

SHARED RESEARCH RESOURCES

CARDIOLOGY

RESPIRATORY PHYSIOPATHOLOGY

CLINICAL PSYCHOLOGY

**MEDICAL STATISTICS, BIOMETRY AND
BIOINFORMATICS**

**CLINICAL EPIDEMIOLOGY AND TRIAL
ORGANIZATION**

TISSUE BANK

FUNCTIONAL GENOMICS CORE FACILITY

CANCER PROTEOMICS-MOLECULAR MECHANISMS

ANIMAL HOUSE

CARDIOLOGY

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The Cardiology Unit mainly carries out activities related to preoperative evaluation of surgical patients, tightly collaborating with anesthetists and thoracic and abdominal surgeons to reduce pre- and peri-operative risk and to manage complications. Evaluation and consultation is also carried out for patients of Fondazione IRCCS Istituto Neurologico C. Besta.

The Cardiology Unit, among its main obligations, performs general cardiac evaluation of all candidates for chemo-radiotherapy treatment, with the aim of monitoring potential cardiovascular toxicity related to antineoplastic treatments.

Several Phase II and Phase III clinical studies have been followed-up during 2010, with routine, mandatory, cardiologic surveillance for the possible cardiotoxicity of new experimental drugs.

Keywords: preoperative evaluation, cardiotoxicity, experimental drugs surveillance

2010 RELEVANT NOTES

Publications

The Incremental Prognostic Value of Echocardiography in Asymptomatic Stage. A Heart Failure. J Amer Soc Echocardiography 2010;23:1025-34.

Contributions

Patrizia Piotti and Carlo Materazzo participate in a multicenter study organized by the Italian Society of Cardiovascular Echography



RESPIRATORY PHYSIOPATHOLOGY

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The Respiratory Physiopathology Unit ensures functional pulmonary evaluation to patients who are candidate for thoracotomy, lung resection or abdominal surgery to assess individual risk of postoperative pulmonary complications and provide monitoring of pulmonary function. Lung function is also tested in patients who undergo radiotherapy and chemotherapy regimens known to be associated with the risk of pulmonary toxicity. Specifically, various examinations can be carried out such as: spirometry, 2D-Doppler echocardiography at rest, cardiopulmonary exercise test on cycloergometer and determination of cardiac output by a non-invasive method. Moreover, diagnostic and clinical assistance is provided to oncologic outpatients and patients referred by GPs and external medical consultants. Our activity focuses on the diagnosis and treatment of chronic obstructive pulmonary disease, asthma, interstitial pneumonia, and respiratory failure.

Finally, the Unit is engaged in three main branches of tobacco control activity: clinical (smoking cessation), educational, and environmental tobacco smoke (ETS) research.

In collaboration with the Thoracic Surgery Unit, we continue the evaluation of preoperative pulmonary function and risk factors in thoracic surgery patients. Conventional preoperative evaluation of thoracic surgery for lung cancer includes spirometry, determination of lung transfer factor for CO, arterial blood gas measurement, estimate of postoperative function calculated from radioisotopic studies, and exercise testing.

Tobacco Control Unit (TCU)

In collaboration with: Respiratory Unit, Brompton Hospital, London; South Western University, Los Angeles, California; Cornell University, New York; Tobacco Free Research Institute Dublin; National Environmental Research Institute, Roskilde; Department of Epidemiology for Cancer Prevention Victor Segalen Bordeaux University; Unità Operativa di Epidemiologia ambientale e occupazionale, Istituto per lo Studio e la Prevenzione Oncologica (ISPO), Florence; Dipartimento di Prevenzione Regione Veneto. The TCU develops and organizes smoking cessation programs; in about 10 years of activity, TCU has enrolled more than 1,900 smokers, with an average cessation or reduction of 40%, in agreement with data from guidelines. A significant portion of clinical activity is devoted to passive smokers' health, with first diagnoses of obstructive lung disease in non-smokers complaining of respiratory symptoms associated with passive smoke.

In 2005, we started a comprehensive project aimed to offer advice and a SC program to all INT smoker patients. Educational activities of TCU aim to enhance the awareness of no-smoking policies at the workplace, to supply schools with educational programs, and to lobby against tobacco smoke. TCU provided numerous local schools with educational antismoking programs for students and teachers. From 2003, we are holding courses on smoking cessation and tobacco marketing at the University of Milan School for Nurses. Because of the educational importance of explaining the environmental health risks linked to tobacco smoke, a research laboratory section for the study of ETS was implemented in 2001. The laboratory carries out several innovative research programs and scientific articles are published in collaboration with various national and international research institutions.



CLINICAL PSYCHOLOGY

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The Unit is involved in clinical psychology, research, and education in oncology. The mission of the Unit is to support adult patients and families who are living with a life-threatening illness. The goals are to enhance quality of life and well-being, and to relieve suffering in all its dimensions throughout illness, survivorship, and bereavement. This is accomplished by providing expert clinical intervention such as individual psychological counseling, short psychotherapies, verbal and psycho-bodily groups, psycho-educational groups, and family therapies. Multidisciplinary clinical projects are carried out in collaboration with Medical and Surgical Units of the INT.

The Unit aims also to improve knowledge about the psychological experience of cancer through its research activities. The following research projects were in progress during 2010:

- Psychological impact of prevention programs in BRCA1-2 carriers.
- Individual end-of-life preferences: impact and usefulness of the ELPI Interview.
- The role of religious practices/beliefs and of spirituality in the search for meaning during the psychological adjustment process of cancer patients.
- Participants' perspective on information aid for newly-diagnosed MS patients: a qualitative study within the SIMS-Trial (SIMS-Qual)

The Clinical Psychology Unit actively took part in the constitution of multidisciplinary work groups such as the Conflicts Mediation Group and the Work Related Stress Group.

During 2010, the Unit planned educational trainings for healthcare professionals and administrative front line workers. The purpose was to upgrade their communication skills in relationships with cancer patients and their families.

Keywords: psychosocial care, communication, quality of life

2010 RELEVANT NOTES

Collaborations

FACIT Measurement System; University of Milan - Bicocca; ISPO - Florence; Istituto Nazionale per la Ricerca sul Cancro (IST), Genoa; Istituto Regina Elena IRCCS, Rome; Fondazione IRCCS Istituto Neurologico C. Besta, Milan

Publications

SIMS-Trial group. An information aid for newly diagnosed multiple sclerosis patients improves disease knowledge and satisfaction with care. *Mult Scler.* 2010;16:1393-405

What "best practice" could be in Palliative Care: an analysis of statements on practice and ethics expressed by the main Health Organizations. *BMC Palliat Care.* 2010;9:1

Contributions

National Commission: SIPO Psiconcogen

North Italian Transplant - Technical review of the psychological aspects of transplantation



MEDICAL STATISTICS, BIOMETRY, AND BIOINFORMATICS

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The Medical Statistics Biometry and Bioinformatics Unit (MSBB) provides quantitative support to research activities of INT. Moreover, MSBB bridges collaborative relationships with other national and international research groups. The INT group activity is governed by a convention with the University of Milan.

Areas of method development and application pertinent to MSBB activities include assay development and quality control, predictive models for diagnosis and prognosis, planning and design of observational or randomized studies, data management and study monitoring, and techniques to report and interpret clinical study results. The main topics in epidemiological research are the relationships between dietary habits and risk of cancer, to implement innovative statistical multivariate models in the analysis of dietary data, and to develop predictive models for cancer risk.

Biostatistics for Oriented Basic Research and Quality Control (P. Verderio)

The team applies statistical methods to different phases of the biomarker development process in oncology. Specifically, it provides statistical analysis of quality control studies for tumor biomarkers and in vitro-diagnostic tools; studies for the evaluation of inherited diseases in oncology; studies for setting up and validation of biological assays; studies of preclinical pharmacology and testing new molecular detection strategies based on innovative technologies

Biostatistics for Bioinformatics and Translational Research (E.M. Biganzoli)

This team follows the transfer of basic preclinical research to the clinical setting, resorting to quantitative approaches for assessment of the impact of new technologies in oncology, according to cost-benefit principles and sustainability perspectives.

Collaborative studies are ongoing related to the comparison of different high-throughput platforms for miRNA, qRT-PCR, and high throughput assays in cancer.

Keywords: computational tools and algorithms, randomized trials, methods to handle data features and anomalies

2010 RELEVANT NOTES

Collaborations

International Agency for Research in Cancer (IARC), Lyon
 Biostatistics Branch, National Cancer Institute, Bethesda
 Molecular and Nutritional Epidemiology Unit, ISPO Florence
 ISS-ACC Bioinformatics Oncology Network RNBIO
 INNS Biopattern Special Interest Group
 Italian Network for Quality Assessment of Tumor Biomarkers (SPIDIA) – European Project - FP7 Program

Publications

A BRCA1 promoter variant (rs11655505) and breast cancer risk. *J Med Genet.* 2010;47:268-70
 Histology-Specific Nomogram for Primary Retroperitoneal Soft Tissue Sarcoma. *Cancer.* 2010; 116: 2429-36
 Alcohol consumption and lung cancer risk in the Environment and Genetics in Lung Cancer Etiology (EAGLE) study. *Am J Epidemiol.* 2010 171:36-44

Contributions

Paolo Verderio: Editorial Board of Journal of Clinical Oncology
 Elia Biganzoli: co-organiser of the session "Multivariable model-building with continuous variables – a comparison of flexible regression approaches" International Biometric Society Conference Florianopolis, Brazil, 2010
 Editorial Board of Source Code in Biology and Medicine
 Adriano Decarli: member of the Executive Committee of the International Society of Clinical Biostatistics (ISCB) and President of the Biometric Society (Italian Region)

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The Unit provides biostatistical support in a broad array of clinic-based research projects, and is actively involved in methodological research and clinically-oriented teaching activities. The personnel has expertise across a wide range of statistical methods and research designs, and has extensive experience working with biomedical and clinical investigators in diverse disciplines, from design of the investigational plan through analysis and publication of study results.

The Unit has participated in a total of 104 projects (mainly in surgical, medical, or hematologic oncology), of which 78 were activated during the last year.

The Unit's research objectives are: a) methodologies for performing nested case-control studies; b) design and sample size calculation for adaptive trials; c) development of nomograms from piecewise survival models.

Grant-supported specific research projects included:

- Design and analysis of phase I studies: methodological aspects and practical applications in oncology.
- Evaluation of biomarker efficacy in postoperative monitoring of early breast cancer. The utility of CEA and CA15.3 in breast cancer follow up is being challenged in an ongoing multicenter randomized trial comparing biomarker based versus standard follow up.
- Hepato-Oncology: a multidisciplinary approach for an emerging specialty. An integrated project investigating the validity of innovative approaches in prevention, diagnosis, and therapy of liver cancer.
- Translational research on molecular markers in gastric cancer patients treated with adjuvant therapy. Nested case control study focusing on different molecular factors biologically relevant for gastric cancer progression and associated with *Helicobacter pylori* infection.

Keywords: biostatistics, study design, data analysis

2010 RELEVANT NOTES

Collaborations

ABO Association - Identification of serum tumor markers in breast carcinoma (<http://www.fondazioneabo.org/>)

Publications

Histology specific nomogram for primary retroperitoneal soft tissue sarcoma. *Cancer*. 2010;116:2429-36.

Comparison of the prognostic value of assessing tumor diameter versus tumor volume, at diagnosis or in response to initial chemotherapy, in rhabdomyosarcoma. *J Clin Oncol*. 2010;28:1322-8.

TISSUE BANK

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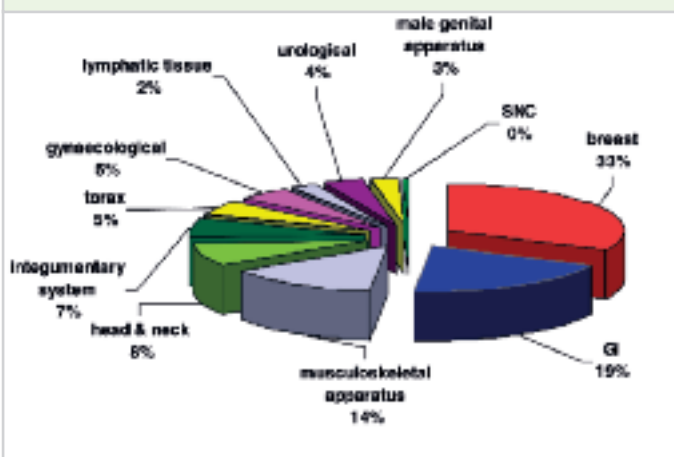
Since 2002, the Tissue Bank Facility of the INT has been dedicated to the collection and distribution of neoplastic, preneoplastic, and normal tissues from human subjects. This resource is a project of INT Scientific Directorate, with day-to-day staff supervision provided by personnel from the Departments of Pathology and Experimental Oncology & Molecular Medicine. The activities are overseen by an inter-department advisory committee, which also evaluates and approves research projects depending on the availability of tissue specimens. Adopting TUBAFROST procedures, although slightly modified to comply with local conditions, the INT Tissue Bank stores frozen samples (primary and metastatic lesions, with corresponding normal tissues) and contributes specimens to more than 30 specific research projects dealing with breast, ovarian, lung, head and neck, thyroid, colorectal, endometrial, and renal cancers, in addition to soft tissue sarcomas, melanoma, and pediatric tumors.

All patients/subjects sign an informed consent document (approved by the Independent Ethics Committee and filed in the patients' record) to donate the leftover tissue/biological specimens after diagnostic procedures have been completed for future studies at the INT Tissue Bank. It is a one-time general consent using a two step decision procedure. At the time of surgical and/or medical procedures, patients are told how samples and health information will be obtained, what risks future research uses pose to them, and whether the research will have any impact on their clinical care. They can choose whether their samples and associated information may or may not be used for future research, relying on an Independent Ethics Committee for the approval of biologically and/or clinically relevant studies. Otherwise, patients will be contacted repeatedly to provide study specific authorization for the use of biological samples and associated personal information. Guidelines have been proposed to define responsibilities for Tissue Bank management, policies, and procedures to protect patient confidentiality and privacy, and establish priorities for specimen distribution. In particular, in 2010 the personnel of INT Tissue Bank collaborated with INT Independent Ethics Committee to develop a set of recommendations on critical aspects pertaining to the use of biological samples for research purposes.

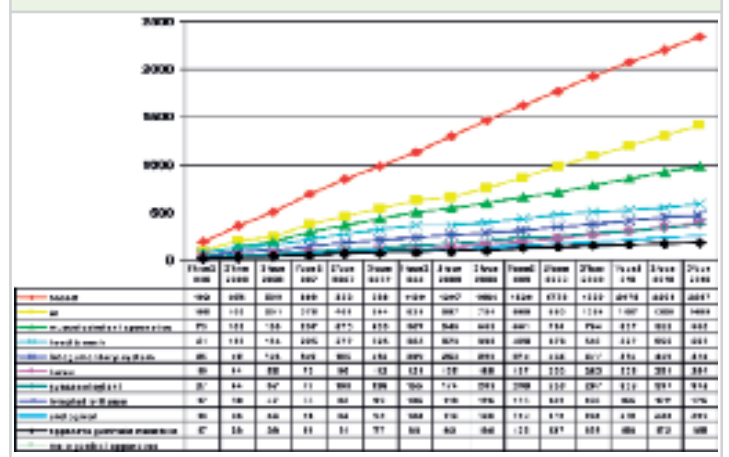
In collaboration with the INT Division of Information Technology and the Politecnico of Milan, approaches for tracking biological specimens through radiofrequency identification technology have been set up, and an integrated data base is now under implementation to link information related to biospecimens to pathologic diagnosis, minimum clinical data set, and follow-up information and to allow a dynamic and user-friendly interface for pre-clinical and clinical studies.

In 2010, the INT Tissue Bank stored frozen specimens from 1,520 new cases. Investigations have been carried out to assess the impact of biospecimen handling on biomarker research in colon cancer tissues and corresponding normal mucosa, to analyze the baseline specimens (frozen within 20 minutes after surgical removal) of these series of cases across 5 miRNA microarray platforms and compare their hybridization performance. Time elapsed between surgery and freezing of samples appears to have a strong impact on sample quality and should be considered as a mandatory variable to control for clinical implications of inadequate tissue handling.

Biological specimens collected in the INTM BioBank from 2006 to 2010 (7261 specimens for an overall of 14676 aliquots)



Cumulative accrual of specimens in the BioBank of Istituto Nazionale Tumori from 2006 to 2010



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The activities of the Functional Genomics core facility are based on wet analyses performed using the Illumina platform and computational analyses using two dedicated workstations. The research group comprises full time personnel involved in wet analyses and personnel dedicating part of their institutional activity to computational analysis of wet and in silico data. Thanks to external training courses, in-house further specialization and fruitful interaction with the Medical Statistics, Biometry, and Bioinformatics Unit, the core facility performs: study design; RNA and DNA extraction; quality controls; all labeling and hybridization methodologies required for high quality analysis; data processing and normalization; full computational analysis. During 2010, 1,700 samples arising from experimental or clinical studies were analyzed for: whole genome expression; Illumina DASL (cDNA-mediated annealing, selection, extension and ligation) assay; miRNA whole expression. Furthermore, the core facility staff elaborated in silico analyses using publicly available datasets from ovary, breast, thyroid, and prostate cancers, as well as melanoma and B-cell lymphomas. Computational and functional analyses are performed using the open source Bioconductor 2.1 and R Software Packages; candidate protein interactions are evaluated using Ingenuity Pathway Analysis 5.0 (Ingenuity Systems Inc, CA, USA) software. A survey of custom satisfaction related to a total of 70 studies conducted from July 2007 to June 2010 indicated that 89% of the results are satisfactory or above expectancy and at least 50% contributed to the generation of new hypotheses.

2010 RELEVANT NOTES

Collaborations

ABO Association - Identification of serum tumor markers in breast carcinoma (<http://www.fondazioneabo.org/>)

Publications

Histology specific nomogram for primary retroperitoneal soft tissue sarcoma. *Cancer*. 2010;116:2429-36.

Comparison of the prognostic value of assessing tumor diameter versus tumor volume, at diagnosis or in response to initial chemotherapy, in rhabdomyosarcoma. *J Clin Oncol*. 2010;28:1322-8.



CANCER PROTEOMICS - MOLECULAR MECHANISMS

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The laboratory develops proteomics applications in cancer including the discovery of novel cancer and treatment signatures, the investigation of oncogenesis mechanisms, and the discovery of novel protein targets for therapeutic intervention.

Main research projects include:

1) discovery of biomarkers potentially useful for developing a multiparametric analysis to identify individuals at high risk of lung cancer. A potential cluster of cytokines useful for evaluation of lung cancer risk was recently identified. The effective power of this pattern is now the object of further studies in a larger number of subjects. Several methods of breath analysis have been set up, ranging from measurement of exhaled breath biomarkers and volatile organic compound (VOC) assessment using mass spectrometry, to analysis of various proteins and metabolites in exhaled breath condensate (EBC);

2) signaling pathway profiling of renal cell carcinoma for targeted therapy. Laser capture microdissection (LCM) and reverse-phase protein arrays (RPPAs) were used to determine the signaling pathway status in tumor cells of a large panel of primary clear cell renal cancers. The results demonstrate that clear renal cell carcinoma could be stratified on the basis of the activated signaling proteins and this type of analysis could be useful in the rationale selection of the most appropriate therapeutic approach;

3) relationships between FAK signaling, microtubule dynamics and drug response. The results support the concept that FAK activity in various cancer cell line types is associated with constitutive activation of anti-apoptotic signaling pathways and drug resistance.

Other projects:

- identification of immunodominant non-Hodgkin lymphoma-restricted antigen(s) as novel biotarget(s) for therapy.
- signaling pathway profiling of colorectal cancer liver metastases for targeted therapy.
- cerebrospinal fluid proteome from central nervous system pediatric tumors: patient-related patterns.

Keywords: mass spectrometry, cancer biomarkers, human fluids, signaling pathways, targeted therapy

2010 RELEVANT NOTES

Technologies

1-D and 2-D electrophoretic protein separations, DIGE technology, MALDI-TOF mass spectrometry (Voyager DE-STR), and SELDI-TOF technology (PCS 4000)

Collaborations

Istituto Superiore di Sanità

Istituto Nazionale per la Ricerca sul Cancro (IST), Genoa

IRCCS Ospedale Oncologico, Bari

IRCCS S. Maria Nuova, Reggio Emilia

Applied Biology at the University of Brescia

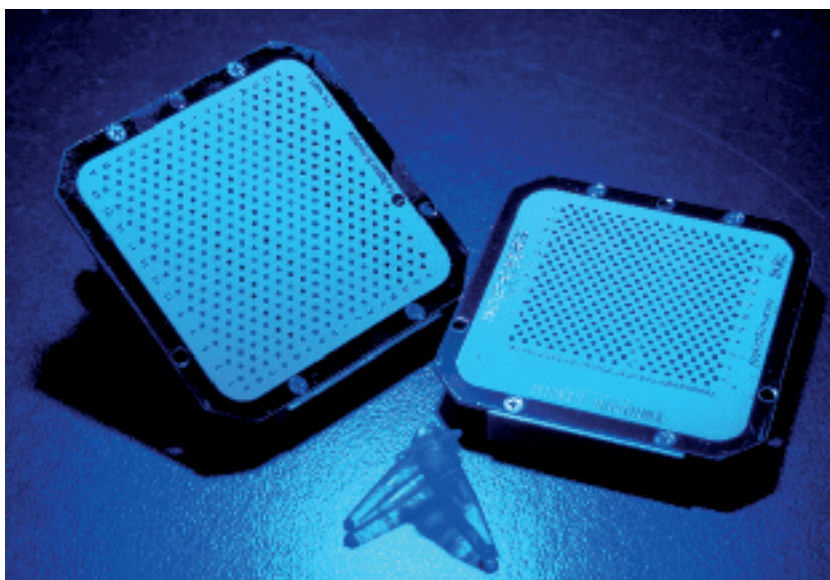
George Mason University, Center for Applied Proteomics and Molecular Medicine, Virginia, USA

Laboratori d'Investigació UdL/HUAV Dept. Medicina Experimental Universitat de Lleida, Spain

Publications

Elevated levels of the acute-phase serum amyloid are associated with heightened lung cancer risk. *Cancer*. 2010;116:1326-35

Dasatinib reduces FAK phosphorylation increasing the effects of RPI-1 inhibition in a RET/PTC1-expressing cell line. *Mol cancer*. 2010;9:278



ANIMAL HOUSE

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Modelling human cancer in mice is an unsurpassed need to validate candidate genes involved in transformation and cancer progression as well as to study new therapeutic options. Microarray technology, gene expression profiles, and genomics provide an multitude of genes that require validation. The search for molecules that interfere with their function requires a complex biological system wherein to test efficacy in clinical applications. Technologies for the manipulation of the mouse embryo including homologous recombination and the similarity of human and mouse genome have allowed the creation of mouse models of human pathologies, which are essential for studying complex cancer traits and testing novel therapeutics. Carcinogenesis is associated with disruption of tissue architecture, with consequent induction of proinflammatory cytokines and chemokines in a milieu in which leukocytes are present and further recruited. Despite such an inflammatory environment, tumors can evade immune surveillance through mechanisms of resistance or induction of tolerance. In this context, mice knockout (KO) for ECM genes and inflammatory molecules, when crossed with transgenic mice carrying oncogenes, permits study of the role of inflammation within variable tumor microenvironments. Cancer immunotherapy has long been studied at INT, and tumor prone transgenic mice complement such studies by testing cancer vaccines in the setting of immunoprevention and therapy of small and large tumors rather than in more artificial transplantable models.

At INT, several transgenic mice reproducing the characteristics of human cancers occurring in prostate, mammary gland, thyroid, colon, and melanocytes have been created and collected. Other transgenic mice carry clonotypic T cell receptors (TCR) or correspondent antigens under tissue specific promoters. The collection includes several mice KO for genes encoding certain cytokines and their receptors, chemokines, signal transduction molecules, ECM proteins, and metalloproteases.

The mouse facility includes several areas for breeding, and a dedicated laboratory is equipped with an X-ray irradiator, and a non-invasive imaging system using micro-ultrasound and microPET. This large mouse collection has had an impact on studies at INT, allowing the discovery of new processes related to tumor biology, immunotherapy, and chemotherapy, and, more importantly, enabling us to investigate the underlying mechanisms. During 2010, published papers reporting animal studies contributed for about 24% of the total Impact Factor of the Department of Experimental Oncology and Molecular Medicine.

Ethics Committee for Experimentation on Animals (CESA)

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Mario P COLOMBO
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In compliance with the national legislation (D.L. 116/92), the Research Projects requiring animal studies are critically evaluated for approval by the CESA before being submitted to the Italian Ministry of Health.



