ncept

Delivering a one-two punch to cancer

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Australian Nuclear Science and Technology Organisation

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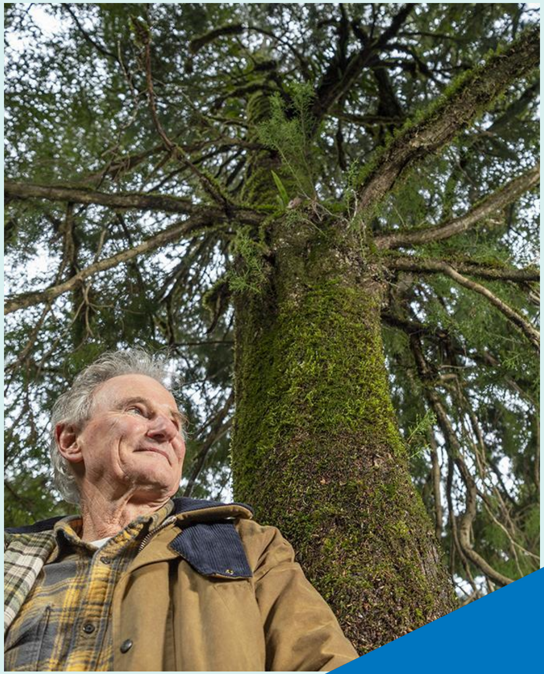

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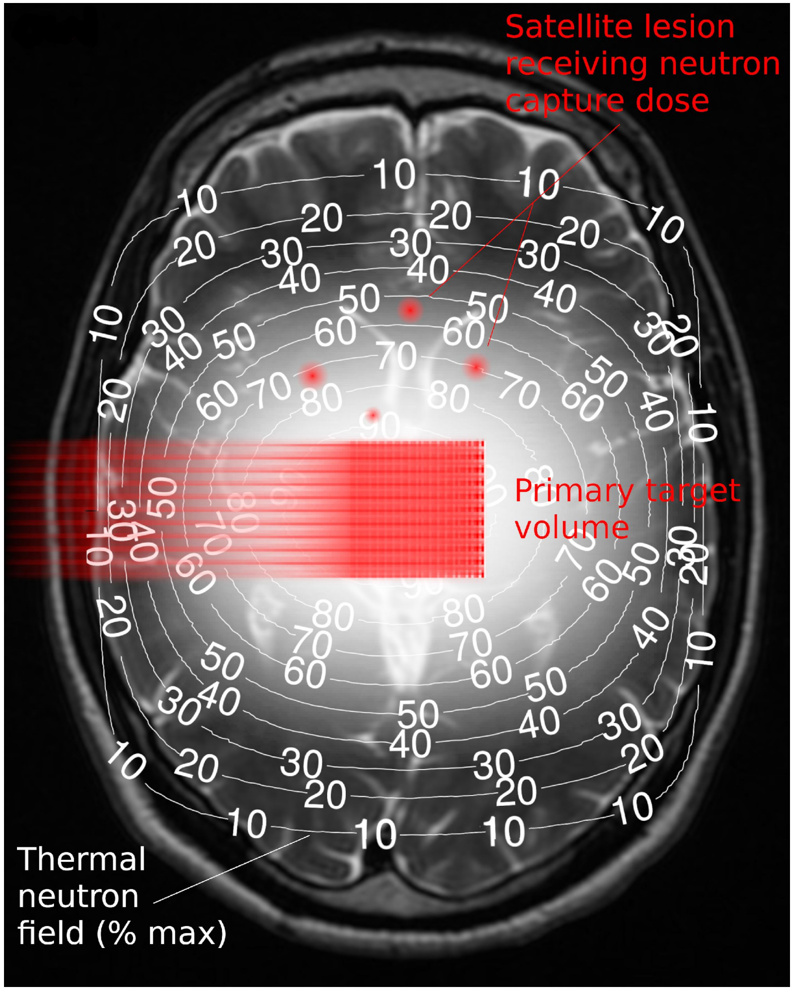
NCEPT: Scientific team

Physics:
Mitra Safavi-Naeini
Susanna Guatelli
Andrew Chacon
Keith Bambery

Biology :
Ryan Middleton
Nicholas Howell

Chemistry:
Benjamin Fraser
Naomi Wyatt

NCEPT: A novel adjunct to particle therapy



Neutron **C**apture **E**nhanced **P**article **T**herapy – a major ANSTO-led international collaboration

Captures **internally generated slow neutrons**, produced at and around the target volume to:

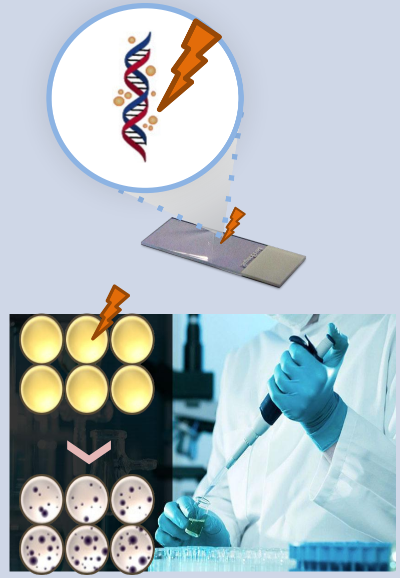
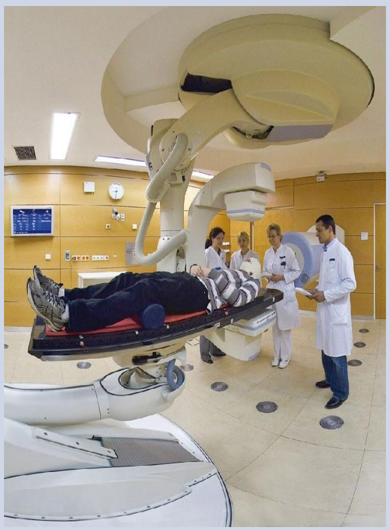
- **Enhance** the dose to **target**
- **Reduce** the dose to **normal tissue**
- **Simultaneously** target **out-of-field satellite lesions**

Leverages ^{10}B and ^{157}Gd-enriched neutron capture agents used in neutron capture therapy

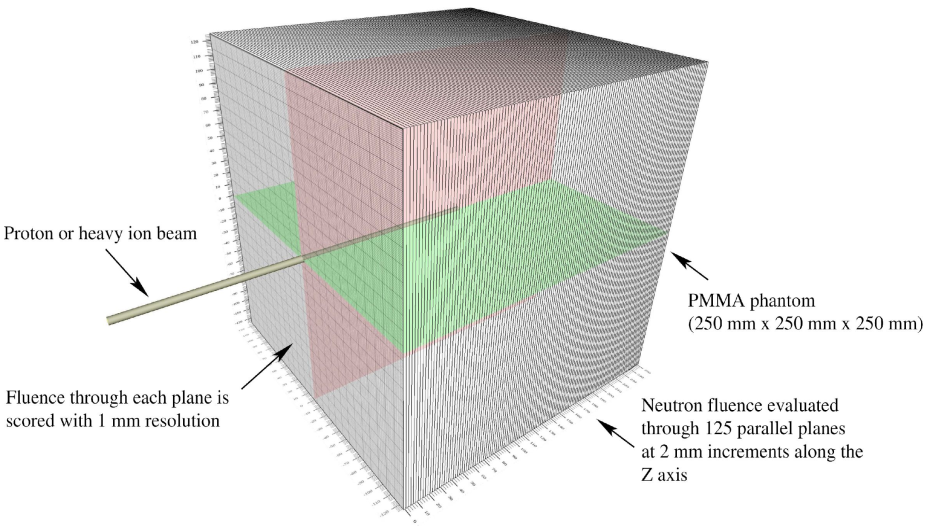
Experimental proof of concept obtained in 2018-2019 in Japan

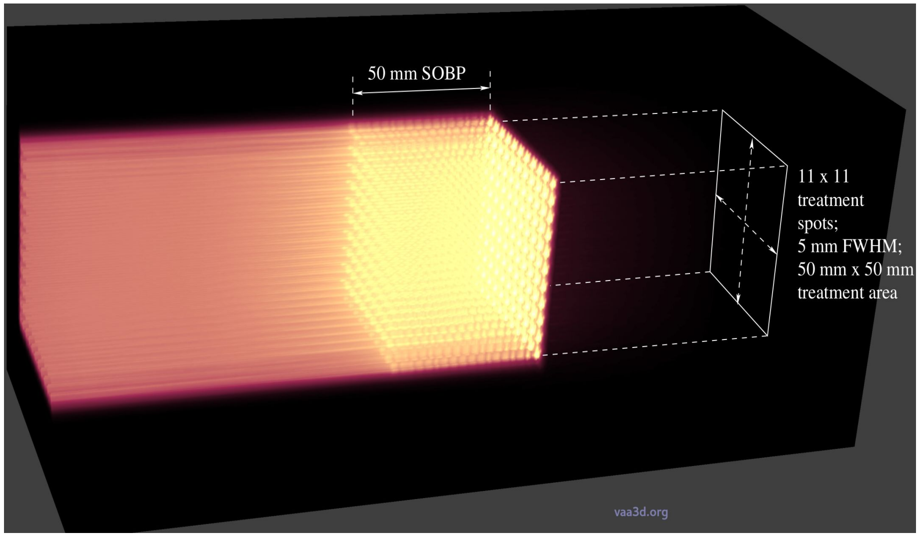
Safavi-Naeini et al., 2017 ***"An irradiation system and method"*** **WO2019051557A1**
https://patents.google.com/patent/WO2019051557A1/

The story so far

2017	2018-2019	2019-2021	End goal
			
Simulation model and proof of concept	Development of methodology and validation in vitro	Development of methodology and validation in vivo	Clinical translation, adjunct to particle therapy

Simulation campaign: why and how





- Realistic treatment plan delivered with carbon and proton beams:
  - Quantification of the neutron fluence at predefined target volumes within a phantom
  - Evaluation of ^{157}Gd and ^{10}B NCA concentrations required to achieve a 10% increase in BED

Safavi-Naeini *et al.* (2018). “Opportunistic dose amplification for proton and carbon ion therapy via capture of internally generated thermal neutrons”. In: Scientific Reports (Nov. 2018). doi: 10.1038/s41598-018-34643-w.

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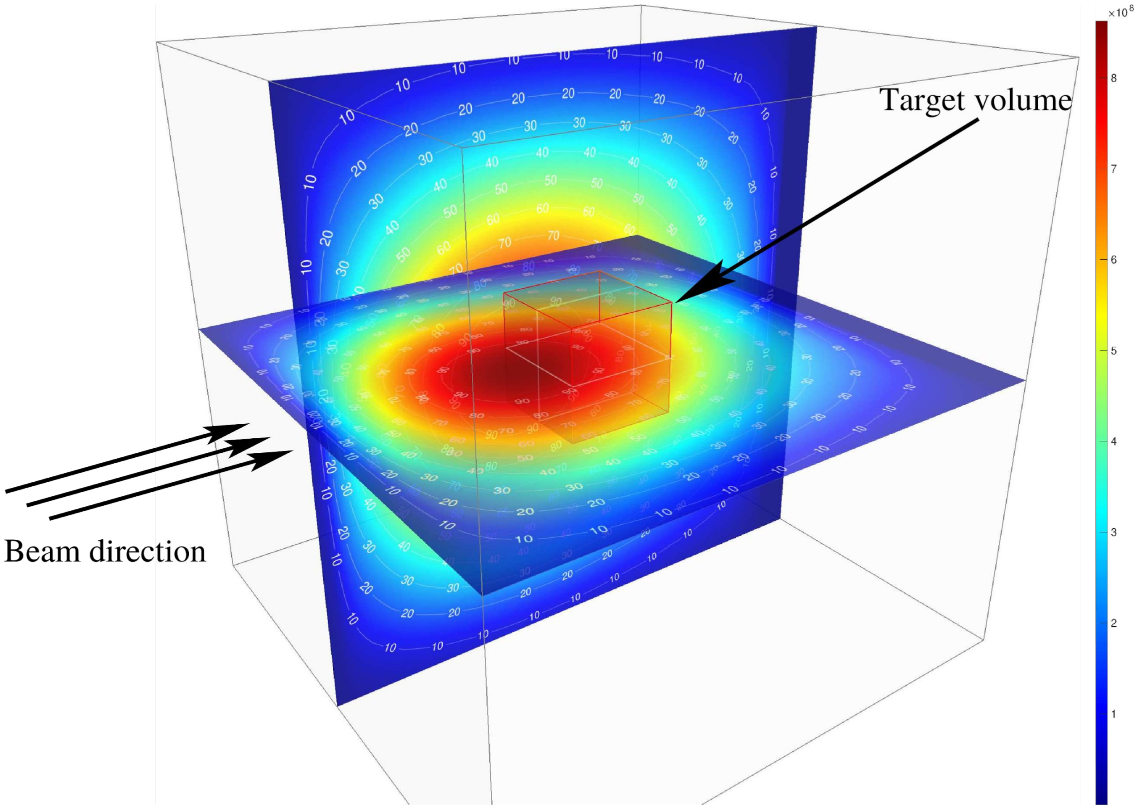
Thermal neutron fluence: proton SOBP

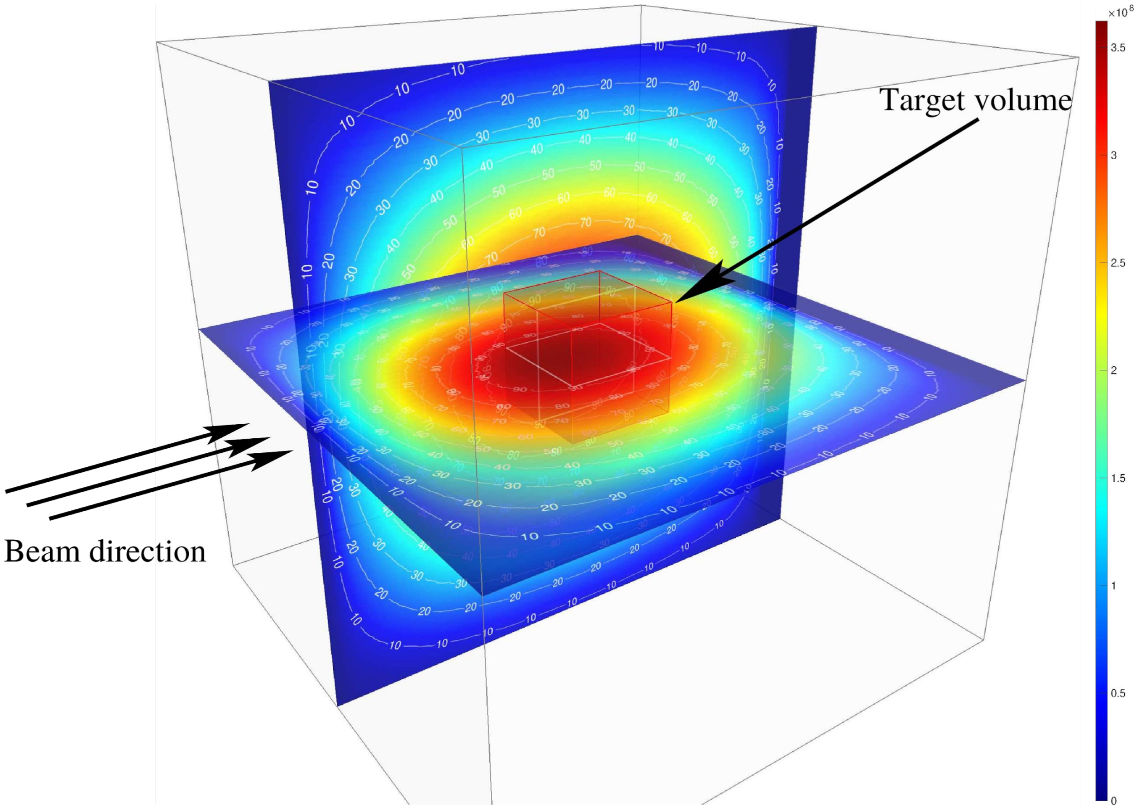


Thermal neutron fluence ($n/cm^2/Gy(RBE)$)	
Minimum	6.3×10^8
Mean	8.8×10^8
Maximum	1.1×10^9

Estimated ^{10}B-BPA required for 10% dose boost: 132 ppm (liver), 345 ppm (brain)
Estimated ^{157}Gd-TPP-DOTA required for 10% dose boost: > 616 ppm (depending on Gd distribution)

Safavi-Naeini *et al.* (2018): Scientific Reports (Nov. 2018). doi: 10.1038/s41598-018-34643-w.

Thermal neutron fluence: carbon SOBP



Thermal neutron fluence ($n/cm^2/Gy(RBE)$)	
Minimum	3.2×10^8
Mean	4.1×10^8
Maximum	4.7×10^8

Estimated ^{10}B-BPA required for 10% dose boost: 285 ppm (liver), 744 ppm (brain)
Estimated ^{157}Gd-TPP-DOTA required for 10% dose boost: > 1330 ppm (depending on Gd distribution)

Safavi-Naeini *et al.* (2018): Scientific Reports (Nov. 2018). doi: 10.1038/s41598-018-34643-w.

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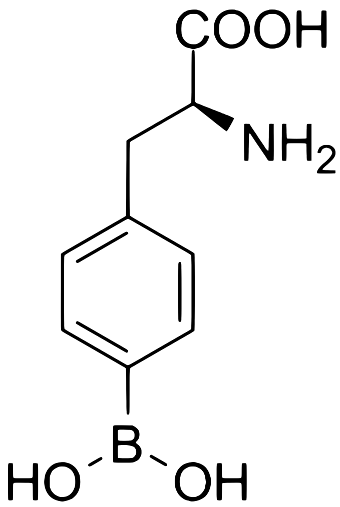
Neutron Capture Agents

^{10}B-borono-L-phenylalanene

- Thermal neutron cross-section of ^{10}B is 3838 barns
- Neutron capture results in release of damaging high-LET alpha particles and ^{7}Li nucleus:

$$^{10}B + n_{th} \rightarrow [^{11}B]^{*} \rightarrow \alpha + {^{7}Li} + \gamma \ (0.48 \ \& \ 2.31 \ MeV)$$

- BPA is preferentially absorbed by cancer cells & is **clinically approved for use in neutron capture therapy** in Japan and elsewhere

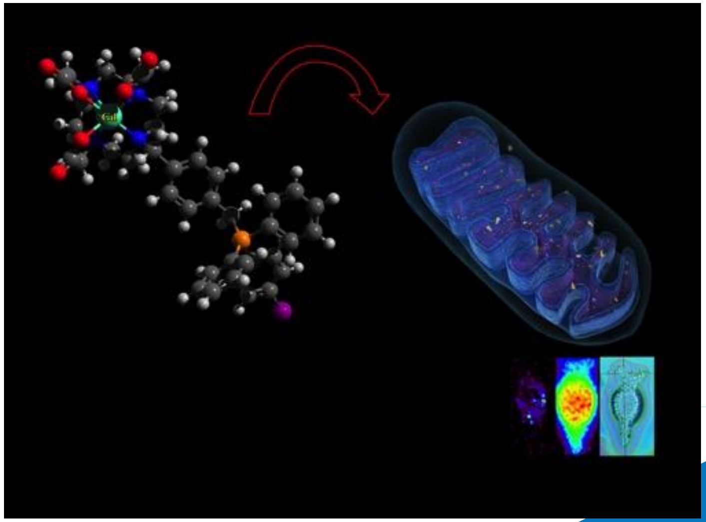


^{157}Gd-TPP-DOTA

- Thermal neutron cross-section of ^{157}Gd is ~254000 barns
- Neutron capture results in release of high-LET Auger and internal conversion electrons - highly damaging & short-range:

$$^{157}Gd + n_{th} \rightarrow [^{158}Gd]^{*} \rightarrow {^{158}Gd} + \gamma \ (7.94 \ MeV)$$

- TPP-DOTA chelates Gd and targets mitochondria membrane in cancer cells
- **Very high specific uptake**



Morisson *et al.* (2014): Chemical Communications (2014, **50**, 2252-2254). doi: 10.1039/C3CC46903D

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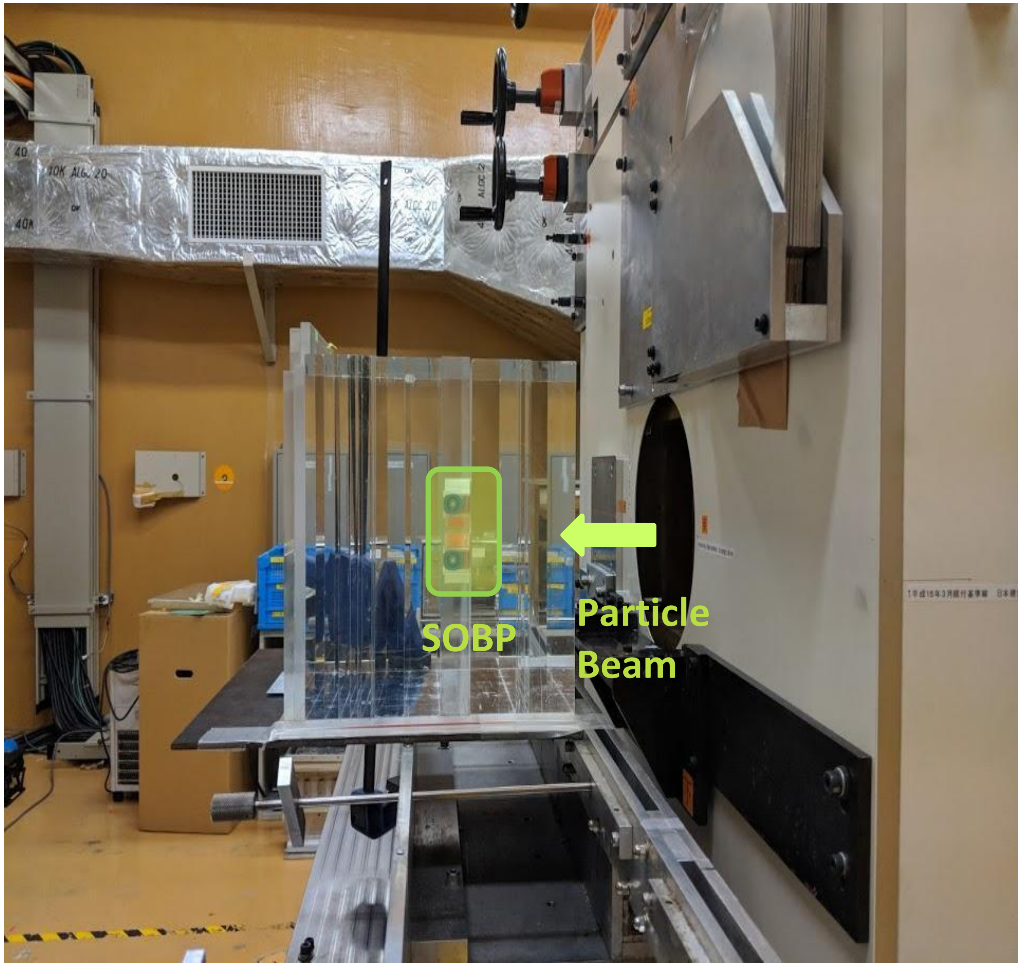
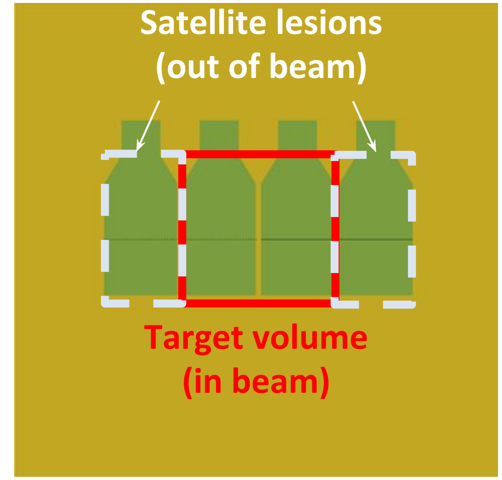
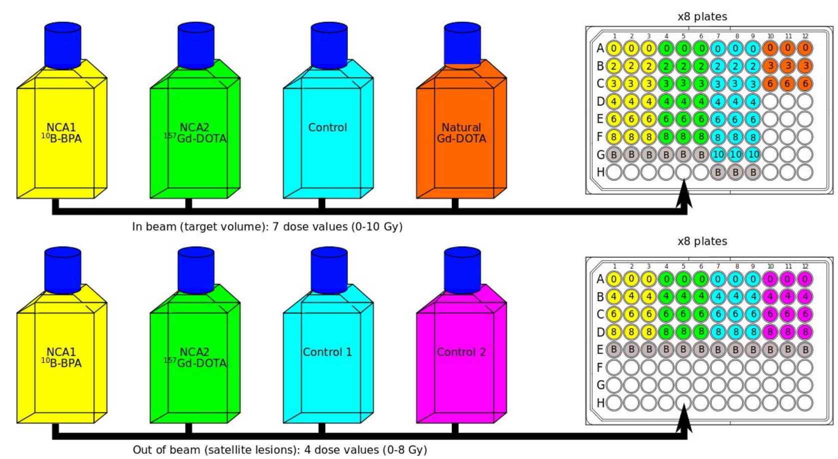
In vitro proof of concept: HIMAC

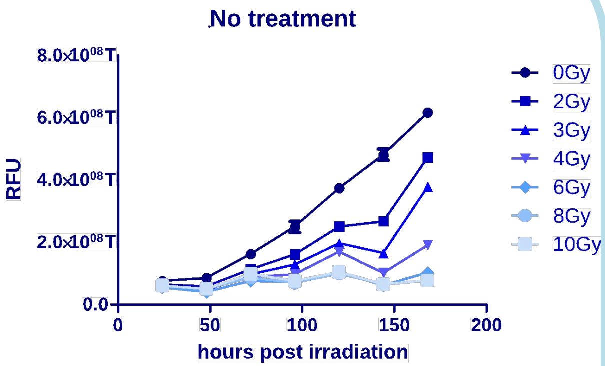




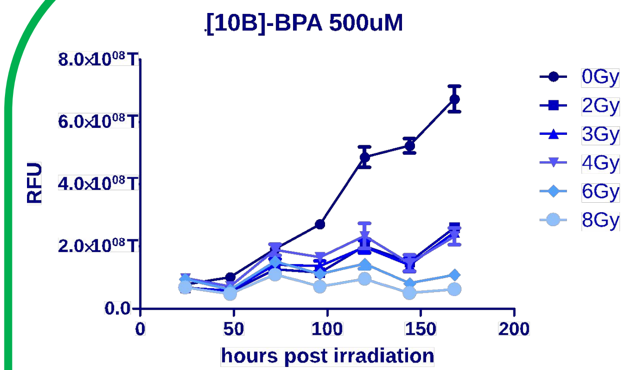


- Impact of radiation on T98G cell proliferation measured for 6 doses (0 to 10 Gy) , with and without two neutron capture drugs (NCAs):
  - ^{10}B-4-borono-L-Phenylalanine and DOTA

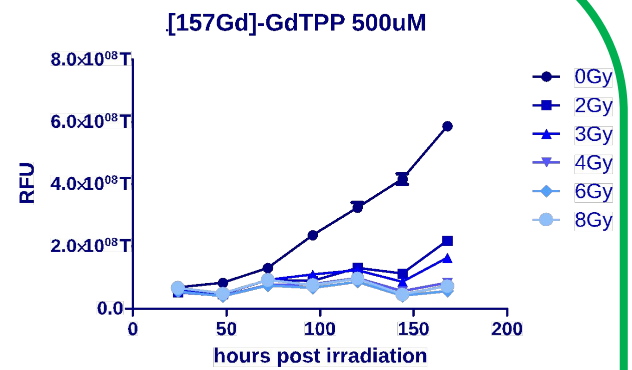
Ion therapy vs NCEPT: Dose response



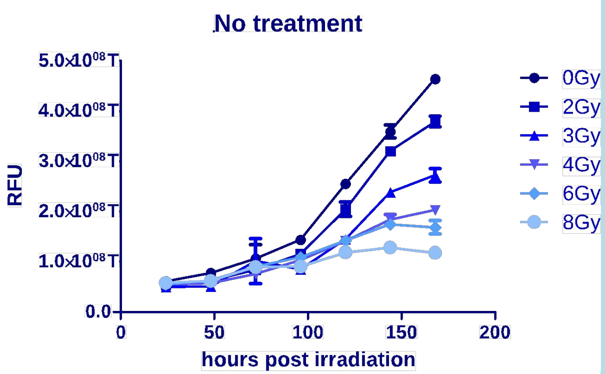
Carbon beam



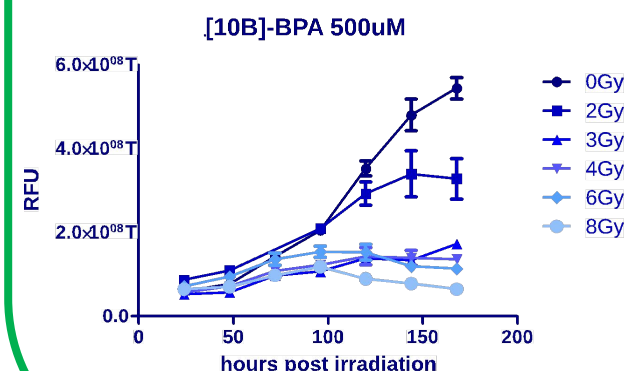
Carbon + ^{10}B-BPA



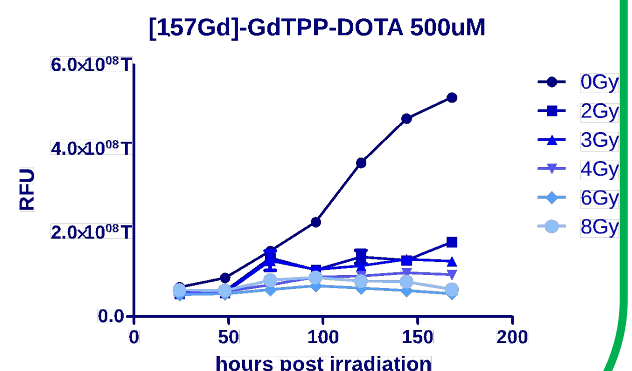
Carbon + ^{157}Gd-TPP-DOTA



Helium beam



Helium + ^{10}B-BPA



Helium + ^{157}Gd-TPP-DOTA

Ion Beam

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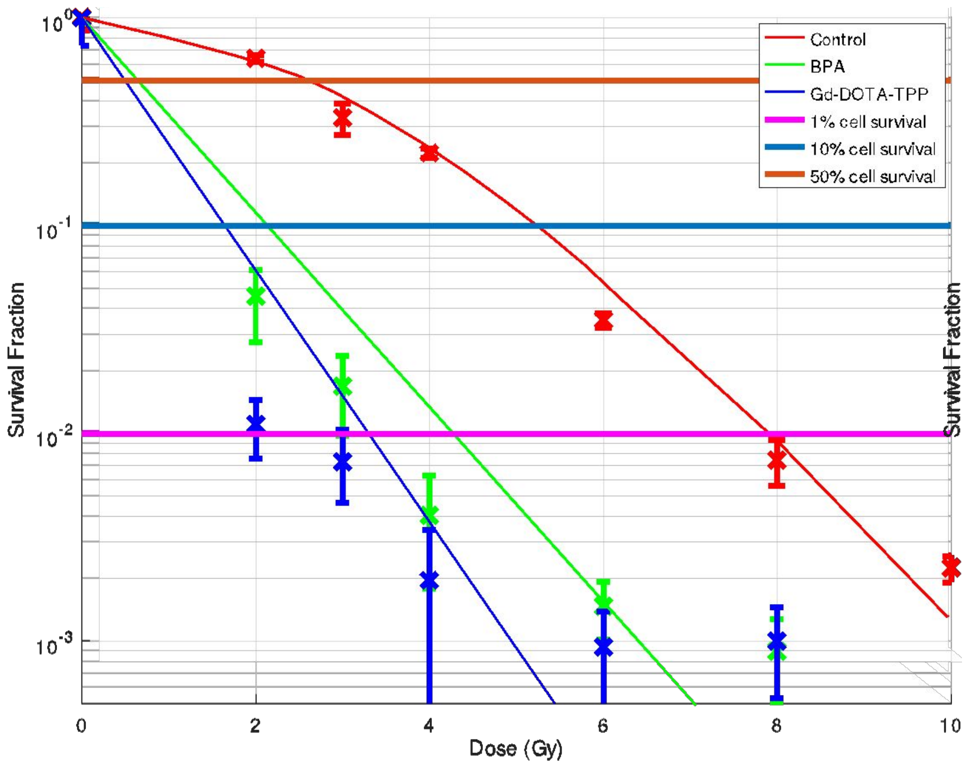
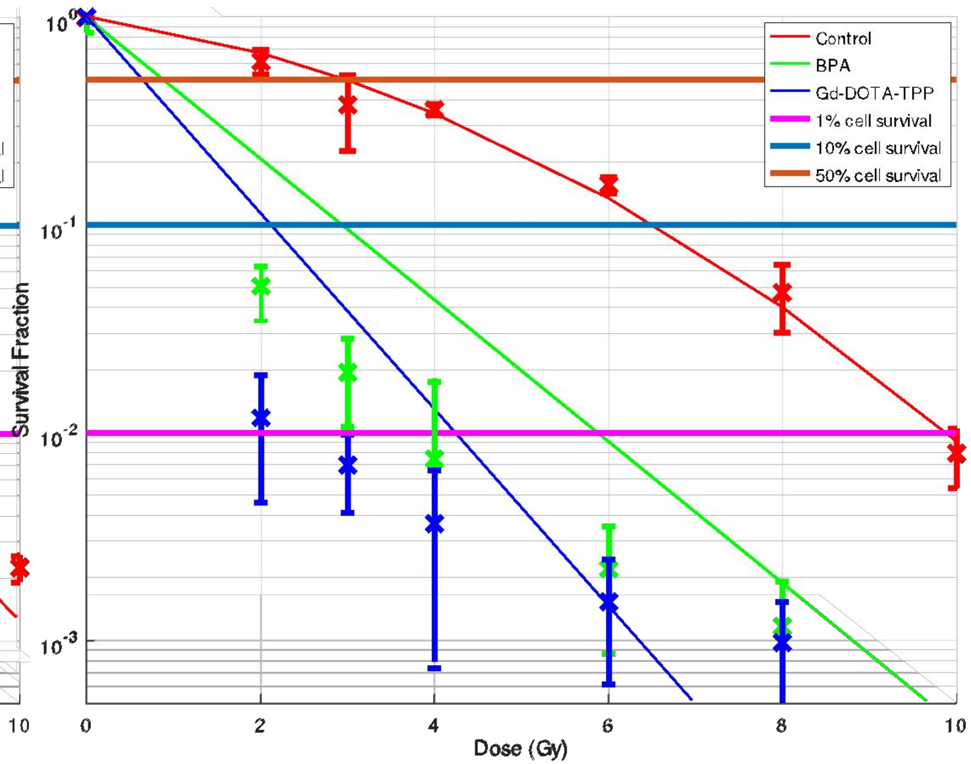
Ion therapy vs NCEPT: clonogenic assay

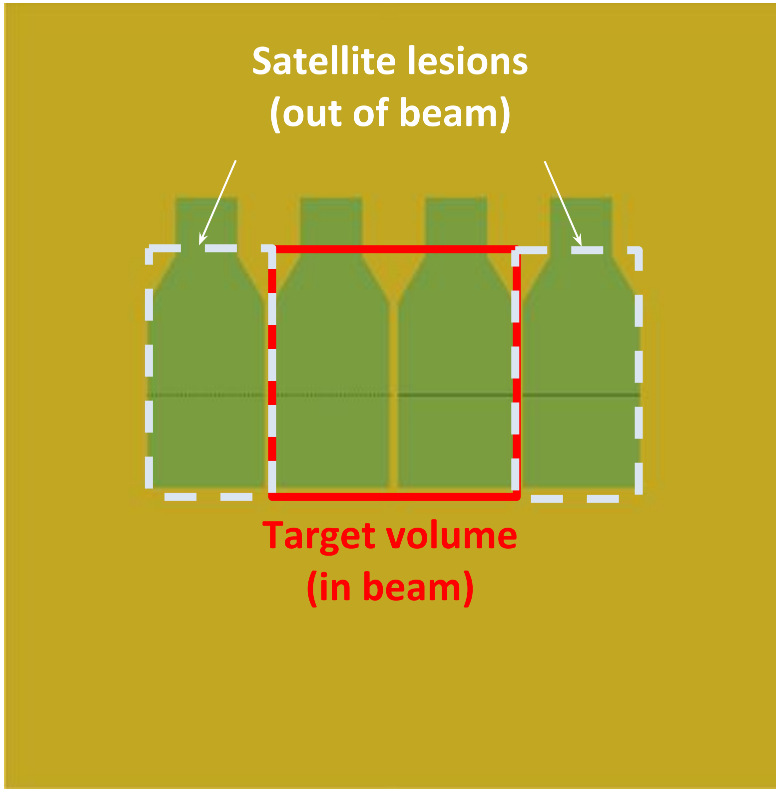


Carbon beam



Helium beam

Ion therapy vs NCEPT: IC50



In-beam IC50

	C IC50 (Gy)	He IC50 (Gy)
^{10}B-BPA	1.77 ± 0.11	2.41 ± 0.07
^{157}Gd-TPP-DOTA	0.89 ± 0.49	1.41 ± 0.13
No compound (ion beam only)	3.09 ± 0.11	3.54 ± 0.41

Out-of-beam IC50

	C IC50 (Gy to SL)	He IC50 (Gy to SL)
^{10}B-BPA	3.33 ± 0.15	3.78 ± 0.08
^{157}Gd-TPP-DOTA	3.11 ± 0.60	2.81 ± 0.10
No Compound (Ion beam only)	7.46 ± 0.44	8.81 ± 0.19

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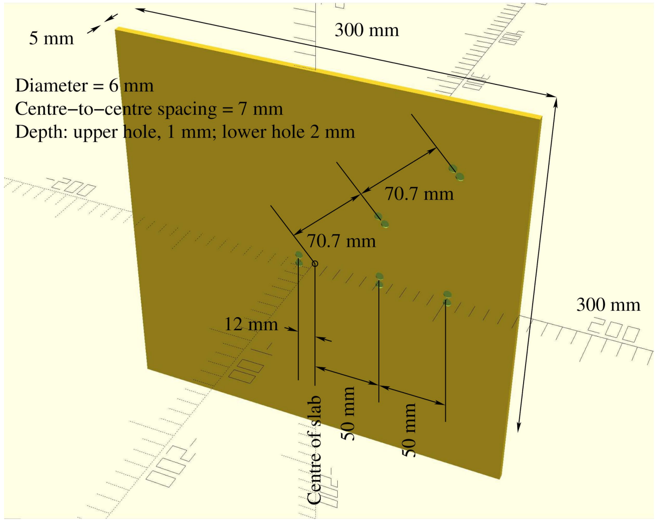
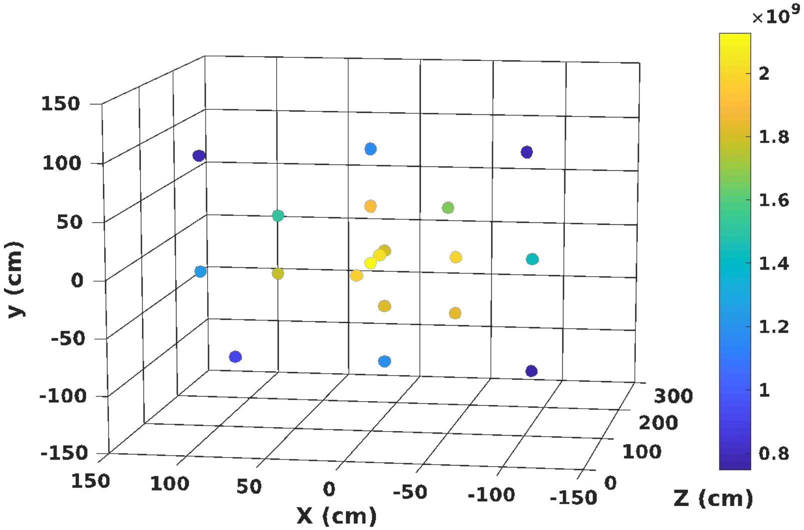
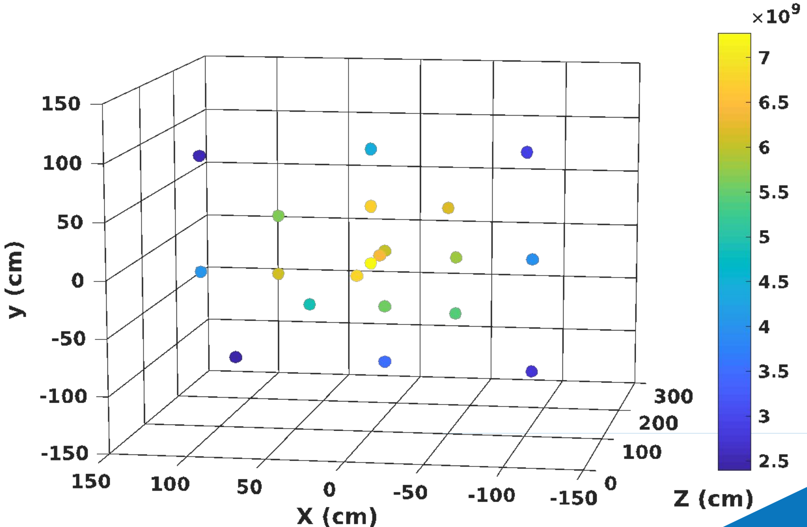
Thermal neutron quantification

- Thermal neutron fluence measured using gold activation method
- Fluence quantified by differential activation of irradiated bare and cadmium-shielded gold foils
- 5 positions evaluated at each of 4 depths, inside and outside of beam







Carbon: mean fluence @ centre of SOBP = $2.4x10^9$ n/cm^2/Gy(RBE)

Helium: mean fluence @ centre of SOBP = $6.5x10^9$ n/cm^2/Gy(RBE)

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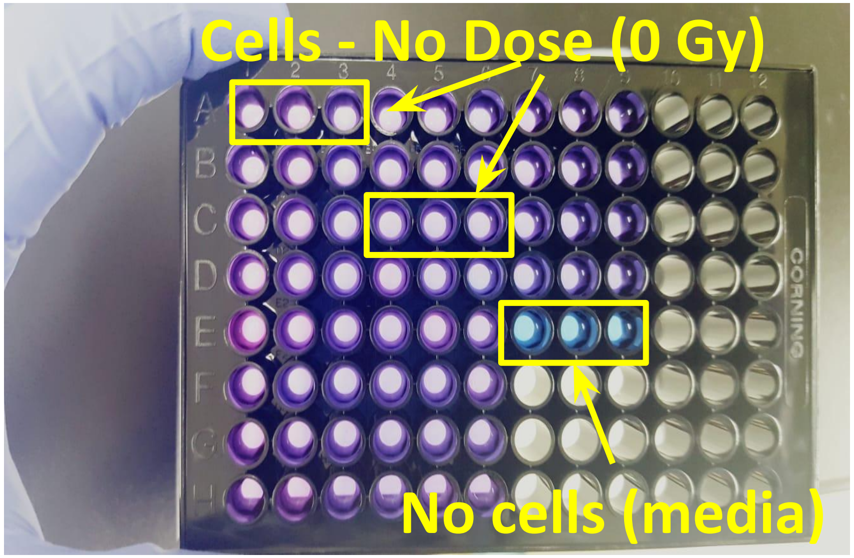
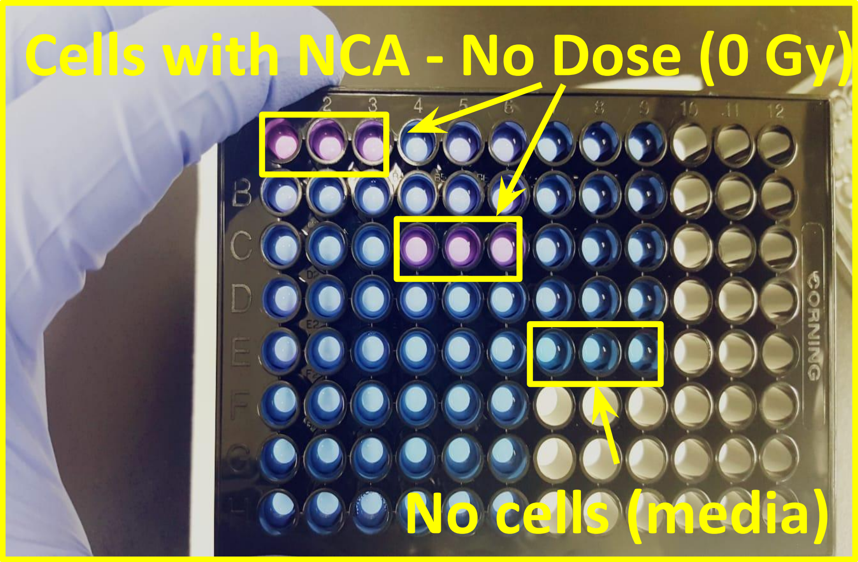
In vitro campaign outcomes





- In vitro results with carbon and helium are extremely compelling:
  - In beam: NCEPT achieves 10% survival with < 50% ion-only dose
  - Out of beam: NCEPT IC50 similar to in-beam ion-only IC50
- Measured neutron fluence 6x > magnitude compared to simulation
- Existing biophysics models (LQM/MMKM) inadequate to explain magnitude of effect

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Project plan

- **In vivo experiments with C/He** (mice) planned for 2020
  - 3 populations (control, BPA and Gd-TPP-DOTA)
  - Tumour growth delay measured in each population in response to dose escalation
- In vitro & in vivo **experiments with proton therapy** is planned for USA in 2020-2023 (+NIH grant proposal)
- In vivo **biodistribution and pharmacokinetics** of ^{157}Gd-based compounds targeting mitochondria are in progress.
- ^{10}B-BPA is clinically approved for BNCT in some jurisdictions, including Japan: **pathway for fast-tracked clinical trials**
  - Terminal head & neck secondary melanoma patients (2021)
  - ^{10}B-BPA is also reported to have high pancreatic uptake - another potential target

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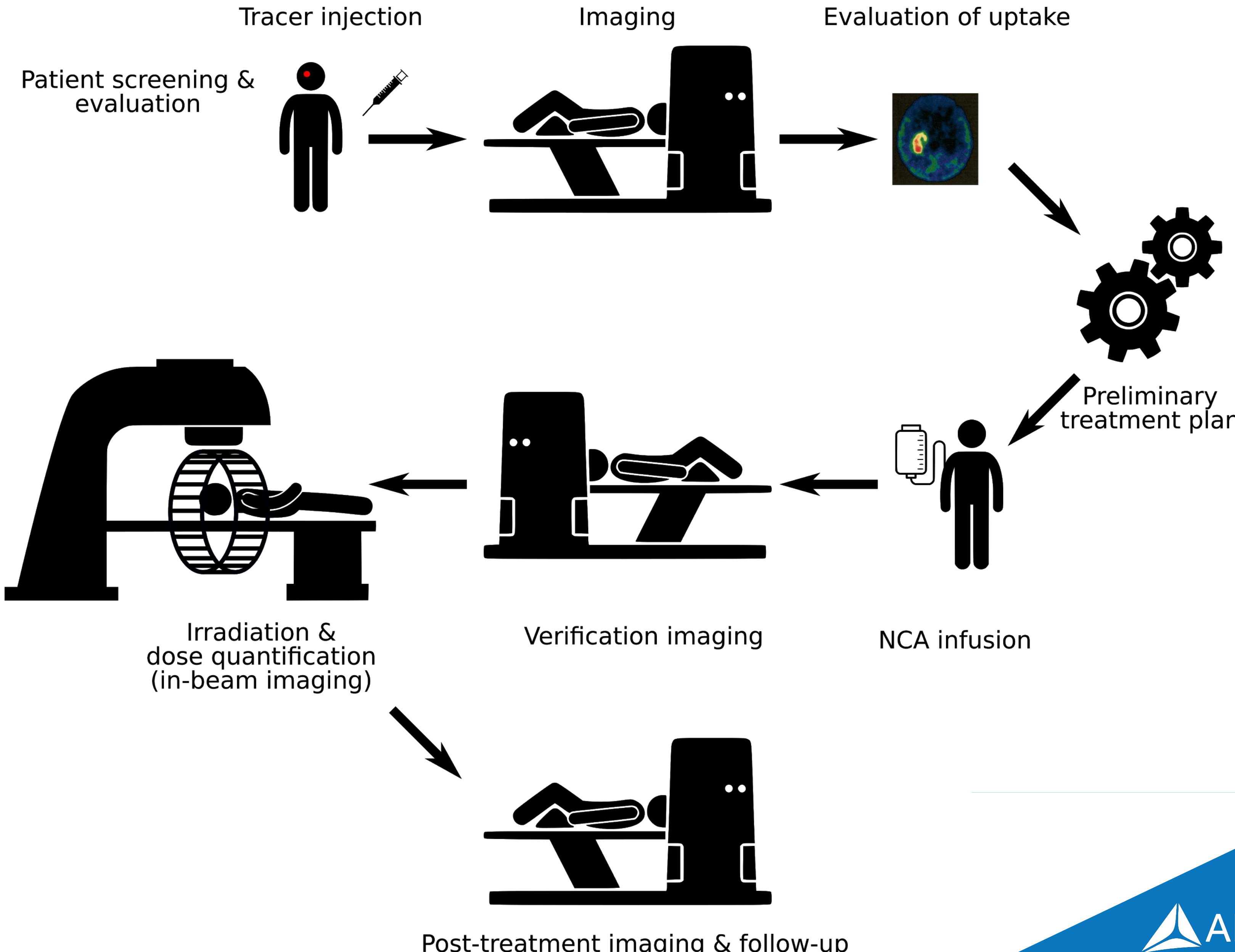
Translation



Missing pieces of the puzzle

- Treatment planning with NCEPT is complex
  - Dose now includes both **ion dose** and n**eutron capture dose**
  - **Iterative dose optimisation** is required
  - Critical need for **absolute quantification of NCA uptake** (e.g. using ^{18}F-BPA PET for ^{10}B-BPA or MRI for ^{157}Gd-TPP-DOTA)

- Opportunities for development of new theranostic agents

- Quality assurance: quantitative imaging techniques are required to verify the total deposited dose:
  - Beam on: prompt gamma (Gd) and SPECT (boron)
  - Beam off: PET (direct dose estimation from positron-emitting fragments)

- We are seeking **opportunities for collaborating with you** on these and other aspects of the project

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NCEPT Collaboration

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- **Mr. Nicholas Howell**
- **Dr. Ryan Middleton**
- **Dr. Benjamin Fraser**
- **Dr. Naomi Wyatt**
- **Dr. Keith Bambery**
- **Dr. Justin Davies**
- **Dr. Ulf Garbe**
- **Dr. Joseph Bevitt**
- **Mr. Attila Stopic**
- **Dr. Timothy Boyle**
- **Ms Shakila Fernando**
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- Mr. Harley Rutherford
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- A/Prof. Susanna Guatelli
- Dist. Prof. Anatoly Rosenfeld

University of Sydney

- **Prof. Louis Rendina**

Westmead Hospital

- Dr Alison Salkeld
- A/Prof. Verity Ahern

Prince of Wales Hospital

- Prof. Michael Jackson

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- Dr Ryoichi Hiryama
- Dr Akram Mohammadi
- Prof. Masashi Koto
- Prof. Shigeru Yamada
- Prof. Hiroshi Tsuji

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- Dr Zuofeng Li
- Prof. Nancy Mendenhall

Loma Linda University, US

- Prof. Reinhard Schulte

Northern Illinois University, US

- A/Prof. Linda Yasui

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