CURRICULUM VITAE of ANDREA OTTOLENGHI

Professor of Medical Physics and of Radiobiology at the University of Pavia,
Member of the Physics Department,
Head of the laboratory of Radiation Biophysics and Radiobiology.

DEGREES

National Scientific Qualification as Full Professor.
Specialization in Medical Physics, *cum laude* (also in all courses), University of Milan, Italy
Doctor in Physics, *laurea cum laude*, University of Milan, Italy
High School Diploma in Electronics, ITIS Feltrinelli, Milan, Italy
High School Diploma, Oshkosh High School, Oshkosh Wi, USA, after a one year permanence in U.S.A. with an AFS scholarship

POSITIONS

- September 2015 – present: **Full Professor** (02/D1-FIS/07: Applied physics) at the University of Pavia, Department of Physics.
- October 2001-August 2015 : **Associated Professor** at the University of Pavia, Faculty of Medicine, member of the Department of Nuclear and Theoretical Physics (since 2012 Department of Physics), head of the laboratory of Radiation Biophysics and Radiobiology
- April 1992 - September 2001: **Researcher** at the University of Milano, Faculty of Medicine, member of the Physics Department.
- December 1969 - April 1992: **Teacher** with continuity (permanent position since 1970 and staff member ("di ruolo") since 1974) in public secondary schools. In 1992 I leave the position of teacher of Mathematics and Physics in High school for the position of researcher at the University of Milan.

DIRECTION AND COORDINATION OF RESEARCH PROJECTS (approved by competitive agencies)

I have been **Principal Investigator** or **Local Scientific Manager** of several international and national research projects, funded by the *European Commission, MURST, ISS, ASI, ESA and INFN*. In particular:

Funded by the EUROPEAN COMMISSION (Horizon 2020, 7th, 6th, 5th and 4th frameworks):

- 2016-2018 ***Scientific manager*** of the Italian partner UniPv of the ***European project*** **ANNETTE** - *Advanced Networking for Nuclear Education and Training and Transfer of Expertise*, within which UniPv contributes to the Education and Training on the effects or radiation, also as Chair of the WG on Education & training of the European Platform MELODI (Multidisciplinary European Low Dose Initiative) (Horizon 2020 EU contract 661910)
- 2015-2019 ***Scientific manager*** of the Italian partner UniPv of the ***European Joint Programme*** **CONCERT** - *European Concerted Programme on Radiation Protection Research*, within which UniPv (A. Ottolenghi) is member of the Executive Board, coordinator of the Work Package on Education & Training and responsible of the task on the Development of Strategic Research Agenda, roadmap and priorities for research with the medical scientific community (Horizon 2020 EU contract 662287).
  CONCERT is a European Joint Programme (EJP) for which **UniPv has been nominated Programme Manager by the Italian Ministry of Education and Research (MIUR)**
- 2014-2015 ***Scientific manager*** of the Italian partner UniPv ***project TREND*** (*TRacking damage at ions' track ENDs*) funded by the EU (by the NoE DoReMi) after the 2014 DoReMi's Internal Call for ad hoc funding (Partners: HMGU, Munich, Germany and UniPv, Pavia, Italy)
- 2014-2016 ***Scientific manager*** of the Italian partner UniPv of the project **SOPRANO** - (subproject of ***OPERRA***) - *Systems Oriented Prediction of Radiation Risk*, funded by the EU after the 1st OPERRA's competitive RTD Call
- 2013-2017 ***Scientific manager*** of the Italian partner UniPv of the **European project OPERRA (Combination of Collaborative project & Coordination and support action)** - *Open Project for the European Radiation Research Area* (VII framework EU contract 604984)
- 2013-2016 ***Scientific manager*** of the Italian partner UniPv of the **European project EUTEMPE-RX (Coordination and support action)** - *EUropean Training and Education for Medical Physics Experts in Radiology* (VII framework EU contract 605298)
- 2012-2015, ***European Coordinator*** of the **European project ANDANTE (Collaborative project)** - *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* (7th framework EU contract 295970).
- 2012-2014, ***Coordinator*** of the ***project INITIUM*** (*Track structures and initial events: an integrated approach to assess the issue of radiation quality dependence*) funded by the EU (by the NoE DoReMi) after the 1st competitive DoReMi's Internal RTD Call (Partners: UniPv, Pavia, Italy and HMGU, Munich, Germany)

- 2011-2015, ***Scientific manager*** of the Italian partner UniPv of the **European project EpiRadBio (Collaborative project)** - *Combining epidemiology and radiobiology to assess cancer risks in the breast, lung, thyroid and digestive tract after exposures to ionizing radiation with total doses in the order of 100 mSv or below* (7th framework EU contract 269553).
- 2010-2015, ***Scientific manager*** of the Italian partner UniPv (and ***member of the Management Board***) of the **European Network of Excellence DoReMi** - *Low Dose Research towards Multidisciplinary Integration* In DoReMi I also ***coordinate*** the *Work package on Training & Education* (7th framework EU Contract 249689).
- 2009-2011, ***European Coordinator*** of the ***European project ALLEGRO*** **(Collaborative project)** - *Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy* (7th framework EU contract 231965)
- 2006-2010, ***Scientific manager*** of the Italian partner UniPv of the ***European Consortium NOTE*** - *Non-targeted effects of ionising radiation* (6th framework EU Contract FI6R 036465).
- 2004-2008, ***Scientific manager*** of the Italian partner UniPv of the ***European Consortium RISC-RAD*** - *DNA damage responses, genomic instability and radiation-induced cancer: the problem of risk at low and protracted doses* (6th framework EU Contract FI6R-CT-2003-508842).
- 2000-2003, ***Scientific manager*** of the Italian partner UniMi of the **European Consortium Low Dose Risk Models** - *Improved cancer risk quantification for environmental, medical and occupational exposures to low doses of ionizing radiation by mechanistic models* (5th framework, EU Contract F1GH-CT CT1999-00005).
- 1996-1999, ***Scientific manager*** of the Italian partner (UniMi) of the **European Consortium** on *Biophysical Models for the Induction of Cancer by Radiation* (4th framework, EU Contract F14P CT 950011c).

Funded by the NATIONAL INSTITUTE OF NUCLEAR PHYSICS (INFN)

- 2014 ***Scientific manager*** of Pavia Unit of the ***experiment INFN MERIDIAN*** on *Measuring the Effects of Radiation on Immunity and DIfferentiAtioN* (Units: Trieste and Pavia).
- 2012-2014 ***Scientific manager*** of Pavia Unit of the ***experiment INFN RADIOSTEM*** on *Radiobiological response mechanisms to photons and charged particles, of cell stems derived from tumours and healty tissues* (Units: National Institute of Health and Pavia).
- 2009-2011 ***National Coordinator*** of the ***experiment INFN TENORE*** on *Damage mechanisms and response (at molecular, cellular and supra-cellular levels) in targeted and non targeted effects of ionising radiation: dependence on radiation quality* (Units: Pavia and National Institute of Health).
- 2006-2008 ***National Coordinator*** of the ***experiment INFN EPICA*** on *Effects of charged particles: mechanisms of induction of molecular damage and modulation of intercellular signalling* (Units: Pavia and National Institute of Health).
- 2003-2005 ***National Coordinator*** of the ***experiment INFN MIDPAC*** on *Mechanims of radiation damage induced by charged particles in human cells: experimental measurements and theoretical models* (Units: Pavia and National Institute of Health).
- 1999-2002 ***Scientific manager*** of Milan Unit of the ***experiment INFN DOSBI*** on *Biological dosimetry from lymphocytes: cytogenetic monitoring in radiation therapy*.
- 1999-2002 ***National Scientific manager*** (within the ***experiment ATER-2/INFN***) of the project **FIBIONCA** (partners: INFN sections of Milano, Torino, Legnaro, Genova, Roma), for the *Development and validation of physical and biophysical models for the simulation of Carbon ion beams in tissue*.
- 1996-1998 ***National Scientific manager*** (within the ***experiment ATER/INFN***) of the project ***ATER-I/MC*** (partners: INFN sections of Milano, Torino, Legnaro, Ferrara, Roma), for the *Development of simulation codes for applications in proton therapy.*
- 1996-1998 ***Scientific manager*** of Milan Unit of the ***experiment FILMEDA/INFN*** (*Light Ion beams and mechanisms of radiation damage*).

Funded by the ITALIAN MINISTRY OF RESEARCH

- 2004-2006 ***Scientific manager*** of Pavia Unit of the Programme of Scientific Research of Relevant National Interest (PRIN-2004), co-funded by the Ministry of Research (MURST) on *Fragmentation of heavy ions in hadrontherapy and in space radiation protection* Specific topic: *Development and application of the FLUKA transport code coupled with anthropomorphic phantoms, to estimate damage at cell and organ levels*.
- 2000-2002 ***Scientific manager*** of Milan Unit of the Programme of Scientific Research of Relevant National Interest (PRIN-2000), co-funded by the Ministry of Research (MURST) on *Biological effects of cosmic radiation: experiments on lymphocytes with charged particles and simulated microgravity, and relative biophysical models*.
- 1995-1996 ***responsible of Milan Unit*** on *Mechanims of Interaction Radiation-biological tissues*, within the *national project "40% - Fisica Medica*" coordinated by A. Stefanini.
- 1995 ***Coordinator*** of the "Murst 60% projects on "*Studio della struttura di traccia e dei danni al DNA indotti da radiazioni ionizzanti, per l'identificazione delle caratteristiche fisiche della radiazione correlate al*

danno biologico and on *Aberrazioni cromosomiche indotte da radiazioni ionizzanti: modelli meccanicistici e simulazioni Montecarlo per lo studio della cinetica e della dipendenza dal tipo di radiazione.*

Funded by the NATIONAL INSTITUTE OF HEALTH

- 1997-1998 ***Principal investigator*** of the research on *Biophysical models for the optimization of proton therapy* (Conv. N. 93/M/T6) within the Project on: *Development of proton studies for oncologic therapy*.

Funded by the ITALIAN SPACE AGENCY (ASI)

- 2016-2018 – ***Principal Investigator*** of the project **PERSEO/ASI** *PErsonal Radiation Shielding for intErplanary mission* (in the negotiation phase). Subcontractors: Thales Alenia Space Italia (TASI), Società Metropolitana Acque Torino (SMAT), Altec, avite, Univ. Roma Tor Vergata
- 2006-2007 ***PA/QA***, 2008-2010 ***Principal Investigator*** and ***national coordinator*** of the subproject **COUNT** (7 partners working on *Countermeasures For The Exposure To Galactic Cosmic Rays In Deep Space*) of the project **MoMa** (*From molecules to man: Space research applied to the improvement of the quality of life in aged population*) and Scientific Manager of the partner UniPv.
- 2000-2004 ***Scientific manager*** of Milan Unit MI1 and (from 2002 of Pavia Unit, Department of Nuclear and Theoretical Physics) of the project *Influence of the shielding in the space radiation biological effectiveness*.

Funded by the EUROPEAN SPACE AGENCY (ESA)

- **2014-2015 Contractor's Representative** (for technical matters, together with Dr. G. Baiocco) for the project **PERSEO/ESA** - *PErsonal Radiation Shielding for intErplanary mission* (after the 2014 Ariadna Call For Ideas - Innovative Radiation Shielding Approaches - ESA Interaction with Academia on Advanced Research Topics), Contract Number: 4000111396

Other research collaborations

- 2006-2008 I ***participate*** in the ***INFN-FLUKA2*** experiment on the *Proposal for the continuation of the activity of development, maintenance and diffusion of the Monte Carlo cod FLUKA*.
- 2002-2005 I ***participate*** in the *INFN-FLUKA experiment* on the *Development the MC code FLUKA and of its interdisciplinary and technological applications*.
- 1995 I start a ***collaboration*** with the Karolinska Hospital and the Department of Medical Radiation Physics of Stockholm University, and I co-ordinate a research on the *techniques to calculate complication probabilities in radiotherapy*.
- 1994 I become ***member of the TERA project (Handrontherapy).*** In this project I ***co-ordinate*** the research on the *use and development of Monte Carlo codes for the l'Evaluation of radiobiological effectiveness of therapeutical proton beams*. I also participate in a project for *An automatic system for a beam feedback control.*

COMMITTEES, BOARDS AND CHAIRS

- ***Director*** of the International Course on *Modelling radiation effects from initial physical events - Learning modelling approaches and techniques in radiation biophysics and radiobiology research, from basic mechanisms to applications*, to be held in Pavia, May 23rd - June 3rd, 2016, Department of Physics, University of Pavia, Pavia, Italy, funded by the European Joint Programme CONCERT.
- ***Main Scientific Organizer (MSO)*** of the two day event on *Space Radiation Risk and Counter-measures: Physical and Biophysical Mechanisms, Modelling and Simulations* within the 41st COSPAR Scientific Assembly, to be held in Istanbul, Turkey, 30 July - 7 August 2016.
- ***Director*** of the International Course on *Modelling radiation effects from initial physical events - Learning modelling approaches and techniques in radiation biophysics and radiobiology research, from basic mechanisms to applications*, Pavia, June 1st - June 12th, 2015, Department of Physics, University of Pavia, Pavia, Italy, funded (after selection) by the European Network of Excellence DoReMi.
- ***Director*** of the International course on *Radiation Biology for Medical Physicists*, Pavia, 13th - 18th April, 2015, Department of Physics, University of Pavia, Pavia, Italy, funded by the *European project* **EUTEMPE-RX**.
- ***Main Scientific Organizer (MSO)*** of the two day event on *Space Radiation Risk Assessment and Counter-measures: Physical and Biophysical Mechanisms, Modelling Simulations and Future Experimental Roadmaps* within the 40th COSPAR Scientific Assembly, Moscow, Russia, August 2014.
- ***Director*** of the International Course on *Modelling radiation effects from initial physical events - Learning modelling approaches and techniques in radiation biophysics and radiobiology research, from basic mechanisms to applications* , Pavia, May 26th - June 6th, 2014 Department of Physics, University of Pavia, Pavia, Italy, funded (after selection) by the European Network of Excellence DoReMi.
- ***Member of the Assembly and of the Board*** of the ***MELODI Association*** (*Multidisciplinary European Low Dose Initiative*), also ***representing the Rector of the University of Pavia.***
- ***Main organiser and chair*** of the DoReMi/MELODI Training & Education Forum, towards the integration for European low-dose radiation risk research. Brussels, Belgium, 8 October 2013.

- ***Chair of the Working group on Training and Education of the MELODI Association*** (*Multidisciplinary European Low Dose Initiative)*
- ***Observer in the Working group on the Strategic Research Agenda of the MELODI Association*** (*Multidisciplinary European Low Dose Initiative)*
- ***Observer in the Working group on Infrastructures of the MELODI Association*** (*Multidisciplinary European Low Dose Initiative)*
- ***European coordinator*** of the eight DoReMi two/three week courses (2013-2014) on Effects of low doses of ionising radiation to be held in Munich (Germany), Pavia (Italy), Stockholm (Sweden), Mole (Belgium), Paris (France), Oslo (Norway)
- ***Chair*** and ***Main Organizer*** of the **DoReMi Radiation Quality Workshop,** SCK-CEN Headquarters, Brussels. 9-10 July 2013
- ***Member of the Joint Committee*** lecturers-students of the Physics department of the University of Pavia
- ***Director*** of the *International Course on Modelling radiation effects from initial physical events - Learning modelling approaches and techniques in radiation biophysics and radiobiology research, from basic mechanisms to applications* May 27th - June 7th, 2013 Department of Physics, University of Pavia, Pavia, Italy, funded (after selection) by the European Network of Excellence DoReMi.
- ***European coordinator*** of the nine DoReMi two/three week courses (2012-2013) on Effects of low doses of ionising radiation to be held in Munich (Germany), Pavia (Italy), Stockholm (Sweden), Mole (Belgium), Paris (France), Oslo (Norway)
- ***Main Organizer and Chair*** of A one day course on Systems Radiation Biology - Learning about how the systems biology approach can be used for research into the biological response to ionising radiation, Sunday 2 September 2012, St Anne's College, Oxford, UK
- ***Director*** of the International Course on Modelling radiation effects from initial physical events - Learning modelling approaches and techniques in radiation biophysics and radiobiology research, from basic mechanisms to applications May 28th - June 8th, 2012 Department of Physics, University of Pavia, Pavia, Italy, funded (after selection) by the European Network of Excellence DoReMi.
- ***Director*** of the International Course on Modelling radiation effects from initial physical events - Learning modelling approaches and techniques in radiation biophysics and radiobiology research, from basic mechanisms to applications May 30th - June 10th, 2011 Department of Nuclear and Theoretical Physics, University of Pavia, Pavia, Italy, funded (after selection) by the European Network of Excellence DoReMi.
- ***Main Scientific Organizer (MSO)*** of the two day event "Space Radiation Risk Assessment and Counter Measures: Physics and Biophysical Mechanisms, Modeling and Simulation" within the 39th COSPAR Scientific Assembly, Mysore, India, 14-22 July 2012.
- ***Main organiser and chair*** of the DoReMi/MELODI Training & Education Forum, towards the integration for European low-dose radiation risk research. Helsinki, Finland, 11 September 2012.
- ***Main organiser and chair*** of the DoReMi/MELODI Training and Education Workshop: towards the integration for European low-dose radiation risk research. 2 November 2011, National Health Institute, Rome, Italy.
- ***Member of the Scientific Committee*** of the 3rd International MELODI Workshop - Multidisciplinary European Low Dose Initiative, November 2-4, 2011, National Health Institute, Rome, Italy.
- ***European coordinator*** of the six DoReMi two week courses (2009-2010 and 2010-2011) on Effects of low doses of ionising radiation held in Munich (Germany), Pavia (Italy), Stockholm (Sweden), Mole (Belgium).
- February 2010: ***member of the visiting committee*** for the evaluation of the Institut de Radiobiologie Cellulaire et Moléculaire (IRCM), Commissariat à l'Energie Atomique (CEA), Fontenay-aux-Roses, Paris, France
- ***Member of the Expert Group*** on Radiation effects on humans - THESEUS – Towards Human Exploration of Space: A European Strategy (European Science Foundation)
- 2007-2008 ***member of the High Level Expert Group (HLEG)*** on Low Dose Risk Research (established in order to better structure and integrate European research in this area and link it with similar research being carried out elsewhere) as high level expert in the area of radiobiological modelling.
- 2006-2013: ***member of the Comitato Tecnico-Scientifico of LENA*** (Laboratory of Applied Nuclear Energy) University of Pavia.
- 2004-2009 ***Deputy Director*** of the Specialization school in Medical Physics, jointly managed by the Universities of Milan, Pavia and Varese.
- 2003 - present: member of the Graduate School Committee of the Graduate Program in Physics (PhD courses), University of Pavia.
- 1999-2002 ***member of the Graduate School Committee*** of the Graduate Program in Physics (PhD courses), University of Milan.
- ***Member of the Organizing committee*** of the workshop on "Medicina: ruolo dello specialista in Fisica Medica", Milan, 16 November 2009.

- ***Member of the International Scientific Committee*** of the "Heavy Ions in Therapy and Space Symposium 2009" Cologne, Germany, July 6-10, 2009
- ***Main Scientific Organizer (MSO)*** of the two-day event "Models and Simulations for Space Radiation Risk Assessment and Countermeasures" within the 38th COSPAR Scientific Assembly, Bremen, Germany, July 2010.
- ***Main Scientific Organizer (MSO)*** of the 1½ -day event "Models and Simulations for Space Radiation Risk Assessment and Countermeasures" within the 37th COSPAR Scientific Assembly, Montreal, Canada , 13-20 July 2008.
- ***Member of the Programme committee*** of the course on Fundamentals of oncological radiotherapy and hadrontherapy Pavia, 28 February - 1 March 2008.
- ***Member of the Scientific and Organising Committee*** of the 3rd FLUKA course, Pavia, March 27-31, 2006
- ***Member of the international FLUKA Coordinating Committee*** (FCC) (2005)
- ***Main Scientific Organizer (MSO)*** of the one-day event "Physical and Biophysical Models and Simulation Codes for Space Radiation Risk Assessment" within the 36th COSPAR Scientific Assembly, Beijing, China, July 16-23, 2006
- ***Member of the Committee for Space Research*** (COSPAR).
- ***Member of the Organizing Committee*** of the 11th International Conference on Nuclear Reaction Mechanisms, Varenna (Italy), Villa Monastero June 12 - 16, 2006
- ***Co-chairman of the 14th International Symposium on Microdosimetry***, Venice, November 2005
- ***Co-chairman of the 24th Miller Conference on Radiation Chemistry***, 10-15 September 2005, La Londe les Maures, France.
- ***Member of the subcommittee on Biological Effects of Ionizing and Nonionizing Radiation*** del 14th International Conference of Medical Physics, Nuremberg, Germany, Sept. 14-17, 2005
- ***Member of the International Program Committee*** of the XIX Nuclear Physics Divisional Conference New trends in nuclear physics applications and technology, September 5-9, 2005 – Pavia, Italy
- **Member of the Scientific Committee** of the XII Convegno SIRR Genoa 9-12 November 2004
- ***Member of the Scientific Committee*** of the II Riunione SIRR and I Convegno Nazionale FIRR on Radiazioni in Medicina e Biologia: stato delle ricerche e applicazioni cliniche, Legnaro-Padova, 20-22 November 2003
- ***Member of the Scientific Committee*** of the VII International Workshop on Radiation damage to DNA, Orléans, 2-7 September 2001.
- ***Co-chairman of the 13th International Symposium*** on Microdosimetry and of the Satellite meeting 5th International Workshop on Microbeams, Stresa 26 May – 1 June 2001.
- ***Member of the Scientific Committee*** and of the Organizing Committee of the X convegno nazionale SIRR, Frascati, November 2000.
- ***Member of the Scientific Committee*** and of the Organizing Committee of the Prima Runione Nazionale organized by SIRR, INFN and ENEA) on Stato dell'arte della radiobiologia in Italia, Padova, 28-30 November 1999.
- ***Main organizer and Chair*** of the one-week AIFB-SIRR course on Method for the deveopment of models and simulations in biomedicine and biophysics. (Como, 23-26 June 1997).
- 1997-2001 ***member of the executive committee of the Physics Department of*** the University of Milan.
- 1997-2000 and September 2002- September 2006 ***member of Board of SIRR*** (Società Italiana Ricerca sulle Radiazioni, Italian Society on Radiation Research), also organizing courses and workshops.
- ***Organizer and co-chair*** of a national co-ordination on methods and techniques of Monte Carlo Simulations for radiotherapy with protons (1995)
- ***Responsible for computing of the Medical Physics section*** of the Physics Department (University of Milan) (1992-2001).
- ***Organizer*** (together with P. Cotta-Ramusino and L. Lanz) ***of a series of seminars each year***, on nuclear weapons, at the Physics Department of the University of Milan (1984-1987).
- ***Member of the simulation group for the development of treaties on Nuclear Weapons***, on invitation, for one month at the University of California, Santa Cruz, with the role of technical adviser (1988).
- Two week meeting (and course) on nuclear weapons and arms control on invitation by J. Ruina (M.I.T., Cambridge, U.S.A.) (1987).
- ***Member or the Advisers group of the World Health Organization***: WHO Management group on Follow-Up of Resolution WHA 36.28 (on the effects of nuclear explosions), on invitation by J. Rotblat (London, formerly member of the Manhattan Project, chair of Pugwash and Nobel Prize in 1995) (1986).

REVIEWING ACTIVITIES

- **Peer reviewer** for International journals, including: Radiation and Environmental Biophysics, The International Journal of Radiation Biology, Radiation Research, Radiation Protection Dosimetry,

Advances In Space Research, New Journal of Physics, Radiation Measurements, PLoS Computational Biology, International Journal of Radiation Oncology • Biology • Physics, PlosOne, Frontiers.

- **Evaluator of Scientific Proposals** for international and national institutions, including: DOE (Department of Energy, USA), Universities of Padua and Trieste, Praha Academy, National Institute for Health Research (UK), Swedish National Space Board, Cancer Research UK.

INVITED LECTURES (selected)

84. *Education and Training for radiation protection research in Europe*, 41st COSPAR Scientific Assembly, to be held in Istanbul, Turkey 30 July - 7 August 2016.
83. *Space radiation risk and counter-measures for human exploration*, 41st COSPAR Scientific Assembly, to be held in Istanbul, Turkey 30 July - 7 August 2016.
82. *European Joint Programme for the Integration of Radiation Protection Research (CONCERT),* Euratom: Giornata Nazionale di Lancio dei Bandi 2016-17 in Horizon 2020, ENEA Roma, 18 febbraio 2016
81. *DoReMi research on Mitochondria - The INITIUM project (Track structures and initial events: an integrated approach to assess the issue of radiation quality dependence),* DoReMi workshop "Mitochondria and Radiation" Munich, 14 – 15 December 2015.
80. *Research on radiation quality and hadrontherapy: where are we? What is to be done?* Technical Meeting (TM), Radiobiology of Charged Particle Therapy (RBPT) IAEA Headquarters, VIC, Vienna, Austria 11 – 13 November 2015.
79. The *ANDANTE project,* MELODI 7th Workshop, Next Generation Radiation Protection Research, Munich, 9 – 11 November 2015
78. *Proposal for an organisation of the task on "dosimetry", including track structure and links with radiobiology*, Crosscutting support to improved knowledge on tritium management in Fission&Fusion facilities. International Workshop: Brussels, 8-9 October 2015
77. 'Heterogeneous learning': participants come with different background and experience (examples, questions, few answers, more questions and stimuli for discussion), Mid-term open workshop of the EUTEMPE-RX project, Sofia, Bulgaria September 25, 2015
76. DoReMi - Low Dose Research towards Multidisciplinary Integration: Education and Training actions, 15th International Congress of Radiation Research (ICRR 2015), Kyoto, Japan, May 2015.
75. Research on radiation quality and hadrontherapy. Seminar on research activities in hadrontherapy, April 29th, 2015, CNAO, Pavia
74. Is there a role for universities in future radiation protection research programs? Meeting with representatives from universities with the aim to make recommendations on how to make full use of the universities research potential for radiation risk research. Rånäs slott, Sweden: December 2014
73. Early events, radiation quality and dose. The experience of the ANDANTE project, TC-IR Ionizing Radiation EURAMET Technical Committee, Oslo, Norway, October 2014
72. *Track structures and initial events: an integrated approach to assess the issue of radiation quality dependence* DoReMi Periodical Meeting, Munich, 2014
71. Round table on the roadmap for future space radiation research 40th COSPAR Scientific Assembly, Moscow, Russia, August 2014.
70. The ANDANTE project: progress towards a re-evaluation of the risk from scattered neutrons during proton therapy. ESTRO 33, Vienna, Austria, 04-08 April, 2014
69. Radiobiology and Hadrontherapy, Le frontiere della medicina tra futuro e attualità: i risvolti della ricerca nella pratica clinica, Collegio Ghislieri, 31 marzo 2014
68. MELODI Working Group on Education and Training 5th MELODI Board of Directors Paris, 10th of February, 2014
67. Education and Training in DoReMi, MELODI and OPERRA, Fifth International MELODI Workshop, October 7-10 2013, Brussels
66. Summary of the Radiation quality workshop, DoReMi Cross cutting meeting 7 October 2013, Brussels
65. Education and Training in the DoReMi project, EUTEMPE-RX kick-off meeting, Leuven, Belgium, 1-2 October 2013
64. From early events to biological damage: the radiation quality issue. Italian Physics Society Meeting, 2013, Trieste
63. Welcome and introduction DoReMi Radiation Quality workshop, SCK-CEN Headquarters, Brussels. 9-10 July 2013
62. Support and integration of education and training on low dose radiation research in europe, ETRAP 2013, 12 - 15 March 2013, Vienna, Austria
61. ANDANTE: The project: a multidisciplinary approach to neutron RBE**.** 2nd ESTRO Forum, Geneva, Switzerland from 19-23 April 2013.
60. Introduction to the Forum, DoReMi/MELODI Training & Education Forum 11 September 2012 Helsinki, Finland

59. ALLEGRO to ANDANTE: An application of radiotherapy data to low-dose radiation research. 4th International MELODI Workshop, 12-14 September 2012 Helsinki, Finland
58. Introduction to session F2.2 “Space Radiation Risk Assessment and Counter Measures: Physics and Biophysical Mechanisms, Modeling and Simulation”. 39th COSPAR Scientific Assembly, Mysore, India, 14-22 July 2012.
57. The ANDANTE project: refining risk estimates from neutrons. ESTRO 31, Barcelona, Spain, 9-13 May, 2012.
56. ALLEGRO, Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy and 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. Giornata informative nazionale nell’ambito del programma EURATOM – presentazione del bando FP7-Fission- 2012, Roma. 17 February 2012
55. Dosimetry for second cancer risk: the EU projects ALLEGRO and ANDANTE. EURADOS Annual Meeting 2012- AM2012, IAEA, Vienna, 6-10 February 2012
54. Early events relevant for biological damage Third MELODI Workshop Rome, 2 - 4 November 2011
53. Invited lecture on Modelling of DNA damage dependence on radiation quality. 14th International Congress of Radiation Research Warsaw, Poland, August 28 - September 1, 2011
52. DNA fragmentation after heavy ion irradiation. DoReMi Modelling Workshop. 7 July 2011. Brussels
51. The ALLEGRO Project: an overview. ESTRO Anniversary Congress, London 8 – 12 May 2011.
50. Modelli del rischio di tumori secondari dopo RT. Corso AIFM su Modelli Predittivi Degli Effetti Della Radioterapia Con Fasci Esterni Firenze 24-26 November 2010
49. Effetti dell’irraggiamento sui sistemi cellulari Corso AIFM su Modelli Predittivi Degli Effetti Della Radioterapia Con Fasci Esterni Firenze 24-26 novembre 2010
48. Track structure, radiation quality and initial events in radiobiological damage, MC2010, Stckholm, 9-12 November 2010
47. ALLEGRO: understanding the risks of normal tissue complications and second cancers following radiotherapy. ESTRO 29 Congress, Barcelona, Spain from 12-16 September 2010.
46. La struttura di traccia come determinante dell'efficacia biologica. La Radiobiologia degli adroni carichi con acceleratori INFN: ricerca, sviluppo, applicazioni. Istituto Superiore di Sanità, Roma, 08 June 2010
45. Stato della ricerca radiobiologica a basse dosi. Corso Dosimetria In Radiodiagnostica Centro Congressi Villa Cagnola Gazzada (VA) 5-7 May 2010
44. Allegro project, Radiogenomics meeting, The University Of Manchester, Manchester, 17-18 November 2009
43. Il rischio di complicanze ai tessuti sani e di tumori secondari in radioterapia: la ricerca in ambito EURATOM, L’ottimizzazione nell’impiego delle radiazioni ionizzanti in Medicina: ruolo dello specialista in Fisica Medica, Milano, 16 November 2009.
42. Effetti radiobiologici della dose integrale e stima del rischio nelle tecniche radioterapiche con fasci esterni. VI Congresso Nazionale AIFM, Reggio Emilia, 16-19 September 2009
41. Nuovi aspetti radiobiologici per la comprensione degli effetti delle radiazioni ionizzanti sull’uomo Seminario - Dal dato dosimetrico all’indice di rischio per pazienti sottoposti ad esami di diagnostica per immagini Polo Didattico Formativo S. Maria a Colle Maggiano (Lucca) 24 March 2009
40. The ALLEGRO project: a European consortium on Early and late health risks to normal/healthy tissues from the use of existing and emerging techniques for radiation therapy. Heavy Ions in Therapy and Space Symposium. Cologne, July 6-10, 2009
39. Il contributo della modellistica, Workshop su La valutazione dei rischi sanitari delle basse dosi di radiazioni ionizzanti: la ricerca italiana e le sue prospettive nel contesto europeo 27 February 2009 Istituto Superiore di Sanità, Roma
38. I modelli di valutazione degli effetti biologici delle dosi somministrate al di fuori del target. al XVIII Congresso Nazionale AIRO, Milano, 15-18 Novembre 2008.
37. Radiation induced inflammation processes and carcinogenesis: from in vitro to in tissue and ex vivo, an integrated experimental and theoretical approach, Workshop: Cancer risk derived with models of carcinogenesis, based on radiobiological measurements and epidemiological data (EpiRadBio), Dublin, Sept. 2009.
36. The “High Level Expert Group on European Low Dose Risk Research (HLEG) su Challenges for understanding and predicting ionizing-radiation health effects al workshop su Radiazioni ionizzanti: nuovi modelli per la stima del rischio. Rome, ENEA, 1 October 2008
35. F22 Session Introductory talk at the COSPAR Meeting, Montreal, Canada, July 2008,
34. I modelli radiobiologici per la terapia con ioni carbonio at the course on Fondamenti di Radioterapia Oncologica e Adroterapia, Pavia, 28 febbraio- 1 marzo 2008
33. Problematiche attuali della ricerca in adroterapia. Convegno AIFM, Lucca, September 2007
32. Modeller biologist interaction at the NOTE training course on Protocols and Pitfalls in the study of Non-Targeted Effects of Radiation, Crete, September 2007

31. Radiobiologia degli adroni carichi: conoscenze attuali e attività di ricerca Convegno Congiunto IGM-CNR, 22-23 Febbraio 2007, Pavia
30. Aspetti fisico-radiobiologici: conoscenze attuali e attività di ricerca La radioterapia con adroni: basi razionali e impiego clinico, Giornata Seminariale Inter-Universitaria. Novara, 7 July 2006
29. Models and simulations of radiation induced chromosome damage Radiation Damage in Biomolecular Systems, The Royal College of Surgeons, Dublin, Ireland 19th - 22nd June 2007
28. Mechanistic and phenomenological models of radiobiological damage Discussion Seminar About Radiation Quality Assessment in Hadrontherapy - Legnaro, 30-31 October 2006
27. Modelling of cellular and tissue responses after irradiation including bystander effects and genomic instability, Radiation Damage to Biomolecules 17 - 19 October 2006, Bad Honnef, Germany
26. Modelli Biofisici dell'azione delle radiazioni ionizzanti sulle strutture biologiche, Giornata di studio - Adroterapia e Ricerca Radiobiologica: Stato e Prospettive in Italia, Roma 27 June 2005
25. Modelling the evolution of radiobiological damage with focus on target structures, RADAM Conference 2005, 17th-20th March 2005, Potsdam near Berlin, Germany
24. Research activities in Radiobiology. First Workshop of the LNL/GANIL Associate European Laboratory Padova April 7th-8th, 2005
23. Ab initio modelling of radiation damage: from track structure to biological endpoints. RADAM Conference, Lyon, June 2004
22. Chromosome aberrations as biomarkers of radiation quality: modelling basic mechanisms at the 34rd COSPAR Scientific Assembly, Houston, October 2002
21. From track structure to biological damage: induction and evolution of DNA lesions all' ESRB meeting, Liege, 4-7 September 2002
20. Targeted and non-targeted effects of ionising radiation: Implications for low dose risk al Workshop of NET-EULEP, Bad Honnef, Germany (10-11 July 2002).
19. Biophysical Models of Radiation Effects al European Radiation Research 2001, 31st annual meeting of the European Society for Radiation Biology, Dresden, Germany (1-5 September, 2001).
18. Modelling of radiation effects at the cellular level al 1st Workshop of NET-EULEP, Bad Honnef, Germany (16-19 June 2001).
17. Modelling Radiation induced bystander effect, 11th L.H. Gray workshop, Dublin (2-5 September 2000).
16. Modelling chromosomal aberration induction by ionising radiation: mechanistic approaches based on track structure simulations at the 33rd COSPAR Scientific Assembly, Warsaw, Poland (16-23 July, 2000)
15. Mechanistic bases for modelling space radiation risk and planning radiation protection of astronauts al 1st International Workshop on Space Radiation Research organized by ASI, NASA and ISE, (Arona 27-31 May 2000)
14. AIFM course on Practical use of TCP and NTCP models for the evaluation of treatment plands in radiotherapy (Como, October 1999).
13. Symposium on "Models from Radiation tracks to molecular damage and cellular effects", all'11th International Congress of Radiation Research, 18th-23rd July, 1999
12. Introductory lecture at the session "Modelling radiation induced biological lesions: from initial energy depositions to chromosome aberrations" al 9th L.H. Gray workshop, 10-13 September 1998, Harwell, UK.
11. Introductory lecture at the session "DNA damage and radiation quality: experiments versus modelling al 12th Symposium on Microdosimetry (29th September - 4th October 1996)
10. su Uso delle strutture di traccia per la comprensione dei meccanismi di induzione dei danni radiobiologici, Congresso Nazionale SIF 1995
9. Simulazioni di traccia per terapia con protoni: aspetti dosimetrici, radiobiologici e radioterapici. Congresso Nazionale SIF 1996

1.-8. Invited lectures on topics related to the effects of nuclear explosions and of of nuclear accidents at the Universities of Milan, Padoa, Rome, Parma, Pavia, Firenze, International School on Disarmament and Research on Conflict, S. Miniato (Director C. Schaerf), International workshop on Nuclear Weapons and Arms Control In Europe (Castiglioncello, 21-25 october 1985

TEACHING ACTIVITY

Summary

- October 2001-present: main teaching activity at the Faculty of Medicine and Surgery and at the Faculty of Science, University of Pavia.
- April 1992- September 2001: main teaching activity at the Faculty of Medicine and Surgery and at the Faculty of Pharmacy, University of Milan.
- December 1969-April 1992 teacher with continuity (permanent position since 1970 and staff member ("di ruolo") since 1974) in public secondary schools.

Main teaching activities:

- courses of Physics and of Radiobiology at the Faculty of Medicine; courses of Radiation Biophysics and Radiobiology at the Faculty of Science; course of Radiobiology for the Physics Doctorate and for the

specialization in Medical Physics (for physicists), and in Radiology and in Radiation Therapy (for medical doctors). Member of the Faculty committee of the Physics Doctorate (previously at Milan University and now at Pavia University); Deputy Director of the School of Medical Physics of Milan, jointly managed by the Universities of Milan, Pavia and Varese.
- Lecturer (and organizer of courses – see section above, on "committees, boards and chairs) on low dose effects, in international courses.

Supevision of Master, PhD, and Specialization Theses, and of post-doc and scholarship fellows
- Responsible for supervising several dozens of MPhys and PhD final year projects and theses ("Laurea" in Physics, PhD in Physics, Specialization in Medical Physics, European Master of Science in Radiation Biology (University College of London, UK)).
- Supervisor and Scientific responsible of dozens of post "laurea" scholars and postdoctoral researchers.

Details on courses
- A.Y. 2014-2015: Course of Medical Physics for the 6-year degree course in Medicine and Surgery, taught in English, University of Pavia.
- A.Y. 2014-2015: Course of Mathmatics for the 6-year degree course in Medicine and Surgery, taught in English, University of Pavia.
- A.Ys. 2007/08–2009/2010: course on Modelling in Radiobiology at the European Master of Science in Radiation Biology (University College of London, UK).
- A.Ys. 2003/04 – 2010, 2012/13: Course of Radiobiology for the International Master on Nuclear and Ionizing Radiation Technologies organized by the University Institute for Advanced Studies (IUSS), Pavia
- A.Ys. 2003/04 – 2013-2014: Course of Physics and Biomedical Technologies for the PhD students at the Graduate School of Physics, University of Pavia.
- A.Ys. 2001/02 - 2013-2014: Course of Physics and Statistics for the three year degree course in Physical education and sport, University of Pavia.
- A.Y. 2001/02 - 2013-2014: Course of Physics in the three-year degree courses in Health Rehabilitation and in Prevention techniques in the environment and at the workplace, Faculty of Medicine and Surgery, University of Pavia.
- A.Y. 2001/02: Course of Radiobiology for the specialization in Radiology and Radiotherapy of the Faculty of Medicine and Surgery, University of Pavia.
- A.Ys. 2001/02 - present: Course of Radiobiology in the three-year degree courses in Medical Radiology Techniques, Imaging and Radiotherapy, Faculty of Medicine and Surgery, University of Pavia.
- A.Ys. 2001/02–2010: Course of Radiobiology for the specialization in Medical Physics Specialization school in Medical Physics, jointly managed by the Universities of Milan, Pavia and Varese.
- A.Ys. 2000-01, 2001/02, 2002/03, 2008/09 - present: Course of Radiobiology for the Master's degree in Physics (University of Pavia).
- A.Ys. 1999/00, 2000/01, 2001/02, 2002/03, 2003/04 and 2004/05: Course of Physics for the Master's degree in Pharmacy, University of Milan.
- A.Y. 1999/00: Course of Medical Physics for the 6-year degree course in Medicine and Surgery (University of Milan).
- A.Ys. 1996/97, 1997/98: Course of Medical Physics for the Master's degree in Odontology (University of Milan).
- A.Ys. 1995/96, 1996/97, 1997/98, 1998/99, 1999/00: Course of Medical Physics for the following three year degree course (at the University of Milan): Orthoptist and Assistant in Ophthalmology (with Laboratory), Techniques of Psychiatric Rehabilitation, Logopedia, Techniques of Audiometry e Hearing aids
- A.Y. 1994/95: tutorials and exams of Medical Physics for the 6-year degree course in Medicine and Surgery, for the three year degree course for Orthoptist and Assistant in Ophthalmology, University of Milan.
- A.Y. 1993/94: tutorials and exams of Medical Physics for the 6-year degree course in Medicine and Surgery, for the three year degree course for Orthoptist and Assistant in Ophthalmology, and for the specialization in Preventive hygiene and medicine, and in Ophthalmology University of Milan.
- A.Y. 1992/93: tutorials and exams of Medical Physics for the 6-year degree course in Medicine and Surgery, for the three year degree course for Orthoptist and Assistant in Ophthalmology, and for the specialization in Preventive hygiene and medicine, University of Milan.
- A.Y. 1991/92: tutorials and exams of Medical Physics for the for the 6-year degree course in Medicine and Surgery, University of Milan.
- 1991-2001 coordinator of the development of teaching software and the tutor activities for Medical Physics in the Faculty of Medicine and Surgery of the University of Milan.
- December 1969 - April 1992 teacher with continuity (permanent position since 1970 and staff member ("di ruolo") since 1974) in public secondary schools. In 1992 he leaves the position of teacher of Mathematics and Physics in High school for the position of researcher at the University of Milan.

RESEARCH ACTIVITY – Summary

The research activity has mainly been on ionizing radiation effects, initially at the Physics Department of the University of Milan and then at the Nuclear and Theoretical Physics Department of the University of Pavia. In particular the activity consisted in the development of models and simulations and experiment designs and data analysis, relative to: radionuclide transport in atmosphere after nuclear explosions and accidents; dose estimates in organs using compartment analysis, short- and long-term effects on humans; cell growth, inactivation, transformation and chromosomal aberrations after in vitro irradiation, and their dependence on radiation characteristics, dose rate etc.; radiation induced DNA damage and repair processes (and relevance in inducing biological end-points); bystander effects; radiation track structure and transport codes (with the integration of radiobiological models); shielding effects using anthropomorphic phantoms; optimisation studies for radiotherapy, with photons and hadrons. In the last years specific attention was dedicated to: theoretical and experimental basic research on the effects of low doses of ionizing radiation of different qualities (with the development of systems radiation biology approaches; clinic radiobiology for the optimization of radiotherapy treatment plans (in particular the risk of complications and of secondary tumours in radiotherapy).

Today I coordinate the **Radiobiology and Radiation Biophysics** group (at the Physics Department of the University of Pavia) and I carry on experimental and theoretical studies on the effects of ionizing radiation on biological structures, with applications in radiation therapy, diagnostics and radiation protection (particularly for the effects of low doses and for space radiation). The activities are carried on as collaborations involving physicists, biologists, physicians and epidemiologists.

The general objectives of basic research are:

- to understand the mechanisms of ionizing radiation action on biological targets from physical interactions (track structure, studied using Monte Carlo methods) to biological damage, at sub-cellular, cellular, tissue, organ and systemic levels. The research activities include radiation induced DNA damage and repair processes (and their relevance in inducing other biological endpoints), intra- and extra signalling perturbation (bystander effect), and their anti and pro carcinogenesis implications. To deeply understand the mechanisms associated with radiation risks (cancer and non-cancer, including cardiovascular effects) and develop predictive and robust models, a holistic approach needs to be associated to a step by step description of radiation action. Ionizing radiation needs to be analysed as a perturbing agent of a complex system that will react with complex behaviours and feedback phenomena, and may end up with a homeostatic equilibrium or with a pathological condition. Together with a classical reductionist study, a system, multi-scale approach is therefore developed, based on the *systems radiation biology*;
- to use radiation as a probe to study mechanisms and behaviours of biological structures, and the response to external stimuli.

The general objectives of applied research are:

- to predict radiation risk particularly from low doses (cancer and non cancer) and its dependence on dose, dose rate and radiation quality (particularly for neutrons);
- to optimize the clinical use of radiation in diagnostics and therapy (e.g. risk of complications and of secondary tumours in radiotherapy, with photons and hadrons);
- to assess the risk assessment and develop countermeasures for missions in open space (e.g. mission to Mars).

RESEARCH ACTIVITY – Description and results

1. Effects of nuclear explosions
2. Biophysical mechanisms of radiation action and effects of experimental conditions: in vitro effects at cellular level
2.1 Growth kinetics of in vitro irradiated cells
2.2 Effects of initial cell density on radiation-induced neoplastic transformation in vitro
2.3 Biological effects of alpha particles
2.4 Criteria and techniques for analyzing cell radiation-induced inactivation data
2.5 Microdosimetry- and biophysics-based predictions, of the dose-rate effects on radiation-induced cell transformation – the inverse dose rate effect.
2.6 Chromosome aberrations induced by high LET radiation and X rays.
3. Biophysical mechanisms of radiation action: radiation interaction with biological structures and damage evolution
3.1 DNA damage complexity and dependence on radiation quality
3.2 Evolution of DNA damage: chromosome aberrations
3.3 Evolution of DNA damage: cell inactivation
4. A systems radiation biology approach
4.1 Cell communication perturbation induced by ionizing radiation: the example of IL-6 signaling
5. Research finalized to radiotherapy: development and application of techniques to evaluate and compare treatment plans in radiotherapy and to optimize radiation treatments.
5.1 Risk to the heart and to the respiratory system
5.2 Biological mechanisms of normal tissue damage: Importance for the design of NTCP models
5.3 Risk of complications and secondary tumours in radiotherapy – the European projects ALLEGRO and ANDANTE (European coordination).
5.4 New Methods for patient alignment in radiotherapy
6 Development and application of Monte Carlo Codes for application in hadrontherapy and space-radiation protection.
6.1 Protontherapy
6.2 Ions and neutrons
6.3 Radiation protection in space
7. Bio-element kinetics studies using stable tracers and nuclear activation techniques.

1. Effects of nuclear explosions

I carried out a research on the theoretical aspects relative to the physics of nuclear weapons and to the consequences of explosions (in particular thermal and mechanical effects, prompt radiation and fallout) and, more in general, on models and simulations of radiation effects. The fundamental aspect of the work was the design of a model (and of corresponding simulation code) initially used for a simulation of a nuclear conflict in Italy. In 1986 I was invited by the World Health Organization and Joseph Rotblat (London, formerly member of the Manhattan Project and chair of Pugwash, Nobel Prize in 1995) to become member or the Advisers group of the World Health Organization "WHO Management group on Follow-Up of Resolution WHA 36.28 (on the effects of nuclear explosions). I was specifically invited to carry out a simulation of the effects of a limited nuclear war in Europe. The results of the simulation were adopted by the WHO Management group and were published in 1987 by the WHO 10 languages: Arabic, Chinese, English, French, German, Russian, Spanish, Czech; Italian, Swedish (see list of publications).

I initially analyzed the physical phenomena that occur after nuclear explosions and the corresponding biological effects and I then formulated a general model adopting a system theory approach. The model was therefore formally described by means a 7-tuple: T (time basis), U (input set), Y (output set), X (state set), Omega (set of the admissible input functions), Phi (state transition function), eta (behaviour function). This approach has allowed a structure of the model and of the simulation codes, where direct comparisons where possible with specific researches and results from other research groups. The input set was described by a matrix containing the explosions characteristics. The state set was described by matrixes that describe on a grid the conditions of the territory (radioactivity as a function of time, and meteorological conditions) and of the population (distribution on the territory, protection conditions, etc.). The state transition state was built starting from the models of the phenomena described below, with the corresponding biological effects and synergisms.

The probability of death and injury from the prompt effects of the explosions, namely thermal radiation and blast wave, are first calculated. The initial nuclear radiation (gamma-rays and neutrons) was ignored, since its range of action falls well within the range of damage from heat and blast for I5O-kt bombs (assumed to be used in the conflict). The effect of fallout was then considered and added to the combined prompt effects. To obtain the number of casualties, the whole area of Europe (exclusive of the Soviet Union, because studied by another research group) was divided into squares of 1 kilometre side. Within each square an average value was assumed for the several variables, i.e. population density, thermal and blast

effects, and radiation exposure from fallout. The total number of fatalities was obtained by summing the deaths in all squares. A similar procedure was adopted in the calculation of the number of injuries, with the qualification that persons suffering injuries from both prompt and fallout effects, or those injured by more than one explosion, are counted as fatalities.

Mathematical formulae and computer programmes were developed to establish the magnitude of the physical phenomena and their effects on the population:

- Shock wave: about 50% of the energy from a nuclear explosion is released as shock wave and a large part of the destruction caused by a nuclear explosion is due to blast and shock phenomena. I adopted functions that describe the peak pressure of the blast wave as a function of the height H and of the distance from the explosion (or of the distance d from ground zero) taking account of scaling possibilities on the bases of the energy released by the explosion. Indeed the dynamic variables relative to energies W1 and W2 assume the same values when d1 = d2 (W1/W2)^(1/3). The overpressure value can therefore expressed as a function of one parameter only (W/(d^3)). An overpressure model was therefore used, relative simple for ground bursts and more complex for air bursts
- Thermal radiation: the radiation fluence was described as *a function of the explosion energy,* and of the height H and of the distance from the explosion. Radiation fluence and rate of delivery (expressed as a function of the explosion energy), were combined into one parameter by defining the effective radiation fluence on the bases of the experience from Hiroshima.
- Fallout: to estimate the effects of local fallout a model is needed that describes the spatial distribution and the rate of the radioactive debris, as a function of the characteristics of the explosion and the meteorological conditions. During the 1970s, detailed models had been developed which considered the meteorological conditions point by point over the contaminated area for weapons of the order of 100 kilotons. The complexity of these models required such a large amount of data and computer time that it made their use difficult for a simulation of multiple explosions over a territory. A simplified model was therefore developed and adopted for this simulation. The adequacy of this model was confirmed by the agreement between predicted and observed fallout patterns following several United States test explosions.
- The number of casualties from radiation exposure depends greatly on the assumed value of the LD-50. Many of the standard casualty models used an LD-50 (measured at the surface of the body) of 4.5 Gy. But a survey of a large group of persons inside their houses during the explosion in Hiroshima, reported by J. Rotblat indicated a much lower LD-50 value under wartime conditions. Consequently, two LD-50 values, 3.5 and 2.5 Gy, were used in the calculation of the number of fatalities. Persons exposed to sub-lethal doses, but who may die due to their susceptibility to infection resulting from the lowering of their immune response, were considered as radiation injuries. The calculation of the probability of death was therefore described by a purposely built model. To allow for the fact that exposure to fallout radiation takes place over a period of time, the concept of the maximum, effective biological dose was used, that is the equivalent of the dose that, if absorbed within a few minutes, would produce the same effect as that from fallout.
- Protection factors: the behaviour of people after the beginning of the attack makes a big difference to the risk of radiation exposure. In this connection it must be pointed out that the first hours after fallout deposition are the most dangerous, since the activity decreases very rapidly with time. Computation of an individual's average protection factor must take into account that it is very unlikely that people would shut themselves into basements or shelters (if available) right after the beginning of the conflict. In fact, experiences from disasters of various kinds - including accidents with release of radioactive debris - show that most people try to reach their relatives and accumulate stocks of food and water, which means staying outside during the most dangerous period. This is especially so in the case when there is lack of communication and information on the dimension of the conflict and the level of involvement of the area. The experience of Chernobyl has shown that even in peacetime and at a low level of radioactivity the information about the real situation was dramatically inadequate. I introduced an approach based on distribution of protection factors to avoid threshold effects present in several simulations previously carried out by other authors.
- Meteorological conditions: the meteorological data were provided by the Global Weather Central (U.S.A.), in the form of typical monthly winds; speeds and directions were given at different levels over each point of a grid covering the northern hemisphere. The calculation of casualties was made for typical winds in four months, February, May, August and November.

2. Biophysical mechanisms of radiation action and effects of experimental conditions: in vitro effects at cellular level

2.1 Growth kinetics of in vitro irradiated cells

Growth curves and size of the colonies of C3H10TI/2 cells exposed to low-LET radiation (31 MeV protons) were determined after 0, 1, 3, 5, and 7 Gy . The data showed that: cell density at confluence was 3 .3 x 104 cells/cm2; the initial division delay was very small; in the first 15 h the increase in the cell number

was essentially the same at all doses; at 100h the colony size distribution was very large, ranging from 0 to 7 generations, even within the control population. I developed a model able to represent the temporal dependence of the growth properties of surviving and non-surviving cells, to describe the number of cells as a function of surviving fraction, time of sampling, growth rate, delay per unit dose, and the rate per unit of dose at which the non surviving cells lose their ability to divide. The parameters of the model were determined experimentally and we found that (in the specific experimental conditions adopted in the experiment) growth curves are affected by non-surviving progeny up to 150, 200 and 250 h after irradiation at 3, 5 and 7 Gy, whereas at longer times the population consists essentially of progeny of surviving cells .

2.2 Effects of initial cell density on radiation-induced neoplastic transformation in vitro

This research was carried out to try to answer to questions related to the effects of the experimental conditions on the in vitro studies on biological effects of ionizing radiation. More specifically the objectives were the development of sound based predictive models to interpret the experimental results. In this case, the effects of cell density on transformation frequencies were studied in C3H10T1/2 cells exposed to 0 .5 to 7 Gy of 200 kVp X-rays. Initial cell density strongly influenced transformation frequency; this decreased by a factor of between 4 and 10 when the initial seeding density was changed from 50 to 2500 cells/ 10 cm diameter Petri dish. I analysed and fitted the data with two equations: (a) an allometric function represented on a log-log scale by a straight line and (b) a sigmoidal function with plateaux between 50 and 250 cells/dish and above 600. The two curves were compared and their probabilities discussed. Our data indicated that the region between 50 and 250 cells/dish would be the most suitable region for dose-effect measurements . A study of the growth curves at 0.5 and 8 .5 Gy shows that cell growth rates are not influenced by initial cell density

2.3 Biological effects of alpha particles

Cytotoxicity and oncogenic transformation incidence were studied in C3H lOTl1 cells irradiated with 4.3 MeV alpha particles and were compared with results previously obtained with low LET protons. The alpha particles were more effective than low LET protons both in cell inactivation and for oncogenic transformation. The survival curve with alpha particles was an exponential function of the dose with a mean lethal dose of 0.61 ± 0.02 Gy. The corresponding RBE was a decreasing function of the dose varying from 15 to 4 when alpha particle doses ranged from 0.1 to 2 Gy. The transformation curves showed complex shapes with a region of apparent constancy at low doses followed by a linear increase with dose. RBE values decreased from 20 to 4 in the dose region between 0.1 and 2 Gy. There was a significant transformation incidence at doses that have very little effect on cell survival. No effect of the dose rate was found at total doses of 0.05 and 0.1 Gy with dose rates of 0.11 and 0.005 Gy/min.

2.4 Criteria and techniques for analyzing cell radiation-induced inactivation data

Cell survival was studied by analyzing the inactivation probability density function and its fundamental parameters. Mean D, variance sigma and mode Dmode were evaluated and a set of equations relating these parameters to the usual parameters of the multitarget, multihit and linear-quadratic models Do and n, alpha and beta, k and lambda were reported. The multihit equation used was an extension of the usual equation, to allow parameter k to assume values that are not necessarily integers. In the multitarget curve, the mode of inactivation probability density function, proved to be the quasi-threshold dose Dq = Do ln(n). I showed that relative variance, degree of asymmetry and degree of peakedness can be directly calculated from the shape parameters n in the multitarget model, kappa in the multihit model, and alpha/(square root of beta) in the linear-quadratic model. From an analysis of eight published cell survival sets of data, on C3H10T1/2 cells exposed to low LET radiations, we found that mean D, sigma, and SF2 (surviving fraction at 2 Gy) are the parameters which exhibit the least variation from experiment to experiment and the least variation in selecting the range of data available for estimation.

2.5 Microdosimetry- and biophysics-based predictions, of the dose-rate effects on radiation-induced cell transformation – the inverse dose rate effect.

There is substantial experimental evidence that protracted exposure to high-LET radiation can have a greater effect than single exposure in inducing cell transformation, the so-called «inverse dose-rate effect». The magnitude of this enhancement is due to the complex interplay between dose, dose rate and radiation quality. I developed a model that explains the complex trend of the experimental results. This model is based on the assumption that there is a brief period of high sensitivity to transformation in the cell cycle (as originally proposed by Rossi and Kellerer) and takes into account the saturation observed at high doses in the dose-effect curves. I developed specific equations for acute, protracted and fractionated irradiation. I analyzed findings with C3H10T1/2 cells in the light of this model. Assuming best fitted parameters of the model obtained from acute-irradiation data (e.g. a sensitive period of 18+/-4 min), transformation frequencies due to protracted or fractionated exposure were predicted and compared with experimental findings on fission and monoenergetic neutrons and on charged particles of LET between 20 and 150 keV/μm. The model's predictions were found to be closely consistent with the available experimental data.

2.6 Chromosome aberrations induced by high LET radiation and X rays.

Cell-cycle stage radiosensitivity for the induction of chromosome aberrations has been investigated in C3HI0T1/2 cells . Exponentially growing cells were irradiated with 3 Gy Xrays (80 kVp) or 0.6 Gy alpha particles (LET= 101 keV/µm) . The two doses were chosen to produced the same survival level (37%) in the asynchronous population. Cells were harvested at four different times following irradiation and cell-cycle phase at the time of irradiation was assessed by using the differential replication staining technique. The frequency of chromosome aberrations produced in a given stage of the cell cycle was not constant as a function of the sampling time, but this could not be simply related to the existence of subphases exhibiting different radiosensitivity (see also section 2.5), because of cell-cycle perturbation introduced by radiation. X radiation induced more exchanges than deletions, whereas a predominance of isochromatid deletions was observed after alpha irradiation This can be interpreted on the basis of the different patterns of energy deposition of densely- and sparsely-ionizing radiation. Both X- and gamma-rays produced a significant increase in the frequency of Robertsonian translocations when cells were exposed in G1 or S phase, but not in G2 phase.

3. Biophysical mechanisms of radiation action: radiation interaction with biological structures and damage evolution

The investigation of the action of ionizing radiation on biological structures requires a detailed analysis of the various stages underlying damage induction and evolution. In order to consider the stochastic aspects characterising the process of interest, “ab initio” models and MC simulation codes are required, which start from the physical track structure and follow its time evolution, taking into account the various levels of organization of the biological targets (DNA, chromosomes, etc.).

3.1 DNA damage complexity and dependence on radiation quality

At the beginning of the 90’s a solid collaboration started with Herwig Paretzke (GSF, now Helmholtz Institute, Munich) for the development of track structure studies and initial damage induced by ionizing radiation and its dependence on radiation types. The collaboration startied with a study on the quality of DNA damage induced by protons and alpha-particles of various linear energy transfer (LET). The aim was to single out specific lesions in the DNA molecule that might lead to biological endpoints such as inactivation. A DNA model coupled with a track structure code (MOCA-15) were used to simulate the lesions induced on the two helixes. Four categories of DNA breaks were considered: single-strand breaks (ssb), blunt ended double-strand breaks (dsb, with no or few overlapping bases), sticky-ended double-strand breaks (with cohesive free ends of many bases), and deletions (complex/cluster lesions which involve at least two dsb within a small number of base pairs). Calculations were carried out assuming various sets of parameters characterizing the production of these different DNA breaks. No large variations in the yields of ssb and blunt- or sticky-ended dsb were found in the LET range between 10 and 200 keV/micrometer. On the other hand, the yield of deletions increases up to about 100 keV/gm and seems to reach a plateau at higher LET values. In the LET interval from 30 to 60 keV/micrometer, protons proved to be more efficient than a-particles in inducing deletions. The induction of these complex lesions is thus dependent not simply on LET but also on the characteristics of the track structure. Comparison with RBE values for cell killing showed that this special class of dsb might play an important role in radiation-induced cell inactivation.

Track structure studies evolved in the late 90’s with the development of the Monte Carlo PARTRAC code (with the fundamental role of Werner Friedland, GSF, now Helmholtz Institute, Munich), moving from a geometrical description of DNA, the use of liquid water cross sections (in MOCA-15 water vapour cross sections were used) and explicitly simulating the production, diffusion and interactions of radicals. A specific study on the parameters controlling the early stages of liquid water radiolysis provided new more reliable values implemented in the PARTRAC code, together with sensitivity studies to quantify the role of the uncertainties in radical production, diffusion and interactions.

To quantify the protective effects of (non-histonic) OH radical scavengers and DNA higher-order structures in induction of single- (ssbs) and double-strand breaks (dsbs) by gamma-rays, spatial distributions of energy depositions by gamma-rays in liquid water were modelled with the track structure modules of the biophysical simulation code PARTRAC. Such distributions were superimposed on different DNA structure models (e.g. linear DNA, SV40 ‘minichromosomes’ and compact chromatin), and direct energy depositions in the sugar–phosphate were considered as potential (direct) ssbs. The diffusion and interaction of the main chemical species produced in liquid water radiolysis were explicitly simulated, and reactions of .OH with the sugar–phosphate were considered as potential (indirect) ssbs. Two ssb on opposite DNA strands within 10 base pairs were considered as one dsb. Yields of ssb and dsb /Gy /Dalton in different DNA target structures were calculated as a function of the .OH mean lifetime, whose inverse value was taken as representative of the scavenging capacity of the DNA environment. A further validation of the models implemented in the PARTRAC code has been provided, thus allowing a better understanding of the mechanisms underlying

DNA damage. More specifically, the protection due to .OH scavengers was separately quantified with respect to that due to histones and chromatin folding, which could be 'switched off' in the simulations. As expected, for a given value of the environment scavenging capacity, linear DNA was more susceptible to strand breakage than SV40 minichromosomes, which in turn showed higher damage yields with respect to cellular DNA due to the larger accessibility offered to .OH. Furthermore, by increasing the scavenging capacity, the break yields decreased in all structures and tended to coincide with direct damage yields. Very good agreement was found with available experimental data. Comparisons with data on 'nucleoid' DNA (i.e. unfolded and histone-depleted DNA) also suggested that the experimental procedures used to obtain such structures might lower the environment scavenging capacity owing to the loss of cellular scavengers.

Always in collaboration with the Helmholtz Institute, we implemented heavy ions in the PARTRAC code. The new PARTRAC code (originally developed on the bases of gamma rays results) was tested, by comparing predictions provided by the code simulations, with experimental data, relative to DNA fragmentation induced by high LET ions. In collaboration with the radiobiology group of the National Health Institute, the new code was then used to study the dependence of DNA damage characteristics on the quality of radiation.

Recently we have investigated DNA fragment spectra induced in human fibroblasts by irradiation with nitrogen and iron ions of different energies and doses. The simulations data for both types of ions were analyzed in terms of DNA mass distribution as a function of fragment size, to have a direct comparison with the available experimental data. A relevant result obtained from the simulations is the large production of very small fragments in the size range lower than 1 kbp, usually not accessible experimentally. In particular, the simulations with nitrogen ions were compared with the experimental results published by Höglund and Stenerlöw (Radiat. Res. 155, 818 (2001)). The agreement between the PARTRAC and the experimental DNA mass distributions is very good in all cases. In the analysis of the experimental data the fragment number distribution is obtained from the mass distribution using the mean fragment size of each size range. This unavoidable approximation was good for intermediate and large fragment sizes, but it introduces large errors for the smallest fragments. In fact, the PARTRAC and the experimental fragment number distributions are in excellent agreement except for the point at the smallest size range, which is greatly underestimated by the experimental evaluation. Thus, experimentally the total DSB yield is heavily underestimated, and so is the RBE for DSB production, since gamma rays do not produce a large number of very small fragments

3.2 Evolution of DNA damage: chromosome aberrations

Track structure simulations, providing a detailed description of the spatial distribution of energy depositions and relevant DNA lesions, represent a useful starting point for the development of '*ab initio*' biophysical models of chromosome aberration induction. Various aspects of the processes determining the induction and the formation kinetics of chromosome aberrations are still under debate, concerning in particular the target description (interphase chromosome organization), the characterization of relevant DNA lesions, the possibility of inducing exchanges starting from single radiation-induced lesions, the rejoining mechanisms (proximity effects and possible induction of incomplete exchanges, i.e. one-way exchanges) and the influence of specific scoring criteria adopted both in experiments and models. Also in collaboration with the radiation biophysics group of Naples University (M. Durante et al) a continuing evolving model (and a corresponding Monte Carlo code) was developed, to provide insight on the mechanisms governing the time dependence of radiation induced CA formation and the dependence on dose and radiation quality.

3.3 Evolution of DNA damage: cell inactivation

The results of cluster lesions' simulations were the basis for simulating cell inactivation and its dependence on radiation quality. In particular cell inactivation in V79 Chinese hamster fibroblasts exposed to to low-energy protons, deuterons and alpha-particles in the LET range 10-200 keV/micrometer. The starting assumption was that the induction of clustered lesions in DNA is a fundamental step for cell inactivation. A non-homogeneous cell population was simulated by a computer program, using as input measured morphological parameters reported in the literature. Variations in the number of traversals through each cell of the population and in the length of the traversal, depending on actual nuclear thickness and position of the traversal, the energy spread of the incident beam, and the change of LET along the tracks were included in the simulation. Microdosimetric spectra were computed and compared with spectra obtained neglecting particle slowing-down and stochastic aspects of cell morphology. Simulated cell survival was estimated under the assumption that surviving cells are those with no clustered DNA lesions or no passages. The main features of experimental RBE versus LET and particle type were reproduced by the simulations. The influence of stochastic aspects of target-cell morphology and of the energy of the incident particles on survival were investigated under different assumptions about the correlation between morphological parameters. Results supported the hypothesis of a relevant role of clustered DNA damage in cell killing and pointed out the importance of target-cell morphology and its variability in beam dosimetry and computer simulations of low-energy particle radiation effects.

4. A systems radiation biology approach

With the increasing efficiency of the experimental biological techniques (and irradiation technology), more mechanistic understanding of the induction and response to radiation damage has been discovered, starting from the analysis of gene expression in irradiated cells. In the past few years, with the evolution of experimental detection techniques, the vision of the biological damage has also evolved, passing from a focus on the damage in terms of the DNA molecule, to a new one, wherein the final results of the radiation insult is seen as a broader response of the system (single cell, tissue, organ, etc.) to the perturbation induced by the radiation exposure. It has become clear that the paradigm of DNA damage alone that held sway for the last part of the 20th century, was overly simplified, and that the response to radiation is more than induction and resolution of DNA damage.

Particularly for studying the (cancer and non cancer) risk of low doses (within the EC-EURATOM funded projects) a systems holistic approach looking at the global features of the system (such as the interrelationship networks, modularity, robustness, etc.) became mandatory to provide information about the complex systems dynamics and perturbations.

Amongst all the mechanisms studied, we devoted particular attention to the role of cell communication in the induction of the radiation effects at a multicellular level. One of the main techniques to evaluate the supra-cellular radiation effect is to look at the damage in cells "in contact" – i.e. physically, through gap junction, through soluble factors, etc. - with irradiated cells (bystander effect). Unlike the investigation of DNA damage induced by radiation (especially complex/clustered lesions, see section 3.1), the study of the radiation effects on cell signaling examines processes which are always present, that regulate cell homeostasis, and where radiation acts only to modulate or perturb already activated processes.

Besides the obvious complexity related to the potentially high number of molecules (e.g. reactive oxygen species and proteins) involved in signalling, another "layer of complexity" resides in the complicated and non-linear (complex) ways in which these proteins interact (often through the coordinated activation of self-sustaining feedback loops after transient stimuli). Further peculiar features of cell communication are the very large ranges of time/spatial scale and the common lack of separation between responses to external stimuli versus internal programs.

4.1 Cell communication perturbation induced by ionizing radiation: the example of IL-6 signaling

In order to evaluate the complex response of the system, we performed a series of experiments to establish protocols for reliable studies of the mediators that regulate the bystander processes. The study focused in particular on protein mediated signals, including cytokines and growth factors. These experiments gave quantitative information of the perturbation induced by irradiation and were coupled with different modeling approaches in order to control for the different possible scenarios involved: we developed a Monte Carlo code and an analytical model to quantify both the local mechanisms and the average quantity dynamics, respectively, that regulate the transmission of the signals. Our findings showed a key modulation of IL-6 (Interluekine-6) induced by radiation for up to 20 hours after irradiation, suggesting a possible involvement of this molecule for the long-term induction of bystander effects.

In order to quantify the perturbing role of radiation on this system it was necessary to evaluate the peculiar features of the systems without radiation (sham irradiated cells). The experimental results illustrated a major role of IL-6 release for unexposed cells induced by a change of the cell culture medium (one of the common techniques developed to investigate the bystander phenomena), indicating that these messengers could also be part of the response of the cells to generic stimuli (stress response). The examination of the irradiated cells pointed out that the radiation induced response in this context is approximately one-third of the response induced by a change of the medium. From the analysis of these data, the perturbation induced by radiation seems to modulate the already perturbed signaling generated by change of the cellular culture medium. We demonstrated that it is difficult (or even not possible) to investigate the role of radiation in a 'totally isolated' system and that it is necessary to move the focus from the pure linear interpretation of cause–effect of cell response, to a more 'circular' interpretation which is more sensitive to feedback and self-corrective changes typical of complex systems.

Together with radiation-induced modulation of cytokine release, experimental and theoretical studies where carried out, on the modulation of signalling mediated by ROS/NRN and the modulation of the expression of membrane receptors

5. Research finalized to radiotherapy: development and application of techniques to evaluate and compare treatment plans in radiotherapy and to optimize radiation treatments.

The techniques introduced for analysing cell survival data (see section 2.4) were refined for the linear quadratic model with the objective of identifying the best parameters for comparing different treatment modalities and optimizing treatment plans.

5.1 Risk to the heart and to the respiratory system

In collaboration with the Karolinska Hospital and the Department of Medical Radiation Physics of Stockholm University (G. Gagliardi and co-workers), I contributed to the development of a technique for

follow-up data analysis, relative to patients treated for breast cancer. Indeed effects on the heart constitute a potentially significant and serious clinical problem in primary radiation therapy of early breast cancer. Increased cardiac mortality among irradiated patients may offset the potential benefit in terms of a reduced risk of recurrence or of death from breast cancer. Clinical data on long-term cardiac mortality among breast cancer patients included in two randomized trials (the Stockholm and Oslo studies) of radiation therapy as an adjunct to primary surgery were analysed using the relative seriality model of radiation response. Five different radiation therapy techniques were used in the trials. The original treatment plans were recalculated on a group of model patients using a three-dimensional treatment planning system. Both heart and myocardium, i.e. excluding circulating blood within the heart, were separately investigated as risk organs. Model parameters (D50, i.e. the dose giving 50% complication probability; y, i.e. the maximum relative slope of the dose-response curve; s, describing the organ relative seriality) were determined by a chisquare fitting of the calculated probability of excess cardiac mortality, based on the DVHs, to the incidence data. Computed complication probabilities for each treatment technique were modelled within the 95% confidence interval (CI) of the clinical incidence data. It was shown that the relative seriality model, assuming a homogeneous radiation sensitivity within the volume of the heart/myocardium can be used to describe the incidence data. A small dependence on the volume was found. The results do not, however, exclude the possibility that more sensitive structures within the myocardium are the main target for radiation.

This work was among the first ones showing the importance of cardiovascular risk associated to radiation. This issue is now considered as one of the major research areas not only for the risk of complications but also for cancer and non cancer effects of low dose irradiation (also for radiation protection).

The method was then refined and applied to the study of the risk for the lung again as possible complications after breast cancer radiation therapy, starting from a group of patients treatd in Radiumhemmet. In this case individual dose volume histograms were available. The model parameters were calculated and the model predictions were compared with the complications observed in 5 other centres.
Model and parameters were tested for a possible application in breast cancer treatment planning.

5.2 Biological mechanisms of normal tissue damage: Importance for the design of NTCP models

Within the activity of the ALLEGRO project (see 5.1.3) we carried out a study on the biological mechanisms of normal tissue damage of importance for the design of the normal tissue complication probability (NTCP) models. The NTCP models currently being proposed for estimation of risk of harm following radiotherapy are mainly based on simplified empirical models, consisting of dose distribution parameters, possibly combined with clinical or other treatment-related factors. These are fitted to data from retrospective or prospective clinical studies. Although these models sometimes provide useful guidance for clinical practice, their predictive power on individuals seems to be limited. We examined the radiobiological mechanisms underlying the most important complications induced by radiotherapy, with the aim of identifying the essential parameters and functional relationships needed for effective predictive NTCP models. The clinical features of the complications are identified and reduced as much as possible into component parts. In a second step, experimental and clinical data are considered in order to identify the gross anatomical structures involved, and which dose distributions lead to these complications. Finally, the pathogenic pathways and cellular and more specific anatomical parameters that have to be considered in this pathway are determined. This analysis was carried out for some of the most critical organs and sites in radiotherapy, i.e. spinal cord, lung, rectum, oropharynx and heart. Signs and symptoms of severe late normal tissue complications present a very variable picture in the different organs at risk. Only in rare instances is the entire organ the critical target which elicits the particular complication. Moreover, the biological mechanisms that are involved in the pathogenesis differ between the different complications, even in the same organ. Different mechanisms are likely to be related to different shapes of dose effect relationships and different relationships between dose per fraction, dose rate, and overall treatment time and effects. There is good reason to conclude that each type of late complication after radiotherapy depends on its own specific mechanism which is triggered by the radiation exposure of particular structures or sub-volumes of (or related to) the respective organ at risk. Hence each complication will need the development of an NTCP model designed to accommodate this structure.

5.3 Risk of complications and secondary tumours in radiotherapy – the European projects ALLEGRO and ANDANTE (European coordination).

The ALLEGRO Project has the full title "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 2010-11 (13 partners, A. Ottolenghi European coordinator) 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 also set the direction for future research efforts. The project investigations were divided into:

a) measurement and modelling of radiation doses outside the treatment volume from photon, proton, and carbon ion beams;

b) review and development of current best practice in normal tissue complication probability (NTCP) modelling in head and neck, lung, and prostate cancer;
c) review and test of current research capability on the risks of second cancer following radiotherapy.

As well as results from the individual investigations, a series of report documents have been produced that summarise the experience gained during the project and providing recommendations for clinical practice in both current and emerging therapy modalities in order to minimise normal tissue risk without compromising treatment efficacy, and also to indicate valuable areas for further research.

In January 2012 we started the activity of the European consortium ANDANTE (duration: 4 years, 8 partners, A. Ottolenghi European coordinator) on *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 will integrate the disciplines of radiation physics, molecular biology, systems biology modelling, and epidemiology in order to investigate the relative risk of induction of cancer from exposure to neutrons compared to photons. The project will focus on three specific cancers that may be detected as second malignant neoplasms following paediatric photon radiotherapy: salivary gland, thyroid gland, and breast tissue. Stem cells from each of the types of tissue will be exposed to well characterised beams of neutrons, and biological markers of possible tumorigenesis will be used to develop RBE models. In parallel a track structure model will be developed to simulate the exact experimental conditions and to explore the relationships between exposure parameters and response. The combination of radiobiology and biophysics/systems biology will generate a strongly directed epidemiological investigation to validate the RBE model using clinical data from paediatric proton therapy patients compared to existing cohorts of paediatric photon radiotherapy patients. The limitations of the epidemiological approach alluded to above will be addressed on the one hand by using the discipline for model validation rather than model generation, and on the other hand a prospective study will be designed in order to accumulate sufficient statistical power. To establish a multi-centre cohort of paediatric patients is a decisive task at the current phase where proton therapy is on the advance world-wide. The overarching objective of the project is to determine values of RBE for neutrons, for specific tissues and neutron energies, which can then be validated using paediatric proton therapy data.

Each task in the project forms an essential component part of this objective. The individual task objectives can be split up as follows:

a) Physical characterisation, using measurements and modelling, of the neutron fields of various energy spectra used for experimental irradiation of cells, and generated during paediatric proton radiotherapy for the purpose of accurate dosimetry and track structure simulation and model development of the damage response;
b) Investigation of the damage induction in stem cells as an indicator of the relative carcinogenic effectiveness of low and intermediate doses from neutrons compared to photons; use of the results to generate provisional values for RBE and explore the dependence on neutron energy and dose;
c) Integration of functional relationships from biophysical simulations and radiobiological stem cell experiments to develop predictive neutron risk models for second primary malignancies following paediatric proton therapy that can be validated using clinical treatment and follow-up data: proof-of-principle pilot study leading to design of a multi-centre prospective study.

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.

5.4 New Methods for patient alignment in radiotherapy

Accurate and repeatable patient positioning has been a research activity since long time. The topic is of particular importance for 3D conformal radiotherapy and for hadrontherapy. The problem is to take into account of the needs of both increasing precision and accuracy, and of optimizing the use of the resources. An interdisciplinary collaboration was established to initially study various possible strategies for patient positioning, with the specific objective of developing optically guided patient positioning techniques to improve patient localization. This research was carried on as a collaboration involving the departments of Physics of the Universities of Pavia and Milan and the departments of Bioengineering of the Polytechnic of Milan.

6 Development and application of Monte Carlo Codes for application in hadrontherapy and space-radiation protection.

6.1 Protontherapy

The physical and radiobiological features of the fully-modulated 72 MeV proton beam of the therapy unit (OPTIS) of the Paul Scherrer Institut (Switzerland) were analyzed in deep detail by adopting both an experimental and theoretical approach. The spatial distribution of the physical dose was calculated by using the FLUKA MC transport code; the role of nuclear interactions was taken into account and the geometry of

the apparatus was faithfully reproduced. The contributions of the various beam components were analysed separately. The simulation results were compared with measured depth-dose distributions and very good agreement was found. The depth-dependence of cell survival along the completely spread-out Bragg peak (SOBP) was simulated with a biophysical model, based on the assumption that clustered DNA damage is a relevant step of the process leading to cell inactivation. The yield of DNA Complex Lesions (CL, which were found to play a relevant role in cell inactivation (see 3.4) and other radiobiological endpoints), reflecting the radiation clustering properties, had been previously calculated using an event-by-event code (see 3.1) and were integrated in FLUKA. The code this way obtained provided the spatial distribution of CL per cell, which can be regarded as a "biological dose". Experiments on clonogenic survival of V79 cells were performed at PSI and the results were compared with the simulations, showing very good agreement.
The method was then applied to a 160 MeV proton beam, modulated to obtain a therapeutic Spread-Out Bragg Peak (SOBP). The contribution of the secondary hadrons to the biological dose was found to be much more relevant with respect to the case of the physical dose and therefore cannot be neglected. An RBE of approximately 1.2 was found along the plateau and in most of the SOBP (due to secondary hadrons), with a sharp increase in the distal part (due to the presence of low energy protons). The "biological peak" resulted to be shifted towards larger depths with respect to the physical peak. The results are in good agreement with experimental data reported in the literature.

6.2 Ions and neutrons

Within the experiment INFN FLUKA snf in collaboration with CERN (Geneve, A. Ferrari et al) the FLUKA code was developed with and interface with the code RQMD (Relativistic Quantum Molecular Dynamics, Sorge) to allow simulations of ion-ion interactions at energies between 100 MeV/n and 5 GeV/n. In parallel an original QMD was developed. Within the collaboration with the National Laboratory of Legnaro (INFN, Garfield experiment) the cross sections CC and O-C at energies between 6 and 20 MeV/u and compared with the theoretical predictions based on Boltzman Master Equations (developed by E. Gadioli et al), in view of their implementation in FLUKA.

I developed new criteria for studying mixed field effects and the action of neutron fields on biological structures was investigated on the basis of chromosome aberration induction in human cells. Available experimental data on aberration induction by neutrons and their interaction products were reviewed. Present criteria adopted in neutron radiation protection were discussed. The linear coefficient alpha and the quadratic coefficient beta describing dose-response curves for dicentric chromosomes induced by neutrons of different energies were calculated via integration of experimental data on dicentric induction by photons and charged particles into the Monte Carlo transport code FLUKA. The predicted values of the linear coefficients for neutron beams of different energies showed good agreement with the corresponding experimental values, whereas the data themselves indicated that the neutron quadratic coefficient cannot be obtained by 'averaging' the beta values of recoil ions and other nuclear reaction products. This supports the hypothesis that neutron induced aberrations increase substantially linearly with dose, a question that has been object of debate for a long time and is still open.

6.3 Radiation protection in space

One of the important concerns about long term missions of astronauts, especially in deep space (such as in the case of a possible mission to Mars) is the biological risk from radiation. The effective dose per day due to galactic cosmic rays is ≈ 1 mSv, which is the order of magnitude of the natural background dose on Earth in one year. Moreover, one must take into account the risk of solar particle events, which are very intense and almost unpredictable fluxes of particles (mainly protons) lasting up to few days, that in absence of appropriate shielding may determine a dose of several Sieverts. Estimating biological risk from GCR and planning countermeasures require investigations on both the physical aspects of the problem (essentially the fluences of the various primary-radiation components and of the secondary particles produced by interactions with the spacecraft walls, the shielding structures and the human body) and the radiobiological aspects, i.e. the effects of mixed fields on biological targets at different levels, from DNA and cells up to tissues, organs and organisms. Space radiation is comprised of high energy protons and high charge (Z) and energy (E) nuclei (HZE), whose ionization patterns in molecules, cells and tissues, and the resulting initial biological insults, are distinct from typical terrestrial radiation. HZE nuclei dominate the exposure in deep space (interplanetary travels), whereas trapped protons also contribute to the equivalent dose absorbed by crews in low-earth-orbit, with remarkable differences in energy deposition in biomolecules, cells and tissues. Because swift charged particles produce fragments in the spacecraft materials, it is very important to identify the best shielding solutions to protect astronauts from space radiation. The FLUKA Monte Carlo code was therefore coupled with two anthropomorphic phantoms (a mathematical model and a ‘‘voxel’’ model) and we calculated organ-averaged dose, dose equivalent and ‘‘biological dose’’ in the various tissues and organs following exposure to the August 1972 Solar Particle Event and to Galactic Cosmic Rays under different shielding conditions. The ‘‘biological dose’’ was characterized by the average number of induced ‘‘Complex Lesions’’ (CLs) per cell in a given organ or tissue (see section 3), where CLs are clustered DNA breaks which can play an important role in chromosome aberration induction. Separate calculation of the

contributions from secondary hadrons – in particular neutrons – with respect to primary particles allowed us to quantify the role played by nuclear interactions occurring in the shield and in the human body. This research activities were carried out in within projects funded by the Italian Space Agency, in particular on the "Influence of the shielding in the space radiation biological effectiveness", also as local coordinator at the University of Milan and, when in Pavia (as national coordinator) within the subproject COUNT (7 partners) of the project MoMa (From molecules to man: Space research applied to the improvement of the quality of life in aged population) with a systematic analysis of the possible countermeasures.

During the last four (and in the next) edition of the COSPAR assembly I have organized sessions (the last ones of two days, with about 35 speakers and 100 participants) on the "Space Radiation Risk Assessment and Counter Measures: Physics and Biophysical Mechanisms, Modeling and Simulation" to improve space radiation risk assessment and on the design of passive, active and biological countermeasures in order to reduce risk.

7. Bio-element kinetics studies using stable tracers and nuclear activation techniques.

In the Medical Physics section of the Physics Department (University of Milan) in the group originally lead by N. Molho, a technique was developed for metabolism studies, based on the simultaneous use of two stable tracers and the analysis based on Proton Nuclear Activation (PNA). The evident advantage compared with radioactive tracers is the possibility of carrying out studies on humans, without radiation exposure.
The technique to study Molybdenum, Ruthenium and Tellurium was optimized and feasibility studies has been carried out on animals and humans. Personally I specifically contributed in the development of mathematical models and optimization techniques and procedures, with data analysis and simulations. In particular I introduced and developed the compartmental approach for determining biokinetic parameters.

The technique consists in the simultaneous administration of two isotopes of the element under study, one given orally and one injected intravenously. Venous blood samples are withdrawn at different post administration times. From each of the venous blood specimens, given amounts of plasma are taken and mixed with a known amount of an appropriately chosen reference element, used for the quantitative determination. PNA method is based on the bombardment of the target with a proton beam to induce nuclear reactions. The different isotopes of the same element can be distinguished by analyzing the characteristic gamma-rays emitted by the radionuclides produced through activation. The concentrations as afuction of time allow the estimation of biokinetic parameters. Data were initially analyzed using a "non compartmental" approach based on a convolution integral, based on the assumption that the oral administration can be assumed as an intravenous administration with a variable rate. This rate (of great importance to quantify biokinetic processes) and its dependence on time can be calculated through a de-convolution procedure. The introduction of a compartmental approach (e.g considering the compartments stomach, intestine, transfer compartment, organs) based on differential equations that describe the various kinetics, has allowed the estimation of parameters more directly correlated to metabolic processes. Applications are of importance both for nutritional and for radioprotection purposes, given the continuous discussions on ICRP approaches for the estimation of organ absorbed doses and "biological" doses in case of accident with the realise of radioactive materials.

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