Presentation 8 – Session 3

Neutron Capture Enhanced Particle Therapy: A new frontier in hadron therapy

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Australian Centre for Neutron Scattering

Biography

Mitra-Safavi-Naeini is a research leader at the Australian Nuclear Science and Technology Organisation (ANSTO). She has a PhD in Medical Radiation Physics from the University of Wollongong, and a BE in Electrical Engineering from the University of Toronto. Her research activities span two main areas: medical imaging quantification (with a specific focus on PET) and radiotherapy (brachytherapy, hadron and heavy ion therapy, and synchrotron microbeam radiotherapy). Her current research also includes several projects which span both of these fields.

In the field of medical imaging, her research activities include the design and development of novel imaging instrumentation (advanced solid-state PET systems featuring ultra high resolution, depth of interaction and high performance scintillation materials coupled to highly pixelated silicon detectors the use of multi-modal molecular imaging tools (PET/MR and PET/CT) for elucidation of biological pathways in rodents, and the development and application of new algorithms for 3D and 4D image reconstruction, aimed at both improving the speed of image reconstruction and maximising image quality to achieve precise and automatic quantification of physical and physiological parameters of interest in research, preclinical and clinical settings.

In radiotherapy, She has performed extensive research and development on quality assurance systems for low and high dose rate prostate brachytherapy based on an in-body pinhole camera imaging system, and research into the biological processes involved in synchrotron microbeam radiotherapy applied in-vitro to cultured gliosarcoma and kidney epithelial cells. More recently, her research has focused on proton and heavy ion therapy - developing algorithms to estimate the delivered dose distribution based on intra- and immediate post-treatment 4D PET imaging of the target volume, quantitative evaluation of a range of Monte Carlo physics simulation models compared to experimental measurements, and most recently, exploitation of the thermal neutron field generated within the treatment volume as a result of proton or heavy ion radiotherapy for an additional dose boost via boron and/or gadolinium-based neutron capture.

Experiments related to the latter research topic (for which a provisional patent has been filed and one research paper presenting our simulation results is currently in preparation) are the focus of her presentation.

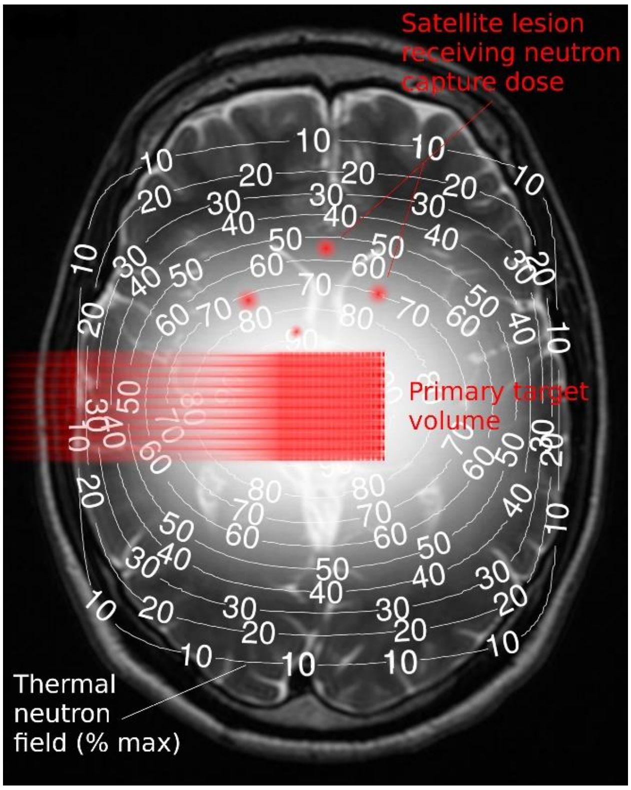
Her primary research goal is to achieve a meaningful improvement in outcomes for patients treated with heavy ion and proton therapy, both through PET image-based quality assurance and improved utilisation of the radiation dose for therapeutic effect. She has a strong track record in research and development in medical radiation physics and engineering, and is supported by a strong multidisciplinary team with the right set of skills to confirm the recent simulation results via preclinical studies, and ultimately move to clinical translation.

ABSTRACT

Neutron Capture Enhanced Particle Therapy (NCEPT) is a radical new paradigm in radiotherapy being developed by an international team led by ANSTO. NCEPT combines the precision of particle therapy with the cancer-specific targeting capability of neutron capture therapy (NCT).

NCEPT magnifies the impact of particle therapy by capturing neutrons - produced internally at the target as a by-product of treatment - inside cancer cells, where they deliver extra dose to the tumour (Fig. 1). NCEPT uses low-toxicity agents containing boron-10 and gadolinium-157 which concentrate in cancer cells, already approved or under development for other medical applications.

Simulations and experiments on cancer cells have yielded extremely compelling results, indicating that NCEPT achieves equivalent cancer cell control with between ⅓ and ⅕ of the radiation dose compared to particle therapy alone. NCEPT has generated considerable excitement within the radiation oncology communities in Australia, USA, and in particular in Japan, where it has been dubbed “the future of ion-beam radiotherapy”. Initial discussions regarding the first clinical trials in Japan are currently in progress.



Conformal delivery of planned radiation dose to the primary target volume with particle beam (red); the resulting thermal neutron field (white) is utilised to (1) enhance the dose at target and (2) deliver a comparable dose to satellite lesions vvia targeted delivery of a neutron capture agent.

ncept

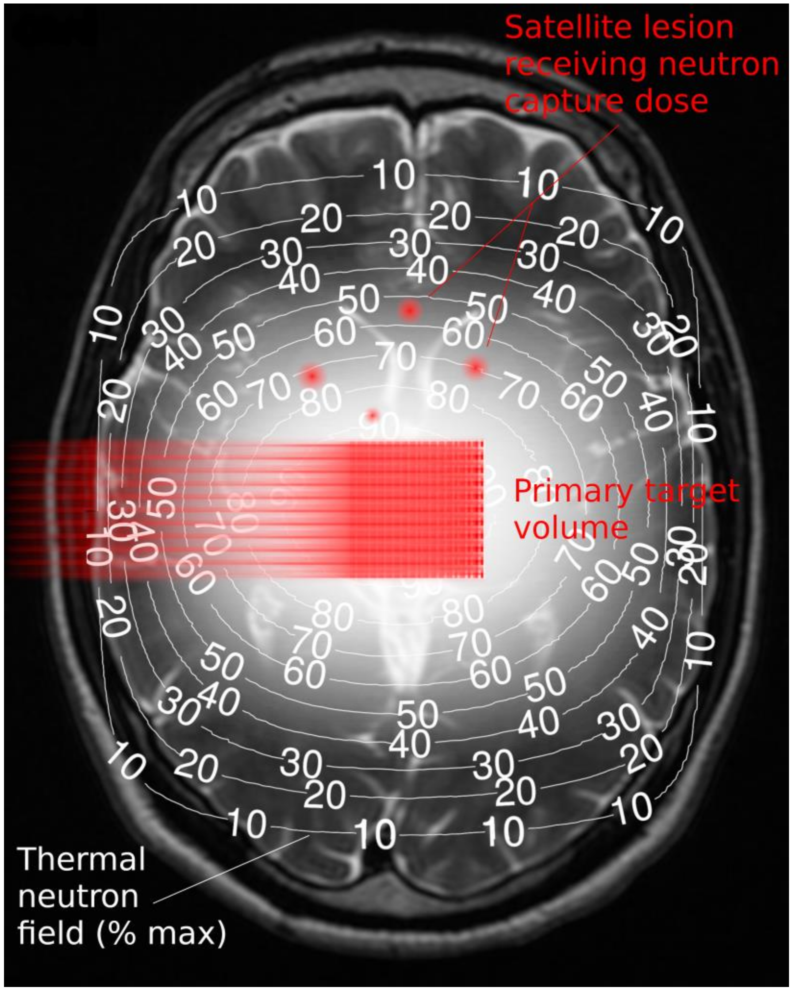
Delivering a one-two punch to cancer

Dr Mitra Safavi-Naeini
Australian Nuclear Science and Technology Organisation

September 2019

ANSTO

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 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/

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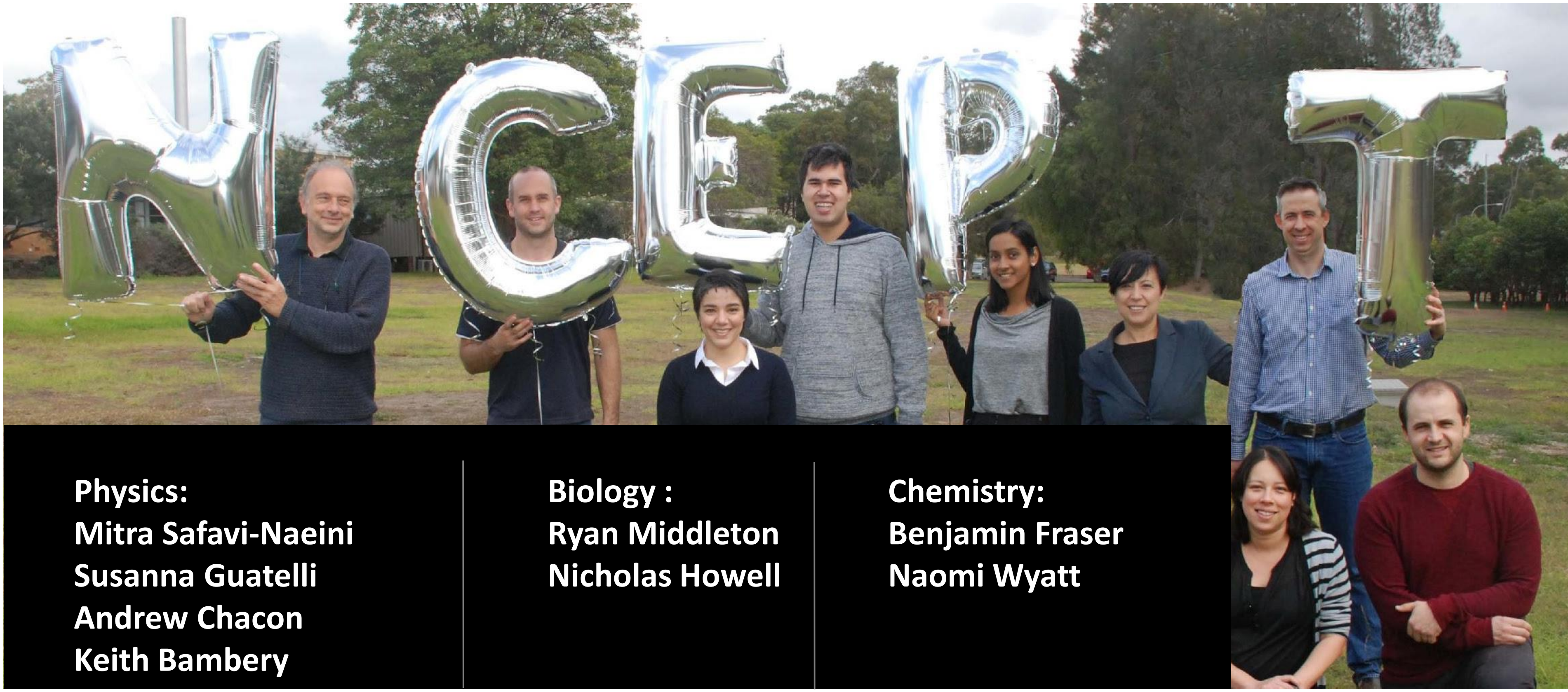
NCEPT: Scientific team

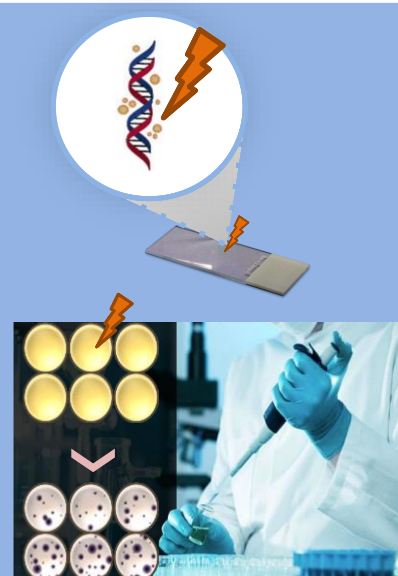


Physics:
Mitra Safavi-Naeini
Susanna Guatelli
Andrew Chacon
Keith Bambery

Biology :
Ryan Middleton
Nicholas Howell

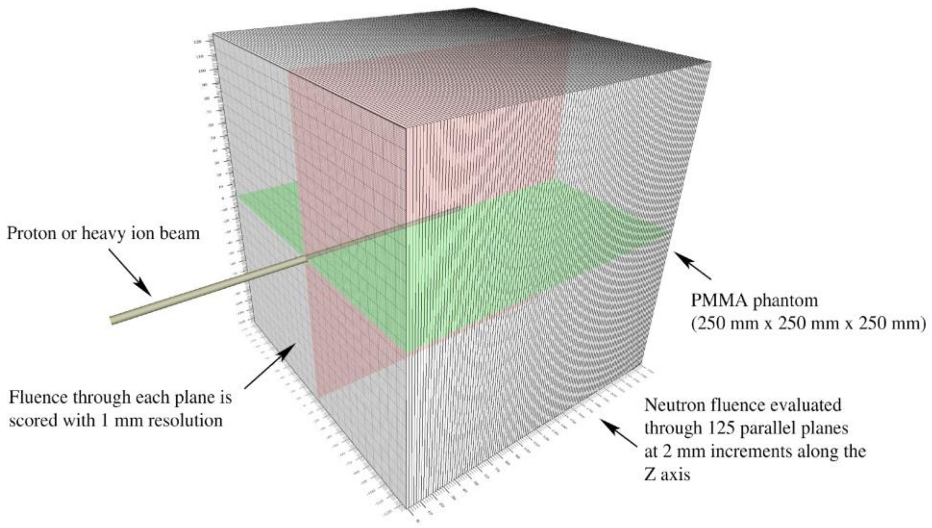
Chemistry:
Benjamin Fraser
Naomi Wyatt

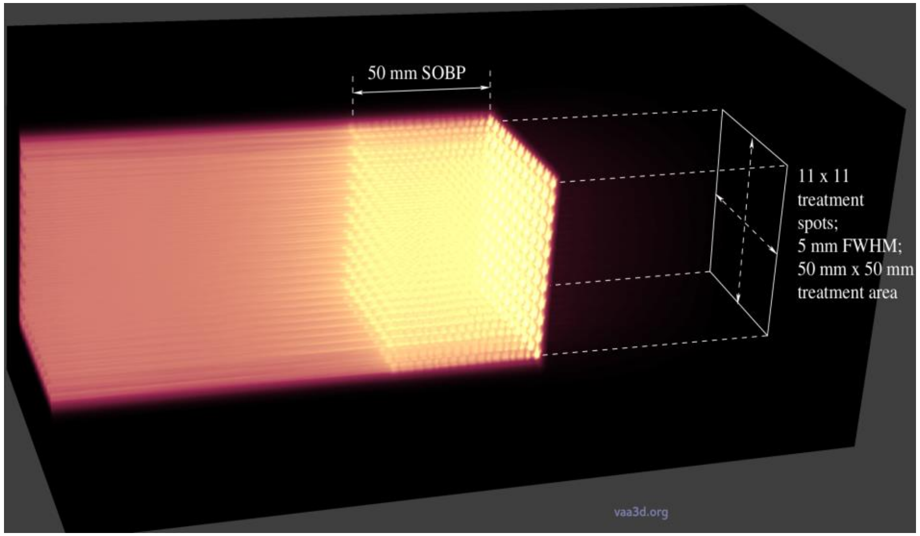
The story so far

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

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.

Simulation campaign: why and how

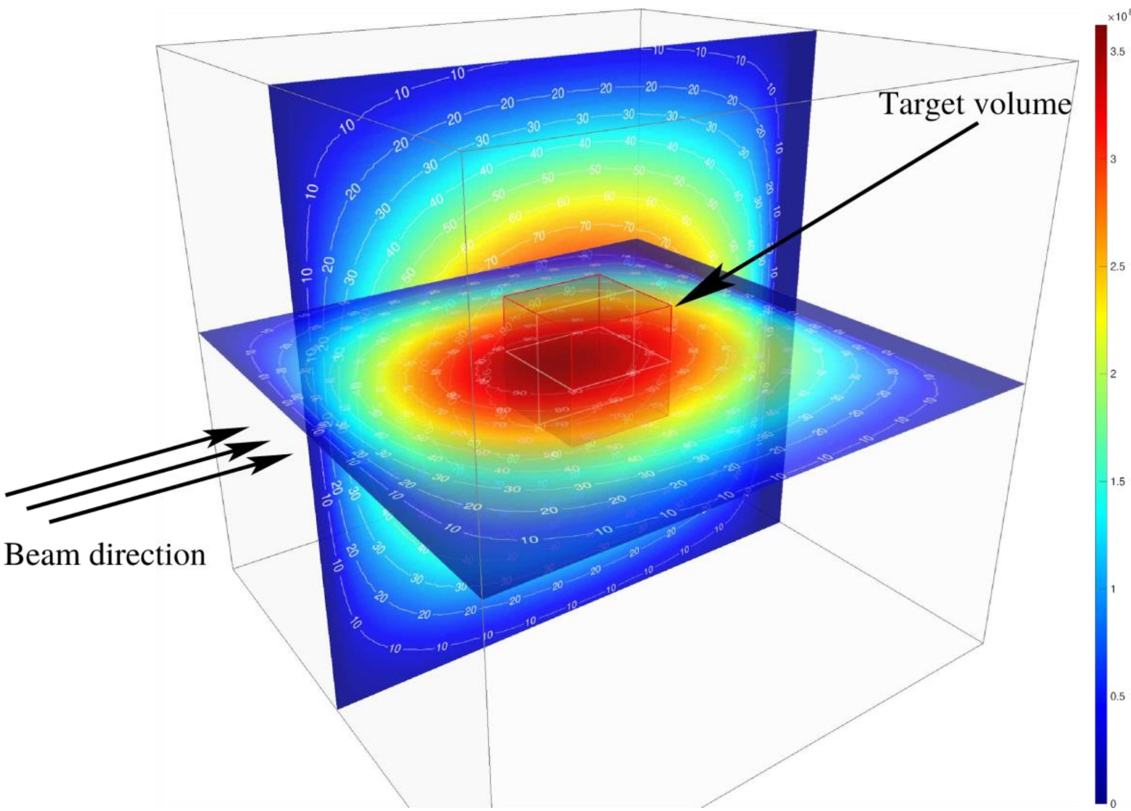




- Realistic treatment plan delivered with carbon and proton beams:
  - Quantification of the neutron fluence at predefined target volumes within a phantom
  - Evaluation of ^{157}Gd and ^{10}B NCA concentrations required to achieve a 10% increase in BED

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.

Thermal neutron fluence: carbon 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.

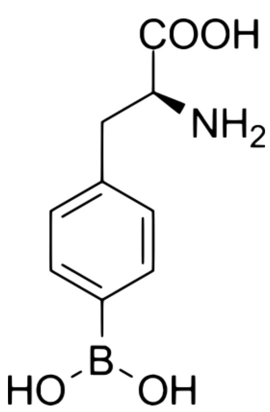
Neutron Capture Agents

^{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

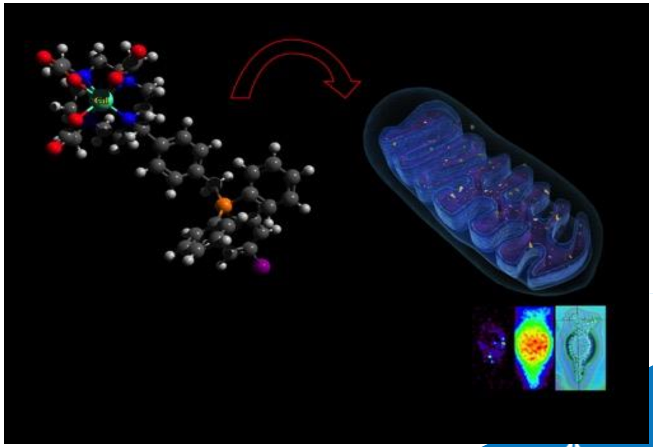


^{157}Gd-TPP-DOTA

- 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:

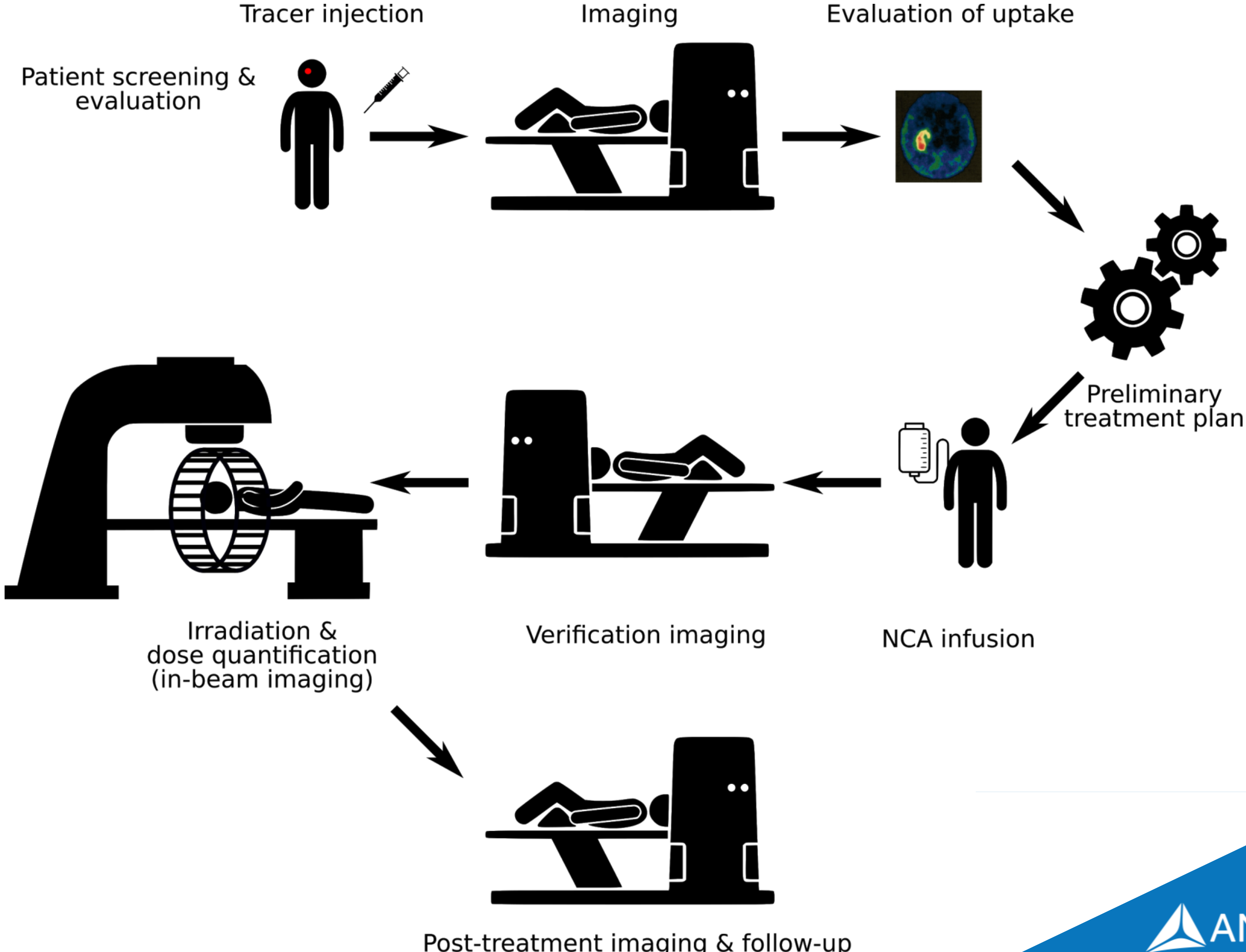
$$^{157}Gd + n_{th} \rightarrow [^{158}Gd]^{*} \rightarrow {}^{158}Gd + \gamma \ (7.94 \ MeV)$$

- 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

Translation



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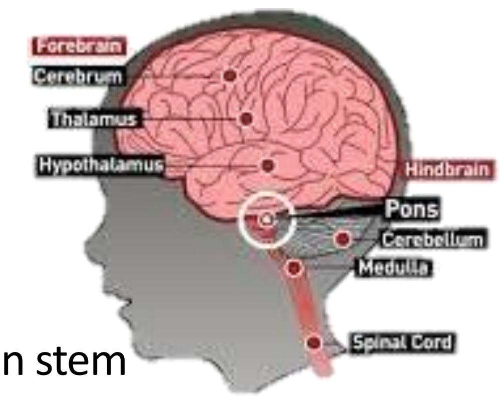
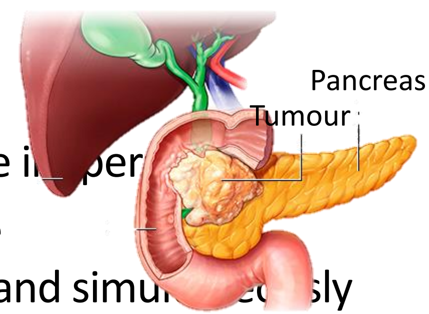
Expected impact

- Diffused intrinsic pontine glioma
  - Attacks 5-9 yr old children
  - Kills 99% of child patients (median survival of 9 months)
  - Malignant cells entwine with healthy cells in brainstem (inoperable)
  - Radiation therapy and chemotherapy don't work
  - NCEPT can provide cellular selectivity, at no cost to the brain stem



- Unresectable pancreatic cancer
  - Vague symptoms (late presenting)
  - Kills 95% of patients within 5 years
  - More frequent in obese patients
  - Second biggest cause of cancer deaths within the next decade
  - 75% of patients are i per
  - NCEPT can provide cellular selectivity and simu sly treat metastatic micro and macro lesions



Expected impact

Ministers
Department of Health

Home | Media centre | The Hon Greg Hunt MP | Senator the Hon Richard Colbeck | The Hon Mark Coulton

Ministers › The Hon Greg Hunt MP › Minister Hunt's media

Inaugural Childhood Brain Cancer Awareness Day

The Morrison Government has launched the annual Childhood Brain Cancer Awareness Day, along with an additional $7 million in research funding, to help support children and their families living with the devastating disease.

The Hon Greg Hunt MP
Minister for Health

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Audience: General public

The Morrison Government has launched the annual Childhood Brain Cancer Awareness Day,

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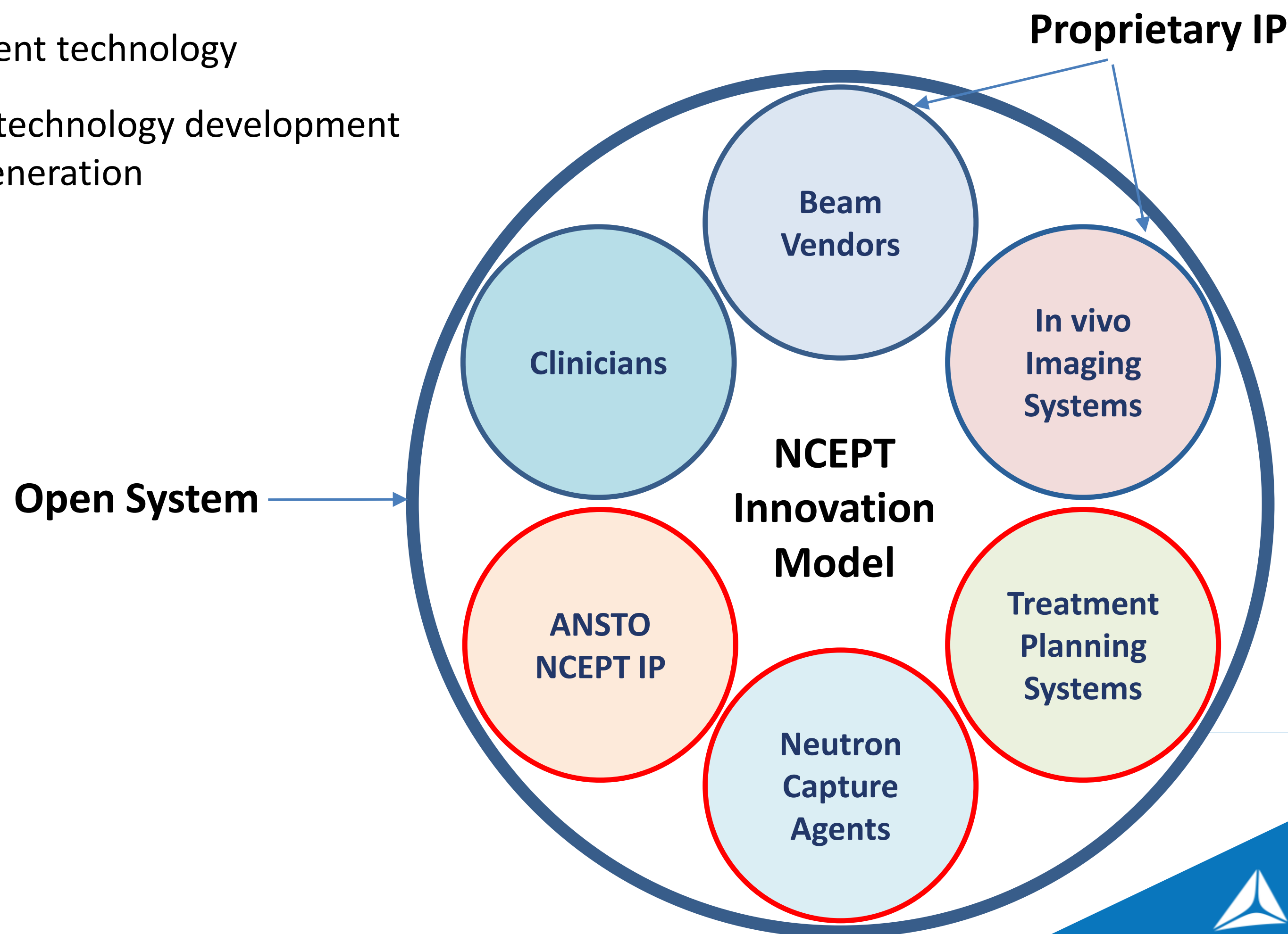
Innovation Model

Proprietary technology in NCEPT open ecosystem

- Uses current technology
- Requires technology development
  New IP generation



NCEPT Collaboration

ANSTO

- **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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University of Wollongong

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- Mr. Harley Rutherford
- A/Prof. Anthony Dosseto
- 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

National Institute of Radiological and Quantum Science (NIRS-QST), JP

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

UF Health Proton Therapy Institute, US

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Loma Linda University, US

- Prof. Reinhard Schulte

Northern Illinois University, US

- A/Prof. Linda Yasui

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