SCIENTIFIC REPORT 2016

EXECUTIVE SUMMARY

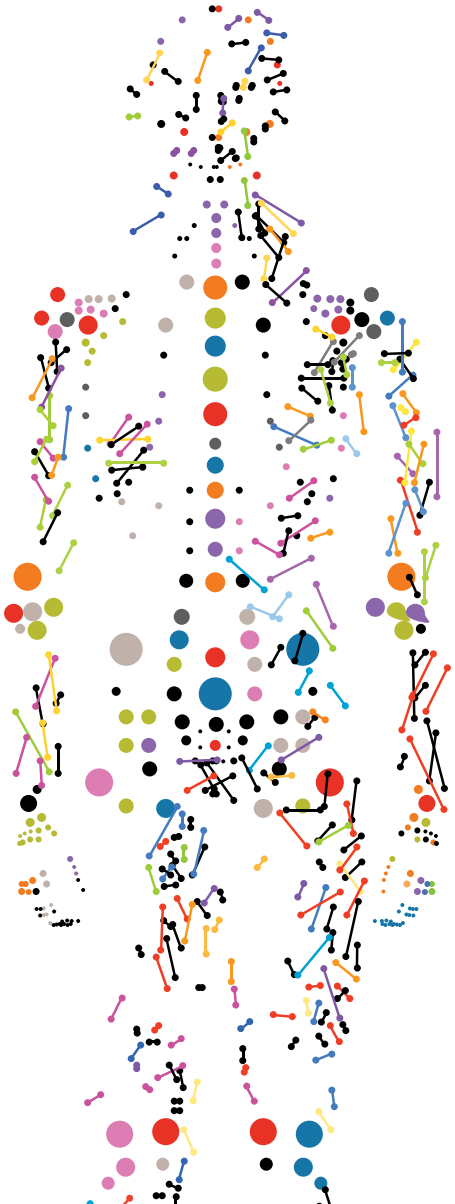
FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Sistema Socio Sanitario
Regione Lombardia

CONTENTS

FROM THE PRESIDENT

ENZO LUCCHINI



Since January 1, 2016 I have been President of the Fondazione IRCCS - Istituto Nazionale Tumori, the historical oncology center envisioned by Luigi Mangiagalli and inaugurated on April 12, 1928, by Vittorio Emanuele III. The Istituto Nazionale dei Tumori in Milan was the first center in Italy to organically address the "dark evil", a term which Carlo Emilio Gadda called cancer in his novel "The pain cognition" of 1941. Today the Institute has grown to the point that it has become a reference of great international prestige for the research and treatment of cancer, a "horizon of hope" for so many patients who come not only from all Italian regions, but also from abroad.

The Institute I chair represents a human, cultural, scientific and technological heritage for both the Lombardy Region, for Italy, and also abroad. INT is an international cancer center certified by the Organization of European Cancer Institutes (OECI) as a "Comprehensive Cancer Center". The Institute site is a composite hospital structure where research activity is closely connected to the clinical dimension of care. In Luigi Mangiagalli's time, the "dark evil" would lethally affect about 25 thousand people because of the lack of good treatment and care, including untold suffering. Today in Italy there are about 365 thousand new cases diagnosed each year. Thanks also to the contribution of our Institute, cancer deaths in recent decades have decreased by 18% among men and 10% among women. These results were achieved thanks to prevention and research activity and thanks to the new therapeutic options which have become available for the most common cancers as well as for the most rare, investigated here and treated with excellence.

Thus, the INT stands for its patients as a "horizon of hope": through its multifold excellence and a continuous collegial effort towards innovative frontiers of research, immediately translating the latest evidence in the fields of prevention, diagnosis and treatment into practice.

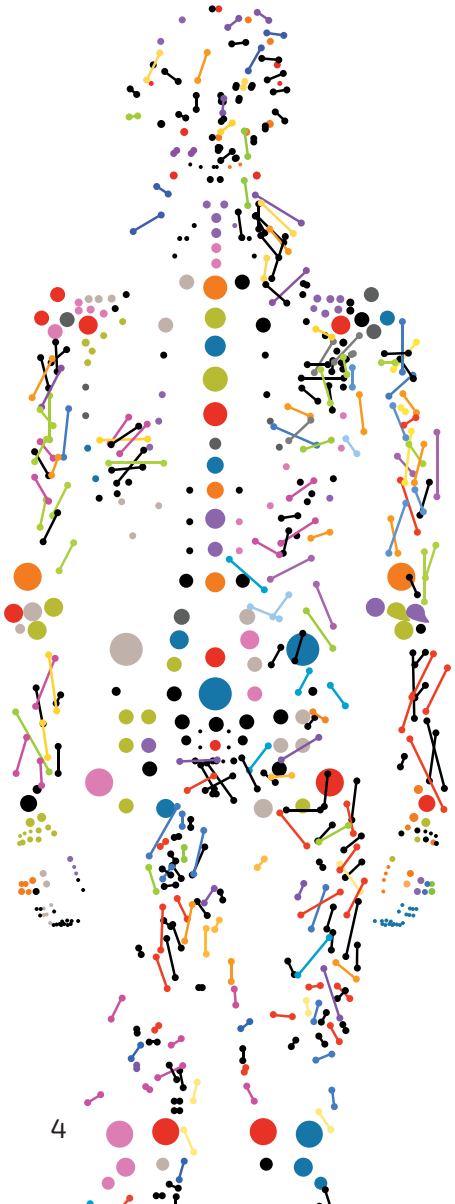
The underlying feature to this is INT's signature: attention and care to the person affected by the disease, not to the disease alone.

FROM THE SCIENTIFIC DIRECTOR

GIOVANNI APOLONE

As part of the mission of any IRCCS, research at INT covers all the most significant areas of cancer research, with structures and scientific programs ranging from basic to clinical and healthcare research. The graphs and figures presented in this report give an overview of these activities; we would like to stress that these could only be achieved thanks to the strong **focus of our Institute on translational research**, where research activities and healthcare are connected through multidisciplinary programs designed and coordinated by teams with diverse clinical and scientific backgrounds.

It is worth remembering that in 2016 the annual independent assessment conducted by the Ministry of Health to evaluate the performance of the 49 Italian IRCCSs confirmed **INT at the first place among Italian Comprehensive Cancer Centers**, against a set of 14 indicators of excellence in scientific research, healthcare and networking.



The **scientific output** in 2016 has enjoyed an upward trend according to all standards conventionally used to classify research activity: 590 clinical trials were conducted, 376 of which classifiable as studies on new drugs or health technologies. Over 25,000 patients had the opportunity to participate in research protocols that, besides offering them the best possible treatment, also gave them access to innovative drugs and devices. In 2016, we published more scientific papers (667 with 3878 IF) than in 2015, thereby upholding the positive trend of recent years. All departments at the Institute contributed to the research activity, as made clear by the affiliations of the authors and the attribution of 60% of the total IF to the clinical departments, 20% to the experimental department, and the remaining 20% to the epidemiology department. It is also worth noting that our researchers were either first or corresponding authors in almost half of the publications by INT-affiliated scientists.

The year 2016 represented a major turning point for research at INT. About six months after his appointment, Dr Giovanni Apolone proposed a Strategic Research Plan for the period 2016-2019 that was agreed upon by the Scientific Institutional Committee and approved by the Board of Directors. The **"INT Research Strategic Plan"** (RSP INT 2016-2019) is a three-year research plan agenda aiming at a better planning of the research strategy, a more consistent decision-making process for research projects and experimentations and a more intensive effort to rationalize research-supporting resources and structures. It also aims at developing and supporting specific initiatives to enhance and strengthen research coordination and governance through the creation of organizational structures - the research infrastructure - supporting research, investigator-initiated (non-profit) clinical trials, leveraging funding from private and public agencies.

In accordance with the RSP INT 2016-2019 and in line with the aim of strengthening INT's presence at international level, INT participates to several European networks. In particular, in 2016 INT started the process

of joining Cancer Core Europe, a consortium of seven leading European Comprehensive Cancer Centers to promote joint translational and clinical research projects, including outcome research, to develop personalized cancer medicine and create standardized diagnostic platforms and large databases. INT is a formal member since July 2017.

Considering the great changes taking place, this *2016 Scientific Report* must be considered a **transition to a new editorial idea**; it presents and outlines, in a summary form, the main results of the implementation of the *RSP 2016-2019* and it aims at promoting innovative areas of research with a strong focus on the constant improvement of clinical outcomes. Starting from 2016, the Scientific Directorate intends to publish the Scientific Report on a two-year basis, the next complete edition will present in an exhaustive way projects, activities and results for the two-year period 2016-2017.

In this way, the renovated two-years Scientific Report could take into consideration the results of the assessment carried out by the Scientific Directorate at the end of the 2013-16 programming period of the 6 lines of research so far pursued and of the available research outcome. This process gave raise to new strategic directions towards 4 novel research lines - Primary prevention, secondary and early diagnosis, Precision medicine and technology innovation (pharmacological and non), Complexity and rare tumors, Health research and "Outcome Research" - that are not just an ex-post justification of the ongoing activities, but offer strong guidance and planning in line with INT mission statement and current priorities, as well as with the available resources.

In order to find the better mechanism for sustaining new projects and initiatives within the new strategic direction, the Scientific Directorate has introduced the necessary organizational changes and identified the funding mechanisms that should give INT freedom to use the resources from the different financing programs in a way that is consistent with the strategic choices INT made. At this purpose, a Fund dedicated to in-house research was created so as to support investigator-initiated projects, not necessarily related with drug research and development. This Fund would enable to plan yearly interventions to promote in-house research and to better meet the needs of our Institute.

In accordance to this, in 2016 the Scientific Directorate started investing part of the available resources of the Fund at supporting in-house research through the **launching of the first competitive call for proposals** with the aim to support preclinical and clinical multidisciplinary projects. The call comprised two separate parts: one focusing on **promoting in-house research** and the second one **supporting researchers in early stages of their career**. The grant has financed 6 long/medium-term multidisciplinary research projects prompted by clinical needs and authored by researchers and MDs working at our institute, with a special focus on early career researchers (under 40 years of age).

THE ESSENTIAL ABOUT **INT** IN 2016

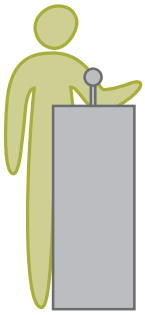
SCIENTIFIC ACTIVITY

693 **PUBLICATIONS**

3727.03 IMPACT FACTOR

46.9% PUBLICATIONS AS FIRST/ LAST AUTHOR

EDUCATION

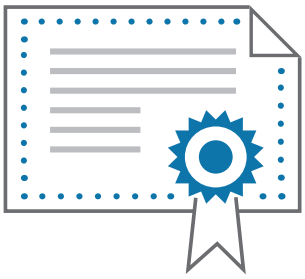


179 **EVENTS/TRAINING COURSES**

4,151 PARTICIPANTS

34,406 FORMATIVE HOURS

PATENT PORTFOLIO

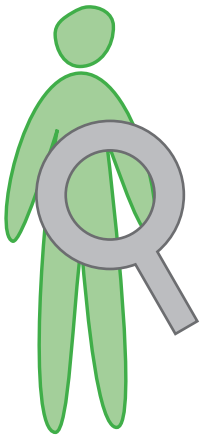


16 **PATENTS**

OWNER OF **7** PATENTS

CO-OWNER OF **9** PATENTS

RESEARCH



640 **CLINICAL STUDIES**

246 OBSERVATIONAL STUDIES

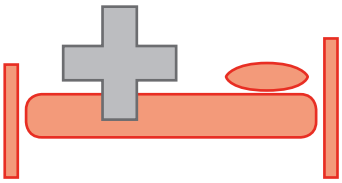
394 EXPERIMENTAL STUDIES

24,445 **PATIENTS INCLUDED IN CLINICAL STUDIES**

21,982 PATIENTS ENROLLED IN OBSERVATIONAL STUDIES

2,463 PATIENTS ENROLLED IN EXPERIMENTAL STUDIES

CLINICAL DATA



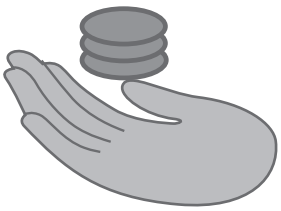
482 **BEDS**

18,294 TOTAL INPATIENTS

4,348 OF WHICH DAY HOSPITAL

1,147,333 CONSULTATIONS

RESEARCH FUNDING



€ 24,343,394.88
TOTAL

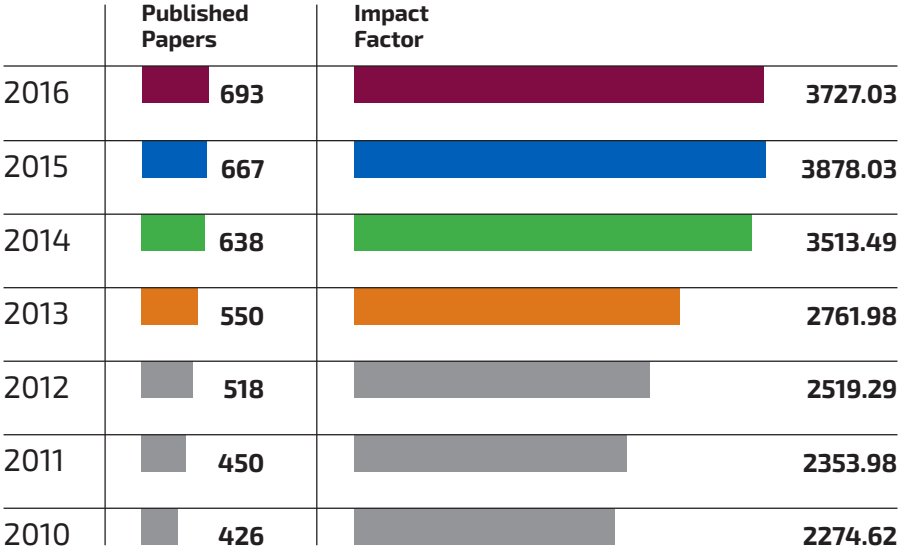
€ 7,546,313.34
MINISTRY OF HEALTH

€ 13,443,081.54
FUNDING AGENCIES

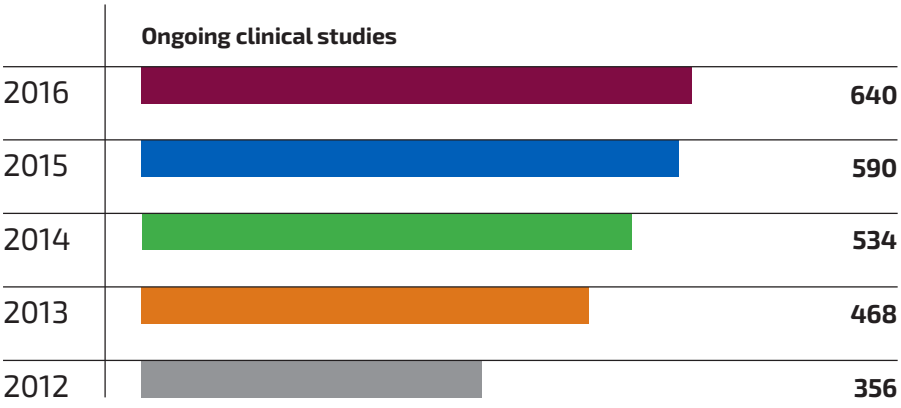
€ 3,354,000.00
CLINICAL TRIALS

FACTS & FIGURES

IMPACT FACTOR AND PUBLISHED PAPERS



CLINICAL STUDIES



Ongoing experimental studies in 2016

	Profit	No Profit
RANDOMIZED	**131** (33.2%)	**95** (24.1%)
NON RANDOMIZED	**74** (18.8%)	**94** (23.9%)

1975 **TOTAL PERSONNEL WORKING AT INT**

OF WHICH

540 PERSONNEL DEVOTED TO RESEARCH

INT's 2016 tenured personnel volumes at a glance

259	MEDICAL DOCTORS
73	HEALTHCARE DOCTORS
20	MANAGEMENT DIRECTORS
430	NURSING PERSONNEL
197	HEALTHCARE PERSONNEL
318	TECHNICAL PERSONNEL
262	ADMINISTRATIVE PERSONNEL
416	NON PERMANENT STAFF (RESEARCHERS, CLINICIANS, FELLOWS, ADMINISTRATIVE, ECC)
1975	**TOTAL**

27 **RESEARCH LABS**

3600 Sqm SURFACE

10 **PARTICIPATION IN CANCER RESEARCH ORGANIZATIONS**

(OECI, UICC, WIN, EORTC, EPCRC, ECCO, IAEA...)

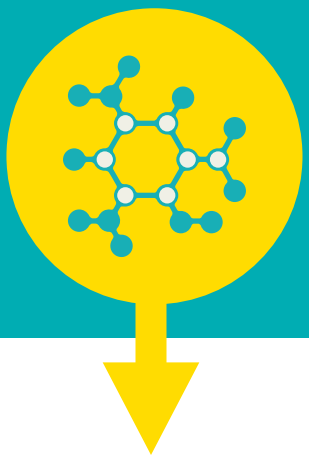
258 **TOTAL RESEARCH COLLABORATIONS WORLDWIDE**

OF WHICH

16 EU COLLABORATIONS

RESEARCH AREAS

INT RESEARCH IS AIMED AT IMPROVING PREVENTION, EARLY DIAGNOSIS AND TREATMENT OF CANCER DISEASES, AND THE QUALITY OF LIFE OF CANCER PATIENTS. RESEARCH ACTIVITY IS BASED ON INTEGRATION AND SYNERGY BETWEEN...



PRECLINICAL AND BASIC RESEARCH

Basicresearchinoncologyaimsatinvestigating cellular and molecular mechanisms underlying the complex nature of tumors, from the transformation of a normal cell into a tumor, to the different processes leading to metastatization, evading immune defense systems and resistance.

TRANSLATIONAL RESEARCH

Translational research in oncology deals with transforming the laboratory's scientific discoveries into clinical applications to treat tumors and, backwards, reporting the outcomes of interventions and clinical questions to foster new ideas in preclinical research. This approach involves a close collaboration between clinicians and lab-biologists facilitating the exchange of ideas, for the identification of new treatments and therapeutic approaches for patients benefit.

CLINICAL RESEARCH

The identification of mechanisms of tumor transformation by basic and translational research may lead to innovative therapies and targeted drugs, whose real effectiveness has to be demonstrated through clinical trials. The patient is actively involved in the study at all levels, making himself available to clinical and radiological controls over time and referring about his quality of life during the therapy. In this way it is possible to identify those therapies that in the future will become a new standard able to prolong patients' life and/or increase the recovery rate from disease.

QUALITY OF LIFE RESEARCH

It is aimed at improving rehabilitative and palliative care, defining personalized plans of psychological assistance to patients and families, and developing more effective approaches to clinical nutrition.

EPIDEMIOLOGICAL RESEARCH

Epidemiology investigates all the factors that determine the presence or absence of diseases and disorders, contributing to understand how many people have a disease or disorder, if those numbers are changing, and how the disorder affects our society and our economy. It is aimed at developing national cancer registries, international cohort studies on the role of diet and prevention interventions. In particular INT carries out research projects related to primary prevention, supporting the message that lifestyle, diet, and smoking cessation have impact on cancer risk.

HIGHLIGHTS

A SELECTION OF RESULTS OBTAINED IN 2016, COVERING THE MAJOR RESEARCH ACTIVITIES PUBLISHED ON PRESTIGIOUS JOURNALS

Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases after surgical resection of localised soft-tissue sarcomas *(Callegaro D. et al, Lancet Oncology)*

We have developed and externally validated two prediction nomograms representing reliable prognostic methods that can be used to predict overall survival and distant metastases in patients after surgical resection of soft-tissue sarcoma of the extremities. These nomograms can be offered to clinicians to improve their abilities to assess patient prognosis, strengthen the prognosis-based decision making, enhance patient stratification, and inform patients in the clinic.

Prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients: The MITO 15 trial (Lorusso D. et al Annal of Oncology)

In the context of a prospective phase II trial of trabectedin in BRCA-mutated and/or BRCAness phenotype recurrent ovarian cancer patients (The MITO 15 trial) our data confirmed that the signature of 'repeated platinum sensitivity' identifies patients highly responsive to trabectedin. In this setting, the activity of trabectedin seems comparable to what could be obtained using platinum compounds and the drug may represent a valuable alternative option in patients who present contraindication to receive platinum.

Development and validation of a microRNA-based signature (MiROvaR) to predict early relapse or progression of epithelial ovarian cancer: a cohort study (Bagnoli M. et al, Lancet Oncology)

We identified 35 miRNAs predicting risk of progression or relapse and used them to create a prognostic model, the 35-miRNA-based predictor of Risk of Ovarian Cancer Relapse or progression (MiROvaR). MiROvaR is a potential predictor of epithelial ovarian cancer progression and has prognostic value independent of relevant clinical covariates. MiROvaR warrants further investigation for the development of a clinical-grade prognostic assay.

Toward the molecular dissection of peritoneal pseudomyxoma *(Pietrantonio F. et al, Annal of Oncology)*

Outcome of pseudomyxoma peritonei (PMP) after cytoreductive surgery (CRS) and hypertermic intraperitoneal chemotherapy (HIPEC) is heterogeneous even after adjusting for clinico-pathological prognostic variables. Our NGS approach allowed the discovery of potentially druggable mutations such as KRAS, whose poor prognostic role we demonstrated for the first time.

Reprogramming the lung microenvironment by inhaled immunotherapy fosters immune destruction of tumor *(Le Noci V. et at, Oncoimmunology)*

Results obtained in our preclinical model indicate that an effective antitumor response can be obtained against established lung multiple foci of a highly aggressive tumor using airway delivery as a convenient and non-invasive way to administer immuno-therapy. The inhalation therapy can be a feasible strategy to deliver immunodulatory molecules, including antibodies and cytokines that reprogram the lung tumor microenvironment to foster immune destruction of tumors.

MET-Driven Resistance to Dual EGFR and BRAF Blockade May Be Overcome by Switching from EGFR to MET Inhibition in BRAF-Mutated Colorectal Cancer *(Pietrantonio F. et al, Cancer Discovery)*

Our studies identified - clinically and preclinically - MET amplification as a new mechanism of resistance to EGFR and BRAF dual/triple block combinations in BRAF-mutated colorectal cancer. Switching from EGFR to MET inhibition, while maintaining BRAF inhibition, resulted in clinical benefit after the occurrence of MET-driven acquired resistance. We believe that specific targeting of MET-driven resistance to dual EGFR and BRAF block may lead to the design of biomarker-driven trials of second-line targeted therapy.

Subtype-specific metagene-based prediction of outcome after neoadjuvant and adjuvant treatment in breast cancer *(Callari M. et al, Clinical Cancer Research)*

We developed metagene-based predictors (linked to proliferation, ER-related genes, and immune response) able to define low and high risk of relapse after adjuvant/neoadjuvant therapy in breast cancer. In triple-negative breast cancer an immune-related metagene associated with prognosis and benefit from chemotherapy was identified, reinforcing the rationale for testing a combination of immunomodulating agents and chemotherapy in this subset of highly aggressive tumors. Clinical trials enrolling only these patients would reduce the overtreatment and increase the chance of demonstrating a clinical meaningful benefit.

Functional genomics uncover the biology behind the responsiveness of head and neck squamous cell cancer patients to cetuximab *(Bossi P. et al, Clinical Cancer Research)*

Our study first specifically investigates cetuximab/platinum resistance in head and neck squamous cell carcinoma patients with recurrent-metastatic disease (RM-HNSCC) and illustrates the feasibility of gene expression profiling of pretreatment tumor to identify candidate biomarkers of response to anti-EGFR treatment in this subset of patients. Our data uncover the biology behind response to platinum-based chemotherapy plus cetuximab in RM-HNSCC cancer and may have translational implications improving treatment selection.

TNF-related apoptosis-inducing ligand (trail)-armed exosomes deliver proapoptotic signals to tumor site *(Rivoltini L. et al, Clinical Cancer Research)*

We investigated the ability of membrane TRAIL-armed exosomes to deliver proapoptotic signals to cancer cells and mediate growth inhibition in different tumor models. TRAIL-armed exosomes can induce apoptosis in cancer cells and control tumor progression in vivo. Therapeutic efficacy was particularly evident in intra-tumor setting, while depended on tumor model upon systemic administration. Thanks to their ability to deliver multiple signals, exosomes thus represent a promising therapeutic tool in cancer.

NFATc2 is an intrinsic regulator of melanoma de-differentiation *(Perotti V. et al Clinical Cancer Research)*

In this study, we identify NFATc2 as major intrinsic regulator of human melanoma de-differentiation, a process implicated in resistance to chemotherapy, target therapy and immunotherapy. By different approaches, we found that the expression of NFATc2 is associated with a $CD271^{+}$ de-differentiated phenotype which, in turn, is controlled by NFATc2 through a pathway that involves mTNF-α, c-myc and Brn2. Moreover, we show that targeting of NFATc2 improves tumor recognition by MDA-specific cytotoxic T cells. Taken together, our results suggest that the expression of NFATc2 promotes melanoma dedifferentiation and immune escape.

miR-9 and miR-200 regulate PDGFRβ-mediated endothelial differentiation of tumor cells in triple-negative breast cancer *(D'Ippolito E. et al., Cancer Research)*

We investigated the role of miRNAs as a therapeutic approach to inhibit PDGFRβ-mediated vasculogenic properties of triple-negative breast cancer (TNBC), focusing on miR-9 and miR-200. Our results demonstrate that miR-9 and miR-200 play opposite roles in the regulation of the vasculogenic ability of TNBC, acting as facilitator and suppressor of PDGFRβ, respectively. Moreover, our data support the possibility to therapeutically exploit miR-9 and miR-200 to inhibit the process of vascular lacunae formation in TNBC.

Mesenchymal Transition of High-Grade Breast Carcinomas Depends on Extracellular Matrix Control of Myeloid Suppressor Cell Activity *(Sangaletti S. et al Cell Reports)*

Biological and clinical characteristics of breast cancer are determined by both tumor cells and normal cells belonging to the immune system. The last, together with the extracellular matrix (ECM), contribute to form the tumor microenvironment. Information about the prognosis of high grade breast tumors can be obtained by studying the expression profile of genes encoding for ECM proteins. In this context, we have shown that extracellular matrix proteins can influence the recruitment and activity of myeloid cells to support tumor growth and aggressiveness. Additionally, we demonstrated the efficacy of aminobiphosphonates, drugs clinically employed in the treatment of osteoporosis, in blocking myeloid cell functions and consequently improving/restoring response to chemotherapy.

Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EUROCARE-5 *(Trama A. et al. Lancet Oncology)*

Notwithstanding the encouraging results for some cancers, and overall, we showed poorer survival in Adolescents and Young Adults (AYAs) than in children for the eight important cancers. Recent European initiatives to improve outcomes in AYAs might reduce the survival gap between children and AYAs, but this reduction can only be verified by future population-based studies.

Final results of the second prospective AIEOP protocol for pediatric intracranial ependymoma *(Massimino M. et al, Neuro-Oncology)*

In a national multi-institutional collaboration, with the largest sample of ependymoma patients in a prospective trial to date (the second prospective AIEOP protocol for pediatric intracranial ependymoma), we have demonstrated the feasibility of multiple surgical procedures followed by a novel radiotherapeutic approach, with a trend to outcome amelioration in children with residual disease, a patient group that carries a poor prognosis.

Impact of home enteral nutrition in malnourished patients with upper gastrointestinal cancer: a multicentre randomised clinical trial *(Gavazzi C et al, European Journal of Cancer)*

Randomised trials aimed at investigating the effects of Home Enteral Nutrition (HEN) in post-surgical patients with GI cancer are lacking. Our study comparing HEN and counselling in limiting weight loss during oncologic treatment indicates that HEN is a simple and feasible treatment to support malnourished patients with upper GI cancer after major surgery and during chemotherapy in order to limit further weight loss.

Is it possible to encourage hope in non-advanced cancer patients? We must try *(Ripamonti CI et al, Annals of Oncology)*

The relationship among hope, symptoms, needs, and spirituality/religiosity in patients treated in a supportive care unit (SCU) was explored. Hope can be encouraged by clinicians through dialogue, sincerity, and reassurance, as well as assessing and considering the patients' needs, symptoms, psychological frailty, and their spiritual/religious resources. The role for the clinicians in promoting 'overall health' and in supporting the 'healing process' of their patients beyond the stage of the disease is impressive. It is necessary to explore the relationship among physical, relational, and cognitive aspects, along with each patient's needs from their diagnosis throughout their oncological treatment.

A multicenter randomized phase IV 'real life' trial on the variability of response to opioids *(Corli O et al, Annals of Oncology)*

This multicentric study (44 centers participating in the trial with 520 patients recruited) compared the analgesic efficacy, changes of therapy and safety profile over time of four strong opioids given for cancer pain. The main findings were the similarity in pain control, response rates and main adverse reactions among opioids. Changes in therapy schedules were notable over time. A considerable proportion of patients were nonresponders or poor responders.

FOCUS ON INTER-DISCIPLINARITY SELECTED RESEARCH AND CLINICAL PROGRAMMES

EARLY PHASE CLINICAL TRIALS

In line with its mission, INT has always promoted clinical research, both sponsored and investigator-driven. Most of the ongoing or planned early studies originate from three departments, i.e. Medical Oncology, Hematology and Pediatrics.The high rate of clinical studies was clearly facilitated by the activity of the institutional Clinical Trials Center (CTC), created in 2011 as a project of the Scientific Directorate and aimed at supporting investigator-driven, early-phase clinical trials and at helping researchers manage spontaneous projects.
Patients have a variety of opportunities to access innovative treatments such as the possibility to benefit from new drugs by participating in sponsored and investigator-driven clinical trials, and even in early phase studies.

IMMUNOTHERAPY

INT is at the forefront of clinical and pre-clinical research in the field of cancer immunotherapy. Over the past 6 years, INT has carried out and contributed to a large number of phase I to III trials, mostly focusing on the treatment of patients with advanced solid tumors using antagonistic antibodies targeting the CTLA-4 and the PD-1/PD-L1 immune-checkpoints in melanoma, non-small cell lung cancer (NSCLC), renal, bladder, gastric and colorectal cancer. In particular INT pioneered the use of immunotherapy in phase III studies in lung cancer, enabling even heavy smokers - whose target genes have not been identified yet - to receive targeted therapies that are revolutionizing cancer treatment. Further immunotherapy trials, testing immune-checkpoint inhibitors in the adjuvant setting, as well as the association of immunotherapy with target therapy or chemotherapy, are ongoing.

In this context research projects aimed at defining more effective predictive biomarkers of response, as well as at understanding the main mechanisms of resistance are ongoing. Pre-clinical research on tumor immunology is based on the comprehensive analysis of neoplastic tissues and peripheral blood from cancer patients. Taking advantage of experimental *in vivo* models, it aims at identifying new molecular targets to improve the efficacy of immunotherapy; understanding the mechanisms of tumor-mediated immune suppression; deciphering the role of immune evasion in hampering the efficacy of immunotherapy; defining the role in the anti-tumor response of distinct cellular subsets belonging to the innate or adaptive arms of the immune system.

EXPERIMENTAL ONCOLOGY

Cancer complexity is reflected in the Department of Research and the Department of Applied Research and Technological Development, in a variety of combined approaches thanks to the availability of adequate infrastructure and resources, dedicated science technology platforms, and excellent expertise and established internal, national and international research networks/collaborations. Many research projects are aimed at understanding the molecular mechanisms of cancer growth and progression, metastatization, and resistance to therapies, as well as identifying and validating novel targets and strategies for cancer treatment and overcoming resistance.

NGS and high-throughput microarray analyses allowed us to capture the biologic complexity of cancer and to identify and validate (in independent studies and/or public datasets), among others: 1) robust metagene-based predictors, able to define low and high risk of relapse after adjuvant/neoadjuvant therapy in breast cancer; 2) a genomic profile predictive of response to cetuximab in head and neck squamous cell cancers; 3) SEMA6A, a gene belonging to the semaphorin-plexin ligand-receptor pathway in BRAF-mutant melanoma cells that has the potential to be a therapeutic target; 4) and a microRNA signature (MiROvaR) that is a predictor of epithelial ovarian cancer progression independent from other relevant clinical covariates.

MICROENVIRONMENT AND INFLAMMATION

In the last years, a core project involving several Units in INT aimed at the identification of new molecules detectable in blood circulation that may have diagnostic and prognostic value at cancer onset or recurrence. Increasing attention is given to the non-tumoral stromal cell components of the tumor microenvironment as active part in tumor progression. Stromal cell components coevolve with tumors to form functional units, which supports tumor growth. In this context, transforming tissues release the molecules that are necessary for cross-communication with the bone marrow. The last provides the stromal cell components necessary to build the favorable tumor microenvironment. The molecules responsible for such cross-communications intercepted and identified in the blood may be exploited as potential biomarkers of earlier tumors of recurrence. As an example, circulating miRNAs that can be provided by stromal cells are predictor of incipient lung cancer earlier than spiral CT, supporting the feasibility of this approach.
Increasing attentions are now given to the extracellular matrix (ECM) as new determinant of tumor aggressiveness and response to therapy and through its unexpected capacity to regulate innate immune cells of the tumor microenvironment. The last have been shown to support the growth of tumors, which have escaped from adaptive immune-surveillance.

IMMUNO-IMAGING

We have developed an antibody fragment (scFv) targeted against PSMA, an antigen commonly found and overexpressed in prostate cancer cells. Once the antibody fragment has been labeld with ^{123}I, it can then be employed to identify cancer cells and find possible relapses. The same fragment ^{124}I labelled has already been used to conduct preliminary experiments of Positron emission tomography (PET) imaging with very promising results.

OUTCOMES RESEARCH

Outcome research relies on observational studies investigating the effect of specific therapeutic procedures on patients' health: response to treatments, overall and disease free survival, cancer prognosis and survivorship, long and short term side effects of anticancer treatments, quality of life etc. In INT outcomes research is based on: 1) INT clinical/experimental data creation of the institutional Breast Cancer Clinical Registry (BC-CR), now being extended to other neoplasms (lung and pancreas cancer CR are under development). The BC-CR systematically collects clinical, pathological, metabolic and biomolecular data of all cases operated at the INT Breast Surgery Unit. The BC-CR is functionally connected with the INT blood bank. For each patients it is therefore possible to directly consult the original reports, and to retrieve additional information of interest for specific studies; 2) based on data from population based cancer registries INT designed EUROCARE, the largest international collaborative population-based study on survival and care of cancer patients in Europe. The EUROCARE data base includes survival data of over 13,800,000 patients diagnosed since 1978 in 117 European CRs, with vital status information available updated to 31 December 2008 or later. Lombardy Cancer Registry - Varese Province, Lombardy registry of congenital malformations and adverse pregnancy events, Registry of hereditary digestive system tumors.

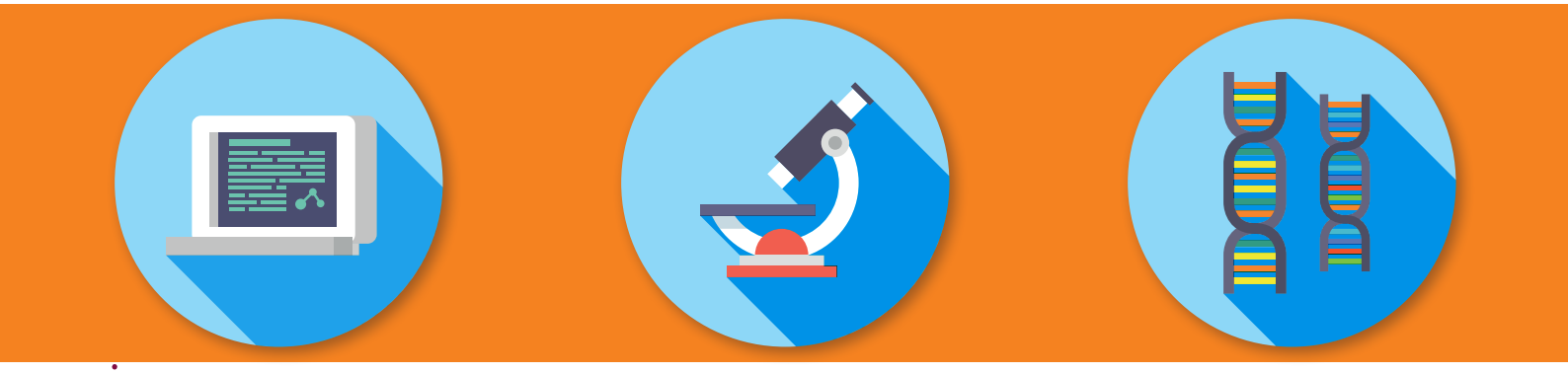
PEDIATRIC ONCOLOGY

The Pediatric Oncology at INT conducts clinical and research projects on pediatric cancers, and represents a referral center for all the country. Patient management is based on a multidisciplinary approach that includes prevention (counselling and genetic testing), diagnosis (with specific histological and radiological expertise), treatment (including interdisciplinary activity with the pediatric surgical unit and the pediatric radiotherapy unit, a Bone Marrow Transplantation service and a team dedicated to experimental therapy in patients with rela psing/refractory solid tumors), psychosocial support, and long term survivors program (for the follow-up of iatrogenic sequele). Dedicated age-specific facilities and projects for adolescents (the Youth Project) have been developed and represent a model to promote the normalcy of our patients.

INT
AND TECHNOLOGY

AVAILABLE TECHNOLOGY FOR DIAGNOSTICS, THERAPY AND SURGERY

In the field of diagnostics and therapy, INT stands out for its latest generation equipment which, in addition to their daily clinical use, is also used for research purposes. Favoured by an adequate hardware and software infrastructure, in INT diagnostic and therapy work in complete synergy, both in the clinical and research fields. In some specific cases, INT contributes in a research context also to the technological evolution and optimization of peculiar equipment, and to the implementation of new applications.



HIGHLIGHT RADIATION ONCOLOGY

Radiation Oncology at INT follows the modern concept of "personalized treatment", thanks to the availability of equipment that meets the highest technological standards (VMAT delivery, integrated CBCT imaging devices, 6D couch, flattening filter free high dose rate beams). In particular, INT is one of the very few centres in Italy with an exclusive system to monitor the movement of the target region during treatment delivery. The system is based on the implantation of small electromagnetic transponders with or very close to the tumour (currently implemented for the prostate).

Available equipment:

- **6** linear accelerators
- **1** brachytherapy unit
- **1** dedicated CT scanner
- **8** workstations for treatment planning and dose calculation

HIGHLIGHT RADIOLOGY AND DIAGNOSTIC IMAGING

Radiology at INT is characterized by the high quality of the obtained diagnostic images, balanced by the continuous search for an optimization (reduction) of the dose of radiation delivered to the patient. Images are managed by a centralized system, locally accessible by the various professional figures on the basis of their clinical and research needs. In particular, INT was equipped in 2016 with a new angiography facility representing the state of the art in this field. The machine consists of a latest generation rotational angiography system, aimed at dose reduction and optimization of rotationally acquired images of crucial importance for oncological interventional procedures. Moreover, the most recent prone stereotactic system for breast biopsy with 2D and 3D imaging was installed. The system provides superior imaging and gives 360-degree access to the breast.

Available equipment:

- **3** Magnetic Resonance scanners (1.5 Tesla)
- **2** CT scanners
- **2** Tomosynthesis and mammographic scanners
- **1** prone stereotactic system for breast biopsy with 2D and 3D imaging.
- **2** angiography facilities
- **20** further radiological equipment

HIGHLIGHT NUCLEAR MEDICINE

Nuclear Medicine at INT meets the highest standards of functional imaging and metabolic therapy. In particular, with regard to the imaging, INT was equipped in 2016 with a new PET/CT scanner provided with a system for the acquisition of images synchronized with the patient's respiratory movement. With regard to therapy, INT is one of the very few centres in Italy treating liver tumours with ^{90}Y microspheres provided with a treatment planning system for 3D dose distribution calculation.

Available equipment:

- **2** PET/CT scanners
- **1** SPECT/CT scanner
- **2** SPECT scanners
- **1** workstation for 3D calculation of the dose delivered with ^{90}Y microspheres

HIGHLIGHT PATHOLOGICAL ANATOMY

In the context of precision medicine as the foundation for personalized medicine, the new Next Generation Sequencing technology is used at INT not only for research aims, but also to support diagnosis, if deemed appropriate by the clinician, especially for lung and colorectal cancer, and melanomas. By systematically using a commercial gene panel of the 50 genes most commonly mutated in cancers, as well as mutational panels designed by INT researchers, it is possible to establish the specific mutational status of each tumor. The quality of the material available for molecular analysis is guaranteed by technologies such as laser capture microdissection (LCM) which allows to collect homogeneous populations of intact cells, selected on the basis of morphological characteristics, from solid sections of tissue.

HIGHLIGHT PHARMACY

The Pharmacy unit is provided with a state-of-the-art facility for centralized and automated chemotherapy preparations. In particular, the 5 clean rooms available are equipped with 2 robots for compounding sterile preparations and with 5 workflow engine systems for the assisted preparation and computerized management of patients tailored treatments. Chemo medications are labelled with a QR Code and delivered to the wards by pneumatic mail.

HIGHLIGHT ENDOSCOPY AND SURGERY

In particular, at INT a broad band wide-angle endoscopy system is now available. The system allows highly accurate diagnostic gastroscopy and colonscopy, given the number and size of the viewing angles of the cameras placed in the distal end of the optic. This allows to improve the detection rate of colon polyps and duodenum and papilla lesions. Among the available surgical instruments, noteworthy is also the videolaparoscopy system for fluorescence imaging, which uses the green indocyanine tracer (non-radioactive) during surgery for neoplastic disease and sentinel lymph node mapping.

NGS TECHNOLOGIES FOR TRANSLATIONAL RESEARCH AND PRECISION MEDICINE

Technology innovation and NGS play a fundamental role in precision medicine whose final goal is providing the right treatment to the right patient at the right moment. INT is at the forefront for using next generation sequencing technologies in diagnosis and translational research in order to identify novel biomarkers and therapeutic targets as well as patient stratification by genomic analysis. Thanks to last generation instrumentation, INT supports basic and translational research in the field of precision medicine, that can find application to patients thanks to high technology instrumentations of diagnostic and therapeutic fields

The functional genomics platform for diagnostic and therapeutic optimization for precision medicine, available at the Functional Genomics Core Facilities, employs high performing instrumentations to perform nucleic acid extraction, purification and quality controls, automation and liquid handling workstations; microarrays platforms for gene, miRNA, lcnRNA expression; DNA methylation, CGH, SNP and copy number variation; Next generation sequencing (Ion Torrent, Ion 5SXL, NextSeq500). In 2016 new instrumentations have been acquired: the ION Ion 5SXL next-Generation DNA sequencer for massive sequencing; the Janus robotic station for liquid handling; the GeneChip System for expression and DNA analysis.

The recently acquired **DEP Array System** combines the ability to manipulate individual cells using DEP technology with high quality image-based cell selection. It identifies and recovers specific intact and viable individual cells of interest from complex, heterogeneous samples, available for further analysis, including next generation analysis.

RESEARCH CORE FACILITIES **INT**

TISSUE AND CELL REPOSITORY

Departments of Pathology and Experimental Oncology have implemented and maintain a large bank of frozen and FFPE normal, tumor tissues and blood/plasma/serum samples, coll ected and stored within a short time from removal following SOPs. Thousands of well-annotated clinical specimens of different tumor histotypes, linked to dedicated databases of patho-biological and clinical information, are currently available. Patients sign an informed consent which allows INT investigators to use the leftover material of biological samples collected during standard surgical and medical procedures for research purposes. Aliquots are attributed to individual studies after approval of Institutional Review Board and specific requests to the Ethical Committee. All leftover material is stored in the Institutional BioBank for at least 20 years from the collection, including residual material of specific project studies.

GRANT OFFICE

The INT Grant Office provides timely advice and information to researchers on funding opportunities; coordinates the participation of the research projects to funding programs; provides information on the internal procedures for submissions of project proposals; supports researchers to the submission and the final financial report and audit processes.

TECHNOLOGY TRANFER OFFICE (TTO)

The INT Technology Transfer Office (TTO) was created in 2009 to address two requirements: improve research results in a scientific and economic key and optimize processes in technology transfer and intellectual property management. The TTO offers support services for patent activities (from the beginning of a new invention to the filing and maintenance of the correspondent patent), spin off evaluation and dissemination of IP culture within researchers.

FUNCTIONAL GENOMICS AND BIOINFORMATICS

The FGBCF provides technological support to translational oncology through the development and implementation of advanced experimental methods with dedicated equipment and platforms. Genomics focus on the genetic information stored in DNA and aim at identifying the different activity of genes in distinct cell populations or in response to different treatments. Bioinformatics develops and applies computational methods for analyzing genetic sequences or gene expression data.

OTHER FACILITIES

- Immunohistochemistry
- Cell imaging facility
- Flow cytometry and cell sorting
- Microbiology service
- Laboratory animal facility
- Proteomics/Mass Spectrometry Laboratories
- Cytogenetics and molecular cytogenetics

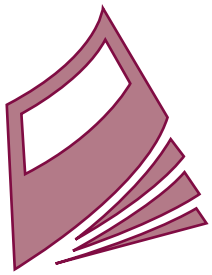
CLINICAL TRIALS CENTER

The Clinical Trials Center supports Clinical Researchers in many aspects of investigational clinical studies, such as study design, statistical analysis/validation, data management, submission to Ethics Committees/regulatory authorities, budget and contract related issues, pharmacovigilance by dedicated personnel including data managers, statisticians, research nurses and administrative personnel.

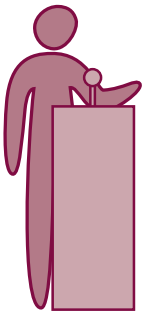
BIOMEDICAL LIBRARY

The INT Library is affiliated to the European Association for Health Information and Libraries. It offers a large collection of basic science journals and reference books, and electronic access to the full text of scientific and clinical journals, databases and books.

EDUCATION IN **INT**

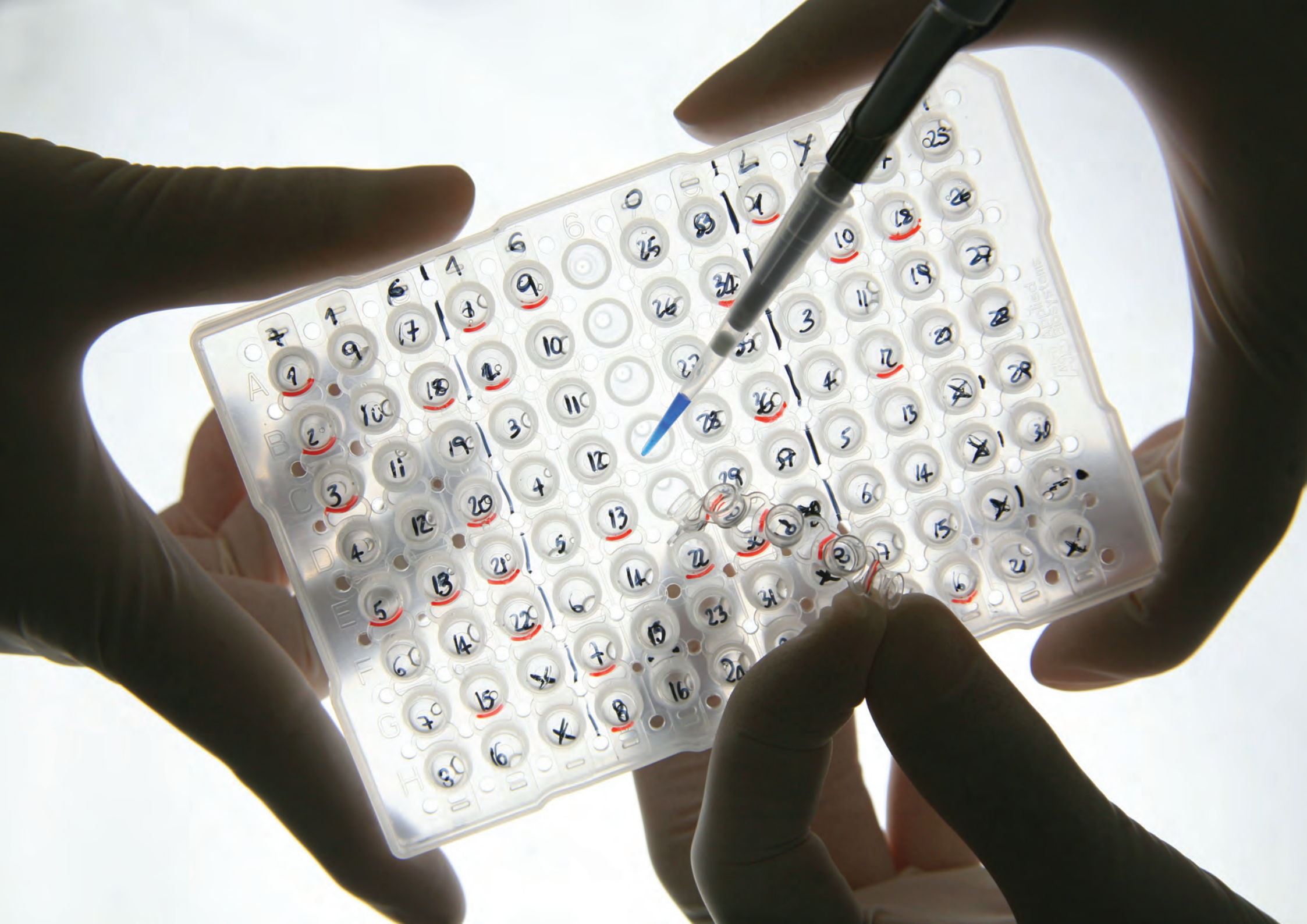


As a comprehensive cancer centre for excellence, INT is deeply committed to quality education and training. Postdoctoral research fellowships, graduate student training, medical residency training, psychology and social work training, as well as many opportunities for continuing medical education are part of the wide ranging academic options available at INT.
To give new impulse to translational research, it is crucial attracting medical doctors working in our Institute, and giving them the opportunity to receive training in cutting-edge research technologies. Our aim is to implement a system that will allow young physicians to gain direct experience in research and help the translation of laboratory discoveries into effective treatments for patients.
Since 1997 INT has partnered with the **Open University (Milton Keynes, UK)** to offer a PhD Programme for young graduates in scientific disciplines. During the course of their studies students conduct their experimental work under the supervision of experienced researchers, have access to modern laboratories and advanced technologies and benefit from a dedicated program of seminars. Academic quality of the educational programme is annually validated.



INT is a **formal partner of the Università Statale degli Studi di Milano** and hosts several professors of the Departments of Oncology and Hematoncology, including the Chairman, Medical Statistics and Biometry, Anesthesiology, and Pathology, with medical students and students from the medical biotechnology and nursingdegree; postgraduate training for the residencies of oncology, hematology, general surgery, radiotherapy, anesthesiology and intensive care are also provided.

Young people have a natural curiosity towards the scientific rules governing the world. To favour this attitude and increase their scientific knowledge, INT offers the possibility of **brief stages to high school students** for visiting laboratories, meeting INT researchers, learning importance of new technologies for advance in oncology research.



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