Biographical Sketch
NIH

BIOGRAPHICAL SKETCH

NAME: Melemenidis, Stavros

POSITION TITLE: Basic Life Research Scientist & Director of Pre-clinical Radiotherapy

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Liverpool, UK	BSc	06/2008	Physics: Medical Applications
University of Liverpool, UK	MSc	06/2009	Physics: Radiometrics
Oxford University, UK	MSc	07/2010	Radiation Biology
Oxford University, UK	DPhil	06/2015	Radiation Biology
Oxford University, UK	Postdoctoral	01/2016	Molecular Imaging
Stanford University, USA	Postdoctoral	09/2020	Radiation Oncology
University of California, LA, USA	MP Certificate	06/2023	Medical Physics

A. Personal Statement

With a foundation in physics and radiation biology, my academic journey has been dedicated to mastering the complex interactions between various forms of radiation and their applications across the breadth of imaging techniques. My expertise extends to the design and execution of primary and metastatic mouse-tumor models, instrumental in advancing early disease detection and therapeutic innovation. I am highly skilled in the nuanced field of *in vivo* contrast-enhanced molecular imaging, utilizing an array of imaging modalities, and in assisting image-guided radiation therapies. My early research was pivotal in creating contrast agents for molecular imaging probes, specifically targeting markers in endothelial cells of primary and metastatic tumors. In the recent phase of my career, I have turned my attention to ultra-high dose rate (FLASH) irradiation technology for preclinical therapy. Through comprehensive research and experimentation, I have been at the forefront of configuring linear accelerators for optimal FLASH radiation delivery, a technique that promises to revolutionize cancer treatment by minimizing harm to healthy tissue while effectively targeting tumor cells. My investigative work has not only illuminated the underlying radiobiological principles of the FLASH effect but has also been pivotal in developing and fine-tuning specific *in vivo* irradiation strategies. This includes the meticulous engineering of mouse shields and collimators for anatomy-specific radiation delivery and the design and fabrication of dosimetric phantoms and protocols that ensure precise and reliable dosimetry.

B. Positions and Honors

Positions and Employment

2015 – 2016 Postdoctoral Scholar, Radiobiology Research Institute, Oxford University
2016 – 2020 Postdoctoral Scholar, Radiation Physics, Radiation Oncology, Stanford University
2020 – date Research Scientist, Radiation Therapy, Radiation Oncology, Stanford University
2023 – date Director of Pre-Clinical Radiotherapy, Radiation Oncology, Stanford University

Awards and Honors

2013 Invited presentation - Oxford Cancer Imaging Center retreat
2014 Poster prize and student bursary - Aegean Conferences
2014 Invited presentation - Oxford Cancer Imaging Center retreat
2014 Invited presentation - Oxford Institute Metastasis symposium
2019 Recognition of excellent research - Aegean Conferences

C. Contributions to Science

1. My contributions to science encapsulate the domain of molecular targeted imaging and the innovation of contrast agents. My first publication described the design and evaluation of an MRI T_2*-weighted contrast agent that targets angiogenesis in subcutaneous tumors. This probe is a conjugation of cyclic RGD variant [c(RGDyK)] peptides, with enhanced affinity for $\alpha_v\beta_3$, to microparticle of iron oxide (MPIO) with 2.8 μm diameter. Additionally, I have furthered the field by formulating a dual-modality PET-MRI contrast agent that facilitates the detection of lung and brain micrometastases by homing in on a vascular inflammation marker. This agent entailed the coupling of vascular cell adhesion molecule-1 antibody (anti-VCAM-1) to 1 μm diameter MPIOs and labeling the complex with $^{[89]}$Zr. These contributions underscore the feasibility of employing iron oxide microparticles, a distinctive alternative to nanoparticles, as preferred intravascular imaging agents.

    a. **Melemenidis S**, Jefferson A, Ruparelia N, Akhtar AM, Xie J, Allen D, Hamilton A, Larkin JR, Perez-Balderas F, Smart SC, Muschel RJ, Chen X, Sibson NR, Choudhury RP. (2015) Quantitative molecular magnetic resonance imaging of angiogenesis *in vivo* using polyvalent cyclic RGD-iron oxide microparticle conjugates. *Theranostics* (PMID: 25767618).

    b. **Melemenidis S.** Knight JC, Kersemans V, Perez-Balderas F, Zarghami N, Sarmiento Soto M, Bart Cornelissen B, Muschel RJ, Sibson NR. (2023) In vivo PET detection of lung micrometastasis by targeting endothelial VCAM-1. *Contrast Media Mol Imaging* (Submission ID: 4099472; *accepted*).

2. My second significant contribution to science resides in the dosimetry of preclinical FLASH)radiobiology. Amidst increasing interest in FLASH radiobiology and the absence of standardized platforms, the field has seen diverse configurations of linear accelerators emerge globally. My research endeavors have been pivotal in the standardization of dosimetric protocols and dose validation across multiple institutions, employing innovative dosimetric phantoms. The initial phase of our study utilized a cuboid PMMA phantom, followed by a study using a 3D-printed, anatomically realistic mouse phantom. Our findings indicate that the employment of these phantoms, coupled with our proposed protocols, facilitates dosimetric consensus among institutions—a key factor for successful FLASH radiobiology experiments.

    a. **Melemenidis S** and Jorge PG, Grilj V, Buchillier T, Manjappa R, Viswanathan V, Gondré M, Vozenin MC, Germond JF, Bochud F, Moeckli R, Limoli C, Skinner L, No HJ, Wu YF, Surucu M, Yu AS, Lau B, Wang J, Schüler E, Bush K, Graves EE, Maxim PG, Loo BW Jr, Bailat C. (2022) Design and validation of a dosimetric comparison scheme tailored for ultra-high dose-rate electron beams to support multicenter FLASH preclinical studies. *Radiother Oncol.* (PMID: 36030934).

    b. **Melemenidis S*** and Ashraf MR*, Liu K, Grilj V, Jansen J, Velasquez B, Connell L, Schulz JB, Bailat C, Libed A, Manjappa R, Dutt S, Soto LA, Lau B, Garza A, Larsen W, Skinner L, Yu AS, Surucu M, Graves EE, Maxim PG, Kry SF, Vozenin MC, Schüler E, Jr BWL. (2023) Multi-Institutional Audit of FLASH and Conventional Dosimetry with a 3D-Printed Anatomically Realistic Mouse Phantom. *ArXiv*. **Preprint** (PMID: 37808098). *Int J Radiat Oncol Biol Phys* (Manuscript ID: ROB-D-23-01452; *accepted*).

3. My third contribution to the field of science outlined in this biosketch is my instrumental role in the development and operation of a clinical linear accelerator setup tailored for preclinical FLASH experiments. The establishment of this FLASH platform has facilitated numerous collaborative ventures, probing various aspects of FLASH radiobiology. Our work established mouse models that allow for precise quantification of radiation toxicity in skin and the gastrointestinal tract, used for evaluating the protective effect of FLASH radiation on healthy tissue (FLASH effect). Additionally, we have conducted comparative studies on tumor control efficacy using FLASH versus conventional dose rate (CONV) irradiation, both with and without the adjunct of immunotherapy, specifically in ovarian cancer models. Our research extends to cellular and organoid experiments, where we have investigated the impact of FLASH irradiation on chromosomal translocations and junctions in cell-lines, as well as the utility of

human enteroids as a novel method to assess the FLASH effect. These endeavors represent substantial advancements in the ongoing exploration of FLASH radiobiology.

a. Soto LA, Casey KM, Wang J, Blaney A, Manjappa R, Breitkreutz D, Skinner L, Dutt S, Ko RB, Bush K, Yu AS, **Melemenidis S**, Strober S, Englemann E, Maxim PG, Graves EE, Loo BW. (2020) FLASH Irradiation Results in Reduced Severe Skin Toxicity Compared to Conventional-Dose-Rate Irradiation. *Radiat Res* (PMID: 32853385).

b. Chow S, Eggold JT, Wang J, Manjappa R, **Melemenidis S**, Loo P, Kidd EA, Engleman EG, Dorigo O, Loo BW, Rankin EB, Viswanathan V, and Natarajan S. (2021) Abdominopelvic FLASH Irradiation Improves PD-1 Immune Checkpoint Inhibition in Preclinical Models of Ovarian Cancer. *Mol Cancer Ther* (MCT-21-0358R1).

c. Barghouth PG, **Melemenidis S**, Montay-Gruel P, Ollivier J, Viswanathan V, Jorge PG, Soto LA, Lau BC, Sadeghi C, Edlabadkar A, Manjappa R, Wang J, Bouteiller ML, Surucu M, Yu A, Bush K, Skinner L, Maxim PG, Loo BW, Limoli CL, Vozenin MC, Frock RL. (2023) FLASH-RT does not affect chromosome translocations and junction structures beyond that of CONV-RT dose-rates. *bioRxiv* [Preprint]. (PMID: 37034651).

d. Klett KC, Martin-Villa BC, Villarreal VS, **Melemenidis S**, Viswanathan V, Manjappa R, Ashraf MR, Soto L, Lau B, Dutt S, Rankin EB, Loo BW, Heilshorn SC. (2023) Human enteroids as a tool to study conventional and ultra-high dose rate radiation. *Integr Biol (Camb)*. (PMID: 37874173).