Out-of-field Radiation Risks in Paediatric Proton Therapy

Charlot Vandevoorde
NRF iThemba LABS
Contact: cvandevoorde@tlabs.ac.za

Seventh NCS Lustrum – Proton Therapy
Amsterdam
27 October 2017

NRF-iThemba LABS: A national research facility in South Africa

30 years of operations with the Separated Sector Cyclotron (SSC)

Collaboration network with South African universities, institutions and international partners

P(66)/Be neutron therapy unit (29 MeV neutrons): routine treatment started in 1989

Passive double scattering proton therapy (PPT) unit (200 MeV protons): routine treatment started in 1993

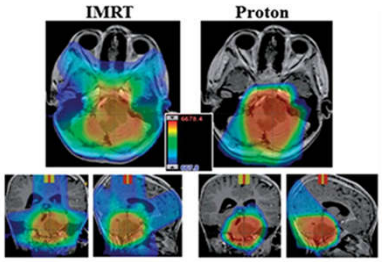
Introduction: Clinical advantage of proton therapy (PT) for childhood cancer

Clinical Rationale for PT: Inverted depth dose profile

- Maximum dose at tumour location
- Sparing of surrounding normal tissue

Integral dose is a factor of 2-3 lower for protons compared to photons

- Impact on secondary cancer induction



Levin et al – Br J Cancer 2005

Children: Higher radiosensitivity and longer life expectancy, resulting in a 2-3 times higher risk for radiation-induced solid tumours and 3-5 times higher risk for radiation-induced leukaemia (UNSCEAR report 2013)
The sparing of normal tissues and the reduction of integral dose makes PT the preferred irradiation technique for treating childhood cancer

Introduction: Stray radiation produced in PT

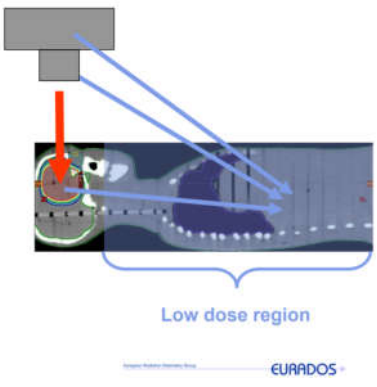
Dose outside the target volume?

- X-ray based RT (incl. IMRT): predominantly photons scattered in linac head and in patient, but when the energy is high enough neutrons are produced due to photonuclear interactions (above 8-10 MeV)
- PT: primary protons and secondary particles, most importantly neutrons, are inevitably produced through nuclear inelastic reactions with components of the beam line and in patients' body

Two beam modulation techniques in PT:

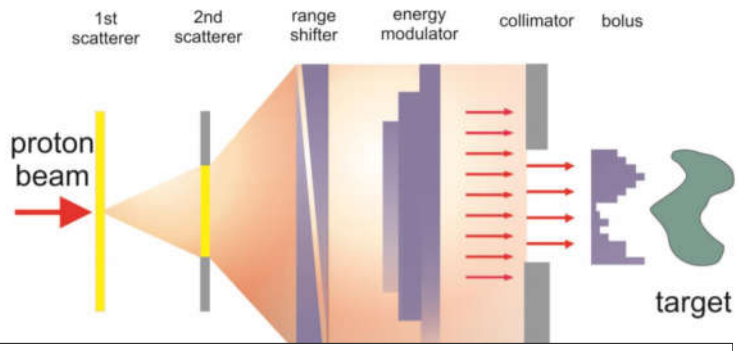
- Passive double scattering proton therapy (passive scattering PT)
- Active pencil beam scanning proton therapy (active scanning PT)

"Internal" and "external" neutron production



Introduction: Stray radiation produced in PT

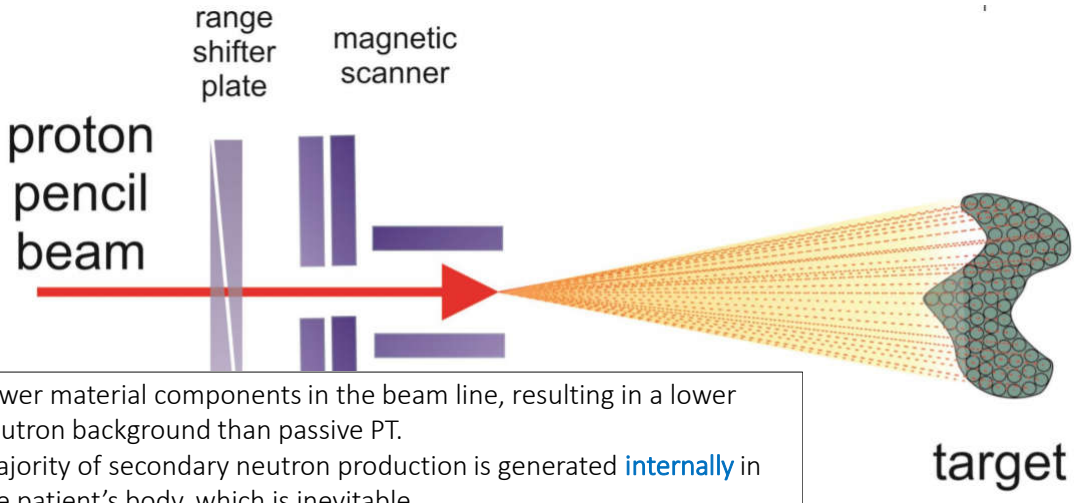
Beam Modulation Technique: PASSIVE



Majority of neutrons is produced by interaction of high energy protons with material components of beam line, with the largest source of neutrons the collimator close to the patients.
Neutron production is dominated by external neutron component

Introduction: Stray radiation produced in PT

Beam Modulation Technique: ACTIVE



Fewer material components in the beam line, resulting in a lower neutron background than passive PT.
Majority of secondary neutron production is generated internally in the patient's body, which is inevitable

Introduction: Stray radiation produced in PT

The mixed radiation field produced in proton therapy where protons are accelerated to therapeutic energies (60-250 MeV) can be divided into high and low LET components:

High LET components: neutrons and charged nuclear fragments (helium ions, deuterons, and tritons)

Low LET components: primary protons, elastically scattered protons, photons and delta electrons

In passive PT, the secondary neutron energy spectra are characterized by a low-energy peak (<10 MeV) and a high-energy neutron peak (>10 MeV up to the proton energy), however, the high energy peak contributes most to the total neutron dose

Next to the influence of the beam line configuration, the proton energy will also influence the neutron production as well as the distance from the field edge. The contribution of the low-energy peak increases with out-of-field distance

Introduction: Impact of neutrons in clinical proton therapy

Neutrons are known to have a high relative biological effectiveness (RBE) and are arguably the most effective particles in inducing late effects. The dosimetric advantage of protons may be negated to some extent by the production of stray neutrons.

This is of particular concern for paediatric patients!

Existing uncertainties in secondary cancer risks due to neutron production in PT:

- Uncertainties on low-dose cancer risks: linear non-threshold hypothesis?
- Controversy in published risk estimations
- Limited epidemiological data
- Dosimetric challenges
- Large uncertainty on neutron RBE and weighting factor

Introduction: Impact of neutrons in clinical proton therapy

Controversies in published risk estimates:

Radiation protection models are used to convert dose to risk.

1. Neutron dose distribution = additional dose burden to the patient (independently of the delivered dose to the tumour)
2. Neutron dose + therapy protons dose distribution = integral dose to the patient

Published comparisons of neutron dose measurements and the corresponding estimates of cancer risk between different treatment modalities differ over orders of magnitude

"Does it make any sense to spend over $100 million on a proton facility, with the aim to reduce doses to normal tissues, and then to bathe the patient with a total body dose of neutrons (…)?"

Hall, Technol. in Ca. Res. Treat., 2007,6,31-34

Introduction: Impact of neutrons in clinical proton therapy

Controversies in published risk estimates:

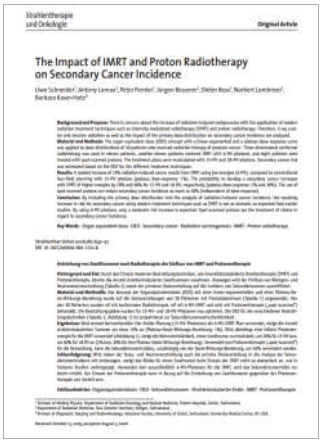
CRITICAL REVIEW

INTENSITY-MODULATED RADIATION THERAPY, PROTONS, AND THE RISK OF SECOND CANCERS

Eric J. Hall, D.Phil., D.Sc.

INTRODUCTION

Hall: secondary cancer risks is up to 20 times higher for passive PT compared to conventional X-ray therapy (Int J Rad Biol Phys 2006)



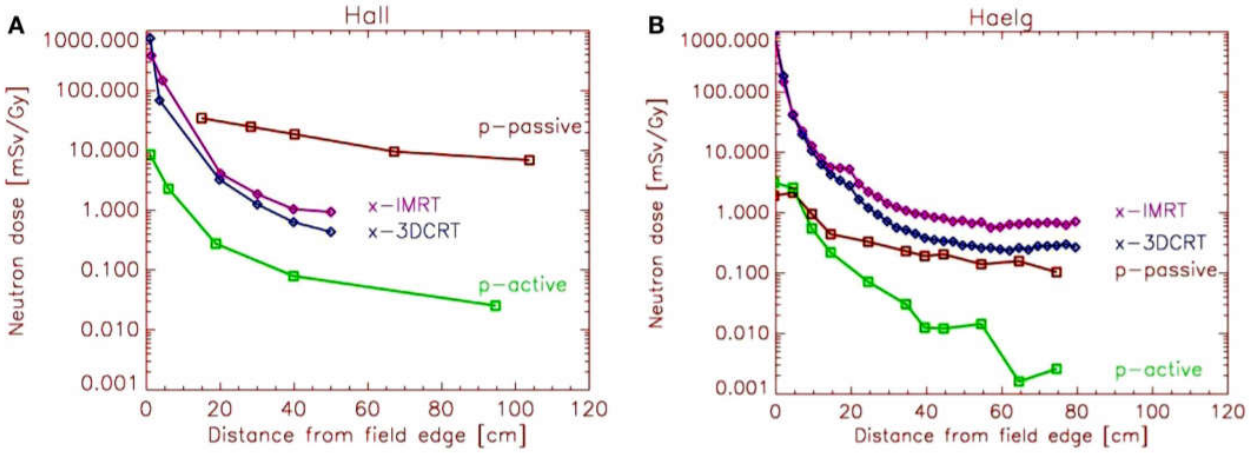
Strahlentherapie und Onkologie — Original Article

The Impact of IMRT and Proton Radiotherapy on Secondary Cancer Incidence

Schneider: Decreased secondary cancer risk for active PT and similar risks for passive PT compared to X-ray therapy (Strahlenther Onkol 2006)

Introduction: Impact of neutrons in clinical proton therapy

Controversies in published risk estimates:



Schneider – Front Oncol 2015

Introduction: Impact of neutrons in clinical proton therapy

Limited epidemiological data:

Data on long-term secondary toxicity and cancer risks in proton therapy is scarce

One of the first epidemiological studies: a reduction in second cancer risks for active and passive PT compared to X-rays.

Int J Radiat Oncol Biol Phys. 2013 Sep 1;87(1):46-52. doi: 10.1016/j.ijrobp.2013.04.030. Epub 2013 Jun 15.

Incidence of second malignancies among patients treated with proton versus photon radiation.

Chung CS[1], Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ.

Author information

1 Department of Radiation Oncology, Alta Bates Summit Medical Center, Berkeley, California, USA. chungc1@sutterhealth.org

Comparison of cancer risks between different treatment modalities should not be oversimplified. The full dose distribution should be taken into account, particularly the integral dose advantage of PT.

Introduction: Impact of neutrons in clinical proton therapy

Large uncertainty on the neutron RBE and radiation weighting factors

Neutron RBE depends on:

- Energy
- Dose (and dose rate)
- Biological Endpoint
- Influence of fractionation

Limited data available on neutron RBE for relevant endpoints (carcinogenesis)

Very limited data is available on high-energy neutrons (20-250 MeV)

Introduction: Impact of neutrons in clinical proton therapy

Large uncertainty on the neut

Neutron RBE depends on:

- Energy
- Dose (and dose rate
- Biological Endpoint
- Influence of fractio

Limited data available on neu

Very limited data is available

Radiation Protection Dosimetry (2010), Vol. 138, No. 4, pp. 299–304
Advance Access publication 19 February 2010

doi:10.1093/rpd/nap028

Editorial

Better radiation weighting factors for neutrons generated from proton treatment are needed

In radiation treatment of cancer, protons and other heavy charged particles offer an attractive clinical advantage when compared to X-rays with respect to healthy-tissue sparing afforded by the charged-particle Bragg peak. Secondary particles, most importantly neutrons, are inevitably produced through nuclear inelastic reactions in the components of particle accelerators and in patients' bodies. Medical proton accelerators are typically operated at energies up to ~250 MeV to ensure an adequate proton penetration in tumours that are located deep within the human body. Secondary neutrons are produced by the scattering system and apertures used in passive scattered proton therapy to shape the dose distribution. Although the majority of neutrons impinging on organs have energies ~1–2 MeV, the dose contribution is predominantly from high-energy neutrons up to 250 MeV[1]. Such irradiation by secondary neutrons leads to a potential risk for patients to develop so-called 'second primary cancers' during the remainder of their life[2]. Modern healthcare has contributed to the longer survival of cancer patients who are now more likely than in the past to live long enough for these potential adverse effects to be manifested.

At present, several proton treatment centres are in operation around the world and a number of others are in various phases of construction or commissioning. Associated with this booming interest in proton therapy is a heightened awareness of potential adverse effects caused by secondary neutrons. In many discussions related to the potential incidence of secondary malignancies resulting from proton therapy[3], the level of secondary neutron irradiation is often adversely compared with a competing technology known as intensity modulated radiation therapy (IMRT) that uses X-ray photons of energies up to 6 MeV. Unfortunately, two dosimetric parameters associated with neutrons, namely the relative biological effectiveness (RBE) and radiation weighting factors, add unnecessary confusion and uncertainty to the ongoing debate, with the consequence that possibly erroneous conclusions may be reached.

It has long been known that neutrons are more effective than photons (X- or gamma-rays) in causing biological damage. However, both the International Commission on Radiological Protection (ICRP) and the International Commission on Radiation Units and Measurements (ICRU) have not always agreed on how to take into account the RBE of neutrons for the purposes of radiological protection[4]. There are several challenges to the establishment of a precise and useful radiation protection dosimetry system for neutrons. In terms of radiobiological data, neutron RBE values vary considerably as a function of the radiation quality, dose, dose rate and biological endpoint. Values of RBE derived from human data and exposure to high-energy neutrons, which would be most relevant, are not available. Most existing RBE values were derived from results on the induction of dicentric chromosomes in human lymphocytes by neutrons <20 MeV. Some of the high neutron RBE values (up to 59) reported by the NCRP-104 were for carcinogenesis in mice involving fission neutrons that have an energy <2 MeV[4]. In contrast, very little information is available on the biological effects of high-energy neutrons in the range of 20–250 MeV that would be most pertinent to applications in high-energy physics research accelerators, civil aviation and, in the present case, therapeutically used particle accelerators.

Radiation protection quantities are known to be often confusing and, as a result, people may fail to fully appreciate the lack of precision in values assigned to the RBE or the radiation weighting factor. As summarized by Edwards[5], the earliest attempt to adopt the RBE was made by the ICRP in 1955 when the permissible dose (expressed in rem) was specified as the permissible dose (expressed in rad) multiplied by an appropriate RBE (for neutrons an RBE value of 10 was suggested at that time). Over time, a number of quantities related to

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

The origin of neutron biological effectiveness as a function of energy

Introduction: Impact of neutrons in clinical proton therapy

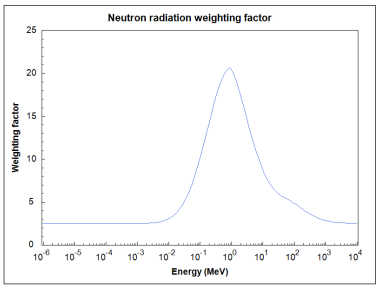
Radiation weighting factor w_R (ICRP) used for cancer risk estimations. Introduced for radiation protection purposes in order to account for the relative detriment of different types of radiation

- Pooling the RBE data from different experiments
- Conversion of absorbed dose (Gy) to equivalent dose H (Sv)

$$H = w_R * D$$

- Depends on energy for neutrons: maximum of 20 around 1 MeV. However, most of the dose deposited indirectly via neutrons in PT is deposited by high energy neutrons
- Recent data obtained with human lymphocytes and 60 MeV quasi-monoenergetic neutrons indicate a mean quality factor that decreases with increasing neutron energy to values of <5: continuous functions used by ICRP

$$w_R = \begin{cases} 2.5 + 18.2e^{-[\ln(E_n)]^2/6}, & E_n < 1\ \text{MeV} \\ 5.0 + 17.0e^{-[\ln(2E_n)]^2/6}, & 1\ \text{MeV} \leqslant E_n \leqslant 50\ \text{MeV} \\ 2.5 + 3.25e^{-[\ln(0.04E_n)]^2/6}, & E_n > 50\ \text{MeV} \end{cases}$$



Radiation Type	Energy	W (ICRP-60)	W (ICRP-92)
Photons	all	1	1
Electrons, muons	all	1	1
Neutrons	<10 keV	5	function
Neutrons	10-100 keV	10	function
Neutrons	>100 keV- 2Mev	20	function
Neutrons	>2 -20 MeV	10	function
Neutrons	>20Mev	5	function
Protons	<2 MeV	5	2
α-particles, fission fragments	all	20	20

Introduction: Impact of neutrons in clinical proton therapy

Strong need for radiobiological input to determine w_R for secondary neutrons produced in PT

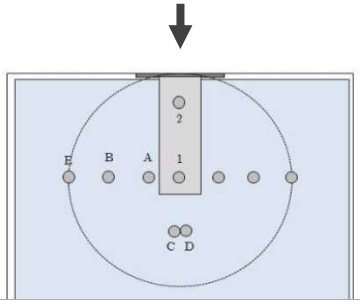
ALLEGRO
Project ID: 231965
Funded under: FP7-EURATOM-FISSION

ANDANTE
Project ID: 295970
Funded under: FP7-EURATOM-FISSION

Material & Methods

Since secondary cancer risk are particularly important for children, all positions are located in a 150 mm radius, representing the diameter of the head of a 5-y old child.

Phantom and Irradiation Set-up:



Beam description:
200 MeV proton beam (PPT)
100 mm R50 range
31mm SOBP
30mm circular field size

Water tank with Perspex sleeves:

Lateral positions (85 mm water equivalent depth):

A: 25 mm from beam axis – 10 mm from field edge
B: 50 mm from beam axis – 35 mm from field edge
E: 75 mm from beam axis – 60 mm from field edge

Longitudinal positions (130 mm water equivalent depth):

Previous studies have shown that the neutron production and the spectral energy distribution were similar in water compared to an anthropomorphic phantom for PT studies

(Mares *et al.* – Phys Med Biol 2016)

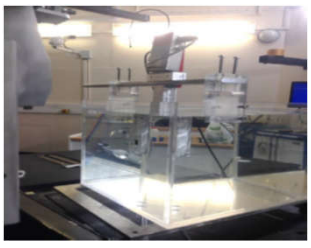
Material & Methods

It is important to study the deposited energy of all stray components

Separate Perspex sleeves were designed for different detectors:

- Neutron bubble detectors (Bubble Technology Industries)
- Li6 and Li7 enriched thermoluminescent dosimeters (TLDs)
- Silicon-on-insulator microdosimeter (MicroPlus™ Probe)
- T2 ionization chamber for measurement of output factors (Gy/MU)

A 'pilot' run of Geant4 Monte Carlo simulations was performed in order to simulate the energy deposition of different stray components in the selected out-of-field positions



MicroPlus™ Probe

Bubble detector

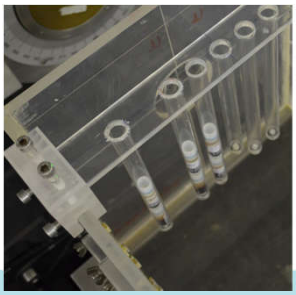
Material & Methods

Radiobiological Endpoints:

Whole blood samples from two adult donors were used: the link between chromosomal aberrations in blood cells and cancer in any organ is strengthened by the evidence that chromosomal aberrations are an indicator of genomic instability, which plays a key role in cancer development.

Cytokinesis-Block Micronucleus Assay (CBMN) - Mutagenesis

Dicentric Assays (DIC) and stable aberrations (mFISH) - Exchange-type aberrations have a link with leukaemia, which is important for childhood cancer survivors



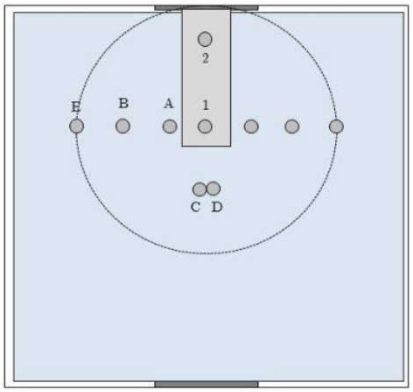
Results

Output Factors:

The output factors indicate that the doses outside the primary field are very low, from 0.6 mGy/Gy for position A down to 0.2 mGy/Gy for position E.

This is in agreement with previous studies illustrating a decrease in absorbed dose outside the primary field with depth.

Positions		Output factor (Gy/MU)	STD (%)	Absorbed dose (mGy/Gy)
Lateral	A	0.00049	1.2	0.6
	B	0.00026	4.7	0.3
	E	0.00015	10.8	0.2
Distal	C/D	0.00027	2.3	0.3
SOBP		1.217	0.1	
Ent. Plat.		0.899	0.1	



Results

Equivalent Dose/Dose equivalent

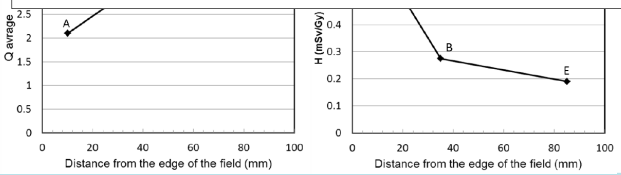
Microdosimetry

Dose equivalent by using quality factor Q(L) recommended by ICRP which depends on the

Bubble detectors

Equivalent dose by using the weighting factor (w_R) based on the continuous function provided by

Are the weighting factors that we use to convert absorbed dose to equivalent dose even appropriate?
Based on this study where we take all stray components into account and determine the RBE of stray radiation out-of-field, the RBE values close to the field edge (<75mm) are not higher than 2…



Romero-Exposito et al – Med Phys 2016: Quality factor and weighting factor are approximately equal for the range of neutron energy in radiation therapy

Discussion and Conclusion

Limitations and future directions:

- Investigation of potential angular dependence of solid-state MicroPlus™ probe
- Secondary neutron production depends largely on the facility
- Lymphocytes of children and adults differ in radiosenstivity
- Based on GEANT4 Monte Carlo data, radiobiological investigation of RBE for neutrons with energies relevant to PT will be performed using iThemba LABS' quasi-mono-energetic neutron beam lines (up to 190 MeV)
- Additional dosimetric and radiobiological investigation of positions close to the field edge (such as position A)
- Passive double-scattering PT beam line at iThemba LABS represents an older generation of PT modalities, there is a need to repeat these measurements and compare our results with more recent active scanning PT systems

Discussion and Conclusion

Conclusions:

- Absorbed doses out-of-field are low, so we have to put radiation risks in perspective
- While there is an exponential decrease in dose, there is an increase in neutron contribution to the total dose as a function from field edge, resulting in higher RBE values
- Although epidemiological evidence indicates that RT makes a crucial contribution to long-term survival of childhood cancer, it is vital that we ensure that any avoidable and detrimental exposures to radiation are as low as reasonably achievable
- Despite large uncertainties, data suggests that particle therapy should lead to a lower risk of secondary cancer compared to conventional X-ray techniques. Modification of treatment units with additional shielding and upgrade to active scanning PT will further reduce the secondary cancer risk in paediatric PT
- Personalised treatment strategies for children, by selecting the radiation type that is likely to have the least detrimental effects

Acknowledgement

NRF iThemba LABS:

- Philip Beukes
- Xanthene Miles
- Monique Engelbrecht
- Julyan Symons
- Jaime Nieto-Camero
- Evan de Kock
- Jacobus Slabbert

DKFZ Heidelberg:

- Steffen Greilich

Ghent University:

- Anne Vral

University of Wollongong:

- Linh Tran
- Lachlan Chartier
- Emily Debrot
- Dale Prokopovich
- Anatoly Rosenfeld

SCK-CEN:

- Marijke De Saint-Hubert
- Sabina Chiriotti
- Alessio Parisi
- Olivier Van Hoey
- Filip Vanhavere

- NRF iThemba LABS Physics Advisory Committee (PAC) for beam time allocation

Thank you for your attention

Any questions???