

Innovative Facility for Isotope GENeration with Efficient Ion Accelerator

Research at the DKFZ

Joao Seco, Martina Benešová-Schäfer

DKFZ, German Cancer Research Center, Heidelberg Germany

Kick-off meeting 3-4 April 2025 Thessaloniki, Greece







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Brief Introduction: <u>DKFZ</u>, German Cancer Research Center

DKFZ Key Facts

Research for a Life without Cancer

3,500 employees

- 1,500 scientists (>800 internationals, >80 nations)
- 600 PhD students, 400 postdocs
- Largest Cancer Research Center in Europe

Translational centers with UMCs

- 8 DKTK sites (11 UMCs)
- 6 NCT sites (11 UMCs)

Top position in Germany and internationally

- 2 Nobel laureates
- 55 ERC Grants
- 2,500 Publications
- Nature Index: 5

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DKFZ Interactions with other WPs



- T4.4 Leader. Collaborating within: WP4 UL, Biokosmos, GNP
- T2.3 Secondments and good practices exchange (DKFZ, GSI, others)
- T6.2 Master Classes in Particle Therapy (M7-M48) [Leader: GSI]
- Additional Training possible via





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Training Component –

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Research Topics at the DKFZ

DKFZ Science

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Expertise in Radiation Biology and Single Cell Analysis of Radiation Effects Seco Lab



DIRECT AND INDIRECT ACTION

The biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA), which is the critical target, as described



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Cell Survival Curves





Single Cell Analysis of Radiation Effects

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What is RNA Sequencing???

- To understand the order/ structure of the molecule
- DNA/RNA sequencing is the process of determining the nucleotide order of a given fragment.
- Nowadays, these techniques are developed to determine ALL the DNA or RNA content of a cell (big data; -omics; high-throughput analyses)



Figure: Structure of DNA and RNA molecule, linear molecules

Ref: https://assets.technologynetworks.com/production/dynamic/images/content/296719/what-are-the-key-differences-between-dna-and-rna-296719-960x540.webp?cb=13068678



Trip back to Biology Lessons in School!



Figure: The connection between the Central Dogma of Biology and the type of 'Omics data obtained from each molecule.

tef: https://wildlifesnpits.wordpress.com/wp-content/uploads/2015/11/centraldogma2-e1447797497421.jpg?w=388



Reasons to study RNA sequencing...

- The whole RNA content of the cell (transcriptome) contains all the information that the cell needs to execute its function under specific conditions. As such, it offers insights on gene regulation, disease states, and cellular responses.
- RNAseq of an irradiated cell reflects all the active gene changes in response to the features of the irradiation (e.g. type, dose, time after treatment).



Figure: Retention of genetic material after transcription Ref: https://media.springernature.com/lw685/springer-static/image/art%3A10.1038%2Fs41390-024-03674-7/MediaObjects/41390_2024_3674_Fig2_HTML.png?as=webp



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Expertise in Radiopharmaceutical Research Benešová-Schäfer Lab



Intro to RadioThera(g)nostics

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Radioactive Elements

- Alpha radiation helium nuclei
- Beta radiation electrons/positrons
- Gamma radiation

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Types of radioactive decay



[1] Inductiveload (https://commons.wikimedia.org/wiki/File:Alpha_Decay.svg), "Alpha Decay", marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-self [2] Inductiveload (https://commons.wikimedia.org/wiki/File:Beta-minus_Decay.svg), "Beta-minus Decay", marked as public domain, more details on Wikimedia Commons: https://commons.wikimedia.org/wiki/Template:PD-self [3] openstax CNX – Radioactive Decay. Accessed from https://cnx.org/contents/lbTLTDQM@1.6:RSq8dk2S@1/Radioactive-Decay on 12.02.2021



RadioThera(g)nostics = RadioTherapy + RadioDiagnostics (therapeuein + gnosis)



Radiopharmaceuticals' Development

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Radiopharmaceuticals' Preclinical Evaluation

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In Vitro Experiments **Cancer cells** Radiolytic (in)stability Cell uptake & internalization **Binding affinity** Cytotoxicity



From Bench to Patient and Back

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Research for a Life without Cancer

Two treatment cycles with [²²⁵Ac]Ac-PSMA-617 14 MBq

PSA: 1301 ng/mL

PSA: <0.5 ng/mL

Radionuclide production and separation **Development of chelating systems Definition of cancer-specific targets** Identification of target-specific ligands Synthesis of compounds' library **Radiolabeling and radio-QC** In vitro experiments (cell lines) *In vivo* experiments (animals) Lead structures' optimization **Clinical transfer (first-in-human) Approval & authorization (routine use)**

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illuccix[®] & LOCAMETZ[®] Diagnostic [⁶⁸Ga]Ga-PSMA-11 Research for a Life without Cancer

[68Ga]Ga-PSMA-11







No Advertisement



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Developed in 2010, first-in-human in 2011, non-patented, published in 2012, produced by ABX from 2013

Marketing authorization by Telix Pharmaceuticals (illuccix[®]), in USA, South America & Australia, 2021 Marketing authorization by Novartis (LOCAMETZ[®]) in USA, Canada & Europe, 2022

Eder et al, Bioconjugate Chem 2012; 23(4): 688–697; Patient's scan acquired from Afshar-Oromieh et al, EJNMMI 2012, 39(6): 1085–1086.

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PLUVICTO[®] Theranostic ([¹⁷⁷Lu]Lu-)PSMA-617



Diagnostic [⁶⁸Ga]Ga-PSMA-617 1 h post-injection

Diagnostic [⁴⁴Sc]Sc-PSMA-617 1 h post-injection 19 h post-injection

Therapeutic [¹⁷⁷Lu]Lu-PSMA-617 Image of the Year 2015 Single dose

Therapeutic [²²⁵Ac]Ac-PSMA-617 Three cycles









Developed at the DKFZ in 2013 First-in-human at the UKHD in 2013 Patented in 2013 Published in 2015

FDA & EMA approval in 2022 Marketing authorization by Novartis (PLUVICTO®) in 2023



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Radelumin[®] Diagnostic [¹⁸F]PSMA-1007

Research for a Life without Cancer

PSMA-1007



[¹⁸F]PSMA-1007

2 h post-injection







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Developed in 2015, first-in-human in 2015, patented in 2015, published in 2016

Marketing authorization by ABX (Radelumin[®]) in AT, BE, F, D, IT, LU, ES & NL, 2022/2023

Focus: Personalized Radionuclides



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Candidate for β**-therapy**



Candidate for β-therapy

[¹⁷⁷Lu]Lu-PSMA-617 [²²⁵Ac]Ac-PSMA-617



Candidate for α-therapy

Focus: Treatment Resistance and Remission

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Focus: Combination Therapies

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Research for a Life without Cancer

TRNT & External Beam Radiation Therapy



Local

TRNT & Brachytherapy



TRNT & Immunotherapy



Systemic

TRNT & Chemotherapy



Seco/Benešová-Schäfer		Radionuclides & Targets in Pineline	dkfz.		
4/3/25	Page 28	Radionaciació a rangeto intripenne	Research for a Life without Cance		
	Diagnostic (PET)				
	F-18				
	Ga-68				
	Zr-89				



DKFZ Interactions with other WPs



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2nd Symposium on **Molecular Radiotherapy Dosimetry:** The future of theragnostics

November 13th-15th 2025, Athens, Greece

https://smrd2025.efomp.org/



QUESTIONS ???





Brief Introduction: Joao Seco and Martina Benešová-Schäfer

Education and Training

Bachelor «Theoretical Physics» - Univ of Lisbon Master «Solid State and Condensed Matter Physics» - Univ of Lisbon/Univ of Paris PhD «Medical Physics in area of Operations Research» - ICR, London UK

Postdoctoral Experience

Postdoctoral Researcher «Monte Carlo tools for Radiation Therapy» - ICR, London UK

Postdoctoral Researcher «4D MC tools for Xray and Protons» - MGH/HMS Boston, USA DABR «Therapeutic Medical Physics» - Harvard Medical School (HMS), Boston USA

Professor Appointments (2016):

Division Head «Biomedical Physics in Radiation Oncology» DKFZ, Heidelberg Chair of Medical Physics – Department of Physics and Astronomy, Univ Heidelberg



Research for a Life without Cancer





Education and Background

Research for a Life without Cancer

- Bachelor «Clinical & Toxicological Analysis»
- Magister «Nuclear Chemistry»

Charles University, Department of Inorganic Chemistry, Prague, Czech Republic

Ph.D. «Radiopharmaceutical Chemistry»

Ruperto-Carola University, Faculty of Biosciences, Heidelberg, Germany German Cancer Research Center (DKFZ), Division of Radiopharmaceutical Chemistry, Heidelberg, Germany

- Postdoctoral Researcher «Radionuclide Production»
- Postdoctoral Researcher «Drug Development»

Paul Scherrer Institute (PSI), Center for Radiopharmarmaceutical Sciences, Villigen, Switzerland + ITM Swiss Federal Institute of Technology (ETH), Institute of Pharm. Sciences, Zürich, Switzerland + Merck & Cie

- Junior Research Group Leader «Molecular Biology of Systemic Radiotherapy»
- Junior Research Group Leader «Translational Radiotheranostics»

Bayer, Targeted Alpha Therapies (TαT) Unit, Berlin, Germany

German Cancer Research Center (DKFZ), Heidelberg, Germany











WPx: title

WP	WP Leader:	
Work Package Name		
Start Month	End Month	
Effort	WP Contributors:	(Institutes)

Objectives



Tasks	Title	Task Leader



Del.	Title	Lead Partner	Dissemination Level	Due On