non-academic): Eindhoven University of Technology (academic).
2. Duration: 3 months (starting in August 2020).
3. Main research objectives: Assessment of the potential of Biogelx hydrogels to act as a nanoparticle delivery system in *in vitro* cultures.
4. New knowledge and competences expected to be acquired during the secondment:
    - Increased knowledge of nanoparticle drug delivery systems.
    - Deeper understanding of state-of-the-art microscopy techniques and hands-on expertise in super-resolution microscopy; i.e. STORM.
    - Hands-on expertise in characterization of Biogelx hydrogels with microscopy techniques.
    - Hands-on expertise in 3D *in vitro* cell culture imaging with confocal and multiphoton microscopy.

**IBEC**

1. Institution and sector (academic/non-academic): Institute for Bioengineering of Catalonia (academic).
2. Duration: 4 months (2021).
3. Main research objectives: Monitoring of nanoparticle drug delivery through stochastic optical reconstruction microscopy (STORM) in 3D *in vitro* cultures.
4. New knowledge and competences expected to be acquired during the secondment:
    - Increased understanding of catalytic systems in a cellular environment.
    - Hands-on expertise in monitoring nanoparticle drug delivery with super-resolution microscopy in 3D *in vitro* cultures.
    - Introduction to monitoring catalysis in 3D *in vitro* cell culture systems through STORM.
    - Improved expertise in 3D *in vitro* cell culture imaging, including confocal and multiphoton microscopy.

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: I want to work in intellectual property, as a patent examiner in the Healthcare, Biotechnology and Chemistry sectors.

2. What further research activity or other training is needed to attain these goals? In addition to my work as a researcher at Biogelx, which evidences a strong technical experience, theoretical training (e.g. course in patent law and patent IT search) and languages (i.e. B2 level of French required for working at EPO). Business experience for a Technology Transfer related path would be also desirable; this could be done in house at Biogelx. For example, I could learn from business development, marketing, communication and quality management areas by getting involved and providing help with these activities. An online course on technology transfer would be also beneficial.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results:
   - Anticipated publications:
     - Potential publication demonstrating the reliability of Biogelx hydrogels to mimic cancer biology.
     - Potential publication comparing *in vitro* bio-orthogonal catalysis in 2D and 3D cell culture.

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations:
     - Attendance at 1-2 large international conferences per year. Attended already "Goodbye Flat Biology: Advancing 3D-based Models for Cancer Biology and Drug Discovery" in Berlin ($10^{th}$-$13^{th}$ November 2019). Potential attendance to "Bioengineering Solutions for Biology and Medicine" in Munich ($24^{th}$ – $26^{th}$ June 2020). Potential attendance to "Organoids Tools for Fundamental Discovery and Translation" in Colorado ($7^{th}$ -$11^{th}$ February 2021).
     - Attendance at relevant meetings/symposiums with Biogelx business team. Attended 3D BioNet/IBIN networking meeting in London ($20^{th}$-$21^{st}$ January 2020).
     - Attendance at seminars by visiting speakers at local universities. I am attending University of Glasgow Biomaterials Seminar Series on a weekly basis and presenting my own scientific work when required.

2. Research skills and techniques:

   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

   - Local training:
     - Trained in theoretical scientific aspects about **Biogelx technology**. I.e. Biocompatible peptide FF-based hydrogels and bioinks. I will **keep myself updated** on these.

- Trained in **industry and business-related activities**. Working in a small company allows me to be directly involved in wide a range of activities, such as developing applications protocols, advising customers on cell culture queries, developing scientific content marketing for Biogelx's website, providing scientific representation in conferences and meetings, and helping Biogelx's business development manager follow up with potential customers. I will **keep on performing these tasks**.
- Trained in **3D *in vitro* cell culture** at Prof Matthew Dalby's lab at the university of Glasgow, and currently working within his cell culture facilities. Expanded my knowledge in bioengineering and the development of innovative 3D cell culture systems. This is being applied to the continuous improvement of my work for the THERACAT project. Also contributed to academic presentations with my own work. As an Affiliated Researcher at the University, I will keep on **performing and benefitting from these activities**.
- In order to continue to develop business skills I will get involved in a project an MBA student from the University of Strathclyde will develop at Biogelx.
- Additionally, there are two **online courses** provided by the University of Glasgow I am interested in: 1) Introduction to Health Economics and Health Technology Assessment and 2) Project Management: turning the theory into practice. The first one would specifically help my long-term career objectives. The second one would generally help long-term career objectives and current work at Biogelx.

- THERACAT training:
  - It is important to provide evidence of biocompatibility of Biogelx 3D *in vitro* tumor models through confocal and multiphoton microscopy. This will be carried out during my secondments at Albertazzi's labs (TUE and IBEC).
  - It would be beneficial to receive training in catalysis reactions in cells at the Unciti-Broceta lab (EDI), what could significantly help in the development of Biogelx 3D *in vitro* tumor models.
  - It would be beneficial to receive guidance in evaluation of THERACAT new developed drugs *in vitro*. Guidance could be provided by Satchi-Fainaro's lab (TAU). Satchi-Fainaro's group has extensive experience in building 3D *in vitro* tumor models with a range of biomaterials (e.g. Matrigel). A comparison between Biogelx and an alternative material-based 3D *in vitro* tumor models would be insightful when evaluating THERACAT drugs activity.

3. Research management:

   *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*

Many international conferences offer competition-based travel bursaries for participants that will be taken into consideration. The online courses offered by the University of Glasgow and cited above in the Local Training section could be also covered by the Scottish Government. An application for funding for one of these courses has been submitted already.

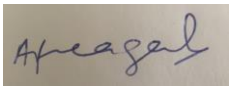
4. Communication skills:
    - Contributed to content marketing at Biogelx; this involves communication of scientific topics to a general audience. I keep on working in content marketing and case studies for Biogelx website.
    - Provided scientific representation in behalf of Biogelx in conferences and meetings and helped Biogelx's business development manager follow up with potential customers. I would like to be further involved in these activities.
    - Disseminated my technical work at Biogelx for the THERACAT project at a local meeting and an international conference through oral communication and poster presentation, respectively. I will keep on disseminating my work at the University of Glasgow Biomaterials Seminar Series when applies and would like to keep on presenting my scientific work in national and international conferences (one of each per year if possible).

5. Other professional training (course work, teaching activity): I am interested in receiving further training in 3D printing, what would be of significant use for the development of Biogelx 3D *in vitro* models; this could be done in house, at Biogelx. As I suggested above, I am very interested in business and entrepreneurship. In addition to the possibility of benefiting from taking part in Biogelx business related activities, I would be benefiting from a convenient training event given by ESADE Business School within the THERACAT training programme.

6. Anticipated networking opportunities: The secondment at IBEC would allow me to maintain professional and scientific links with my native country, Spain. Attending national and international meetings, and conferences would allow me to build further relationships with worldwide scientists and professionals working within the healthcare, biotech, pharma and chemistry sectors.

7. Other activities (community, etc.) with professional relevance: As already pre-established by the consortium, and in collaboration with the rest of early stage researchers, I am happy to participate in the organization of our meetings/symposiums and to the fellows committee. This would enable me to further develop management skills. Besides, I am actively volunteering with a foundation with educational purposes called IMFAHE, which provides high achieving students and young professionals with international mentoring experiences. My role within the foundation consists of leading its Alumni community, what is helping me develop strong project management skills.

Date & Signature of fellow



2 APRIL 2020

Date & Signature of supervisor

2 APRIL 2020

# CAREER DEVELOPMENT PLAN

Name of fellow: Boris Lozhkin

Department and Host Institution: Department of Chemistry, University of Basel

Name of Supervisor: Prof. Dr. Thomas R. Ward

Date: 14.04.2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:**

It is known that i) hCA II is a priviledged host for the creation of artificial metathases and ii) artificial metathases are biocompatible, air stable and can be operate *in vivo*. To target a tumour site, it is proposed to exploit hCA IX to specifically accumulate and activate a metathesis catalyst on the surface of cancer cells. Indeed, hCA IX is overexpressed on the surface of various forms of cancer cells. Accordingly, a fluorinated sulfonamide anchor will be linked via a spacer to a metathesis catalyst. The catalyst precursor is activated upon incorporation within the host protein thanks to the high affinity anchor.
Having identified an active metathesis catalyst for incorporation within hCA IX, the artificial metathase will be screened for its RCM activity towards an heptatriene substrate bearing either a caged fluorophore or a caged drug. Upon RCM, a spontaneous 1,2 or 1,4 elimination occurs via an aromatic transition state, thus uncaging the fluorophore or the drug.
Having identified a suitable catalyst, activated upon incorporation in hCA IX, experiments will be performed in the presence of cells overexpressing hCA IX on their cell surface. To facilitate its delivery to cancer cells, the catalyst precursor will be non-covalently incorporated in a variety of delivery vectors including: hydrogels, micelles, SCNPs, lipidic NPs.

**INDIVIDUAL SECONDMENT PLAN(S):**

1. Institution and sector (academic/non-academic): University of Edinburgh, academic; TEVA Pharmaceutical Industries Ltd., non-academic

2. Duration: 3+3 months

3. Main research objectives:

    1. Synthesis of caged prodrugs;
    2. Uncage a cargo (fluorophore or drug) as a result of ring-closing metathesis;
    3. Adaptation NPs to the delivery of the metathesis catalyst

4. New knowledge and competences expected to be acquired during the secondment:
    1. Become familiar with working with different mammalian cancer cell lines.
    2. Basics of molecular and cellular biology.

3. Master organic chemistry skills in a pharmaceutical industry.
4. Become familiar with the requirements of a pharmaceutical industry.

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: several publications in high-impact journals, postdoc in a complementary research field and permanent position in R&D in pharmaceutical industry

2. What further research activity or other training is needed to attain these goals?
   Postdoc in a foreign country
   Internship in pharmaceutical company.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications: 3 publications in high-impact journals.

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations:

     THERACAT network meetings and conferences, lab seminars, progress report presentations, monthly reports, international conference to present my research results

     XXIV International Symposium on Olefin Metathesis and Related Chemistry (Bergen, Norway, summer 2021)

2. Research skills and techniques:

   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

   - Local training: courses (German, molecular biology, ethics on site, scientific writing, visualization of results)

   - THERACAT training: Trainings and network meetings.

3. Research management:

   *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*
   Swiss National Science Foundation Postdoctoral Fellowship (to carry out a postdoc in a foreign country).

   National Competence Center in Research (NCCR) “Molecular Systems Engineering” award for best oral presentation during NCCR fellow retreat. Swiss Chemical Society best poster award

4. Communication skills: confident, articulate, and professional speaking abilities, participation in lab seminars, progress report presentations, monthly reports, posters on symposia

5. Other professional training (course work, teaching activity):
    - General chemistry practical courses for biology students;
    - Nov 23, 2019, Chemistry Olympiad Workshop for gifted Swiss high school students

6. Anticipated networking opportunities:
    - NCCR Molecular System Engineering (30 groups working in related fields);
    - Science Slam;
    - Regular meetings with BaselArea.swiss (meetings with scientists and potential investors).

7. Other activities (community, etc.) with professional relevance:

    Transferable Skills courses:

    - Writing to Be Published – Academic Writing Conventions and Style;
    - "Out of the Box! Visualize your Science".

    Other activities:

    - Participation in the Locarno Film Festival (BaseCamp 2019).

14.04.2020

Date & Signature of fellow

April 16 2020

Date & Signature of supervisor

# CAREER DEVELOPMENT PLAN

**Name of fellow:** Melissa van de L'Isle
**Department and Host Institution:** University of Edinburgh
**Name of Supervisor:** prof. Asier Unciti-Broceta
**Date:** 15/04/2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:** *half page should be enough*

The aim of this research project is to develop novel applications in the field of bio-orthogonal chemistry and catalysis. More specific, via several sub-projects various biocompatible transition-metal nanoparticle and devices will be created/assembled to enable catalytic prodye and prodrugs release *in vivo.*

The first project concerns a collaboration with ESR 5. The project revolves around the assembly of proteolysis targeting chimeras (PROTACs), which ideally would be assembled *in vitro* and *in vivo* via bio-orthogonal catalysis. The idea behind the PROTAC strategy is to enable degradation of malfunctioning enzymes via linkage to an ubiquitinylated E3 ligase, which can then subsequently be recognized and degraded by the proteasome. More specific, the linkage between these enzymes, is achieved via covalent binding or the E3 ubiquitin ligase and target enzyme to either ends of the PROTAC scaffold. Therefore, the idea of this project is to assemble and improve the bioavailability of PROTACs, via *in vitro* and *in vivo* Cu(I)-catalysed azide-alkyne cycloaddition. In order to achieve this, my part in this project is to deliver the necessary biocompatible beads containing caged Cu(I) particles for the bio-orthogonal catalysis.

The second project will focus on creating bio-compatible Au nanoparticle devices for the selective release of prodrugs in fragile tissue like the brain or spinal cord, targeting chronic pain and degenerative disorders. Moreover, Au particles exhibit some favourable characteristics like their recyclability, capacity to catalyse oxidative reactions at low temperature and biocompatibility. However, it has been known that thiol groups, present in proteins and other cellular components tend to interact with Au. Therefore, the idea of this project is to develop devices that shield the Au from direct contact with proteins, but will allow catalytic interaction(s) with small molecule substrates for prodrug release. In order to achieve this, self-assembled monolayer Au devices have to be synthesized, characterized and tested for their biological activity. In addition, a range of prepared Pd nanoparticles will be tested, since their catalytic cleavage of propargyl moieties from prodyes and prodrugs proceeds in faster and higher rate, than biocompatible Au nanoparticles.

The third project is about dialysis membrane sachets containing transition-metal nanoparticles (i.e. Au, Cu or Pd), in order to increase their catalytic activity in vivo. The idea is to use dialysis membranes with variating cut offs, to enable small molecules/prodrugs to enter the sachet but excluding access for proteins. Therefore, this strategy could be a useful way to circumvent unwanted environmental interactions with the nanoparticles, preventing lower activity or even deactivation thereof. The device is meant to be useful as novel approach to introduce bio-orthogonal catalysts *in vivo*. In addition, to this propargylated fluorophores will be used and developed to demonstrate their activity. Based on earlier publication of Tel Aviv University, a cyanine-based near-infrared fluorophore is being developed for improved *in vivo* imaging.

**INDIVIDUAL SECONDMENT PLAN(S):**

- Institution and sector (academic/non-academic):
  - *Biogelx Limited (BGX), United Kingdom, non-academic*

- Duration:
  - *3 months, M21* (period: 24th of March until 25th of May 2020)
    **Due to the unforeseen COVID-19 pandemic, the secondment was put on hold as soon as the lockdown measurements of the UK became active at the 16th of March 2020**

- Main research objectives:
  - *The assembly of novel nanoparticle devices, as gel-based implants, that could be useful as therapeutic treatment, initiating catalytic prodrug release in vivo. In addition, getting familiar with alternatives to animal testing via the usage of reproducible 3D hydrogel systems.*
    **After the training received at the Biogelx facility, the proof-of-concept for the (hydro)gel-based nanoparticle device/matrix and their catalytic activity was successfully demonstrated**

- New knowledge and competences expected to be acquired during the secondment:
  - *Gain industrial R&D experience. Become familiar with the utilization of innovative 3D models/material that exhibit the nanoscale matrix structure of human tissue, as alternative for animal testing.*

- Institution and sector (academic/non-academic):
  - *Tel Aviv University (TAU) Tel Aviv, Israel, academic*

- Duration:
  - *3 months, M36*

- Main research objectives:
  - *In vivo imaging/monitoring of the catalytic release of prodrugs by the nanoparticle devices obtained during the research projects. Preliminary, design, synthesis and screening of therapeutic agents. Followed by the evaluation and interpretation of derived biological data thereof, to select candidates for in-vivo screening.*

- New knowledge and competences expected to be acquired during the secondment:
  - *Get familiar with animal testing, protocols and gain skills in in vivo imaging of potential therapeutic treatments.*

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

- Goals:
  - Become an all-round researcher and be able to continue to work in the field of drug discovery and development.

- What further research activity or other training is needed to attain these goals?
  - Gain more in-depth knowledge concerning the research topic(s) (c.g. nanoparticles and accompanying cellular assays) through literature studies/review, learn new techniques to improve and/or expand skill set, attend congresses/symposiums to network and industrial placement to experience other steps in the drug development process. In addition, the successful management of the projects, will result into publications to obtain the PhD.

**SHORT-TERM OBJECTIVES (1-2 years):**

- Research results

  - Anticipated publications: Two papers, one focusing on the development of biocompatible Cu(I) carrier to induce PROTACs in vivo, and one focusing on the Au/Pd nanoparticle devices and applications thereof.
  - Anticipated conference, workshop attendance, courses, and/or seminar presentations.
  - Workshops: Scientific writing/communication, instruments workshops i.e. LC-MS, GC-MS and NMR, research planning and management workshops/ online courses.
  - Conferences: Conferences that are focused on bio-orthogonal chemistry, chemical biology, drug discovery, cancer therapies, catalysis i.e. Bioorthogonal & Bioresponsive 2019.
  - Seminars: Attend university organized seminars focusing on organic synthesis, drug discovery, cancer therapies, catalysis, bio-orthogonal reactions.

- Research skills and techniques:

  *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

  - Local training: Organic synthesis, advanced material chemistry i.e. synthesis of nanoparticles, characterization, design and development of assays and animal models, western-blots and proteomics analysis, critical thinking, literary reviews.

  - THERACAT training: Incorporating techniques/methodologies that I as a chemist am not familiar with into my research i.e. *in vivo* studies; translational and outreach activities; industry experience.

- Research management:

  *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*

  - Monthly meetings with supervisor and team to regularly discuss findings, troubleshooting etc. Determine deadlines for the project and meet them. Budget for costs of materials and any tests that may need to be conducted by external parties. Apply for funding opportunities to continue as a post doc.

- Communication skills:
  - Scientific writing/communication workshops. lab meeting presentations, poster presentations at conferences, paper writing, grant applications, lab journal management.

- Other professional training (course work, teaching activity):
  - Undergrad research project supervisor, supervisor of undergrad labs.

- Anticipated networking opportunities:
  - RSC events, seminars, conferences, Marie Curie workshops, post-grad events.

- Other activities (community, etc.) with professional relevance:
  - CRUK public engagement events and involvement on social media like LinkedIn and Twitter, public engagement LEAPS voluntary work.

15-04-2020
Date & Signature of fellow

17-04-2020
Date & Signature of supervisor

# CAREER DEVELOPMENT PLAN

Name of fellow: Maria Vlastara

Department and Host Institution: Tawgorks/Nuclear Medicine

Name of Supervisor: Marc S. Robillard

Date: 14/04/20

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:** *half page should be enough*

The ESR12 position is embedded in the THERACAT project, which aims at the training on the topic of the development of the catalysis-based approaches towards cancer therapy. More specifically, the project is focusing on the application of the bio-orthogonal catalysis in cancer. For this purpose, the ITN foresees training of the fellows, equipping them with the necessary skills in order to succeed both in the academic and the industrial field.

Within the 3-years project of the Marie Curie ITN action, the ESR12 position will aim to apply and develop novel in vivo click and click-to release strategies to achieve and improve the bioorthogonal catalytic activation in cancer therapy. Click-conjugation chemistry will be used to radiolabel and image catalysts and possibly their activity in vivo. Depending on the nature of the catalyst the radiolabeling will occur pre- or post- catalyst administration. In addition, radioimaging agents will be designed that localize at the target following catalyst-mediated uncaging. Regarding click-to-release chemistry, novel strategies will be developed to activate target-localized catalysts, enabling temporal control over catalyst activity, for example to reduce premature catalyst deactivation. Furthermore, an important part of the project will be the development of the click-to-release chemistry in the chelate cleavage of radiolabeled catalysts to improve the tumor-blood ratios.

The position will also include two planned secondments in the University of Edinburgh (EDI) and the University of Basel (BAS). During the mobility in the University of Edinburgh the ESR12 will develop a method for masking and unmasking catalytic nanoparticles using click-chemistry and during the mobility in the University of Basel, click-chemistry will be used to mask and unmask proteins. Also, the training of the ESR12 will be enriched with workshops and courses provided by the host institution (Radboud University Medical Center) as ESR12 has been enrolled in their PhD program. Dissemination of results is also an indispensable part

of this position and the fellow will publish results in peer-reviewed journals and present the scientific results within the ITN framework, the host institution Radboudumc and international conferences.

**INDIVIDUAL SECONDMENT PLAN(S):**

1. Institution and sector (academic/non-academic):
   Host of First Secondment; University of Edinburgh (EDI) / academic sector

   a. Duration: 1.5 months

   b. Main research objectives:

      - Development of a pro-PET agent

   c. New knowledge and competences expected to be acquired during the secondment:

   During this secondment I had the opportunity to gain knowledge in the field of organic chemistry and particularly in the field of Pd-catalysts. The secondment was cut short because of the COVID-19.

2. Institution and sector (academic/non-academic):
   Host of Second Secondment; University of Basel (BAS) / academic sector

   a. Duration: 3 months

   b. Main research objectives:

- In vivo imaging of protein-based catalysts.
- In vivo imaging of radiolabeled substrate being activated by catalyst
- Method of masking/unmasking: using the click-chemistry reaction; activation of protein.
- In vivo release and/or activation of a targeted-bound catalyst by click-release chemistry.

   c. New knowledge and competences expected to be acquired during the secondment:

   During this secondment I will have the opportunity to gain knowledges in the field of the artificial metalloenzymes. During my stay in the University of Basel, I will use the click-chemistry method to mask and unmask proteins. In that way I will aim for the localized activation of the proteins to achieve a localized biorthogonal drug release. In the course of this work I expect to develop skills in protein chemistry and in vitro studies.

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals:
   My long-term objectives are to continue to strengthen my scientific knowledge and to engage myself in the field of biomedical research and industry. Within the ITN TRERACAT program which combines both the academic and the private sector, I could envision a future both in the academia and the industry. My work will be involved around a private company (Tagworks) and the Radboud University Medical Center as the academic sector. Already from my first secondment I witnesses the importance of working in different groups and acquiring new techniques. Both secondments will give me the opportunity to build relationships with two scientific groups, whereas the trainings in the ITN program which involve two private companies will give the advantage of building relationships within the industry.

2. What further research activity or other training is needed to attain these goals?

   - Training in radio-labeling catalysts (Pd, Pt)
   - Enhance my organization, presentation and communication skills by attending courses provided by the Radboud UMC
   - Participation in workshops, weekly department meetings, yearly nuclear medicine conferences
   - Writing a scientific paper

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications:
     Publications in major impact journals are expected to report the progress of my research and my findings with the scientific community. The main topic of them will be related to the in-vivo click-chemistry in tumor therapy, the in-vivo imaging of catalysts and their activation using click-release chemistry

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations:

Weekly research meeting "Nuclear Medicine Department" (1.0/y ECTS)
Weekly research meeting "Radiology and Nuclear Medicine Department" (0.75/y ECTS)

NKRV yearly workshop (0.75/y ECTS)
Yearly PhD retreat (1.0/y ECTS)
EMBL Heidelberg, Germany 2 - 5 Sep 2020, CHEMICAL BIOLOGY EMBO

2. Research skills and techniques:
   *Local and network-wide scientific and complementary skills training necessary to ensure the successful completion of the research project and of the future fellow career*

   - Local training:
     - Cell culture training
     - Affinity assays, cell cultures
     - Biodistribution assays
     - Teaching Sessions in Nuclear Medicine Department

   - THERACAT training:
     - Training event 1 (TUE)
     - Training event 2 (BAS)
     - Training event 3 (EDI)
     - Training event 4
     - Training event 5
     - ESR meeting 2 (EDI)

2. Research management:
   *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*

Applications to several grants within the European Marie Curie Actions program private entities and governmental agencies are expected to be submitted. These applications will be sent at the right time in order to ask for funds to attend summer schools, training sessions, seminars, and congress according to the needs of my research.

3. Communication skills:

   The ITN constitutes a valuable opportunity to train my personal presentation and communication skills. All the international conferences, workshops and seminars that I plan to attend, according to my "career plan" will be crucial in the further development of my presentation and communication skills.

Being an international Marie-Curie fellowship I have the opportunity to work in a multi-cultural environment, in which I can train my communicational skills in different languages, such as English and Dutch. In that purpose, I will attend the Introductory course in Dutch to increase the quality of the period in a foreign country and increase possibilities to learn about another culture.

4. Other professional training (course work, teaching activity):

   Teaching assistantships, mentoring of young researchers and other activities of this kind will be considered in due time, when the opportunity arises from my host University.

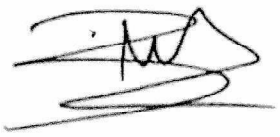
5. Anticipated networking opportunities:

   Develop and maintain within the 3-years project co-operative networks and working relationships as appropriate with supervisors and members in the Department of Nuclear Medicine in the Radboudumc and the Radboud Institute for Molecular Life Sciences. Also, within the Marie Curie ITN framework I will have the opportunity to participate in the research network beyond my home institution, promoting my learning experience and my communication skills. For that purpose, I will spend 2 months in the University of Basel for the synthesis of activable PET probes.

6. Other activities (community, etc.) with professional relevance:

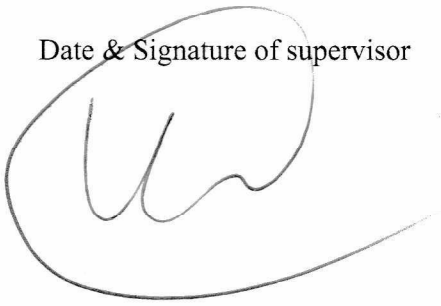
   I intend to participate in the committee of the PhD students in the RadboudUMC to gain communication and organization skills.

Date & Signature of fellow



14-04-20

Date & Signature of supervisor



21-4-2020

# CAREER DEVELOPMENT PLAN

Name of fellow: Daniel Rodríguez Ajamil

Department and Host Institution: Sackler School of Medicine, Tel Aviv University

Name of Supervisor: Prof. Ronit Satchi-Fainaro

Date: 13th May 2020

**BRIEF OVERVIEW OF RESEARCH PROJECT, METHODOLOGY AND MAJOR ACCOMPLISHMENTS EXPECTED:**

We biologically characterized amphiphilic block-copolymers based on PEG-dendron hybrids provided by Roey Amir's group. We will evaluated their biocompatibility and potential toxicity by means of their hemolytic effect on Red Blood Cells (RBC) and cell viability assays in several cancer cell lines and fibroblasts. The nanocarriers that presented the best biocompatibility were selected to asses their penetration capacity in 3D Multi Cellular Tumor Spheroids (MCTS). Afterwards the candidate showing the best pharmacokinetics was chosen to entrap a combination Talazoparib (PARPi) and a small molecule PD-L1 inhibitor synthesized *in house*, which are suitable for targeting BRCA-mutated breast cancer. The rationale behind this combination relies on the observed increase of the expression of PD-L1 in BRCA mutated breast cancer cell lines under Talazoparib treatment. Our small molecule PD-L1 inhibitor was proved to efficiently to compensate this expression.

At this point we will determine the performance of the combined therapy on T-cell-mediated death when 3D BRCA mutated breast cancer MCTS are co-cultured with activated spleenocites, isolated from C57/BL6 adult mice resected spleens in the presence of fluorescence caspase 3/7 substrate with the IncuCyte live-cell analysis system.

Following full in vitro evaluation, we will first stablish BRCA mutated breast cancer orthotopic mouse models using murine mCherry-EMT6 cell line. The mouse models will be characterized for morphology and invasiveness by H&E staining, proliferation by KI67/PCNA immunostaining, microvessel density by CD31 immunostaining and immune cells activation using CD3/CD4/CD8 for T-cells infiltration. Afterwards we will proceed to in vivo assays, including MTD, PK, PD, anticancer efficacy and toxicity of the proposed therapy (e.g. body weight change and blood chemistry following treatment) on breast cancer-bearing mice models stablish.

**INDIVIDUAL SECONDMENT PLAN(S):**

**• Barcelona, Spain**

1. Institution and sector (academic/non-academic): Institute for Bioengineering of Catalonia (IBEC) or University of Eindhoven with Lorenzo Albertazzi's group. Academic

2. Duration: 4 months

3. Main research objectives: Imaging of the proposed nanomedicines internalization and therapeutic effect on microfluidic 3D cell culture system with Super resolution confocal microscopy.

4. New knowledge and competences expected to be acquired during the secondment: *In vitro* super resolution imaging. Stochastic Optical Reconstruction Microscopy (STORM)

**• Kfar Saba, Israel**

1. Institution and sector (academic/non-academic): TEVA Pharmaceutical Industries Limited. Non-Academic

2. Duration: 3 months.

3. Main research objectives: Large scale formulation of prodrugs and nanomedicines and its characterization via light scattering techniques.

4. New knowledge and competences expected to acquire during the secondment: Better understanding of the critical factors that might affect scaling up and manufacturing of newly-discovered drugs

**LONG-TERM CAREER OBJECTIVES (over 5 years):**

1. Goals: Conduct research and development of novel nanoparticle-based drug-delivery systems for cancer therapy by undertaking post-doctoral positions

2. What further research activity or other training is needed to attain these goals?

   I would like to conduct further research on different polymer and catalysts; supramolecular stimuli responsive systems, cancer active targeting and drug pharmacokinetics by collaborating with researchers and research groups having expertise in this domain.

**SHORT-TERM OBJECTIVES (1-2 years):**

1. Research results
   - Anticipated publications: We intend to publish papers on proof of concept of micellar catalysis releasing a synergistic combination of PARPi and PD-L1 inhibitor small molecules to optimize the system for in vitro and in vivo prodrug activation in triple negative breast cancer bearing mice. We also intend to publish a review paper within the scope of targeted nanomedicines and prodrug activation opportunities in breast cancer.

   - Anticipated conference, workshop attendance, courses, and/or seminar presentations: NanoSingapore 2020. Israeli Chapter of the Controlled Release Society (ICRS), NanoBioMed Conference (IBEC). 13$^{th}$ International Activity Based Protein Profiling Meeting (Weizmann Institute)

2. Research skills and techniques:

   - Local training: Synthesis of polymeric nanocarriers for cancer therapy. Physico-chemic-biological characterization of the nanomedicines developed. Immunohistochemistry techniques and cell-based assays including immunooncology assays. Design and conduct in vivo experiments and corresponding techniques required for them such as MRI or Maestro (Intravital non-invasive *in vivo* imaging)

   - THERACAT training: Imaging of nanomedicines with Super Resolution Confocal Microscopy. Pro-drug synthesis. Development of microfluidic 3D cell culture models for nanomedicine screening.

3. Research management:

   *Fellowship or other funding applications planned (indicate name of award if known; include fellowships with entire funding periods, grants written/applied for/received, professional society presentation awards or travel awards, etc.)*

   I intend to apply for local travel grants (CBRC at TAU) and for external travel awards and Marie Curie post-doctoral opportunities e.g. Postdoc COFUND Programs in the future to support myself during my time of employment.

4. Communication skills: Undertake scientific writing and soft skills and dissemination courses. To prepare PowerPoint and posters presentations of my current research progress for further presentation in conferences. To collaborate in the development of an animated movie explaining the concept of THERACAT and its advantages together with IBEC and Eindhoven University of Technology (TU/e).

5. Other professional training (course work, teaching activity): Undertake teaching assistantships by supervising laboratory courses and seminars during my time as a PhD student, starting at my second year following PhD proposal. To assist with workshops of soft skills and dissemination.

6. Anticipated networking opportunities: Conducting collaborative research with my peers by consulting them for my difficulties while also contributing to their research, attending national and international conferences along with the THERACAT meets for understanding newer developments for redesigning and evaluating my research. Attending seminars and workshops of the Tel Aviv University Nanoscience and Nanotechnologies Center which holds a monthly colloquium and a yearly meeting. Acquiring new skills in in vitro imaging techniques and prodrug development

7. Other activities (community, etc.) with professional relevance: Career workshops for opportunities in industry and interview simulations, entrepreneurship strategies, dissemination and searching for postdoc opportunities.

13th May 2020
Daniel Rodríguez Ajamil

13th May 2020
Ronit Satchi-Fainaro