



Deliverable 3.7: Co-supervision of Ph.D. thesis update

Author(s):	Lead author: Yvonne Kohl (FhG) Co-authors: Alena Gabelova (BMC SAV), Bozena Smolkova (BMC SAV), Tatiana Siposova (BMC SAV), Julie Earl (SERMAS), Maria Dusinska (NILU), Agapi Katakaki (NKUA)
Workpackage:	3
Task:	3.3
Version:	1.0
Date:	29. 09. 2022



Contents

Basic information.....	3
Executive summary	4
1 Description of work & main achievements	5
1.1 Co-supervision of PhD thesis	5
1.1.1 Co-supervision of PhD thesis #1	5
1.1.2 Co-supervision of PhD thesis #2	6
1.1.3 Co-supervision of PhD thesis #3	6
1.1.4 Co-supervision of PhD thesis #4	7
1.1.5 Co-supervision of PhD thesis #5	8
1.1.6 Co-supervision of PhD thesis #6	8
1.1.7 Co-supervision of PhD thesis #7	9
1.1.8 Co-supervision of PhD thesis #8	9
2 Deviation from the work plan	10
3 Conclusion	10

This report arises from the VISION project. The content of this report represents the views of the author/s only and is his/her/their sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Research Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains. The authors are not responsible for any further and future use of the report by third parties and third-party translations



Basic information

Project title	Strategies to strengthen scientific excellence and innovation capacity for early diagnosis of gastrointestinal cancers
Project acronym	VISION
Call	H2020-WIDESPREAD-2018-2020
Topic	WIDESPREAD-03-2018
Project type	Coordination and Supporting Action (CSA)
Grant Agreement No.	857381
Nature	R (Document, report - excluding the periodic and final reports)
Dissemination level	PU (Public, fully open, e.g. web)



Executive summary

Involvement of VISION partners in mentoring and co-supervision of PhD will increase the quality of education at universities, mainly medical and natural science faculties. PhD students of the Cancer Research Institute BMC SAS (Bratislava) are supervised by VISION project partners in the form of a co-supervision. Eight Ph.D. students have been allocated specific co-supervisors. Partner NILU co-supervises three Ph.D. students, and FhG and IRYCIS, each two Ph.D. students. NKUA co-supervises one Ph.D. student, who is additionally co-supervised by IRYCIS.



1 Description of work & main achievements

Collaboration and networking between VISION partners will accelerate the personal and professional development of early stage researchers and medical doctors, impact the rate of success in internationally competitive research funding and high-quality peer-reviewed publications. Involvement of VISION partners in mentoring and co-supervision of PhD will increase the quality of education at universities, mainly medical and natural science faculties. PhD students of the Cancer Research Institute BMC SAS (Bratislava) are supervised by VISION project partners in the form of a co-supervision. Seven PhD students have been allocated specific co-supervisors. Partner NILU supervises three PhD students, FhG and IRYCIS both each two PhD students. One of the IRYCIS co-supervised student will additionally be co-supervised by NKUA.

1.1 Co-supervision of PhD thesis

In the following please find details on the topic of the individual co-supervised PhD thesis and the co-supervisors.

1.1.1 Co-supervision of PhD thesis #1

PhD student: Kristína Kopecká, MSc.

Topic of PhD thesis: Distribution, accumulation and biological effects of gold nanoparticles in vivo.

Anotation: Targeted drug delivery is one of the main fields of medicine where nanotechnology can substantially contribute to the breakthrough in treatment efficacy of various diseases. Elucidation of relations that determine enhanced affinity of nanomaterials toward certain organ/tissue is therefore in a spotlight of nanotherapy research. Very promising nanomaterials for targeted delivery are noble metals like gold. Gold nanoparticles show almost no acute toxicity and their unique optical features enable to monitor them in the body. Despite significant benefits nanomaterials hold for nanomedicine, the questions concerning their bio-safety remain insufficiently explored. These are mainly their interactions with cells on the molecular level, mechanism of distribution, accumulation and elimination from the body, as well as their possible biological adverse effects emerging from a long-term exposure. Deeper understanding of these natural patterns will significantly contribute to the development of safer and more effective nanotherapeutics.

Supervisor: Andrea Bábelová, PhD - Cancer Research Institute BMC SAS, Bratislava

Co-supervisor/consultant: Dr. rer. nat. Yvonne Kohl – Fraunhofer-Institut für Biomedizinische Technik IBMT, Sulzbach, Germany (FhG)

Status of the PhD thesis: For the thesis, in vivo experiments have been completed and most of the analyses performed. Additional histological examinations and molecular biology tests are to be finished soon. Preparation of the thesis is currently in progress with several chapters completed. Publication concerning research reported in the thesis is being prepared with the submission planned for the end of the year. PhD student has successfully passed the dissertation examination and has been recently visiting Fraunhofer-Institut für Biomedizinische Technik IBMT for a research stay under the auspice of the VISION project.



1.1.2 Co-supervision of PhD thesis #2

PhD student: Lucia Bálintová, MSc.

Topic of PhD thesis: Biological safety of innovative nanotherapeutics with potential application in regenerative medicine.

Anotation: Development of novel therapeutically active wound dressings which provide the wound protection as well as wound healing promotion has an advantageous potential for clinical applications. Our goal is to assess the biosafety of prepared innovative nanohydrogels in in vitro and in vivo conditions. Nanogel integrates protective (nanohydrogel) and healing functions (iron oxide nanoparticles and targeted miRNA) within one nanocomposite structure; and detailed characterization of nano:bio interactions will contribute to elucidate the mechanisms of action of nanogels in the biological system.

Supervisor: Monika Šramková, PhD - Cancer Research Institute BMC SAS, Bratislava

Co-supervisor/consultant: Dr. rer. nat. Yvonne Kohl - Fraunhofer-Institut für Biomedizinische Technik IBMT, Sulzbach, Germany (FhG)

Status of the PhD thesis: Within the first year of Ph.D. study, experiments were focused on the determination of possible cytotoxic and genotoxic effects of three types of nanohydrogels using selected human skin cell lines. Also, scratch assays were performed to evaluate the effect of nanogels on the migratory activity of skin cells. Moreover, the healing of the puncture wound on full thickness 3D skin model has been studied by H&E staining. Currently, changes in gene expression and inflammatory response is being evaluated.

The written part of the Ph.D. thesis has been submitted and successfully defended in March 2022, along with the state exams that are mandatory.

In the upcoming months, a study stay at the Instituto Ramon y Cajal de Investigación Sanitaria, Madrid, Spain (IRYCIS) is planned.

1.1.3 Co-supervision of PhD thesis #3

PhD student: Jana Hricovíniová, MSc

Topic of PhD thesis: New precursors of pharmaceuticals based on nitrogen heterocyclic compounds and glycoconjugates: structure-biological activity relationship analysis.

Anotation: Development of new drugs with increasing specificity and sensitivity is one of the main aims in the field of medical research. Significant attention has received nitrogen-containing heterocycles that are part of many natural compounds (e.g. nucleic acids, alkaloids, antibiotics, barbiturates). Quinazoline and quinazolinone-based compounds represent a unique class of heterocyclic compounds displaying a wide range of therapeutic and pharmacological properties such as, anticancer, antibacterial, antiviral, antifungal, anti-inflammatory, or antimalarial activities. The aim of this study is evaluation of biological activities of new synthetic quinazolinone derivatives in vitro. A series of new derivatives will be tested by various chemical, biochemical and molecular biology assays utilizing kidney cancer and non-cancer cell lines.

Supervisor: Dr. rer. nat. Katarina Kozics, PhD. - Cancer Research Institute, Biomedical Research Center SAS, Bratislava



Co-supervisor/consultant: Dr. rer. nat. Mária Dušinská, DSc. - Norwegian Institute for Air Research, Oslo, Norway (NILU)

Status of the PhD thesis: The PhD. student Jana Hricovíniová completed her PhD studies in August 2022.

1.1.4 Co-supervision of PhD thesis #4

PhD. student: Verona Buociková, MSc

Topic of PhD thesis: Nanocarrier Mediated Multimodal Anticancer Therapy

Anotation: In the last decade, significant progress has been made in the use of the properties of nanoparticles for medical applications, especially in the field of anticancer treatment. The new generation of nano-drugs not only ensures a synergistic effect of several substances and specific targeting of therapy but also enables an increase in the sensitivity of resistant cell populations and monitoring of drug accumulation in the tumor. The goal is the development of a new generation of multi-functional nano-drug that combines diagnostic and therapeutic potential within one nanostructure. It has four key components: 1. surface ligands for targeting tumor cells, 2. a diagnostic component in the form of inorganic nanocrystals, 3. a cytotoxic component, and 4. an epigenetic drug as a chemosensitizer. As part of the dissertation, the student will realize in vitro experiments aimed at evaluating the expression of stem cell markers on tested cell lines, testing and evaluating the response to treatment in cell lines, and evaluating the safety and efficacy of the developed drug before its in vivo application. In this work, she will learn to reliably use the whole spectrum of molecular biological methods such as flow cytometry, cell culture in 2D and 3D conditions, immunohistochemical staining, western blot, real-time PCR and many others.

Supervisor: Bozena Smolkova, PhD. – Cancer Research Institute, Biomedical Research Center SAS, Bratislava

Co-supervisor/consultant: Dr. rer. nat. Mária Dušinská, DSc. - Norwegian Institute for Air Research, Oslo, Norway (NILU)

Status of the PhD thesis: Verona Buocikova completed her Ph.D. study in June 2022. She obtained the third prize in the Competition for the best dissertation thesis with her work. She published three papers relevant to her PhD thesis research topic as a first author:

1. Buocikova, V. et al. Decitabine-induced DNA methylation-mediated transcriptomic reprogramming in human breast cancer cell lines; the impact of DCK overexpression. *Frontiers in Pharmacology*. In press. <https://doi.org/10.3389/fphar.2022.991751>
2. Buocikova V et al. Decitabine potentiates efficacy of doxorubicin in a preclinical trastuzumab-resistant HER2-positive breast cancer models. *Biomed Pharmacother*. 2022 Mar;147:112662. doi: 10.1016/j.biopha.2022.112662.
3. Buocikova V et al. Epigenetics in Breast Cancer Therapy-New Strategies and Future Nanomedicine Perspectives. *Cancers (Basel)*. 2020 Dec 3;12(12):3622. doi: 10.3390/cancers12123622.



1.1.5 Co-supervision of PhD thesis #5

PhD student: Michaela Blažíčková, MSc

Topic of PhD thesis: Relationship between structure and biological activity of newly synthesized thymol derivatives in colorectal in vitro model.

Anotation: Beneficial effects of thymol (TY), a naturally occurring phenol monoterpene of essential oil from thyme, on human health are well known for many years. The proposed project is focused on the synthesis of hydrophilic derivatives of TY while the antioxidative and antiproliferative properties as well as the effective cellular uptake will remain intact. Using comprehensive approaches from biochemistry, biology, and molecular biology will enable us to assess the biological effects of these derivatives depending on their molecular structure. The project will contribute to gain an insight into the molecular mechanisms of action of hydrophilic TY derivatives. The biological activity will be studied using 2D and 3D colorectal cell models cultured in vitro.

Supervisor: Dr. rer. nat. Katarína Kozics, PhD - Cancer Research Institute BMC SAS, Bratislava

Co-supervisor/consultant: RNDr. Maria Dusinska, DSc. - Norwegian Institute for Air Research, Oslo, Norway (NILU)

Status of the PhD thesis: Status of the PhD is according to the plan.

1.1.6 Co-supervision of PhD thesis #6

PhD student: Kristina Ploth, MSc.

Topic of PhD thesis: Advanced in vitro and in vivo models derived from primary tumour tissue as tool for preclinical research

Anotation: Models based on primary tumour cells such as organoids and patient-derived xenografts (PDX) are recently the most relevant preclinical systems for evaluation of efficacy of anticancer approaches as well as for studies focused on cancer cell biology, chemoresistance and metastasis. Based on existing cooperation with clinicians we will use vital samples of tumour tissue obtained at surgical resection of colon cancer for preparation of organoids and PDX. Subsequently, these models will be used for evaluation of efficacy and safety of combined therapy targeted via nanocarrier as well as for study of mechanisms of chemoresistance and metastasis.

Supervisor: Dr. rer. nat. Miroslava Matúšková, PhD. – Cancer Research Institute, Biomedical Research Center SAS, Bratislava

Co-supervisor/consultant: Maria-Laura Garcia-Bermejo, PhD. - Instituto Ramon y Cajal de Investigación Sanitaria, Madrid, Spain (IRYCIS)

Status of the PhD thesis: The PhD student interrupted her doctoral studies due to maternity duties.



1.1.7 Co-supervision of PhD thesis #7

PhD. student: Peter Dubovan, MD

Topic of PhD thesis: Management of postoperative pancreatic fistula

Anotation: Postoperative pancreatic fistula (POPF) is the most common postoperative complication after pancreatic resection. Even though, there are multiple works dedicated to this problem, there is still missing knowledge of all risk factors contributing towards POPF and there is missing unanimous management preventing creation of POPF or management of POPF after its creation. In the surgical world there are trends towards minimising the use of intraabdominal drainage. This trend is visible also in pancreatic surgery, however in our current practise we routinely use intraabdominal drainage in pancreatic surgery and we think we have very good results regarding overall morbidity and mortality.

Therefore, in this work we aim to conduct retrospective analysis of our single center cohort in the years 2015-2020. We want to compare our data with the data from current literature and eventually create the baseline for a new protocol/recommendations with a prospective phase of the study.

Potential expansion: The additional research goal broadening the focus of the study towards practical aspects of the intervention is related to the routine use of postsurgical intraabdominal drainage in pancreatic adenocarcinoma and potential understanding of the underlying disease, its therapy and impact on further prognosis of patients. There is ongoing discourse focused on radicality in pancreatic cancer surgery, concentrating among else on the significance of the role of peritoneal lavage in overall survival, with unanswered questions on the key related factors impacting survival. Our research would explore utilization of the fluid from the intraabdominal drainage, to identify either carcinomatous cells or biomarkers, to expand our understanding of the pathophysiological processes after surgery and optimise therapeutical interventions based on this insight. Our assumption is that this could help confirm the impact and most optimal administration of excessive peritoneal lavage, nowadays conducted with saline, but maybe in the future with more effective solutions and ultimately increase the effectiveness of oncological treatment and prognosis for patients.

Supervisor: Assoc. Prof. Daniel Pindřák, MD, PhD. – Slovak Medical University, Bratislava

Co-supervisor/consultant: Prof. Manousos M Konstadoulakis - National and Kapodistrian University of Athens (NKUA), Athens, Greece; Julie Earl, PhD. - Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain (IRYCIS)

Status of the PhD thesis: Preparation of the written part of the Ph.D. thesis is currently in progress, and the experimental part (retrospective analysis) proceeds according to the schedule. Two publications concerning research reported in the thesis were published. In addition, in 2021, the Ph.D. student completed a study stay at the National and Kapodistrian University of Athens, Greece.

1.1.8 Co-supervision of PhD thesis #8

PhD. student: Mária Urbanová, MSc.

Topic of PhD thesis: Identification of molecular markers for early detection of pancreatic cancer



Anotation: Slovakia is one of the countries with the highest incidence of pancreatic cancer. Due to the lack of treatment, early diagnosis is key to improving patient survival. The development and introduction of new models, including organoids and xenografts derived from patients' tumors, is an important tool for translational research. These models will be applied to increase understanding of PDAC tumor progression, its microenvironment (TME) as a tumor fate determinant, and the reciprocal tumor-TME interactions that drive clinical outcomes. The dissertation aims to uncover the microenvironmental cross-talk mechanisms that support pancreatic cancer cells' aggressiveness and identify new molecular biomarkers, enabling earlier detection of this deadly disease.

Supervisor: Bozena Smolkova, PhD. – Cancer Research Institute, Biomedical Research Center SAS, Bratislava

Co-supervisor/consultant: Julie Earl, PhD. - Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain (IRYCIS)

Status of the PhD thesis: Maria Urbanova completed the first year of the study. She participates in international research within the NexT project and national projects focusing on pancreatic cancer. During her PhD. she completed two study stays in partner laboratories of VISION consortium (IRYCIS and NILU), and she applied acquired knowledge in her experiments. She published one manuscript as a first author: Urbanova M et al. DNA Methylation Mediates EMT Gene Expression in Human Pancreatic Ductal Adenocarcinoma Cell Lines. Int J Mol Sci. 2022 Feb 14;23(4):2117. doi: 10.3390/ijms23042117.

2 Deviation from the work plan

There are no deviations from the work plan.

3 Conclusion

Eight PhD students with specific reserach topics as well as specific co-supervisors of the consortium partners have been identified. Partner NILU and IRYCIS supervises both three PhD students, FhG two PhD students. One of the IRYCIS co-supervised student will additionally be co-supervised by NKUA.