SUMMARY

The considerable extension of human lifespan during the last century and the increase in the population of elderly individuals necessitate the development of tools that will improve health and quality of life at old age. Many diseases, including cancer, are strongly associated with old age. In order to tackle them and achieve a point where people would age healthy, research towards understanding the fundamental mechanisms that govern the ageing process is vital. During the last decades many of the hallmarks of ageing have been uncovered. Research on progeroid syndromes led to the discovery of defects in genome maintenance pathways as underlying factors of the ageing phenotype and subsequent development of mouse models with similar deficiencies substantiated the role of DNA damage in the ageing process. As research on other ageing denominators progresses, it is becoming increasingly clear their interconnection, as well as the driving role of genomic damage to each one of them.

Adult stem cell exhaustion is a major contributor to the degenerative pathology of ageing tissues. Many lines of evidence indicate that DNA damage accumulates in ASCs with age and leads to their elimination or dysfunction and tissue pathology. In line with accumulated damage, DNA repair pathways were shown down-regulated or dysfunctional in aged ASCs (all the above information is reviewed in **chapter 1**). The requirements of the diverse ASC types for DNA repair pathways and how distinct ASC types in different tissues respond to damage stimuli in order to preserve their function and ensure the best possible outcome for the organism is far from understood. This is partly attributed to insurmountable - thus far - technical challenges in identifying and monitoring individual ASC populations. Another major area of research is the identification of all the means by which ageing-related damage impacts ASC function in the context of the organism. Cell-extrinsic and paracrine factors are shown to affect ASC and progenitor regenerative capacity and the transplantation of only one type of young, healthy ASC type can have remarkable rejuvenating effects on the whole organism (published by Lavasani and colleagues, reviewed in **chapter 1**).

In order to contribute towards better understanding on the role of damage in ageing-associated ASC dysfunction and disease (such as tumorigenesis), we decided to study `the DNA damage responses and cell fate decisions of small intestinal (SI) and liver stem cells in well established mouse model of progeria. The development of genetically engineered mice enabling us to follow fluorescently labeled ASC populations in these two organs and the advent of organoid culture technology facilitated this inquiry. These two stem cell populations were interesting to us since they differ greatly in their proliferative rate and regenerating capacity – a factor long established to affect DNA repair pathway

decisions – but also they share common developmental factors affecting their function, especially in situations of injury-induced regenerative responses.

In **chapter 2** we follow the fate of liver Lgr5+ stem cells and biliary cells in the same progeroid mice. The latter have been proposed as potential ASCs and they give rise to ASC-bearing liver organoid structures. We show both *in vitro* and *in vivo* a multitude of damage-related responses, limiting the function of these ASCs, such as apoptosis, misaligned expression of cell cycle regulators implicated in cell cycle arrest and senescence, polyploidy and reduced proliferating proficiency. Aberrant proliferation of liver cell populations attempts to overcome the limited regenerative capacity of the tissue, which shows dramatic histopathological phenotype.

In addition, we analyze the SI stem cell and progenitor population of 15-weeks-old *Ercc1*$^{\Delta/-}$ mice both in the context of the tissue and in the context of organoids. Our findings revealed damage outcomes in the SI tissue that although they don't result in major histopathology of the tissue may have functional consequences for a tissue such as the intestine. We demonstrate that the fastly dividing Lgr5+ stem cell population is diminished due to endogenous damage, however plasticity in the crypt compartment ensures normal tissue regenerative proficiency. Apoptotic responses in the crypts were recapitulated in the small sized *Ercc1*$^{\Delta/-}$ SI organoids, which additionally suffered from the presence of senescent cells in both crypt and epithelial cells, limiting their growth potential.

Moreover, we compare the sensitivity of intestinal and liver stem cells to exogenously imposed helix-distorting lesions and interstrand crosslinks, revealing a substantial susceptibility of intestinal stem cells to apoptosis. This finding may be related to overall low apoptotic threshold of ISCs, previously suggested for ionizing radiation induced DNA injuries, but also to their insufficient DNA repair capacity, as exemplified by remaining UV induced 6,4 photoproducts, when LSCs have fully recovered their intact genetic material.

In **chapter 3**, we use next-generation genomic sequencing on clonal organoid cultures from *Ercc1*$^{\Delta/-}$ progeroid mice, to unravel the mutagenic consequences of persistent endogenous damage in the two ASC populations. Subsequent analysis revealed a higher number of point mutations in LSCs, compared to ISCs, possibly reflecting the higher proliferation rates seen in the liver tissue, with respect to baseline cell division (**chapter 3**). Interestingly, analysis uncovered a mutational pattern in both mutant ASC types, as well as CRISPR-Cas modified XPC-deficient human ASCs, previously reported in certain cancer types, linking endogenous damage unrepaired by NER to only one specific mutational signature.

In **chapter 4**, we evaluate the consequences of translesion synthesis deficiency on ASCs and organoids. Liver stem cells lacking the translesion polymerase REV1, seem unaffected but intestinal stem cells show a noticeable functional limitation and a dramatic organoid growth phenotype, especially with simultaneous XPC deficiency. This finding implicates translesion synthesis in maintenance of intestinal epithelium as well as in the mutagenicity of *Xpc* depletion.

To conclude, we present important findings linking DNA repair pathways with stem cell exhaustion during ageing, as well as in specific cancer-related mutational patterns. Moreover, we put forward a general model, in which remaining cellular lifespan determines which DNA damage response strategy is used by the cell. Such a model provides an explanation for the segmental ageing phenotypes of human progeroid syndromes and DNA repair-deficient corresponding mouse mutants, as well as the different aging trajectories between organs and tissues during natural ageing.

NEDERLANDSE SAMENVATTING

De levensverwachting is in de laatste eeuw aanzienlijk toegenomen en daardoor groeit de urgentie instrumenten te ontwikkelen die de gezondheid en levenskwaliteit van ouderen verbeteren. Veel ziektes, zoals kanker, dementie, diabetes, hart- en vaatziekten zijn sterk geassocieerd met oudere leeftijd. Om die verschillende ziektes als geheel te kunnen bestrijden en een punt te bereiken, waarbij mensen gezonder ouder worden, is wetenschappelijk onderzoek nodig om de fundamentele mechanismen, die ten grondslag liggen aan het verouderingsproces, te begrijpen en op basis van die kennis het ontstaan van verouderingsziekten tegen te gaan. Gedurende de laatste decennia zijn er veel belangrijke kenmerken van het verouderingsproces ontdekt. Onderzoek naar progeria en daaraan gerelateerde syndromen heeft geleid tot de ontdekking, dat afwijkingen in het onderhoud van het genoom vaak geassocieerd zijn met versnelde veroudering. De ontwikkeling van muismodellen met vergelijkbare defecten in onderhoud van DNA bevestigde de rol van DNA-schade in het verouderingsproces. Naarmate het onderzoek naar factoren van vergrijzing vordert, wordt steeds duidelijker hoe ze onderling samenhangen en hoe belangrijk de rol van genomische schade is als oorzaak van veroudering.

Het uitgeput raken van volwassen stamcellen (ASC: adult stem cells) draagt in belangrijke mate bij aan de degeneratieve pathologie van verouderende weefsels. Onderzoek toont aan dat DNA-schade zich ophoopt in volwassen stamcellen bij oudere leeftijd en dat dit leidt tot celdood of celdisfunctie en weefselpathologie. Geheel in lijn met het concept van ophoping van DNA schade werd gevonden, dat DNA-herstelmechanismen in verouderde adulte stamcellen minder actief zijn of functioneel achteruitgaan (deze informatie wordt in **hoofdstuk 1** besproken). De strategieen van verschillende adulte stamcellen wat betreft DNA-herstel en hoe ze reageren op verschillende soorten DNA schade om hun functie te behouden en de best mogelijke uitkomst voor het organisme te waarborgen zijn ver van begrepen. Dit komt deels door onoverkomelijke technische barrieres bij het identificeren en monitoren van individuele ASC-populaties. Een andere belangrijke beperking is de identificatie en kwantificatie van DNA schades en hun bijdrage aan veroudering van ASC in de context van het organisme. Cel-extrinsieke en paracriene factoren blijken de ASC en het regeneratieve vermogen van progenitorcellen te beïnvloeden en transplantatie van slechts één type jonge, gezonde ASC kan opmerkelijke verjongende effecten hebben in het hele organisme (gepubliceerd door Lavasani en collega's, besproken in hoofdstuk 1).

Om de rol van DNA schade in veroudering-geassocieerde ASC-disfunctie en ziekte (zoals tumorigenesis), beter te kunnen begrijpen hebben we besloten om de cellulaire respons op DNA-schade te onderzoeken van dunne darm (SI) en lever-stamcellen in

goed gekarakteriseerde muismodellen van progeria. De ontwikkeling van genetisch gemodificeerde muizen, die ons in staat stelt om fluorescent gelabelde ASC-populaties in deze twee organen te volgen en de komst van organoïde kweektechiek heeft dit onderzoek makkelijker gemaakt. Deze twee stamcelpopulaties zijn interessant omdat ze opmerkelijk verschillen in proliferatiesnelheid en regene-ratievermogen; factoren, waarvan bekend is dat ze van belang zijn voor de DNA schade respons. Daarnaast delen ze ook een aantal gemeenschappelijke ontwikkelingsfactoren, die hun functie beïnvloeden, vooral in situaties van door letsel geïnduceerde regeneratieresponsen.

In **hoofdstuk 2** volgen we de ontwikkeling van lever Lgr5+ stam- en biliaire cellen van bovengenoemde progeroïde *Ercc1*$^{\Delta/-}$ muisrepairmutanten. Van de biliaire cellen wordt gedacht dat ze de adulte leverstamcellen vertegenwoordigen vanwege het feit dat ze structuren van leverorganoïden tot expressie brengen. We presenteren zowel *in vitro* als *in vivo*, een groot aantal DNA schade gerelateerde responsen, die de functie van deze ASC›s aantasten, zoals apoptose en ontregelde expressie van celcyclusregulatoren, die betrokken zijn bij cellulaire senescence, polyploïdie en verminderde proliferatie. Door snelle toename van polyploidizatie probeert de lever het beperkte regeneratievermogen te compenseren, hegeen de dramatische histopathologische leververoudering in de repairmutant verklaart.

Analyseren we stamcellen uit dunne darm en de progenitor-populatie van 15 weken oude *Ercc1*$^{\Delta/-}$ muizen zowel in de context van het weefsel als in de context van organoïden. Onze bevindingen toonden diverse schadeparameters in het dunne darmweefsel aan. Hoewel deze niet resulteerden in ernstige histo-pathologie van het weefsel, kunnen ze wel functionele gevolgen hebben voor de darm. We vonden dat de sneldelende Lgr5+ stamcelpopulatie is verminderd door endogene schade. Echter de plasticiteit in het cryptcompartiment compenseert dit en zorgt voor een normaal weefselregeneratievermogen. De toename van apoptose in de crypt werd gerecapituleerd in de (kleine) *Ercc1*$^{\Delta/-}$ SI-organoïden, die bovendien senescente cellen herbergen zowel in crypte- als in het epitheel, waardoor hun groeipotentieel wordt aangtast.

Vergelijken we de gevoeligheid van intestinale- en lever-stamcellen voor exogene DNA lesies, die baseparing verstoren en interstrengs-crosslinks veroorzaken. We vonden een sterke DNA schade overgevoeligheid van de darmstamcellen voor apoptose in vergelijing met leverstamcellen. Deze bevinding kan gerelateerd worden aan de algehele lage apoptotische drempelwaarde van ISC's, eerder gesuggereerd voor ioniserende straling geïnduceerde DNA-lesies. Daarnaast kan de geringe DNA-herstelcapaciteit van ISC's hieraan bijdragen, zoals geïllustreerd aan de hand van de trage verwijdering van UV-geïnduceerde 6,4 fotoproducten, vergeleken met LSC's.

In **hoofdstuk 3**, gebruiken we next-gen-sequencing op klonale organoïde-culturen van *Ercc1*$^{\Delta/-}$ progeroïde muizen, om de mutagene gevolgen van persisterende endogene

schade in de twee ASC-populaties te ontrafelen. Analyse van de verkregen data liet een hoger aantal puntmutaties in LSC's zien, vergeleken met ISC's, mogelijk een reflectie van de hogere drempelwaarde van LSC's voor apoptose na DNA schade (hoofdstuk 3). Het is merkwaardig dat de analyse van mutante ASC-typen en CRISPR-Cas gemodificeerde XPC-reparatiedeficiënte menselijke ASC's een mutatiespectrum blootlegde, dat eerder is gerapporteerd bij bepaalde kankertypen, waarbij endogene DNA schade in afwezigheid van NER geassocieerd kan worden met slechts één specifieke mutatiesignatuur.

In **hoofdstuk 4**, evalueren we de gevolgen van deficiëntie van een translesie DNA polymerase op ASC's en organoïden. Leverstamcellen die het translesie-polymerase REV1 missen, lijken niet aangetast, maar intestinale stamcellen vertonen een merkbare functionele beperking en een dramatisch organoïde groeifenotype, vooral in het geval van gelijktijdige XPC-deficiëntie. Deze bevinding impliceert translesie DNA synthese bij het in standhouden van intestinaal epithelium evenals bij de mutageniciteit van Xpc-depletie.

In conclusie, dit proefschrift presenteert belangrijke bevindingen die DNA-herstelsystemen relateren aan uitputting van stamcellen tijdens veroudering, evenals specifieke mutatiepatronen die optreden bij kanker. Bovendien stellen we een algemeen model voor, waarin de resterende cellulaire levensduur bepaalt welke strategie voor DNA-beschadiging door de cel wordt gebruikt. Een dergelijk model biedt een verklaring voor de segmentale verouderingsfenotypen van menselijke progeroïde syndromen en corresponderende DNA-herstel-deficiënte muismutanten, evenals verschillen in verouderingsstrategieen tussen organen en weefsels tijdens natuurlijk verouderen.

PH.D. PORTFOLIO

Summary of Ph.D. training and teaching

Name PhD student: Maria Vougioukalaki
Erasmus MC Department: Department of Molecular Genetics
PhD period: February 2014 – May 2018
Promotor(s): Prof.dr. J.H.J. Hoeijmakers
Supervisor(s): dr.Joris Pothof

PhD training

General courses	**Dates/Year**
Genetics	2014
Biochemistry and Biophysics	2014
Practical introduction to laser scanning microscopy	2014
Functional Imaging and Super Resolution Microscopy	2014
Microscopic Image Analysis, from theory to practice	2015
Laboratory animal science (art.9/FELASA-C)	2015
Biomedical English writing and communication	2015

Seminars workshops, international conferences

Marrie Curie ITN Marriage Skills workshop, Newcastle • Scientific writing • Research integrity • Research communication • Career development	23-25th April 2014
EMBO workshop Developmental Circuits in aging, Heraklion	5-28th May 2015
Workshop Bioinformatics tools for interrogating *Transcriptomes and epigenomes, Heraklion, Crete*	29th May 2015
Workshop Genetic Model Organisms in Ageing research, Cologne	21st Sept 2015
Marriage ITN annual meeting (oral presentation)	22nd Sept 2015
Complemetary skills workshop on Scholarly Publishing and writing, Cologne	23rd Sept 2015
Molecular Biology of ageing Meeting, Groningen	25-28th Oct 2015
Workshop on Mechanisms of age related diseases,Cologne, Germany (poster presentation)	2-7th April 2016

Complimentary skills workshop on Enterpreneurship and career plans
Cologne, Germany 5th April 2016
EMBO meeting on the DNA damage response in cell physiology and disease
Sounio, Athens, Greece (poster presentation) 2-6th Oct 2017
2nd Molecular Biology of ageing Meeting, Groningen (poster presentation)
8-11th Oct 2017

Teaching

Teaching assistant in group-based exercises of the genetics course Nanobiology, Erasmus MC 2014-2017
Teaching and supervising phD students and technitianson culturing and handling of stem cell organoid cultures 2014-2018
Training and supervision of junior phD student on assessing DNA damage repair capacity of ASCs using microscopy techniques on organoid cultures 2017-2018

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EDUCATION

2014-present **Ph.D,** Erasmus MC, Rotterdam, The Netherlands
2004-2006 **M.Sc.,** Molecular Biology and Biomedicine, University of Crete, Greece (grade: 9.35/10)
2000-2004 **B.Sc.,** Biology, University of Crete, Greece (grade: 7.42/10)
1997-2000 1st Nea Filadelfeia public high school, Athens, Greece (grade: 19.2/20)

SCIENTIFIC AREAS OF EXPERTISE

DNA Damage/DNA Repair, Ageing Biology, Cancer Biology/Oncology, Molecular and Cellular Biology, Adult Stem Cell Biology, Genetics, Cancer Immunity, Biochemistry, Protein Biology, Cell signaling, Cancer signaling, Inflammation and Immunity

RESEARCH

Post-Graduate Scientist (PhD thesis) 02/2014 – present
Erasmus MC, Rotterdam, The Netherlands
Advisor: **Prof. dr. Jan Hoeijmakers**
Research project: DNA Damage Response in adult stem cells during aging

- Stem cells of small intestine and liver from *Ercc1*$^{\Delta/-}$ mice and other progeroid repair-deficient models were evaluated for their responses and function upon persistent damage that drives ageing and related pathologies, as cancer.

Senior Research Associate 01/2009 – 07/2013
Institute of Molecular Biology and Biotechnology
& School of Medicine, Crete, Greece
Supervisor: **Prof. Aristides G. Eliopoulos**
Research project: Regulation of inflammatory signaling pathways in cancer.

- Analyzed in molecular detail the regulation of inflammatory signal transduction (TNF superfamily members) by cell adhesion molecules and their relevance to cancer.
- I found and validated target that sensitized tumor cells to LBW242 SMAC Mimetic compound.
- Became familiar with a variety of cellular, molecular biology and biochemistry techniques, as well as xenograft and allograft mouse models of cancer.

Research Assistant 10/2007 – 12/2008
Molecular and Cellular Biology laboratory
School of Medicine, University of Crete
Supervisor: **Prof. Aristides G. Eliopoulos**

- Participated in research project studying the interaction of cell adhesion – mediated and TNF-induced signal transduction pathways.

Post-Graduate Researcher (M.Sc. thesis) 01/11/2005 – 01/09/2006
IMBB & University of Crete
Advisor: **Prof. Kostas Tokatlidis**
Thesis title: Functional characterization of *Saccharomyces cerevisiae* Tim12 mitochondrial protein. (grade: 9.25/10)

- I studied how Tim12 translocase functions to import proteins to mitochondrial inner membrane. I showed that it interacts specifically with inner mitochondrial membrane lipids and small Tim9 protein and which domains mediate these interactions.

Post-Graduate Researcher (laboratory rotation) 08/2005-10/2005
IMBB & University of Crete
Advisor: **Prof. Despina Alexandraki**
Research project: The role of the interaction between Yap1 and Aft1p on the transcriptional activation of iron-dependent genes in *Saccharomyces cerevisiae*. (grade: 9.5/10)

- Implemented Chromatin Immunoprecipitation (ChIP) technique to study the time and nutrient-dependent recruitment of transcription factors to promoters of iron-dependent genes.

Post-Graduate Researcher (laboratory rotation) 04/2005-06/2005
IMBB & University of Crete
Advisor: **Prof. Electra Gizeli**
Research project: Differential detection of DNA molecules based on their viscoelastic properties using an acoustic biosensor. (grade 8/10)

- Designed small DNA molecules of various conformations and examined the differences on the signal emitted when attached to the surface of a Love wave biosensor.

Under-Graduate Researcher (B.Sc. degree) 09/2003-09/2004
IMBB & University of Crete
Advisor: **Prof. Anastasios Economou**
Thesis title: Biochemical characterization of *Escherichia coli* SecA mutants. (grade: 9/10)

- Performed a variety of basic and advanced cellular, molecular biology and biochemical assays to determine the structural alterations and function of numerous point mutants of the SecA translocase ATPase.

AWARDS AND FELLOWSHIPS

Marie Curie Early Stage Researcher fellowship for PhD studies
Erasmus MC, Rotterdam, The Netherlands 2014-2017
Fellowship from the Institute of Molecular Biology and Biotechnology, Crete 2011-2012
Fellowship from the Institute of Molecular Biology and Biotechnology, Crete 2010-2011
Fellowship from the Institute of Molecular Biology and Biotechnology, Crete 2009-2010
Onassis Foundation travel grand July 2004

METHODS/ SKILLS

- Organoid culture development, maintenance, viral transduction, immunofluorescent and immunohistochemical stainings, survival (clonogenic assays) and DDR detection assays in organoid cultures
- Basic and advanced confocal microscopy, immunofluorescence imaging
- Fluorescence activated Cell sorting
- Basic laboratory mouse research techniques
- Histology, immunohistochemistry, immunocytochemistry
- Cell biology – cell viability and proliferation assays in mammalian cells and 3D cultures, colony forming and soft agar assays, tissue culture, DNA and siRNA transfection, shRNA design and generation of stable cell lines, CRISPR/Cas9 in cell lines and organoids
- Molecular biology – qPCR, cloning, mutagenesis, domain swaps
- Biochemistry/protein chemistry : protein expression, purification, FPLC, HPLC, Protein interaction analysis (co-immunoprecipitation, pull-down assays, gradient ultracentrifugation)

enzymatic activity assays (ATP hydrolysis assays, kinase assays etc), SDS and Native PAGE, mitochondria isolation, protein import in mitochondriaGenetic assays in bacteria and yeast

- **Computer literacy:** Microsoft Office, CanvasX, Adobe photoshop, Adobe Illustrator, Graph Pad Prism, Image analysis-quantitation software, basic molecular biology software, basic productivity software, databases and Internet, Programming in Python, Data science fundamentals using Python

TRAINING AND WORKSHOPS ATTENDED

Genetic model organisms in ageing research, Cecad, Cologne 21/09/2016
Complimentary skills workshop on Enterpreneurship and career plans, Cecad, Cologne 05/04/2106
Biomedical English writing and communication, Erasmus MC, Rotterdam 02/2016
Certificate in Laboratory Animal Science, Utrecht University 11/2015
Bioinformatics tools for interrogating transcriptomes and epigenomes in ageing Heraklion, Crete, Greece 29/05/2015
EMBO workshop Developmental circuits in ageing, Heraklion, Crete, Greece 25-28/05/2015
Functional Imaging and Super Resolution Microscopy, Erasmus MC, Rotterdam 03/2015
Microscopic Image Analysis, from theory to practice, Erasmus MC, Rotterdam 01/2015
Marie Curie ITN, MARRIAGE, (transferable) skills workshop
Newcastle University, Newcastle upon Tyne 04/2014
2nd Inflammation, Cancer and Novel Therapeutics Conference and Summer School Malia, Crete, Greece 24-28/09/2012
3rd Summer school on protein biotechnology graduate program, Fodele, Crete 04-07/06/2008
2nd Summer school on protein biotechnology graduate program, Crete 23-27/05/2007

INTERNATIONAL CONFERENCES ATTENDED

2nd Molecular Biology of ageing meeting, Groninger, The Netherlands 08-11/11/2017
EMBO Conference *The DNA damage response in cell physiology and disease*, Sounio, Athens, Greece **(poster presentation)** 02-06/10/2017
2nd Cologne Ageing Conference, Cologne, Germany **(poster presentation)** 3-5/04/2016
Molecular Biology of ageing, Groningen, The Netherlands 26-28/10/2015
3rd annual meeting CodeAge aDDress MARriAGE,
Cologne, Germany **(oral presentation)** 21-23/09/2015
The 5th EMBO meeting, Amsterdam, The Netherlands 21/23/09/2013
2nd Inflammation, Cancer and Novel Therapeutics Conference, Malia, Crete, Greece **(poster presentation)** 24-28/09/2012
3rd INFLA-CARE annual meeting, Athens, Greece 10-11/10/2011
2nd INFLA-CARE annual meeting, Fodele, Crete, Greece 27-30/09/2010
1st International Conference on *Molecular Cancer Research*, Athens, Greece 27-29/11/2009
12th International TNF Conference –
The TNF superfamily and its interactions with other signaling proteins in infection, autoim-

munity, cancer and therapy, Madrid, Spain (poster presenter) 26-29/04/2009

MEMBERSHIP OF PROFESSIONAL SOCIETIES

Hellenic Society of Molecular Biology and Biochemistry
International Society for Stem Cell Research

LANGUAGES

English, Proficiency C2 level
French, Intermediate level
Greek, native proficiency level

TEACHING EXPERIENCE

Teaching assistant in group based exercises
genetics course, B.Sc. programme in Nanobiology, Erasmus MC 2014-2017
Supervising phD students and technicians on culturing, handling
and imaging of stem cell derived organoid cultures 2014-2018
Training and supervision of junior phD student on assessing DNA damage
repair capacity of organoid-resident ASCs using fluorescence confocal microscopy
2017-2018
Teaching high school level students in private biology classes (freelancer) 2007-2008
and present time
Certificate of professional adequacy to teach biology as part of the undergraduate
B.Sc. diploma in collaboration with University of Rethymnon, Crete 2004

PUBLICATIONS

PEER-REVIEWED PUBLICATIONS

Vougioukalaki M., Vermeij W., Bruens S., Brandt R., Kuijk E., Jagger M., van Boxtel R., Cuppen E, Hoeijmakers J., Pothof J. Organ specific differences in genome maintenance strategies impacting ageing. ***manuscript in submission*** (PDF available upon request)

Vougioukalaki M., Hoeijmakers J.H.J., Pothof J. Stem cell aging; genomic instability, checkpoint responses and regenerative therapeutic strategies ***manuscript in preparation*** (PDF available upon request)

Jager M.,Blokzijl F., Kuijk E., **Vougioukalaki M.,** Janssen R., Besselink N., Boymans S., de Ligt J., Hoeijmakers J.H.J., Pothof J., van Boxtel R., Cuppen E. Deficiency of global genome nucleotide excision repair explains mutational signature observed in cancer ***under revision in Genome Research*** https://www.biorxiv.org/content/early/2017/11/17/221168

Vougioukalaki M., Kanelis D.C., Gkouskou K., Eliopoulos AG. (2011) Tpl2 kinase signal transduction in inflammation and cancer. **Cancer Letters** 304, 80-89

Vougioukalaki M., Gialesaki S. and Eliopoulos A.G. Quantitative changes in Focal Adhesion Kinase differentially control NFkB-regulated signal transduction, STAT3 signaling and cell survival. ***in preparation***

Lionaki E., de Marcos Lousa C., Baud C., **Vougioukalaki M.,** Panayotou G. and Tokatlidis K. (2008) The essential function of Tim12 *in vivo* is ensured by the assembly interactions of its C-terminal domain. **J Biol Chem** 283(23), 15747-15753

MEETING PAPERS

Vougioukalaki M., Vermeij W., Bruens S., Brandt R., Kuijk E., Jagger M., van Boxtel R., Cuppen E, Hoeijmakers J., Pothof J. (2017) Consequences of Ercc1 repair deficiency on mouse intestinal and liver stem cells and organoids : tissue specific ageing trajectories. 2nd Molecular Biology of ageing meeting, Groninger, The Netherlands

Vougioukalaki M., Vermeij W., Bruens S., Brandt R., Kuijk E., Jagger M., van Boxtel R., Cuppen E, Hoeijmakers J., Pothof J. (2017) Consequences of Ercc1 repair deficiency on mouse intestinal and liver stem cells and organoids : tissue specific ageing trajectories. EMBO meeting on the DNA damage response in cell physiology and disease, Sounio, Athens, Greece **(selected poster)**

Vougioukalaki M., Brandt R., Hoeijmakers J.H.J. and Pothof J. (2016) DNA damage response in ageing stem/progenitor cells. 2nd Cologne Ageing Conference, Cologne, Germany

Jager M., Kuijk E., **Vougioukalaki M.,** Janssen R., Besselink N., Boymans S., de Ligt J., Kanaar R., Hoeijmakers J.H.J., Pothof J., van Boxtel R., Cuppen E. (2015) Genomic stability of adult stem cells of healthy and *Ercc1*$^{\Delta/-}$ mice. Molecular Biology of Ageing Meeting, Groningen, The Netherlands

Vougioukalaki M., Gialesaki S. and Eliopoulos A.G. (2013) Quantitative changes in Focal Adhesion Kinase regulate secretory signaling for cell survival. 64th conference organized by the Hellenic Society of Biochemistry and Molecular Biology, Athens, Greece **(Award for Best poster-presented work)**

Vougioukalaki M. and Eliopoulos AG. (2012) Regulation of TPL2 signal transduction by Focal Adhesion Kinase. 2nd Inflammation, Cancer and Novel Therapeutics Conference and Summer School, Malia, Crete, Greece

Vougioukalaki M. and Eliopoulos AG. (2010) Anchorage dependency of TNF and CD40 ligand-induced MAPK signaling. 1st Inflammation & Cancer Summer School, Heraklion, Crete, Greece

Vougioukalaki M. and Eliopoulos AG. (2009) Anchorage dependency of TNF and CD40 ligand-induced signal transduction. 12th International TNF Conference-The TNF superfamily and its interactions with other signaling proteins in infection, autoimmunity, cancer and therapy, San Lorenzo de el Escorial, Madrid, Spain