4th International MELODI Workshop, 12-14 September 2012
Hotel Presidentti, Helsinki, Finland

ALLEGRO to ANDANTE: An application of radiotherapy data to low-dose radiation research

Andrea Ottolenghi
Vere Smyth, Klaus R Trott
Dipartimento di Fisica,Università di Pavia

ALLEGRO

Multidisciplinary evaluation of the cancer risk from neutrons relative to photons using stem cells and the analysis of second malignant neoplasms following paediatric radiation therapy
ANDANTE

UniPv
DF

EURATOM

ALLEGRO

Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy

It was funded by EURATOM for 2 years:
February 2009-March 2011

- to define the current state of the art of understanding and assessment of normal tissue risks from radiation therapy,
  - in order to be able to provide advice on clinical treatment choices
  - and set the direction for future research efforts.

Project acronym: ALLEGRO

Project full title: Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy

MCG: A Ottolenghi, K R Trott, V Smyth *February 2009-January2011*

	Beneficiary name	Short name	Country	Resp. scientist
1	Università degli Studi di Pavia (Coordinator)	UniPv	Italy	A Ottolenghi
2	Aarhus University Hospital	AUH AS	Denmark	J Overgaard
3	Chalmers Univ of Technology	CUT	Sweden	L Sihver
4	ESTRO	ESTRO	Belgium	V Gregoire
5	GSI, Darmstadt	GSI	Germany	M Durante
6	Istituto Europeo di Oncologia	IEO	Italy	R Orecchia
7	Katholieke Universiteit Leuven	KULeuven	Belgium	F Van den Heuvel
8	Maastricht Radiat Oncol GROW.	MAASTRO	Netherlands	P Lambin
9	Mt Vernon Hospital	MVH	UK	E Aird
10	Paul Scherrer Institute, Villigen	PSI	Switzerland	EB Hug
11	University of Technology Dresden	TUD	Germany	W Dörr, M Baumann
12	Univ. Medical Centre, Groningen	UMCG	Netherlands	JA Langendijk
13	Universitätsklinikum Ulm	UULM	Germany	Th. Wiegel

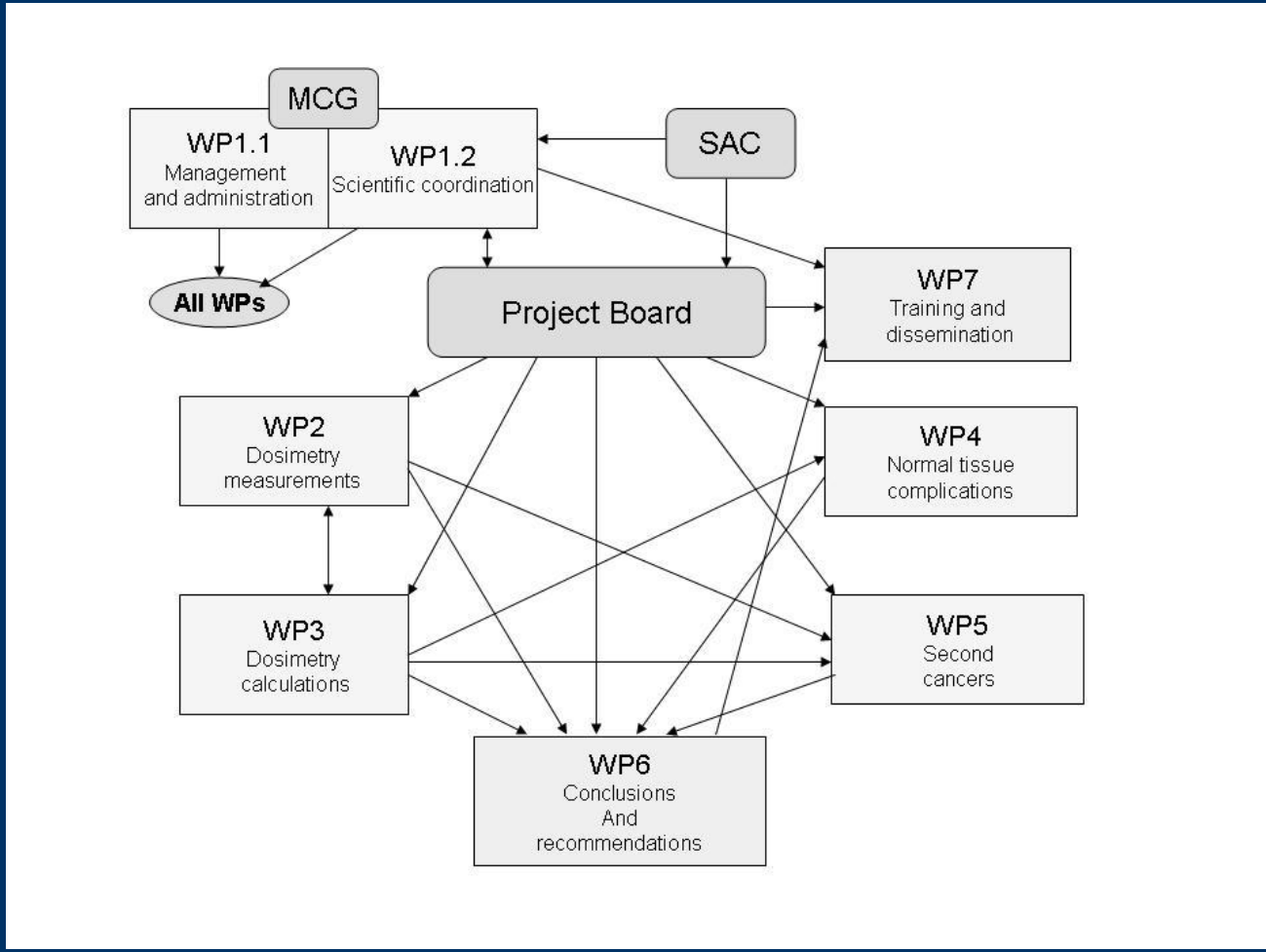
Scientific advisers: A van der Kogel, B Mijnheer, H Suit

The **ALLEGRO** project investigations were divided into:

1. measurement and modelling of radiation doses outside the treatment volume from photon, proton, and carbon ion beams;
2. review and development of current best practice in normal tissue complication probability (NTCP) modelling in head and neck, lung, and prostate cancer;
3. review and test of current research capability on the risks of second cancer following radiotherapy.

ALLEGRO structure

WP1.1	Project management
WP1.2	Project scientific coordination
WP2	Measurement of radiation doses to normal tissue
WP3	Calculation of radiation doses to normal tissue
WP4	Estimation and minimisation of risks of normal tissue complications
WP5	Estimation and minimisation of risks of second cancers
WP6	Survey of knowledge, conclusions, and recommendations
WP7	Training, Education and Dissemination of Results



ALLEGRO objectives

i. Investigation of the magnitude and distribution of radiation doses in normal tissues

ii. Modelling of the risk of normal tissue damage in common and emerging cancer treatments

iii. Investigation of the risk of second cancers from the radiation exposure of normal tissues

iv. Expert forum review of new state of the art

ALLEGRO

Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy

EURATOM Fission-2008-3.2.1: The risk of early and late health effects from the use of radiation therapy.

Expected impact:

- "Quantification of early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy as input to sound judgments on their application and optimisation.
- Identification of future research needs for those techniques where the risks cannot be assessed with sufficient certainty for sound clinical decision making."

...as well as results from the individual investigations,

- a series of report documents have been produced that:
  - summarise the experience gained during the project
  - provides recommendations for clinical practice in both current and emerging therapy modalities in order to minimise normal tissue risk without compromising treatment efficacy,
  - indicates valuable areas for further research.

ALLEGRO results:

- **Dosimetry for normal tissue risk assessment: Measurement and calculation of the doses received by normal tissues from radiation therapy from current and emerging modalities.**
- **NTCP modelling: Current model development, fitting, validation, and applications.**
- **Second cancers after radiation therapy: Potential and pitfalls of the analyses of clinical databases**
- **Conclusions and Recommendations: lessons learned for clinical practice, policy makers, equipment manufacturers, prospective data collection, and questions remaining for future research.**

From

ALLEGRO

to

Multidisciplinary evaluation of the cancer risk from neutrons relative to photons using stem cells and the analysis of second malignant neoplasms following paediatric radiation therapy

ANDANTE

UNIPV-DF

SEVENTH FRAMEWORK PROGRAMME THEME: EURATOM

Nuclear fission and radiation protection

Fission-2011-3.1.1: Contribution to low-dose risk research in Europe.

Project acronym: ANDANTE

Project full title: **Multidisciplinary evaluation of the cancer risk from neutrons relative to photons using stem cells and the induction of second malignant neoplasms following paediatric radiation therapy**

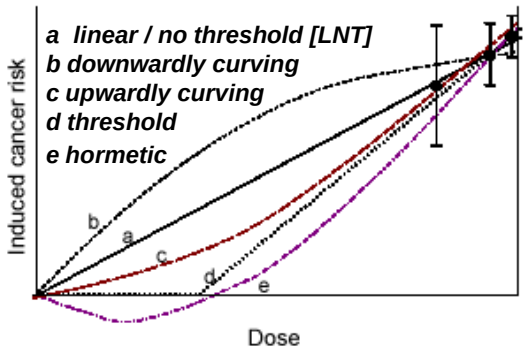
MCG: **Andrea Ottolenghi, Vere Smyth, KlausTrott**

	Beneficiary name	Short name	Country	Resp. scientist
1	Università degli Studi di Pavia (Coordinator)	UniPv	Italy	A Ottolenghi
2	Bundesamt fuer Strahlenschutz	BfS	Germany	L Walsh
3	Chalmers Univ of Technology	CUT	Sweden	L Sihver
4	European Society for Therapeutic Radiology and Oncology	ESTRO	Belgium	E Chimfwembe
5	Loma Linda University	LLU	United States	R Schulte
6	Paul Scherrer Institute, Villigen	PSI	Switzerland	A Lomax
7	Academisch Ziekenhuis Groningen	UMCG	Netherlands	R Coppes
8	Universitaet Rostock	UROS	Germany	G Hildebrandt

Scientific advisers: **Albrecht Kellerer, Herman Suit, Adrian Begg, Charles Land**

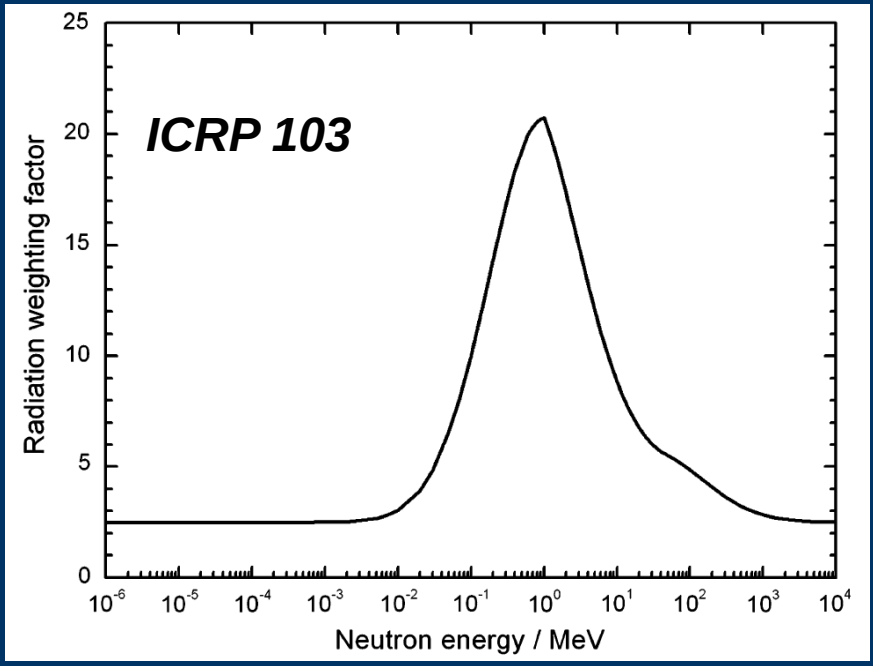
The general EURATOM "radiation protection" question:

low dose risk and shape of the curve



In ANDANTE we address a specific question within the more general quality of radiation question: the neutron risk

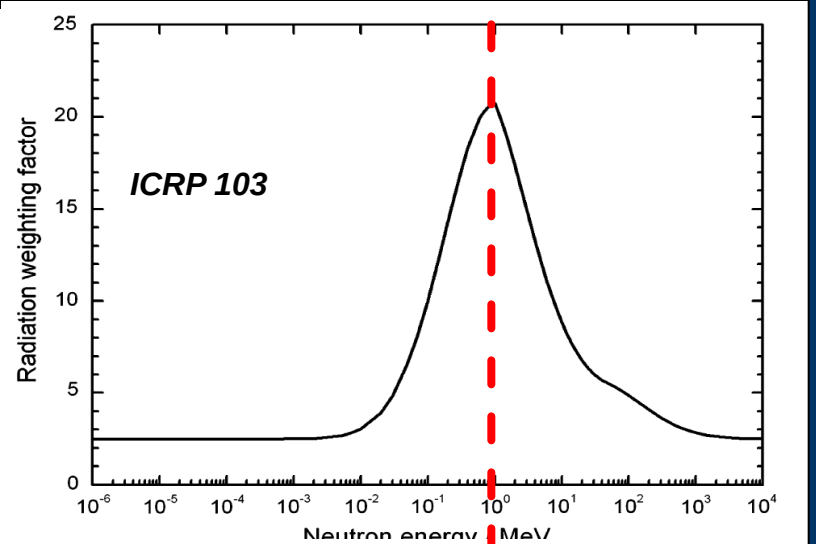
… and this is the kind of "tormenting" plots when we talk about neutron risk:

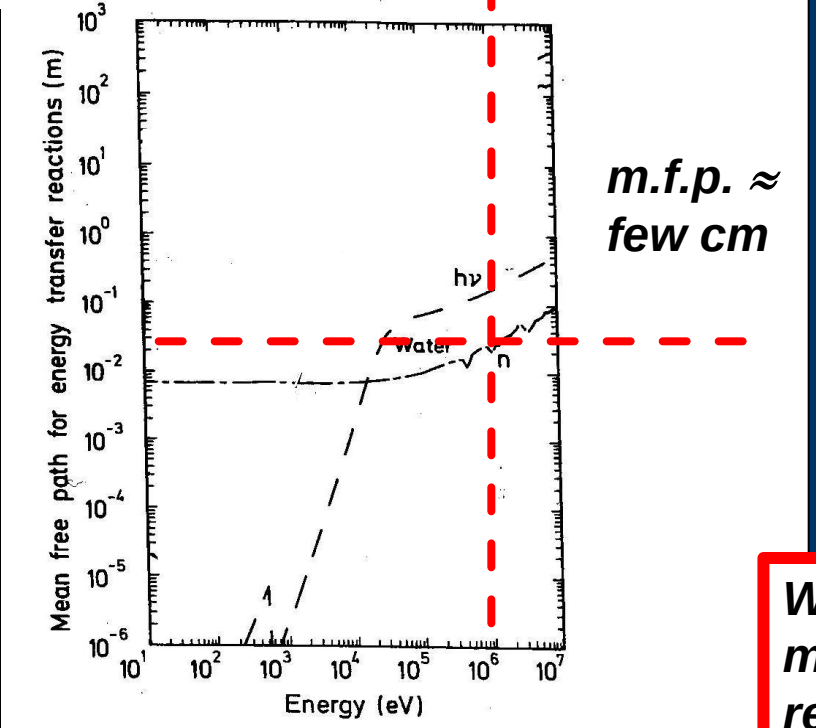


… but here we have a twofold problem:

- ***we don' t "like" W_Rs (the use of W_Rs has intrinsic assumptions on the shapes of the dose-risk curves***
- ***the bases for neutron W_Rs, and the way they depend on the energy, are very much under discussion***

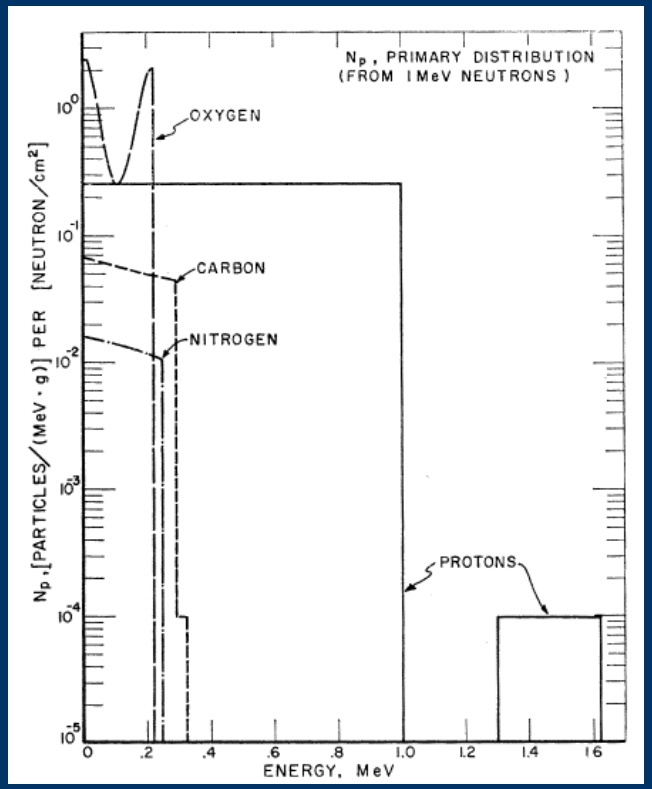
neutrons





m.f.p. ≈ few cm

Mean free path for energy transfer reactions of neutrons and photons in water



Initial energy distributions , $N_p(\varepsilon)$ for six ions produced by the interactions of 1-MeV neutrons with tissue (Caswell and Coyne, 1972) (+ other particles including photons!)

We need to (from the HLEG): "carry out mechanistic studies on early and late responses to different radiation types and dose rates starting from physical interactions"

ANDANTE key ingredients
(phenomena, concepts/hypotheses and methods)

Physics:
- Neutron interactions
- Accelerated charged particles produced by nuclear interactions
- Track structures of charged particles

Biology and Radiobiology:
- The stem cell hypothesis in carcinogenesis

Retrospective and prospective studies on secondary tumours in radiotherapy:
- Secondary neutrons in proton treatments
- Secondary tumours in paediatric treatments with photons and protons

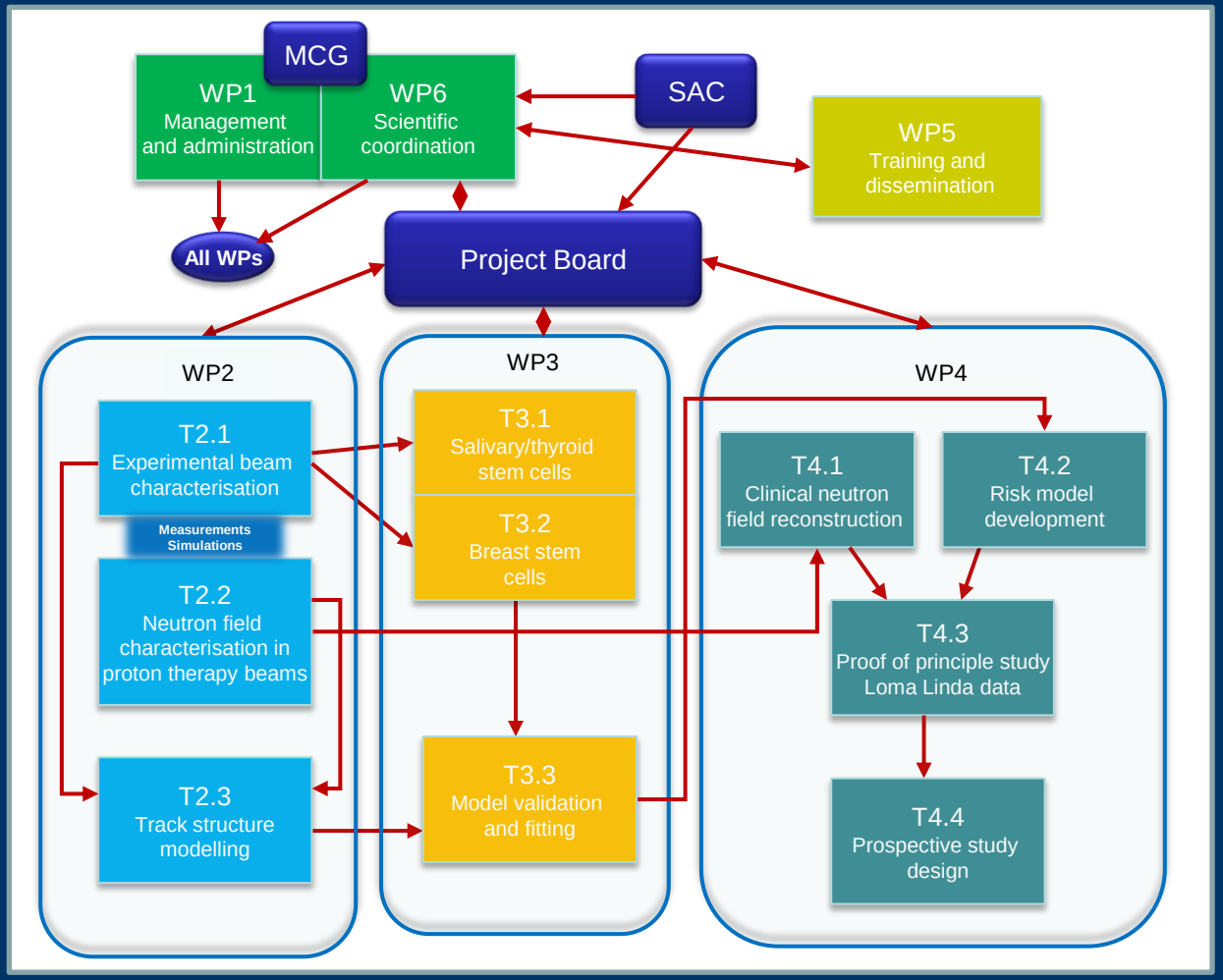
UNIPV-DF

ANDANTE

Multidisciplinary evaluation of the cancer risk from neutrons relative to photons using stem cells and the induction of second malignant neoplasms following paediatric radiation therapy

ANDANTE structure

WP1	Project management
WP2	Physical measurement and modelling of neutron fields
WP3	Relative carcinogenesis of neutrons on stem cells
WP4	Relative carcinogenesis of neutrons on humans using paediatric data
WP5	Training, Education and Dissemination of Results
WP6	Project scientific coordination



WP 2 :**Physical measurement and modelling of neutron fields**

- Characterisation of the experimental radiation beams
- Measurement and modelling of neutron fluence and energy spectra out of the treatment field in proton therapy beams;
- Modelling of neutron and secondary particle track structures (Integration of measurements with modelling activities, e.g.: CUT (transport codes), LLU (micro-/nano-dosimetry), UniPv (track structure studies) to collaborate with PSI in the development of predicting models.

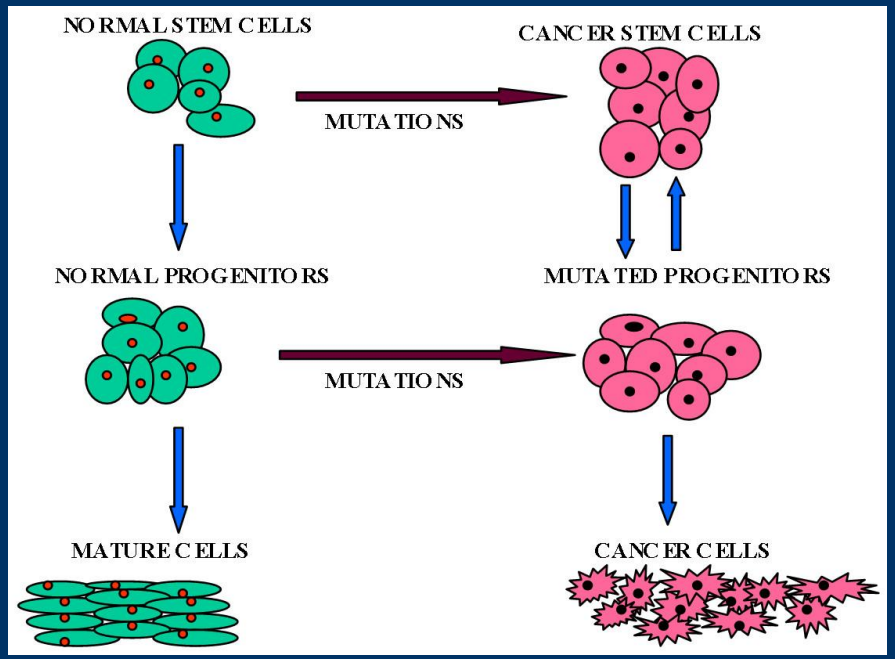
WP3 - **Relative carcinogenesis of neutrons on stem cells**

The question: how low and moderate doses of neutrons can influence the proliferation, differentiation and genome instability of stem cells and are therewith involved in radiation-induced carcinogenesis.

After irradiation with either neutrons or with photons dose response relationships of different stem cell populations will be investigated in vitro and in vivo:

- Determination of radiation effects
  - on salivary gland stem cells
  - on thyroid gland stem cells
  - on breast tissue stem cells
- Validation of track structure model

Cancer stem cell hypothesis



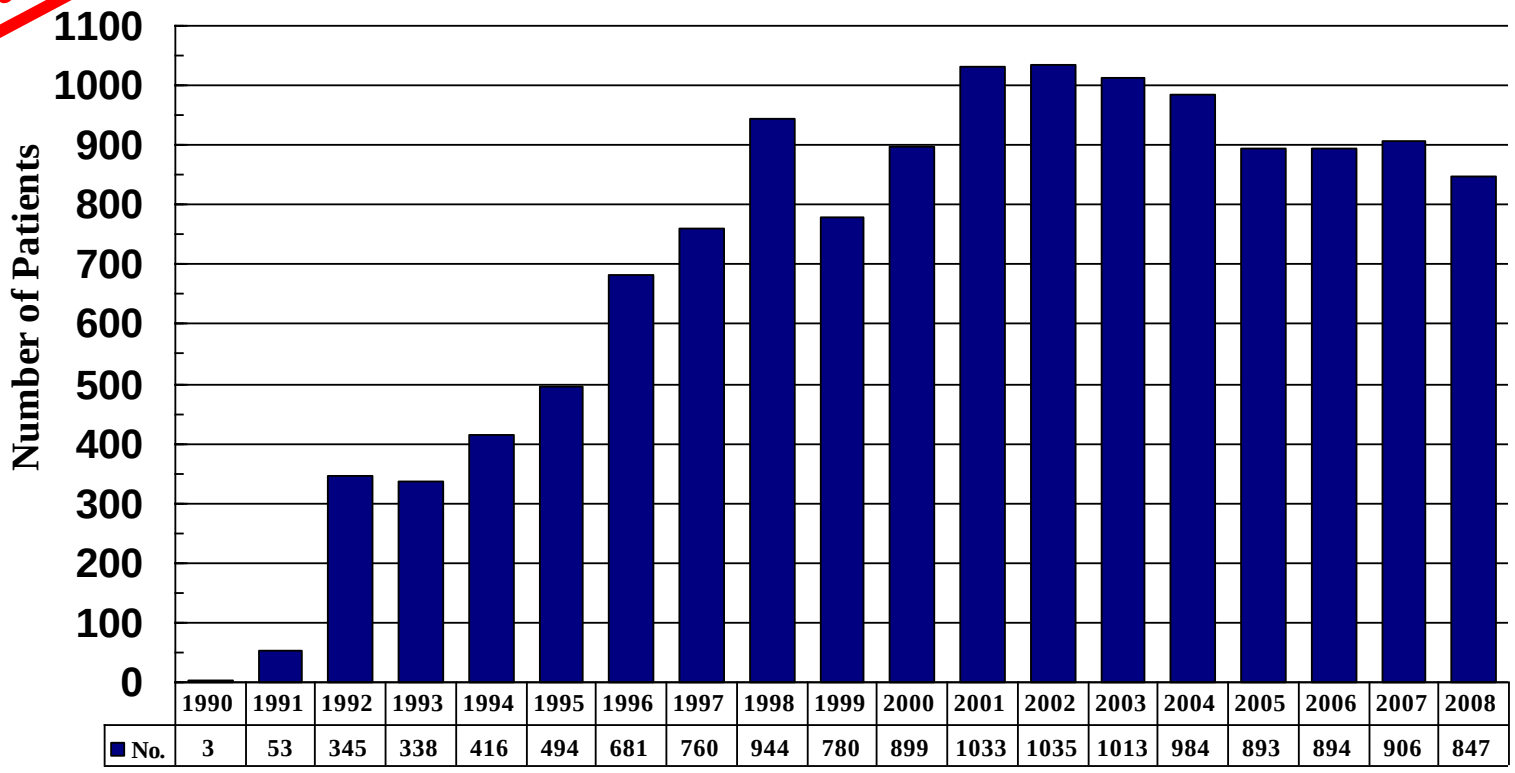
Sagar et al., *Cancer Cell* 2007

WP4: **Relative carcinogenesis of neutrons on humans using paediatric data**

- Develop a methodology for reconstruction of neutron dose and energy outside the treatment volume in proton therapy patients;
- Develop a predictive neutron dose-risk model in order to validate neutron RBE values using proton therapy data;
- Proof of principle study for validation of neutron dose-risk model using paediatric radiotherapy data;
- Design and if possible initiate a prospective multi-centre epidemiological study to validate neutron RBE models and investigate more general tumorigenesis risks from neutrons.

Annual Proton Patients at LLUMC 1991-2008

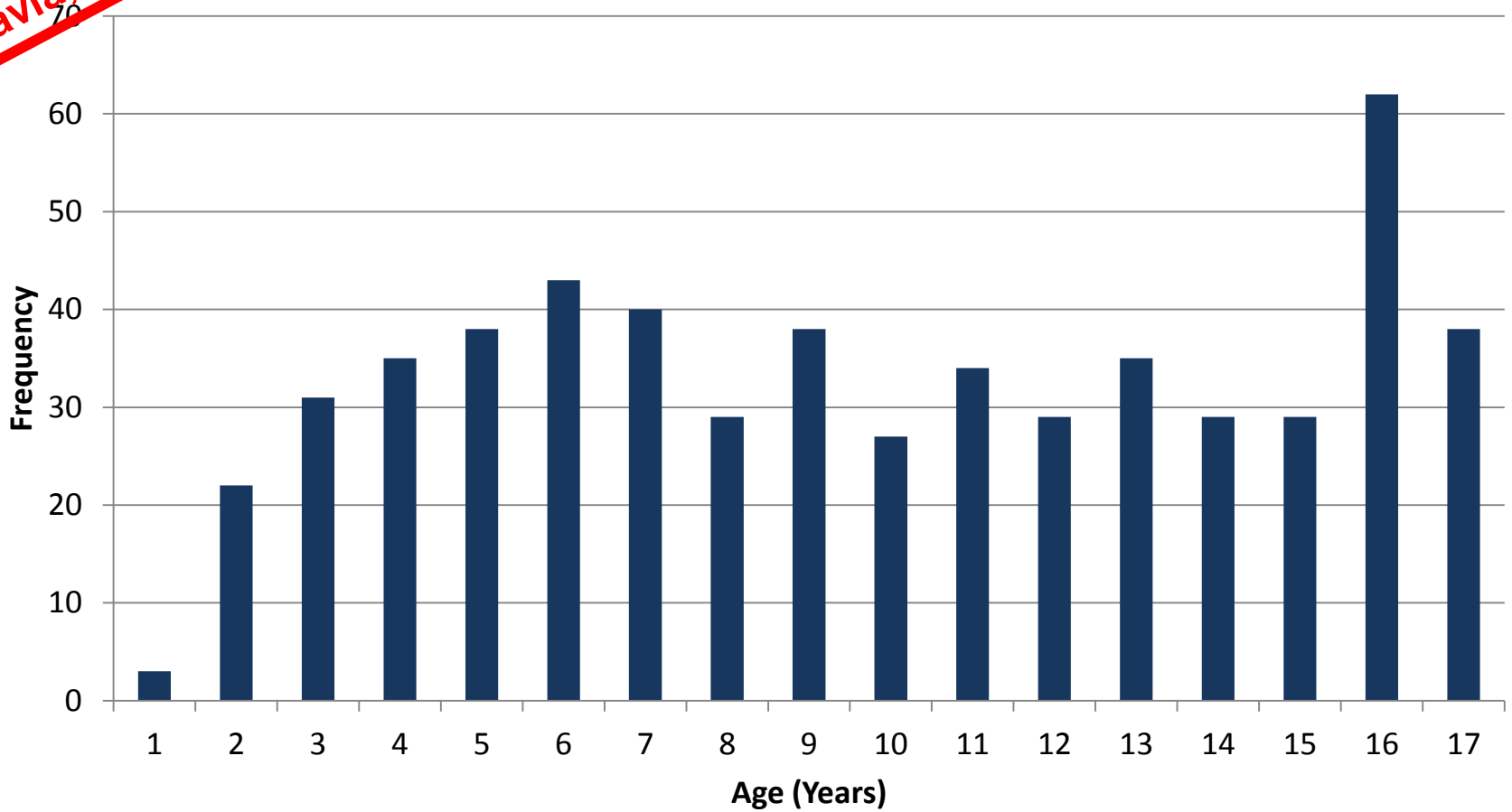
From ANDANTE kick-off meeting, Pavia, Jan 2012



	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008
No.	3	53	345	338	416	494	681	760	944	780	899	1033	1035	1013	984	893	894	906	847

Age Distribution of Pediatric Proton Patients

From ANDANTE kick-off meeting, Pavia, Jan 2012



UNIPV-DF

ANDANTE

Multidisciplinary evaluation of the cancer risk from neutrons relative to photons using stem cells and the induction of second malignant neoplasms following paediatric radiation therapy

- The ANDANTE project is expected to produce results that will have an impact on any facet of radiation protection where neutrons are a significant factor.
- The re-evaluation of RBE for neutrons will provide information of fundamental importance to the ICRP formalism of radiation protection.
- This will have direct implications for any industry where neutrons are produced as a by-product.

Thank you for your attention!