# Microdosimetry-based treatment planning in proton therapy

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6th Annual LLU Algorithm Workshop , July 20-22, 2020

# Acknowledgement of Collaborators


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**CMRP PhD students:** Lachlan Chartier, David Bolst, Emily Debrot, Stephania Peracchi, James Vohradsky, Ben James, *and many others*
**POWH:** Dr Michael Jackson, MD
**ANSTO:** Dr Dale Prokopovich, Dr Mark Reinhard, Prof David Cohen,

*3DMiMiC European-Australian Collaboration*
**SINTEF** : Dr Angela Kok, Dr Marco Povoli and 3DMiMiC team
**SPA BIT** Ukraine , Dr V.Perevertaylo
**HIT facilities in Japan**: Prof N.Matsufuji ,Dr T. Inaniwa (**NIRS**), Prof T.Kanai, (**GUMC**),
**MGH F Burr Proton Therapy Center and Harvard Medical School**
Dr Ben Clasie, Dr Jay Flanz, Dr Nicolas Depauw, Dr Hanne Kooy, Dr Aimee McNamara, Prof Harald Paganetti
**Mayo Clinic** Dr Chris Beltran and team
**iThemba Labs** Drs Vandevoorde C, Beukes P, Miles X, de Kock E, Symons J, Nieto-Camero Vanhavere F, Peterson S, Vral A, Slabbert J
**University of Groningen** Prof Stefan Both, Prof S. Brandenburg, Dr M-J. Goethem, Dirk Wagenaar
**INFN** Dr Cuttone , Dr P.Cirone, Dr G.Petringa


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# Meet the CMRP Team


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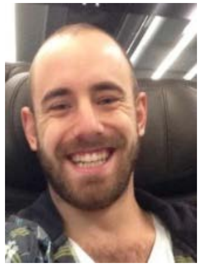
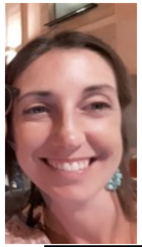
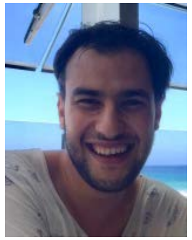

Dr Jeremy
Davis


Dr Iolanda
Fuduli


Dr Giordano
Biasi


Dr Saree
Alnaghy


Dr Linh Tran


Dr Brad Oborn


Dr Dousatsu
Sakata


Dr David
Bolst

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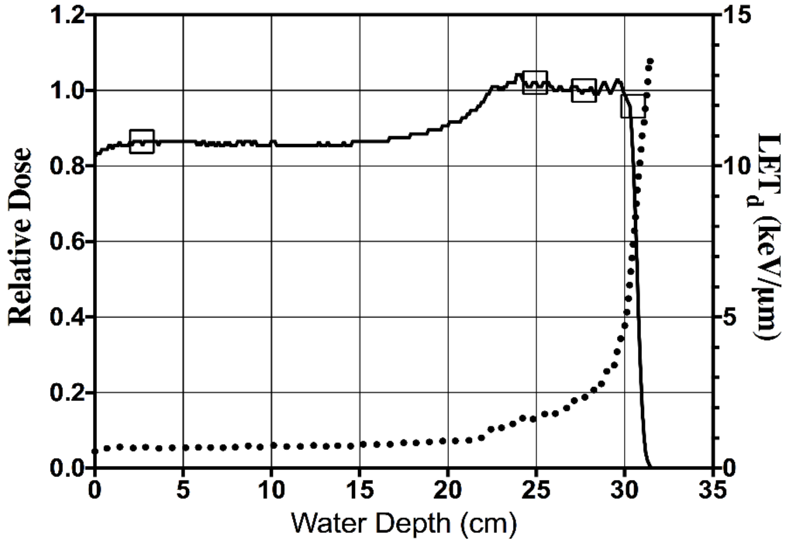
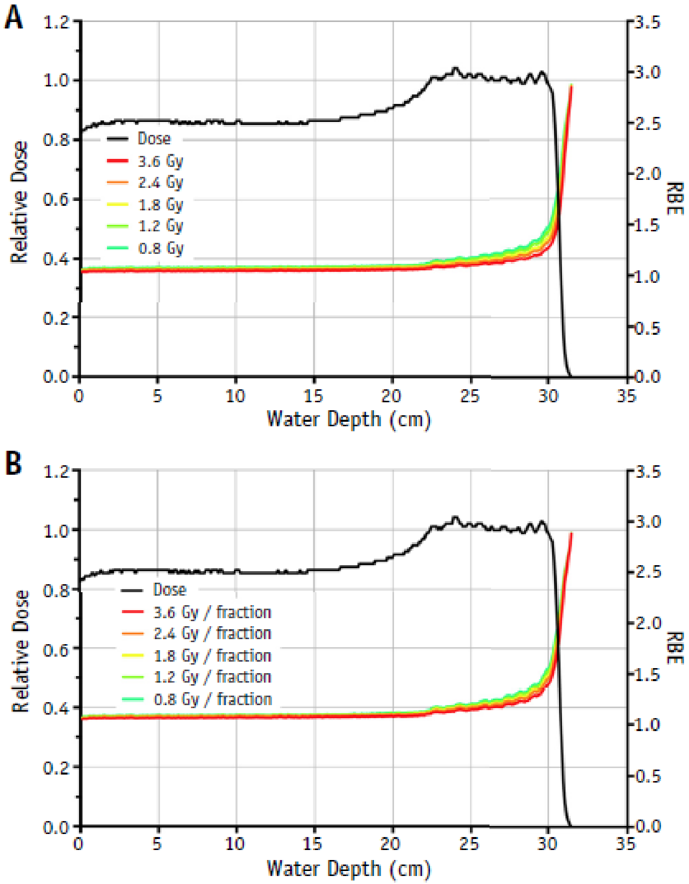
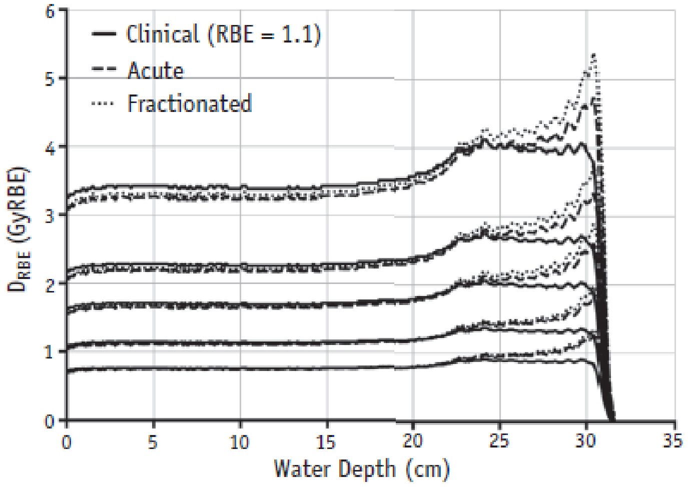
# Clinical Evidence of RBE>1.1



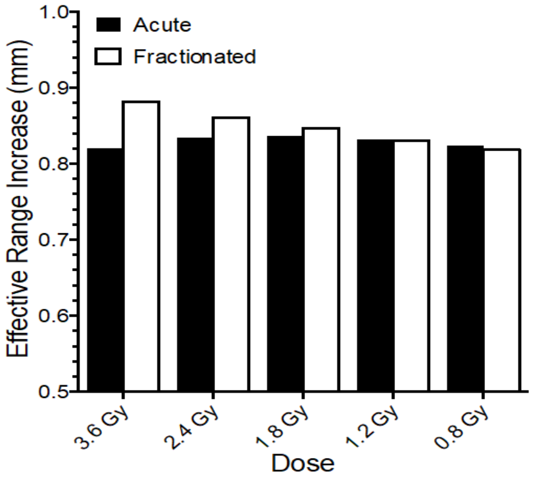




$$RBE_{acute} = \frac{-\alpha_X + \sqrt{\alpha_X^2 + 4\beta_X(\alpha_P D_P + \beta_P D_P^2)}}{2\beta_X D_P}$$

and

$$RBE_{frac} = \frac{\alpha_P + \beta_P d_P}{\alpha_X + \beta_X d_X}$$

$$\alpha_p = \alpha_x + \lambda LET$$




Human fibroblasts (AG01522) at 4 key depth positions on a clinical PBS SOBP of maximum energy 219.65 MeV were subjected to various fractionation regimens with an interfraction period of 24 hours at Proton Therapy Center in Prague

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T.I.Marshall…K.Price et al IJROBP , **95**, No. 1, pp. 70-77, 2016

# Importance of variable RBE in Proton therapy

**IOP** Publishing | Institute of Physics and Engineering in Medicine Physics in Medicine & Biology

Phys. Med. Biol. **60** (2015) 8399–8416 doi:10.1088/0031-9155/60/21/8399

$$\mathrm{RBE}\left[D_{\mathrm{p}},\left(\frac{\alpha}{\beta}\right)_x,\mathrm{LET}_d\right]=\frac{1}{2D_{\mathrm{p}}}\left(\sqrt{\left(\frac{\alpha}{\beta}\right)_x^2+4\left(\frac{\alpha}{\beta}\right)_x\frac{\alpha\,[\mathrm{LET}_d]}{\alpha_x}D_{\mathrm{p}}+4\frac{\beta\,[\mathrm{LET}_d]}{\beta_x}D_{\mathrm{p}}^2}-\left(\frac{\alpha}{\beta}\right)_x\right)$$

Acta Oncologica

Taylor & Francis

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: http://www.tandfonline.com/loi/ionc20

**Varying relative biological effectiveness in proton therapy: knowledge gaps versus clinical significance**

- *More in vivo experiments are needed*
- *Clinical data need to be analyzed with respect to RBE effects.*
- *Use the variable RBE to maximize the potential of proton therapy.*

**IOP** Publishing *Phys. Med. Biol.* 63 (2018) 225009 (12pp) https://doi.org/10.1088/1361-6560/aae8a5

Physic

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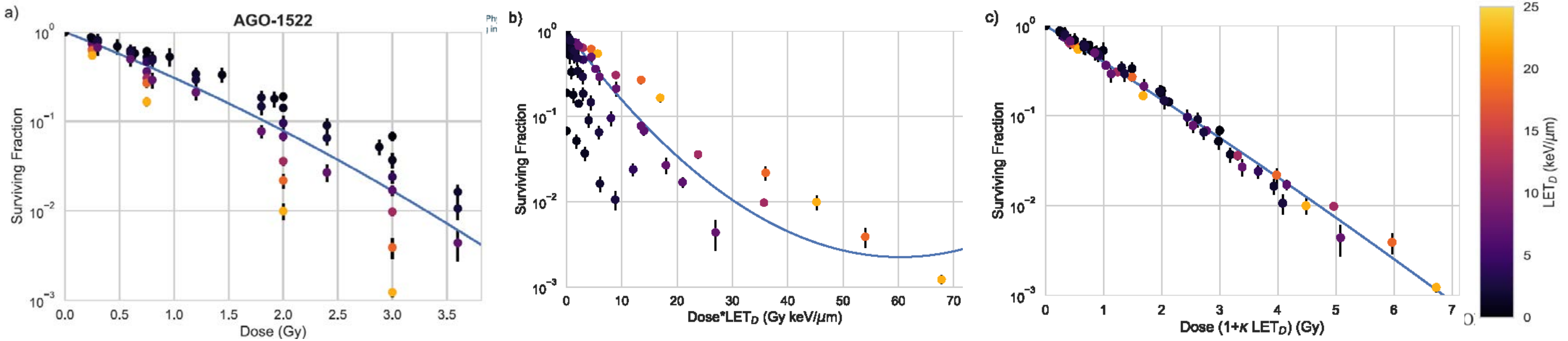
AGO-1522




While not a replacement for full RBE models, simplified metrics such as this LET-weighted dose can be used to account for the majority of variability which arises from the LET-dependence of RBE with reduced need for biological parameterisation

# Microdosimetric Kinetic Model (MKM)

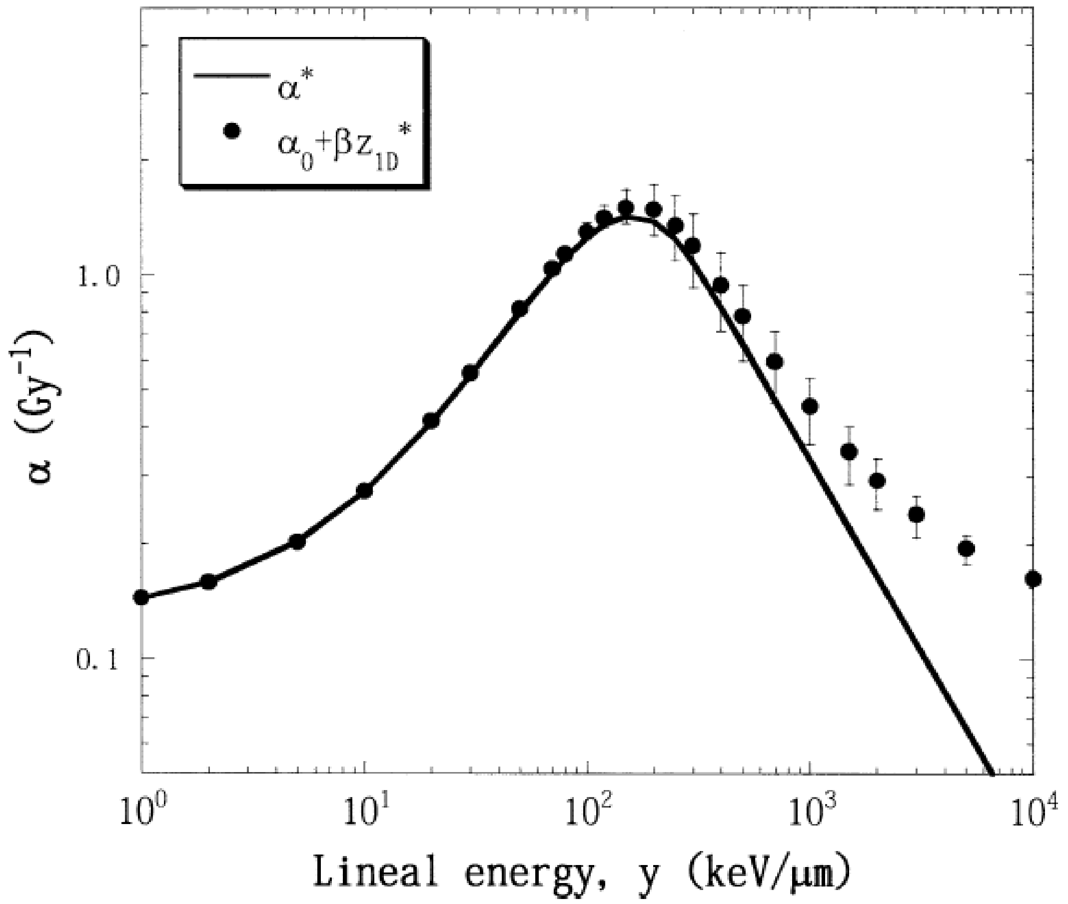



FIG. 4. The $\alpha^*$ value obtained with Eq. (5) and the value of $\alpha_0 + \beta z^*_{1D}$ in Eq. (7) as a function of lineal energy for a single event, with the biological parameters applicable for HSG cells. The error bars show a variation of 20 keV/μm for the saturation parameter, $y_0$ = 150 keV/μm.

**Linear Quadratic Model**

$S(D) = \exp[-\alpha D - \beta D^2]$

Physics/Biology

$$\alpha = \alpha_o + \frac{\beta}{\rho \pi r_d^2} y^*$$

$$y^* = \frac{y_o^2 \int_0^\infty \left(1 - exp(-y^2/y_o^2)\right) f(y) dy}{\int_0^\infty y f(y)\, dy}$$

$$RBE_{10} = \frac{2\beta D_{10,R}}{\sqrt{\alpha^2 - 4\beta ln(0.1)} - \alpha}$$

- $\alpha_o$= 0.13 Gy$^{-1}$; $\beta$= 0.05 Gy$^{-2}$ ; $r_d$ = 0.42 μm is radius of sub cellular domain in MK model, $y_o$ = 150 keV/μm
- Where $D_{10,R}$ = 5Gy is 10% survival of 200 kVp X rays for HSG cells

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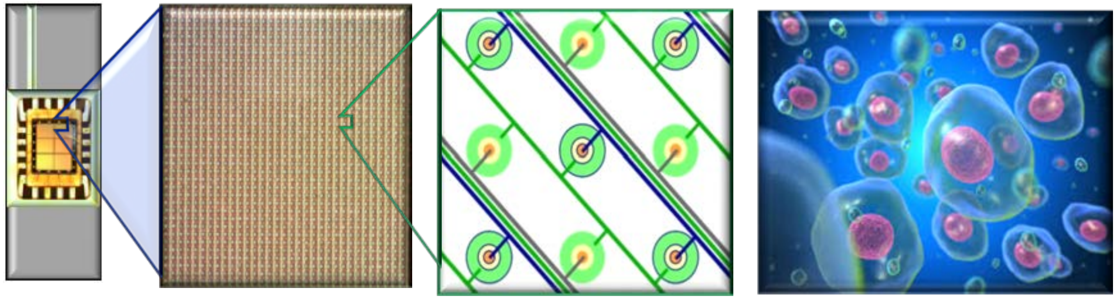
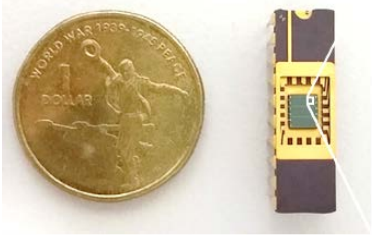
# Conventional microdosimeter

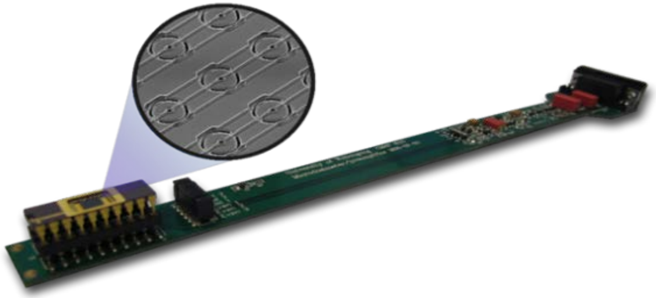
✓Low energy sensitivity **y= 0.05 keV/um**
✓Spherical SV in shape
✓ Tissue equivalency

▪Large size of assembly which reduces spatial resolution and introduces wall effects
▪ Can not measure an array of cells.
▪High voltage applied
▪Low degree of portability

# Silicon on insulator (SOI) Microdosimeter







✓ Can measure an array of cells
✓Micron sized SV
✓ Provide true microscopic SV
✓ Compact size and low voltage for operation
✓ High spatial resolution.

not tissue equivalent

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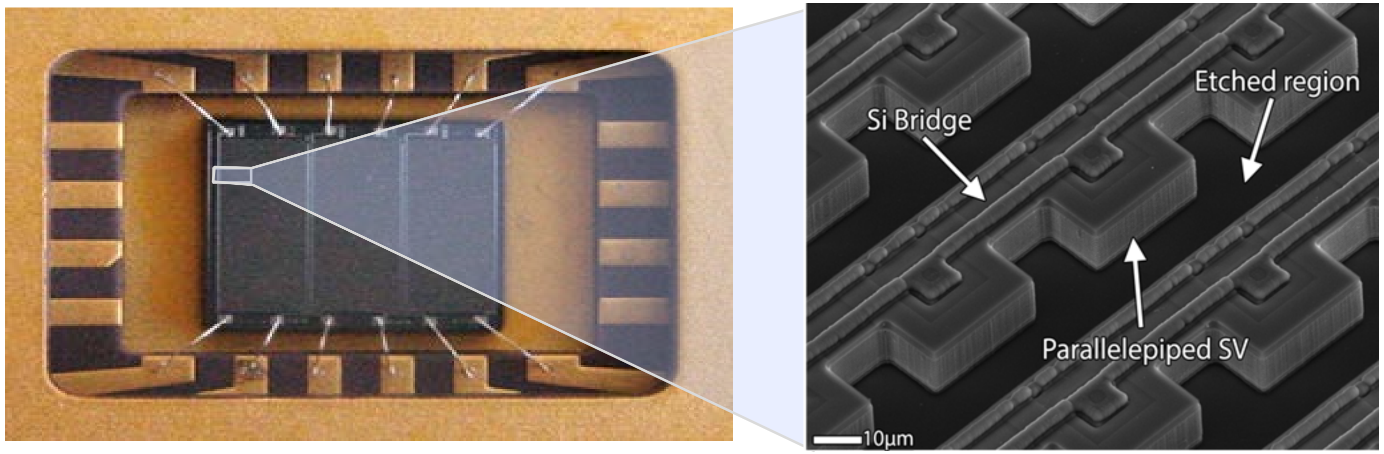
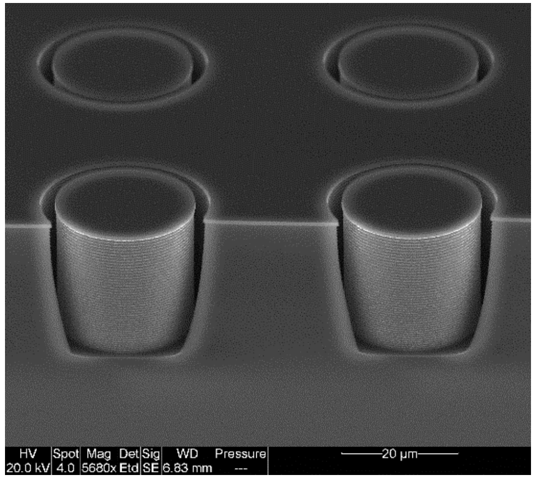
# CMRP Silicon Microdosimeters

Bridge MD Version 2

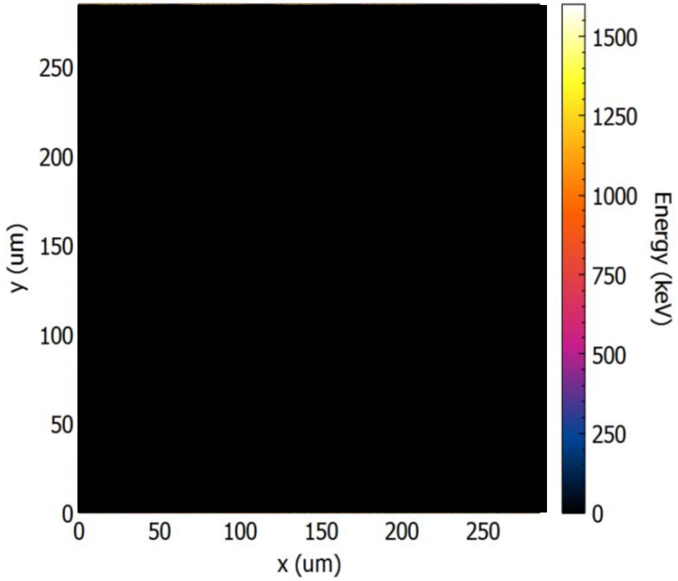


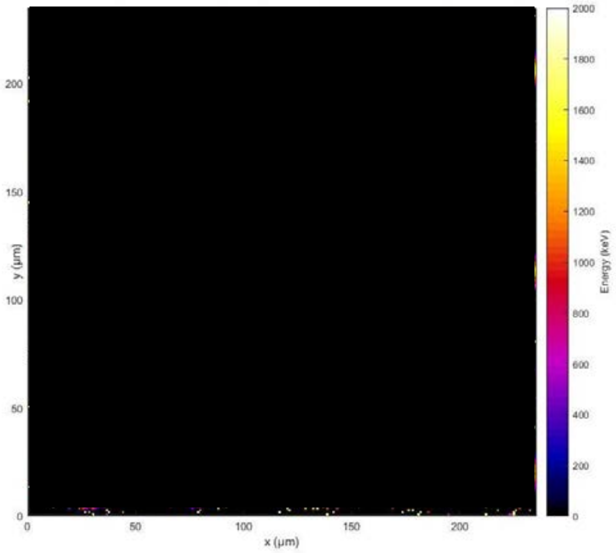





SEM image of Mushrooms

Median energy map showing the charge collection distribution in the BridgeV2 microdosimeter, biased at -10V

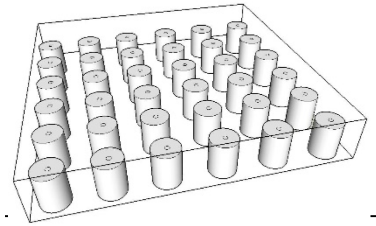



Median energy map showing good sensitive volume yield in the Mushroom microdosimeter, biased at -10 V

**U.S. Patent 8421022**

**EU patent EP 2 102 685 B1**



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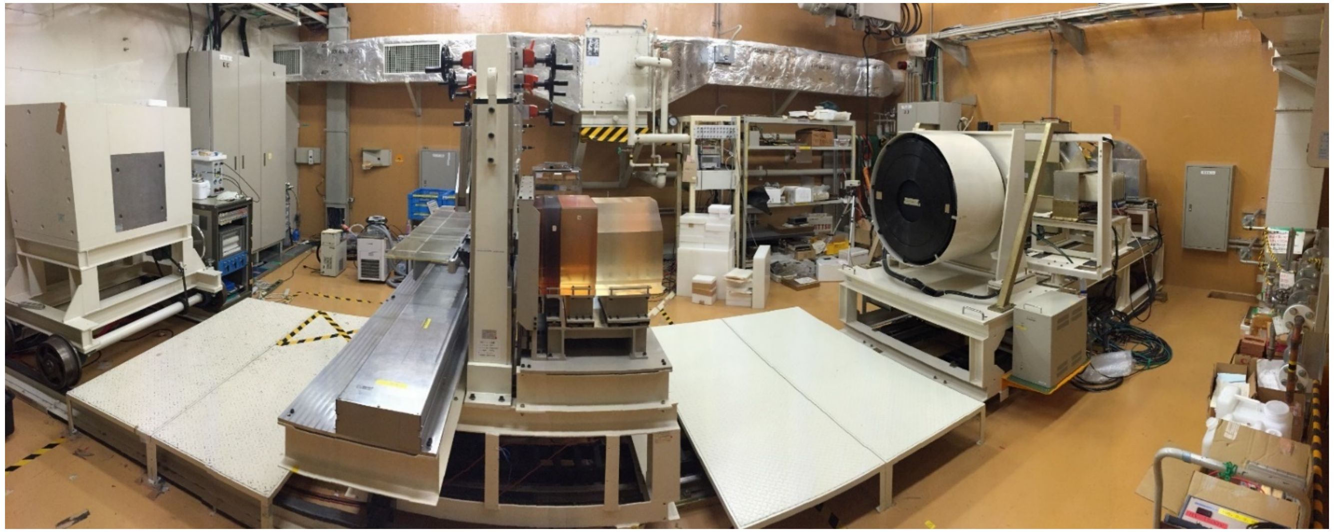
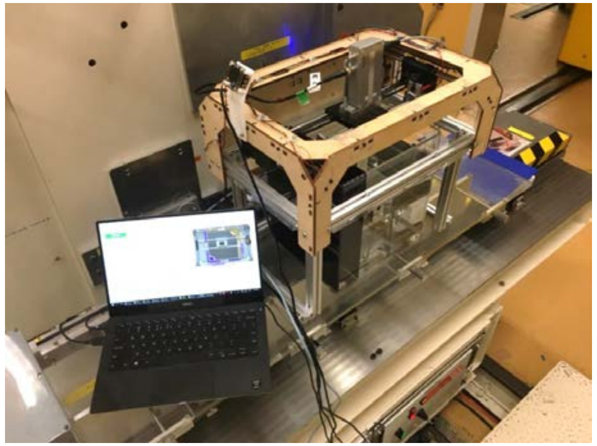
A. Rosenfeld "Novel detectors for silicon based microdosimetry, their concepts and applications", NIM A, 809, 156-170, 2016

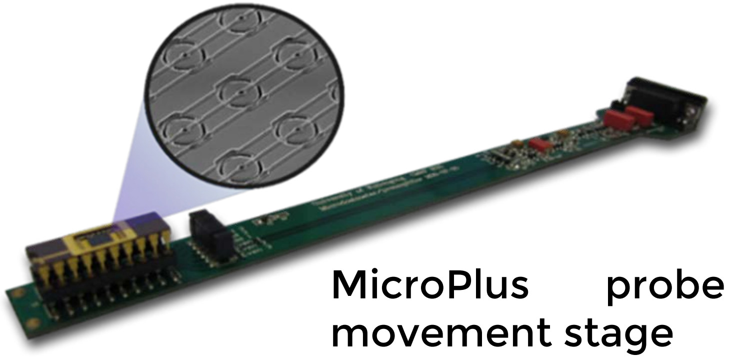
# Heavy Ion Medical Accelerator in Chiba

## HIMAC, Japan

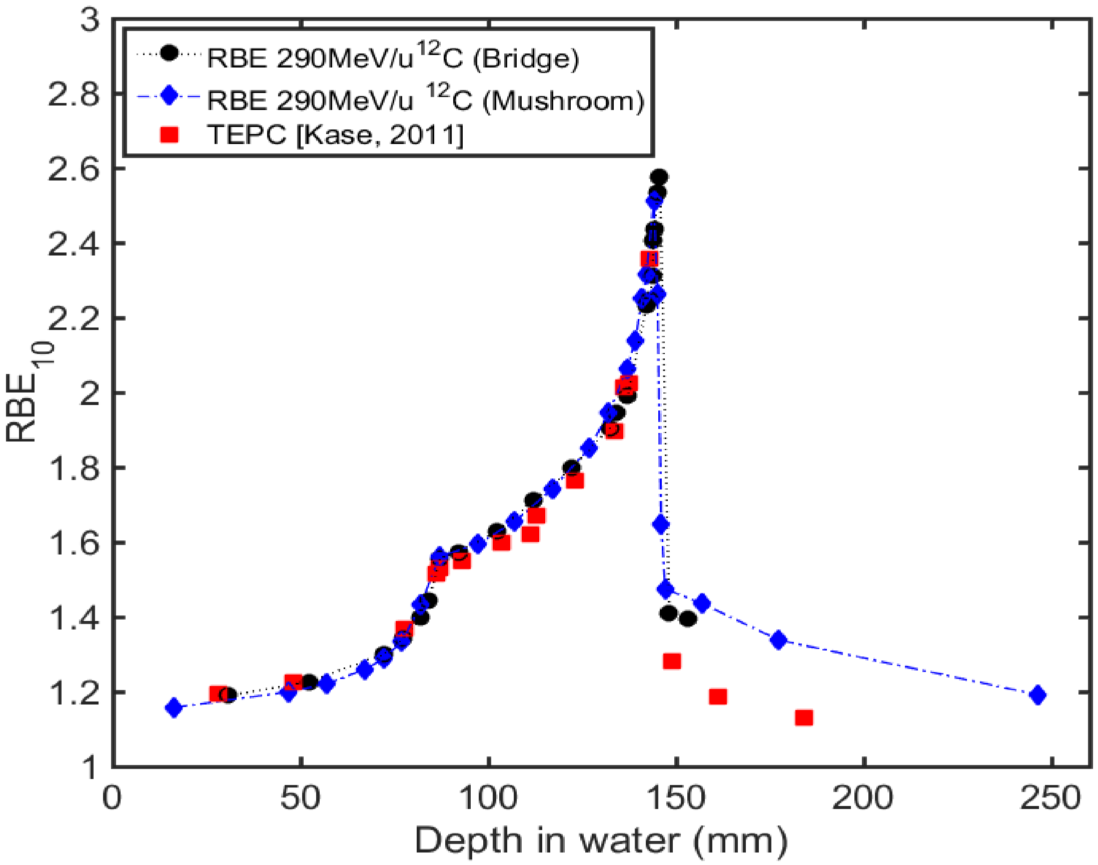


HIMAC Bio-cave beam port with passive scattering delivery





MicroPlus probe with XY-movement stage

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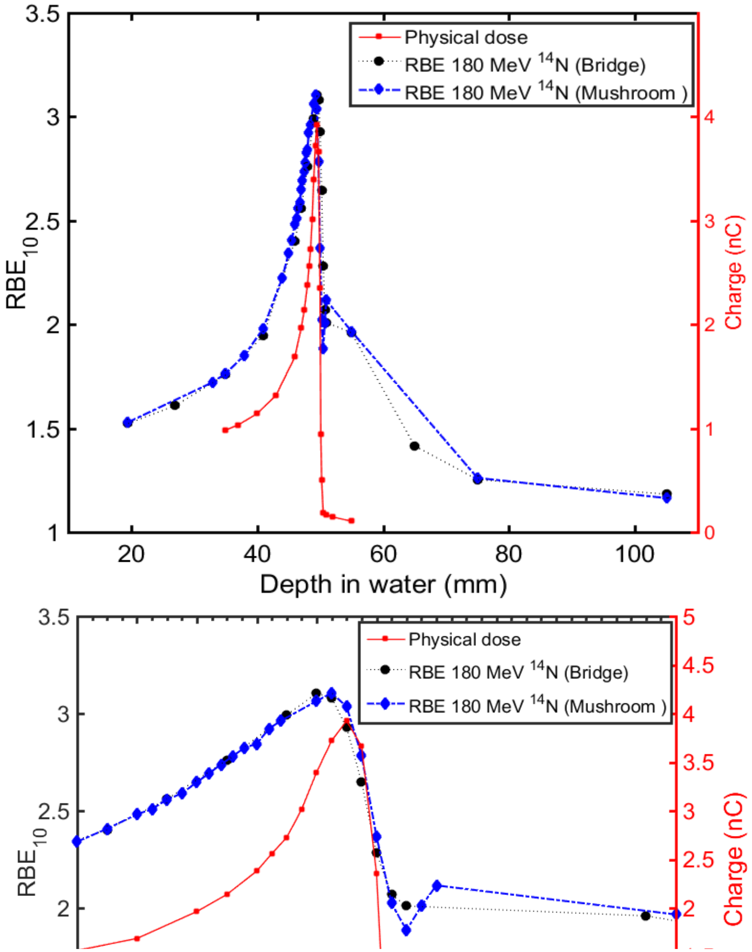
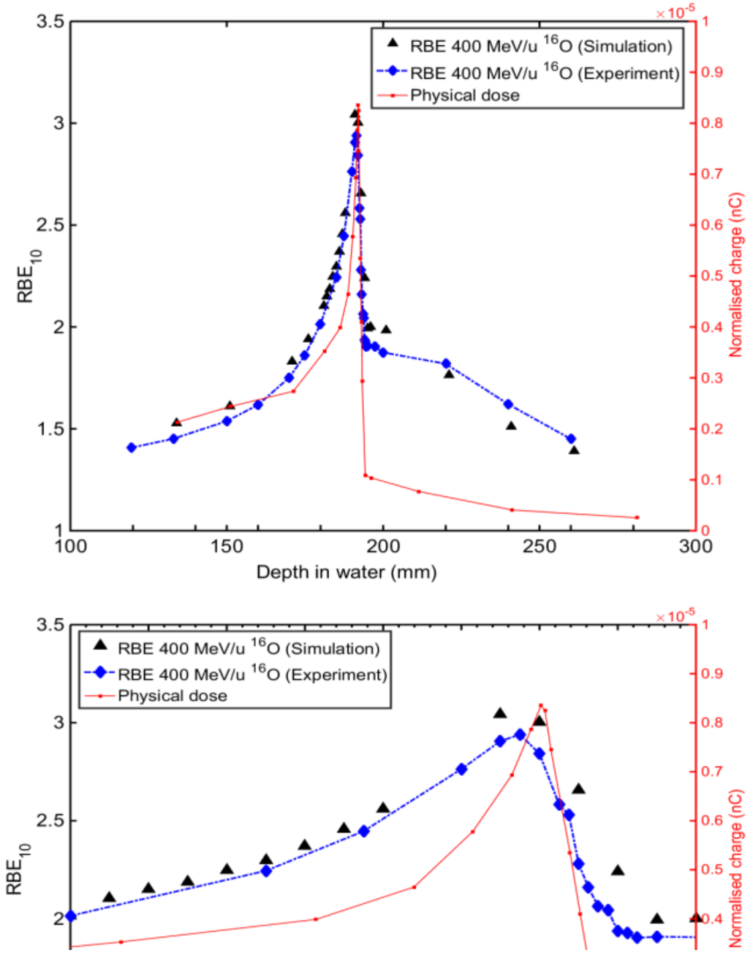
# $RBE_{10}$ obtained with SOI microdosimeter in response to pristine BP of *$^{14}N$, $^{16}O$ and $^{12}C$ ion beam*

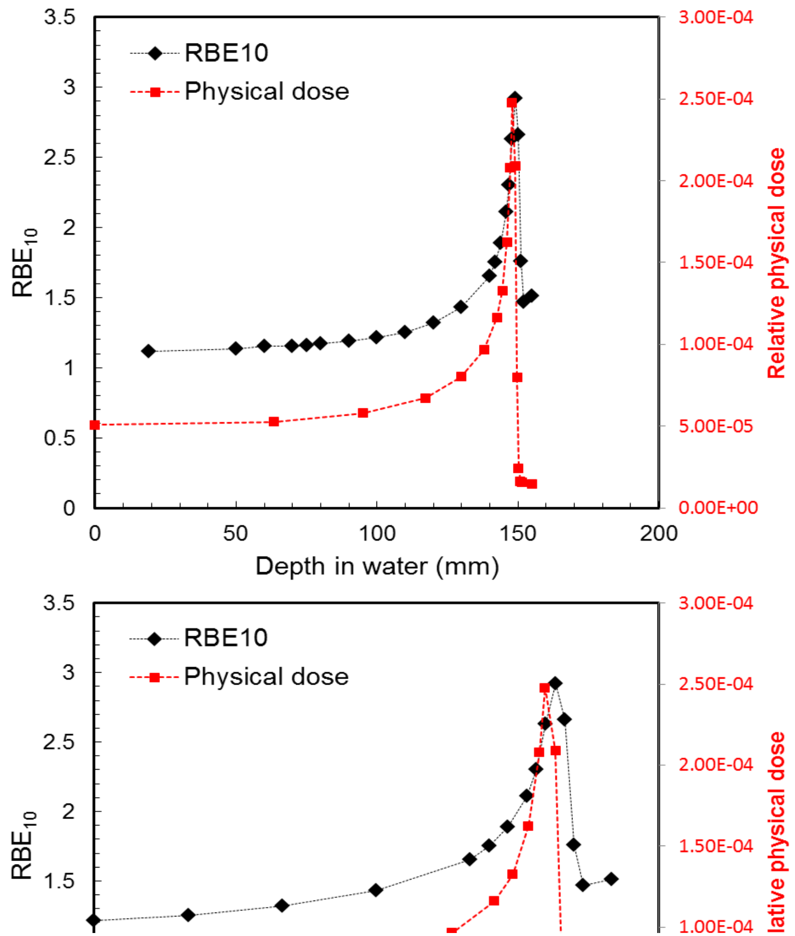
## 180 MeV/u $^{14}N$




## 400 MeV/u $^{16}O$




## 290 MeV/u $^{12}C$



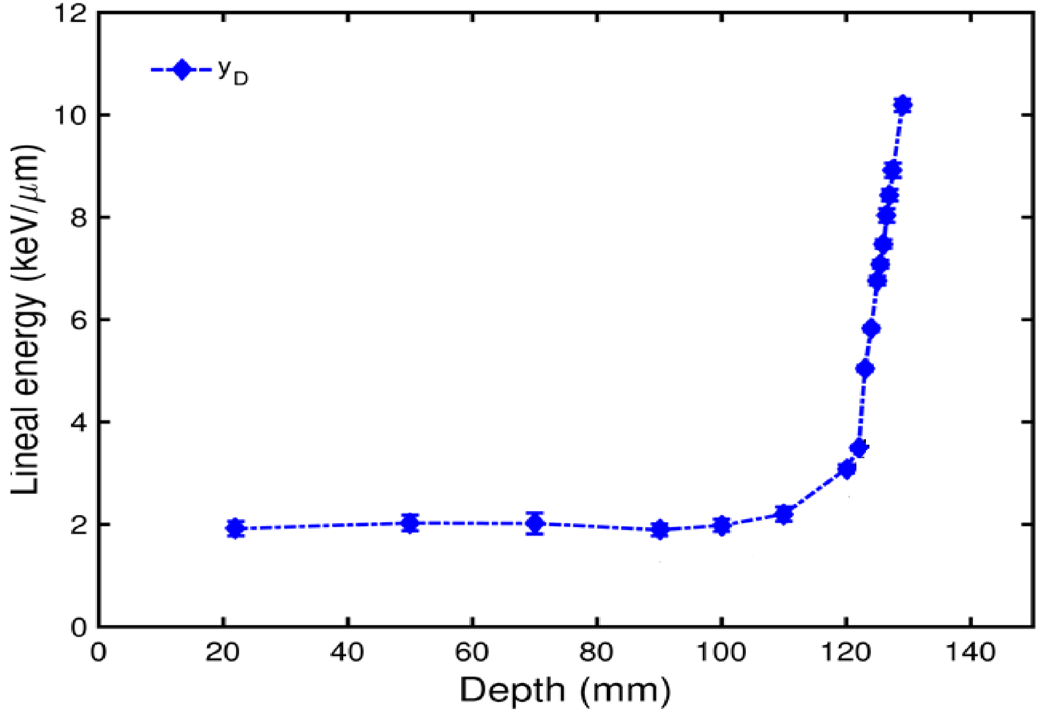

Linh T. Tran, et. al., *"The relative biological effectiveness for carbon, nitrogen and oxygen ion beams using passive an scanning techniques evaluated with fully 3D silicon microdosimeters"* Medical Physics, 2018 , DOI10.1002/mp.12874.

Farrington Daniel award for the best Medical Physics paper FY 2018 selected by the American Association of Physicist in Medicine (AAPM).

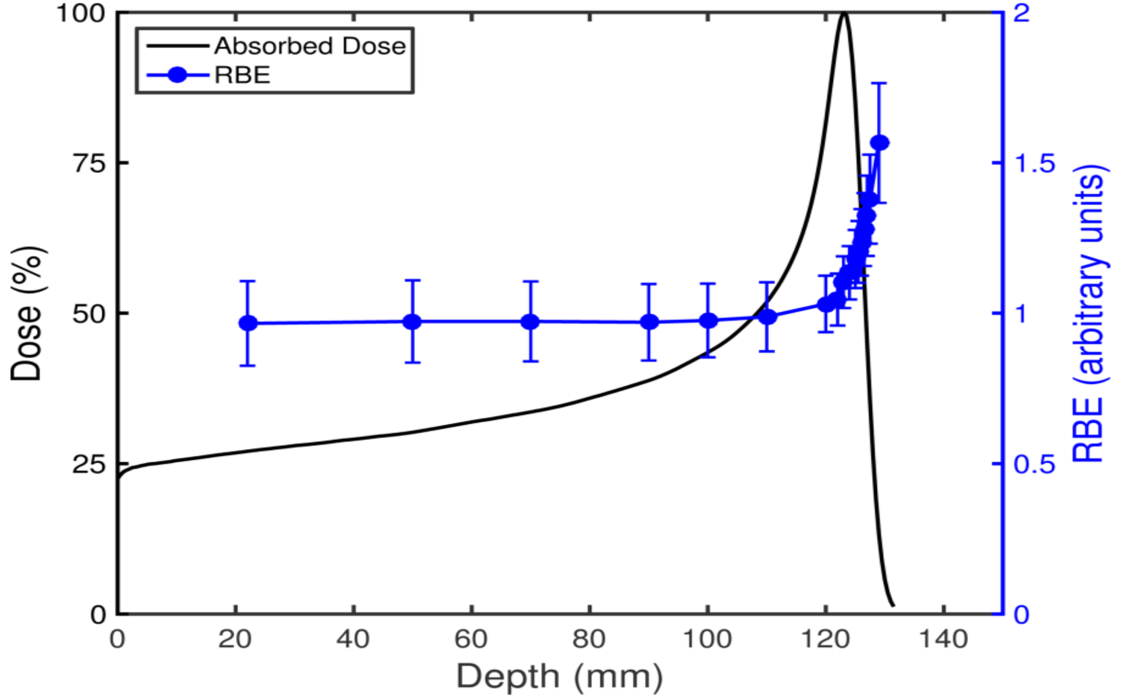
# Characterization of Pencil Beam Scanning in Proton therapy

$$RBE = \frac{D_{S,R}}{D_S} = \frac{\sqrt{{\alpha_R}^2 - 4\beta ln(S)} - \alpha_R}{2\beta D_S},$$

$\alpha_R = 0.13\ Gy^{-1}$
$\beta = 0.05\ Gy^{-2}.$




*a)* $\overline{y_D}$ obtained using Bridge microdosimeter obtained with Bridge m+ probe in water for spot PBS (MGH)




b) Depth dose distribution and RBE for PBS spot for dose in BP 2Gy. (MGH)

Linh T. Tran, et. al., "Characterisation of proton pencil beam scanning and passive beam using a high spatial resolution solid state microdosimeter"" Medical Physics, **44** (11), 2017 , DOI10.1002/mp.12874.

# Proton Scanning Irradiation, Mayo Clinic, Minnesota, USA

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S. Anderson, K Furutani, L. Tran *et. al*. ***"Microdosimetric measurements of a clinical proton beam with micrometer-sized solid-state detector,"*** Med Phys. 2017 Sep 14. doi:

# RBE in proton therapy: Cell survival vs Bridge Microdosimetry

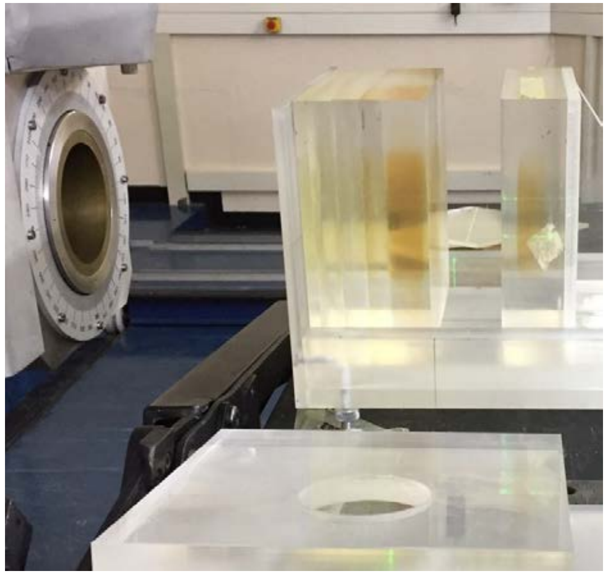


**Fig 1:** In-vitro radiobiology setup in PMMA phantom. Bridge Microdosimeter was placed at the same depth as cells.

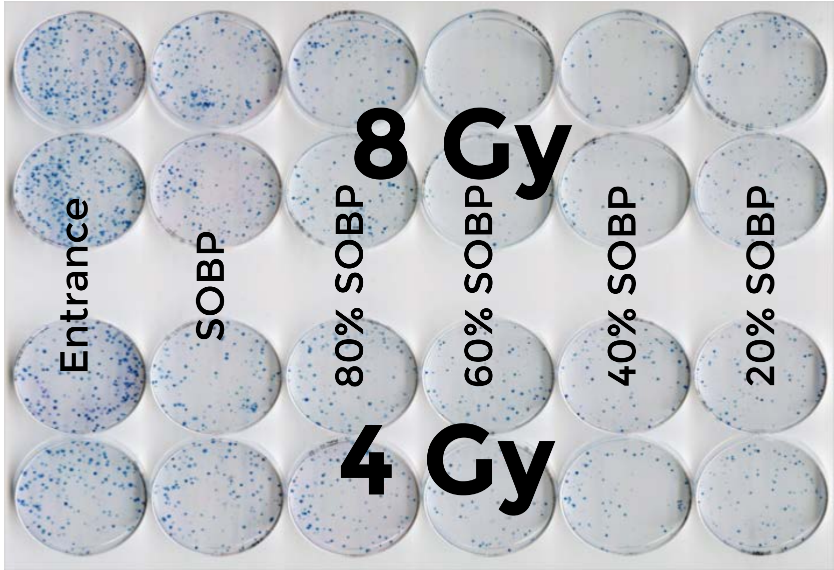
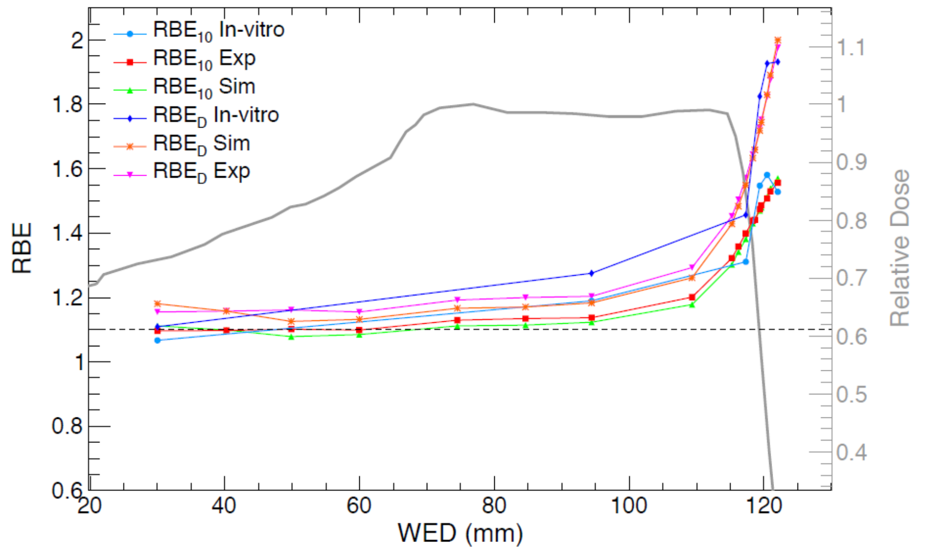



**Fig 2:** In-vitro CHO-K1 irradiated cells




$RBE_D$ : Cells survival vs Microdosimetry prediction . Good agreement. Dose 2 Gy.

## MicroPlus probe predicts $RBE_d$ and $RBE_{10}$ in agreement the CHO-K1 cell line

✓ **Ability to replace time consuming radiobiological RBE experiments**

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dkfz.

NRF
National Research Foundation
iThemba LABS
Laboratory for Accelerator Based Sciences

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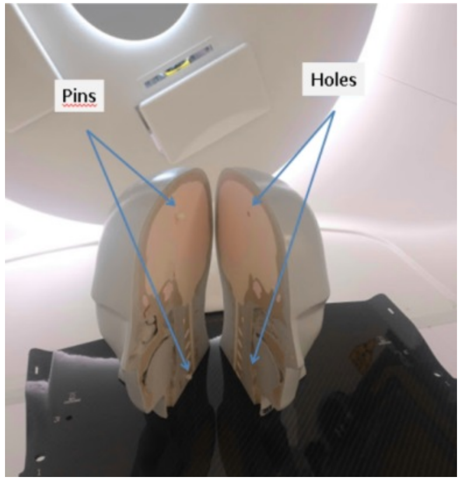
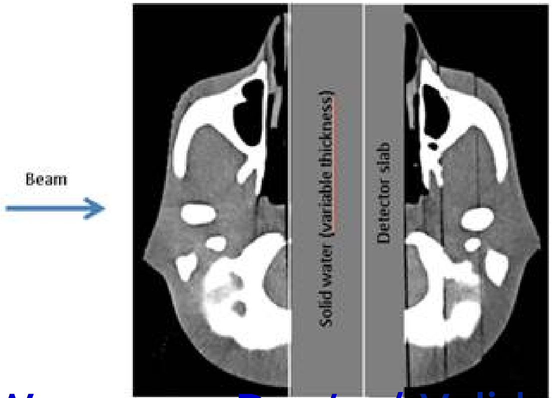
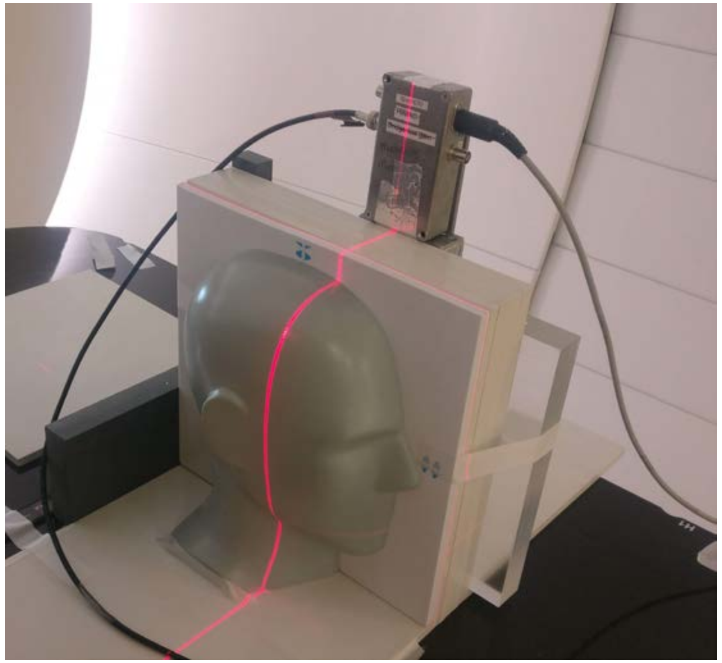
E Debrot, L Tran, L Chartier *et. al.* SOI microdosimetry and modified MKM for evaluation of relative biological effectiveness for a passive proton therapy radiation field, PMB , 2018

# MicroPlus as QA tool for RayStation TPS verification: Experiment in anthropomorphic head phantom with PBS patient treatment plan at proton therapy centre, Groningen University, Netherlands

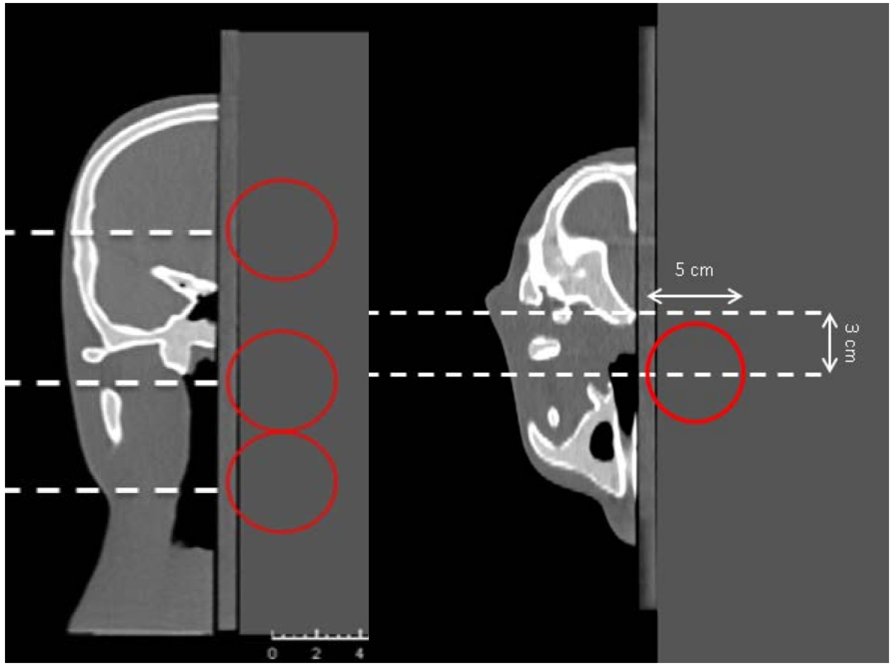



CIRS-head & neck phantom



MicroPlus probe in the CIRS head and neck phantom




A coronal projection of CT scan of the CIRS 731-HN phantom

Wagennar, D, *et. al.* Validation of linear energy transfer computed in a Monte Carlo dose engine of a commercial treatment planning system, Phys.Med. Biol., 65(2):025006, 2020

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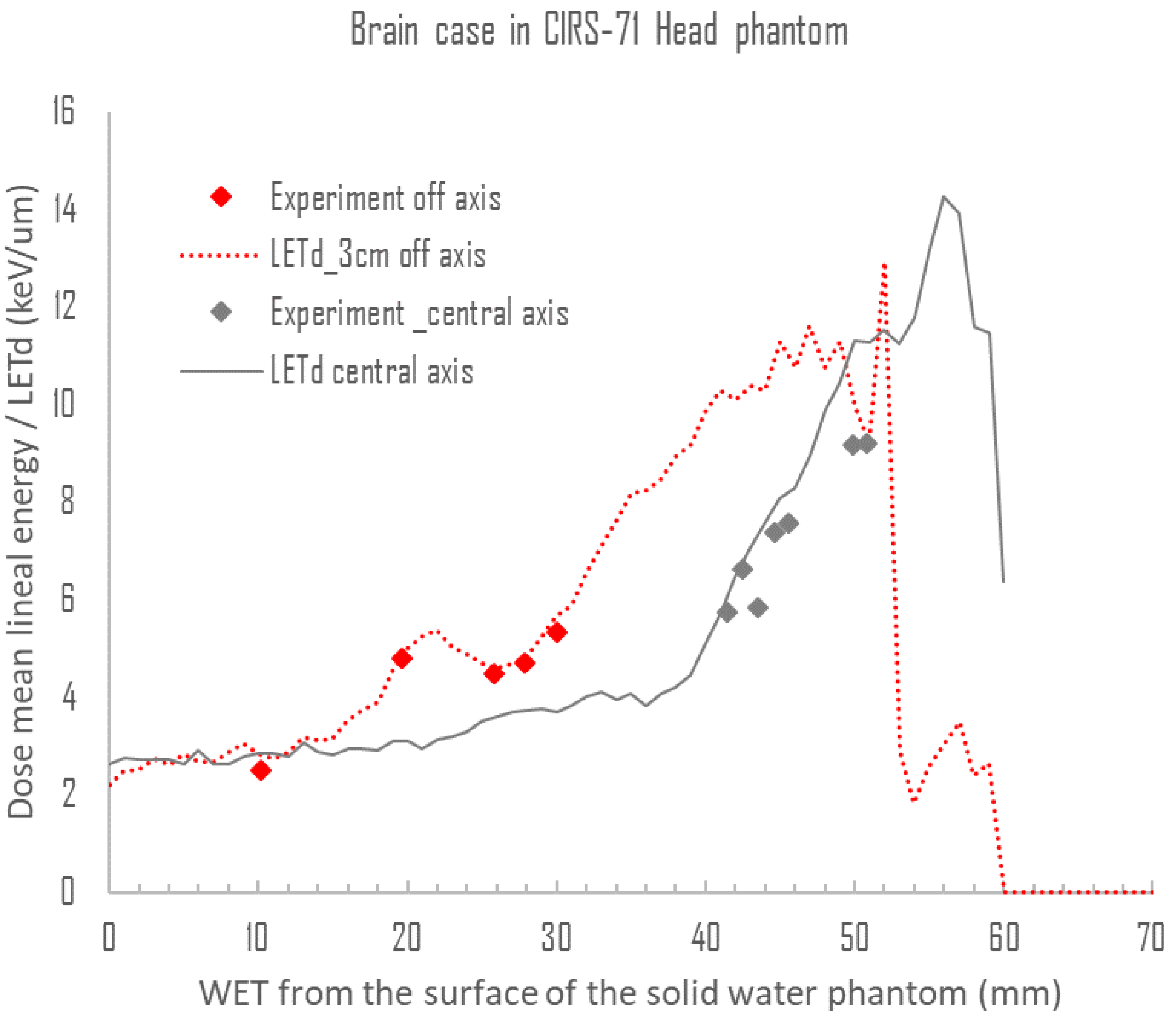
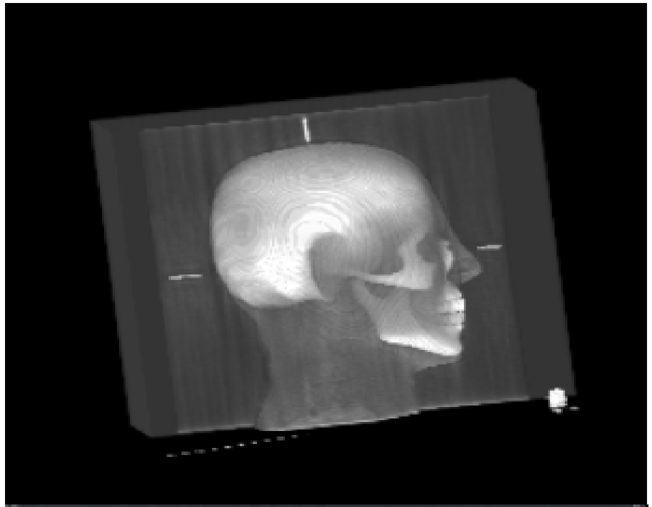
# Comparison of $y_D$ distribution vs $LET_D$ predicted by Raystation

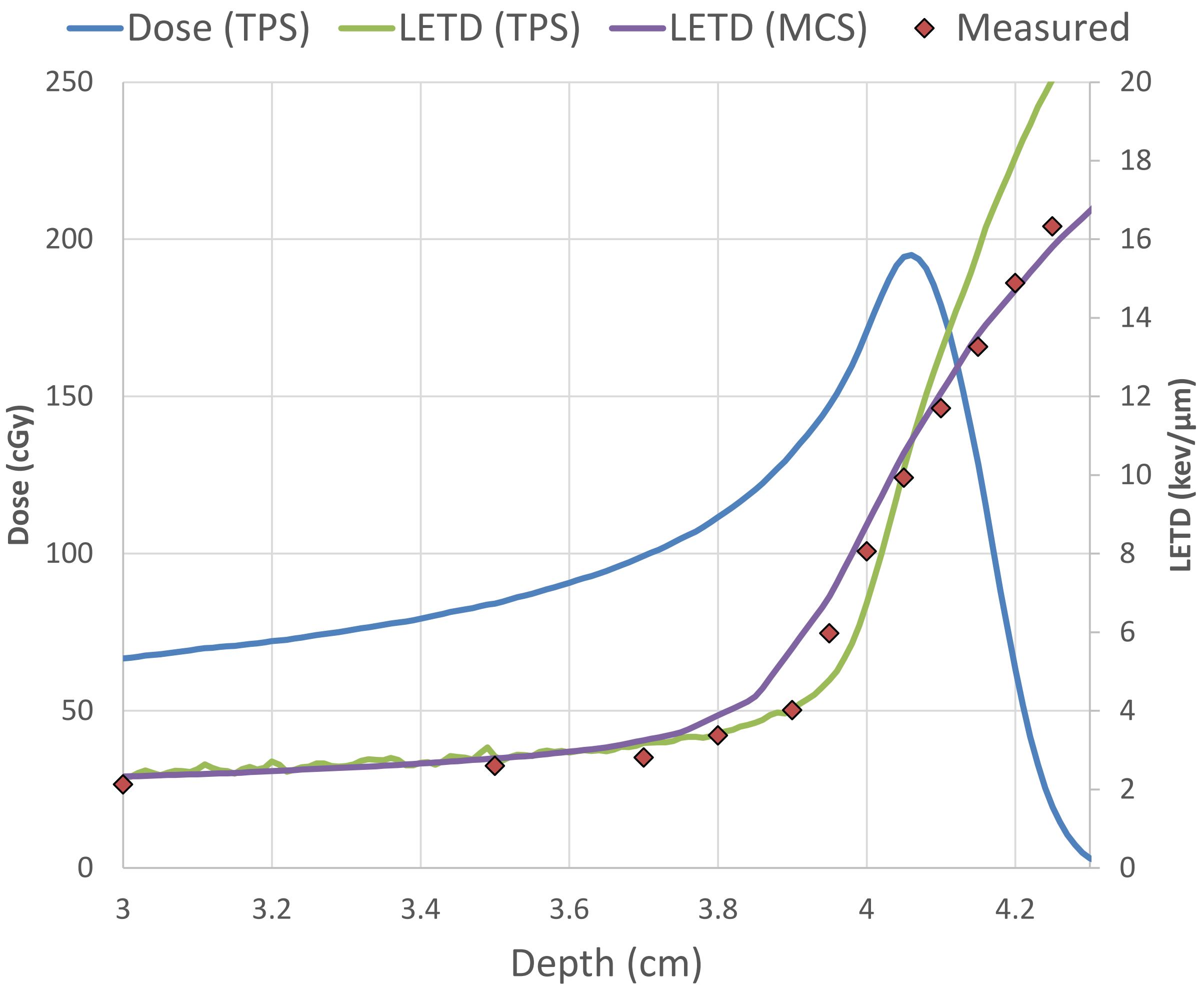


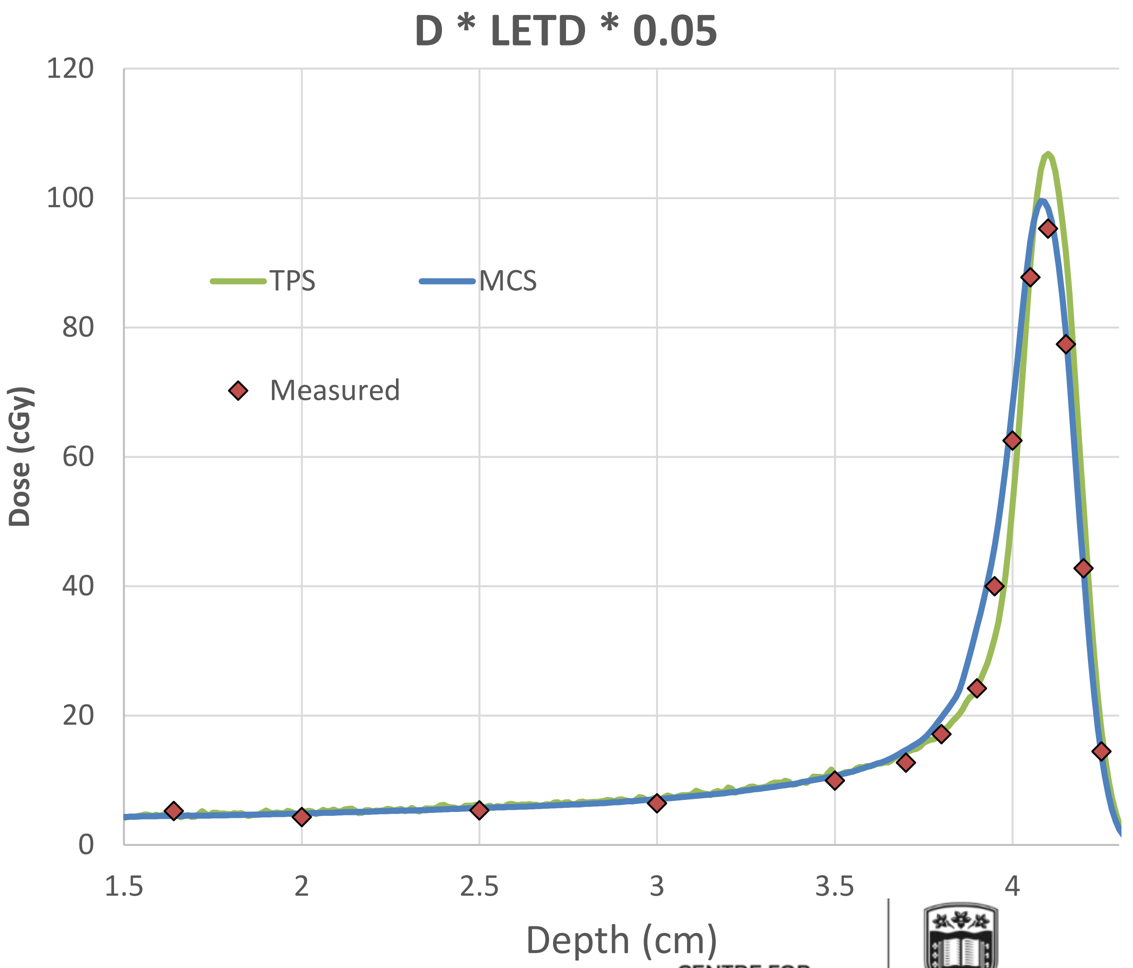



CT scan of a head phantom and a solid water slab

Clinical plan in a head phantom for Brain, Naso and Neck (top to bottom).

# Results: 70 MeV spot in water

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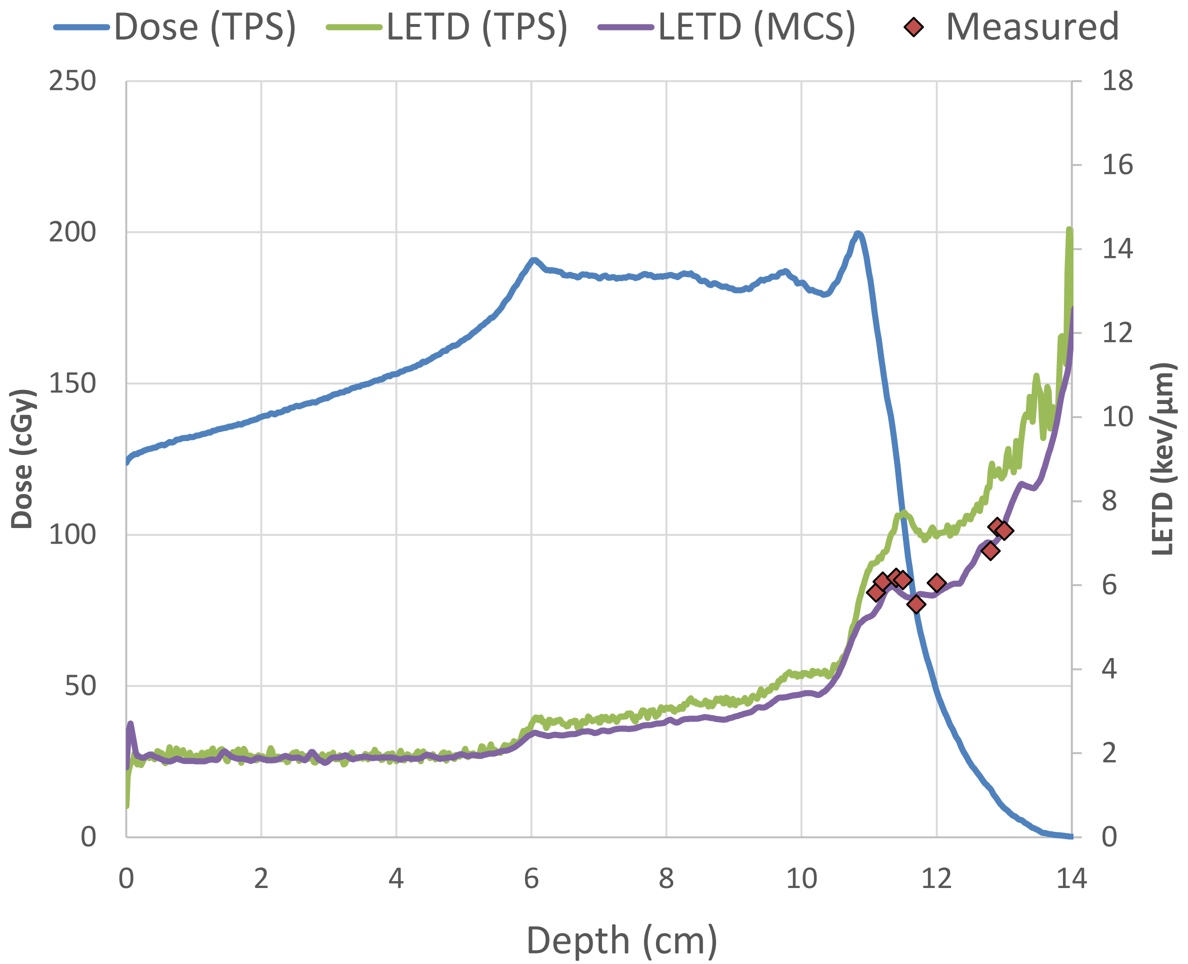
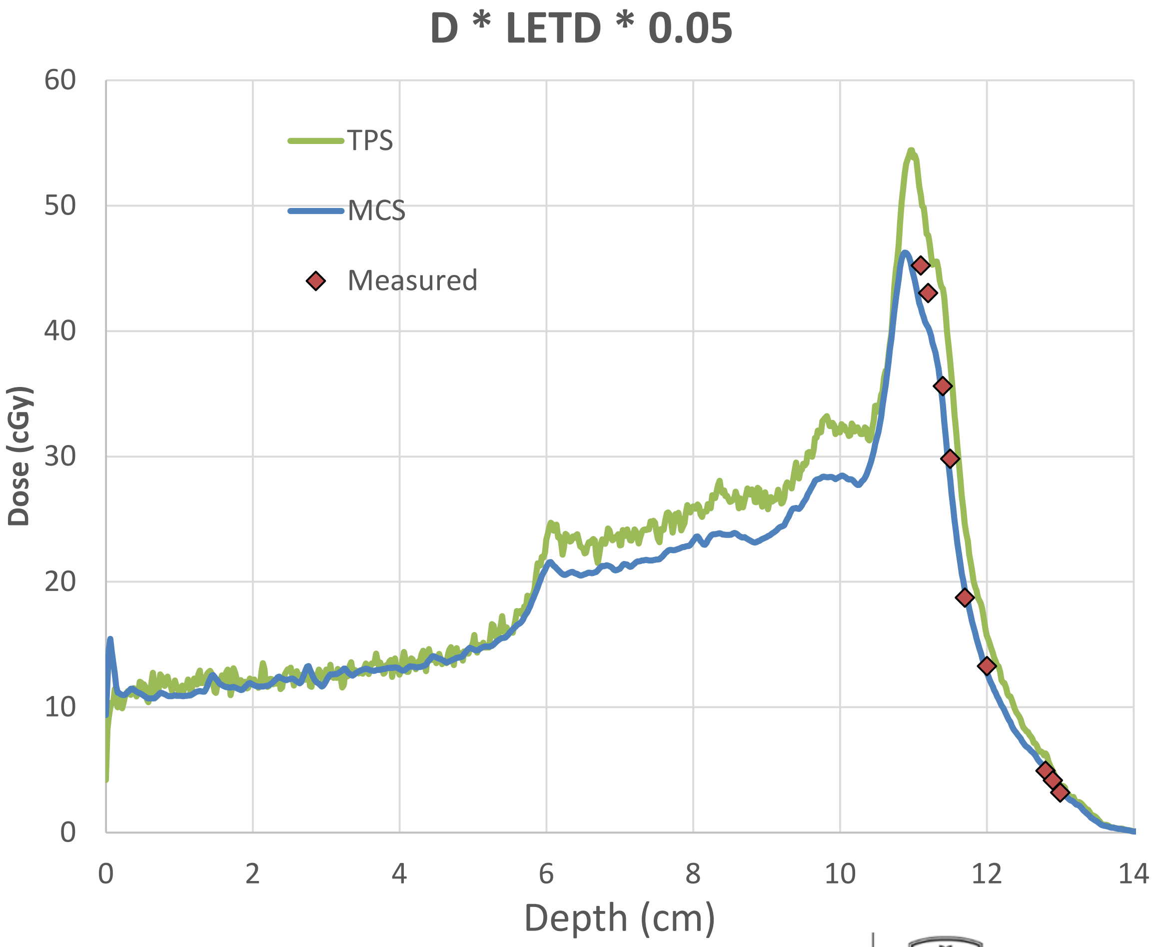
# Results: Nasopharynx plan in water

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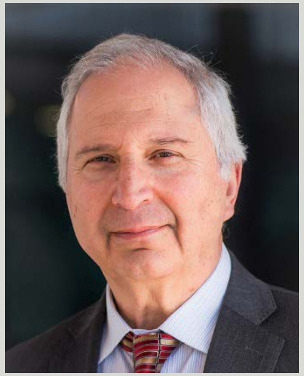
# Meet the CMRP microdosimetry team


Prof Anatoly Rozenfeld

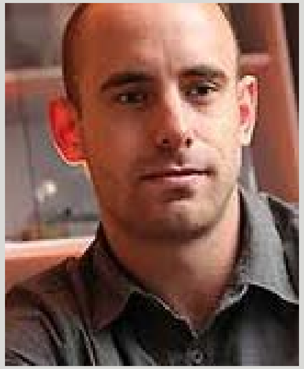

Prof Michael Lerch


A/Prof Susanna Guatelli


Dr Linh Tran


Dr Dale Prokopovich


A/Prof Marco Petasecca


Dr Jeremy Davis


Vladimir Pan


Dr David Bolst


Lachlan Chartier


Ben James


Stefania Peracchi


Dr Emily Debrot

**and PhD students:**

- James Vohradsky
- Vladimir Pan
- Fang Su

**Master student:**

- Federico Pagani

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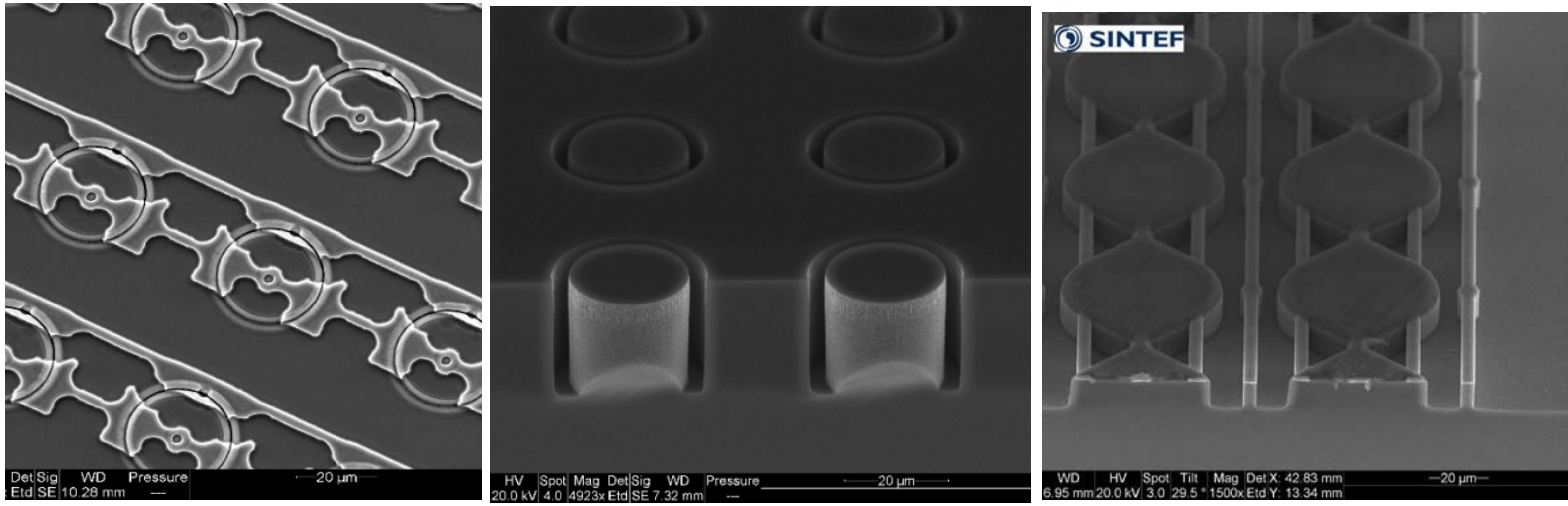
# CMRP-SINTEF business partnership

Microdosimeter sensor “Mushroom”





**CMRP:** Invention, prototyping and licencing to SINTEF
**SINTEF:** 3D detector technology and sensors fabrication
**CMRP:** Implementation to space and clinical practice
**Jointly:** ESA selected radiation sensors for space missions

IEEE NSS MIC 2018, November, Sydney

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# SOI Microdosimeter as a Gold Standard

- Zhu, Hongyu; Chen, Yizheng; Sung, Wonmo ; McNamara, Aimee; Tran, Linh; Burigo, Lucas N.; Rosenfeld, Anatoly; Li, Junli; Faddegon, Bruce; Schuemann, Jan; Paganetti, Harald *“The microdosimetric extension in TOPAS: Development and comparison with published data"* , PMB , **64**(14): 145004 , 2019 doi: 10.1088/1361-6560/ab23a3

# Conclusion

- Solid State SOI microdosimetry concept has been developed
- Optimized geometry of 3D SVs and simple conversion to tissue equivalency
- SOI microdosimeters using 3D detector technology have been fabricated
- SOI microdosimeter in mixed radiation fields is matching to TEPC
- Unique submillimetre spatial resolution in proton and heavy ion fields
- Ability of microdosimetry in a wide range of LET (0.15-50000) keV/um
- Ability operate in GCR environment and low energy ion fields
- Useful for TPS commissioning in terms of $LET_d$
- Useful for space applications: radiation shielding evaluation, personal dosimetry for astronauts and SEU prediction.

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