



**SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA**  
Azienda Ospedaliera di Reggio Emilia  
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Istituto in tecnologie avanzate e modelli assistenziali in oncologia  
Istituto di Ricovero e Cura a Carattere Scientifico

# **Program for the “ricerca corrente”<sup>\*</sup> of the IRCCS 2013 – Institute for Advanced Technologies and Healthcare Protocols in Oncology-Research Lines**



# Program for the “ricerca corrente”\* of the IRCCS 2013 – Institute for Advanced Technologies and Healthcare Protocols in Oncology Research Lines

\*Ricerca corrente means a specific funding program of Italian Ministry of Health that gives economic support to each Research Hospital-IRCCS- on the basis of actual data furnished by the Scientific Directorate to the Ministry on annual basis regarding clinical and research activities.

The IRCCS obtained formal recognition with the M.D.12/4/2011, published in the general series Official Bulletin No.119 of 24 May 2011, and the subsequent period 2011-2012 saw its consolidation in agreement with the plan and the research lines adopted in the process of recognition. In the three-year period, 2013-2015, the IRCCS will continue the activities of hospitalisation and care and basic, clinical and translational research, consistent with its area of recognition (*Advanced Technologies and Healthcare Protocols in Oncology*) and with the National Plan of Healthcare Research, through the three Research Lines already presented during the Ministerial Site Visit and re-defined as follows:

- 1. Complex Oncological Pathology,**
- 2. Advanced Diagnostic and Therapeutic Technologies,**
- 3. Healthcare Protocols and Oncological Pathways**

In addition to these three Lines, there will be a fourth line, focussed on translational research, in particular, on the subject:

#### **4. Targets and innovative therapeutic strategies in Oncology and Oncohematology: microenvironment, inflammation, angiogenesis, immunity.**

Given below are the main research and healthcare activities to be carried out by the IRCCS in the coming three-year period:

- a) in the context of the re-organisation of the entire Hospital on the principles of Intensity of Care, a new hospitalisation ward and department for clinical research in Oncological Medicine will be activated (*early in 2013*) which will house the clinics for Oncological emergencies and Palliative Care;
- b) Inter-departmental and inter-hospital units shall be consolidated and integrated in the current Diagnostic-Therapeutic Care paths (*PDTA - Percorso Diagnostico Terapeutico Assistenziale [Diagnostic Therapeutic Care Path]*): Thyroid Centre, Breast Unit, Skin Cancer Unit and PDTA for lung, colon-rectal, mesothelioma and lymphoma, as well as a new Palliative Care centre (2013-2014);
- c) The new Onco-Hematological centre will be opened, which will house the hospitalisation wards and laboratories (end of 2014, start of 2015);
- d) The network activities at the hospital (*ASMN*), provincial (*Local Health Authority-AUSL*), regional (*with Regional Social and Health Agency and University*) and international level (*by participation in collaborative European projects*) will increase.

As regards the last point, the IRCCS will increase interaction with the ASMN (*with the consolidation of the intra-hospital Oncological Network and with a “research training” path*

aimed at health professionals so that the results of basic research can be easily translated into clinics and the other way around), with the AUSL (through research projects in the field of primary and secondary prevention) and with international networks (on Personalised Medicine). In this regard, the new laboratories forming part of the "Translational Research" Department belonging to the Research and Statistics Infrastructure Department will be completed (last part of 2013). Lastly, the ability to operate on the network will be increased with the creation of actions for consultation and coordination with the Region, University and other IRCCS. These objectives shall be achieved not only through greater interaction at the level of individual researchers, but also by the establishment of specific offices and the creation of coordination and consultation panels, coordinated by the Institute and/or by the Regional Health Agency.

In order to promote research by the IRCCS and ensure its integration in the context of the ASMN multidisciplinary hospital where it is housed, two different tools will be used:

- Consolidation of the Department "Infrastructure Research and Statistics" which, from 2012 has been re-organised and extended, with the aim of supporting all the research activities of the Hospital, both as regards scientific as well as healthcare activities, so that the IRCCS becomes the reference point for the entire Hospital, while at the same time making sure the Hospital is available to the IRCCS;
- Creation of a Research Fund, mainly supported with the funding of Ricerca Corrente\* also in order to support non-profit research activities. The funds shall be allocated to research teams by means of a transparent and "meritocratic" mechanism based on explicit standardised criteria.

Ricerca Corrente\* means means the Annual Research Program financed by the Italian Ministry of Health to the Italian IRCCS network.

## Research Line No.1: Complex oncological pathology

**Person-in-charge:** dr.Corrado Boni (Director of Oncology)

**Description:** The capacity to translate into practice scientific discoveries in the field of genetics, molecular biology and oncology is one of the most innovative and important focal points for a research centre that deals with cancer patients.

"Each patient is different from another and every tumour is different from another". The complexity of the cancer patient and the need to face these complexities by developing pathways which are modelled to suit the needs and clinical, biological, genetic and personal characteristics of the patient, is today the objective that clinicians and researchers have prefixed to be able to treat the patients in the most specific and effective manner.

Therefore, in this context, the term "complex" carries more than one meaning, but, as a whole, identifies a special case to be treated with special care. On the other hand, in Italian, the word has at least two meanings: difficult and/or having a number of aspects. We can therefore use this clue (*complexity as synonym of difficulty and multiplicity*) as the starting point for a reflection on its meaning when used in the context of healthcare. The interest in the complexity in medicine and healthcare derives from the need to be able to distinguish (*identify and classify*) the various cases (*individuals*) on the basis of their intrinsic difficulty/multiplicity since it is from these that greater difficulty/multiplicity may ensue in terms of treatment and also a different quoad vitam o valitudinem prognosis. A complex case will, in fact, require a different, more intense and, sometimes, more expensive treatment. At the same time, as regards research, a complex topic/case

deserves special attention and therefore a dedicated line of research. We therefore recognise at least two aspects that can create/increase the complexity of a case: the rarity (*peculiarity*) of the problem which needs to be dealt with by means of specific approaches not listed in the usual pathways of research and healthcare meant for frequent cases and the presence of certain non-biological conditions (*sometimes referred to as welfare or social*) which, although known and normal from the genetic and biological point of view, make the case particularly complex from the healthcare point of view.

Translational research, which acts as a bridge between basic research and clinical research is the best way to transfer the findings of researchers in the clinical context and to provide insights for new laboratory research deriving from clinical practice and observation of patients.

Thanks to an integrated approach between clinic and research, the ability to look at the world of personalised medicine and pharmacogenomics, makes it possible to classify the disease not only on the basis of the area affected, but according to its specific characteristics and to identify the biological and molecular parameters which sometimes make it possible to predict tumour response to treatment or to report specific risk factors in the patient for the development of toxicity.

And it is precisely in the context of toxicity, thanks to a multidisciplinary integrated approach with the various professionals of the Institute, that the IRCCS of the S. Maria Nuova Hospital of Reggio Emilia aims to evaluate the impact of chemotherapy, new target therapy and the association of some of the most widely used anti-cancer drugs in terms of adverse reactions.

Cardiotoxicity and cerebrovascular toxicity, in particular, are today one of the factors that most limit the use of anti-cancer drugs with a strong impact on the quality of life of the patient.

Our research in this area has the aim of studying the mechanisms of cardiovascular toxicity and cerebrovascular toxicity of anticancer drugs and checking the feasibility of using diagnostic and chemo-preventive approaches to reduce the damage to the cardiovascular and cerebral damage.

In parallel to clinical observation, our studies focus on analysis of the cellular and molecular mechanisms involved in the damage induced by drugs in order to understand the effect in vitro of chemotherapeutic agents on cell populations, as well as to identify biomarkers capable of defining a score risk that predicts the risk of toxicity.

### **Objectives:**

The overall objective is expressed through four specific types of research, listed below: 1) complexity and testing of new drugs and new combinations of antineoplastic drugs; 2) Complexity of the patient due to a genetic-biological-molecular peculiarity of the tumour, such as affiliation to a specific sub-group with rare or little known genetic-biological-molecular profile and 3) Complexity of the cancer patient as a carrier of other specific conditions/diseases, such as the presence of a number of concurrent tumours, the presence of special metastatic areas or multiple non oncological diseases or the presence of multidimensional clinical-healthcare conditions, such as old age and fragility 4) Complexity of the patient due to cultural, social and psychological factors; 5) study of toxicities developed by the complex cancer patient treated with antineoplastic drugs.

With regard to the specific objectives described above, it is proposed to "study" the patient under the various biological, genetic and clinical aspects, in the context of translational research, taking into consideration not only the patient's specific conditions correlated to



the disease, but also the patient's needs related to the family, social and economic contexts.

The main objective of clinical and translational research in oncology by this IRCCS is to implement the knowhow that has until now made it possible to determine how each tumour has specific molecular characteristics which, like finger prints, distinguish and diversify it, modulating and modifying the patient's response to treatment as well as the toxicity of the treatment.

In fact, with the progressive and increasing advent of new treatments targeting molecules, there is a need to gain a better and deeper understanding of the short-term as well as long-term toxicity these treatments can induce. Therefore, the understanding of the molecular mechanism underlying the action of new drugs could result in a more detailed understanding and prediction of risk of toxicity for the patient.

The pharmacokinetic or pharmacogenomic approach, also through the use of new technologies and cutting-edge molecular biology approaches, will allow professionals of this Institute to balance research and clinic to offer the patient customised ad hoc treatment, with great advantage in terms of clinical and staff management for the patient, taking into consideration also an advantage in terms of quality of the service and savings on costs and resources.

#### **Indicator:**

- Articles in magazines (*position, first name and surname; co-authors of publications with other Institutions*).
- Presentations at international conferences.
- Patents.
- Product IF.
- H index for Researcher.
- Chapters of Books.
- Ability to acquire funds for research.
- Collaboration with other institutions.
- Organisation of training Courses and conferences related to the research lines.
- Multidisciplinary procedures for the integrated management of the complex cancer patient.

#### **Result Indicator:**

- Number of publications per Research Line= 45.
- Medium normalised IF per Line for the Year 2013= 5.
- Projects under way funded by external Institutions =5.
- Number of presentations at conferences =90.
- Patents=1.
- Chapters of Books= 10.
- Collaborations with other institutions = 5.
- Multidisciplinary procedures for the integrated management of the complex cancer patient = 7.

#### **Result described:**

The results we propose to obtain will emerge from the publications and research projects related to the complexity and investigation of new drugs and new associations of anti-cancer drugs, the genetic-biological-molecular evaluation of the tumour, study of the toxicity correlated to cancer treatments.

Moreover, we plan to evaluate from multiple points of view the complexity of the cancer patient as a possible carrier of other comorbidities, a number of concurrent tumours, multidimensional clinical-care conditions such as old age and fragility and cultural, social and psychological factors, which are at times difficult to manage.

As regards translational research we propose to "study" the patient under the various biological, genetic and clinical aspects to understand how each tumour has precise molecular characteristics which, like finger prints, distinguish and diversify it, modulating and modifying the patient's response to treatment as well as the toxicity of the treatment.

## **Research Line No.2: Advanced diagnostic and therapeutic technologies**

**Person in charge:** dr. Annibale Versari (Director of Nuclear Medicine)

**Description:** Projects for the study/evaluation of Health Technologies (*drugs, diagnostics, devices, algorithms, classification systems*) characterised by innovativeness (recent/new, promising but not validated, in use but not studied, promising but devoid of formal evaluation of clinical utility). Type of projects/studies: 1) diagnostics (imaging-modulated and advanced technologies) and 2) innovative treatments (*pharmacological and non-pharmacological*).

### **Objectives:**

- Development and validation of advanced technologies in "in vivo", cellular and molecular diagnostics.
- Study of new methods (*algorithms, models, etc.*) for the quantitative and semi-quantitative evaluation of biological processes.
- Integration of molecular biology and imaging methods (*molecular and morphological*) for the development of the most customised oncological treatments.
- Development and validation of new therapeutic techniques for the treatment of oncological diseases.
- Research Effectiveness/Outcome studies to produce additional evidences of the clinical efficacy of diagnostic and therapeutic procedures.
- Study of procedures for the early evaluation of the response to chemotherapy-radiotherapy treatments.
- Promotion of early phase clinical trials for the verification/validation of diagnostic-therapeutic procedures through phase II-III trials.

### **Indicator:**

- Articles in magazines (*position first name and surname, co-authors of publications with other Institutions*).
- Product IF.
- Presentations at international congresses.

### **Indicator result:**

- Number of publication per Research Line: 40.
- Medium normalised IF per Line per Year: 4.
- Number of presentations at congresses (national and international; oral and poster): 60.

### Result described:

Taking into account the objectives of the line of research, i.e.:

- Development and validation of advanced technologies in "in vivo", cellular and molecular diagnostics.
- Study of new methods (*algorithms, models, etc.*) for the quantitative and semi-quantitative evaluation of biological processes.
- Integration of molecular biology and imaging methods (*molecular and morphological*) for the development of more customised oncological treatments.
- Development and validation of new therapeutic techniques for the treatment of oncological diseases.
- Effectiveness/Outcome Research studies to produce additional evidences of clinical efficacy of diagnostic and therapeutic procedures.
- Study of procedures for the early evaluation of response to chemotherapy radio therapy treatments.
- Promotion of early phase clinical trials for the verification/validation of diagnostic-therapeutic procedures by means of phase II and III studies.

## Research Line No.3: Healthcare protocols and oncological pathways

**Person in charge:** dr. Lucia Mangone (Director of Statistics and Quality of Clinical Trials)

**Description:** Healthcare Research is the type of Translational Research conducted within the NHS with the aim of identifying bio-medical and healthcare information obligation through scientific research to fill cognitive gaps and check to see how much their application and implementation is reflected in terms of economically sustainable improvement. Its systematic application would make it possible to produce evidence documenting the real value and potential impact of these interventions in healthcare before and after their actual implementation. The projects and studies are focused on the development, evaluation and validation of complex clinical-organisational-healthcare interventions. Type of projects/studies: Projects for developing/validating new clinical pathways (*PDTA*) and epidemiological/evaluative and experimental studies for checking the impact, efficacy/effectiveness of complex interventions (*new clinical-care strategies*) for tumour of the breast, lung, colon-rectum and lymphoma. Projects for verifying the organisational and communicative aspects of healthcare pathways and attention also to aspects concerning the quality of life of the patients followed in the pathways. New pathways will also be implemented for tumour of the thyroid, melanoma, endometrium, ovaries and mesothelioma and projects which concern the overall quality of life of the cancer patient: age, gender, palliative treatment, fertility, application of integrated approaches of treatment (*physiotherapy*). Finally two crucial aspects of care will be implemented: one concerns the communication and relation among peers and with the patient and the other concerns the promotion of female personnel in the field of research and healthcare.

**Objectives:** Implement the pathways in a coordinated manner integrating these with aspects of healthcare research and methods of evaluation of the knowledge available (*systematic reviews, health technology assessment, appraisal*) in order to be able to evaluate each path in terms of efficacy, safety and sustainability; Start up research programs to document the actual level of application in the context of healthcare, using clinical, "medical humanities" and economic type of outcomes and end-points. The efficacy/effectiveness indicators shall be evaluated for the clinical pathways (*PDTA*) of tumours of the breast, lung, colon-rectum and lymphomas. Pathways will also be implemented for tumour of the thyroid, melanoma and mesothelioma. The aspects concerning communication with the patient and the impact of the training activities on healthcare personnel will also be evaluated.

**Indicator:**

- Articles in magazines (*position, name and surname, co-authors of publications with other institutions*).
- Product IF.
- Presentations at national and international congresses.
- Training and dissemination of the results concerning the Research Line.
- Production of clinical pathways (*PDTA*) of the main tumor sites.
- Divulcation of good Health Literacy practices.



**Indicator result:**

- Number of publications per Research Line 3: 60.
- Medium normalised IF per Line per Year: 3.0.
- Presentations (*oral and poster*) at national and international congresses: 30.
- Organisation of Training courses and Seminars concerning the Research Line: 30.
- Production of clinical pathways (*PDTA*) of the main tumour sites (*breast, lung, colon-rectum, lymphomas*).
- Number of days dedicated to the training on Health Literacy: 10.

**Result described:**

The objectives of the Line are:

- 1) Implementing the standardised methods of evaluation of the knowledge available in order to be able to evaluate the actual cognitive level of each healthcare pathway/protocol model in terms of efficacy, safety and sustainability;
- 2) Activate clinical and healthcare research programs in such a way as to document the level of actual application and the performance in the field of healthcare for 4 specific diagnostic-therapeutic pathways for tumours of the breast, lung, colon, rectum and lymphomas. The results will also be published on the pathways launched for tumours of the thyroid, endometrium, ovaries and mesotheliomas and on the aspects concerning the overall quality of life of cancer patients: age, gender, palliative treatments, fertility, application of integrated approaches of treatment (*physiotherapy*). Finally two aspects will be implemented concerning oncological pathways (*Health Literacy project on correct communication/relation with the patient*) and the healthcare protocols (*preparation of a pathway to favour research among young researchers, during the period of pregnancy and maternity*).

## Research Line No.4: Targets and innovative therapeutic strategies in Oncology and Oncohematology: microenvironment, inflammation, angiogenesis, immunity

**Person in charge:** dr. Francesco Merli (*Director of Haematology*)

**Description:** Projects and activities aimed at the study/evaluation of protocols focussed on microenvironments in oncology and oncohematology. In vivo, the growth of the tumour is influenced in a decisive manner by the cells of the microenvironment (*cells of the vascular and lymphatic network in angiogenesis, cells of the innate and adaptive immune system in inflammation and immune response defects, fibroblasts in the malignant stroma*) and by components of the extracellular matrix (*collagens, fibronectin, laminins and other components of the stroma, proteoglycans, protease*). In recent years there has been a great diffusion of the so-called "biological" drugs which have action mechanisms and targets different from traditional chemotherapy and which, in some cases, have radically modified the prognosis of certain diseases (*e.g. Rituximab in Non Hodgkin B lymphocytes Lymphoma, inhibitors of the tyrosin-kinase in Chronic Myeloid Leukemia, Bortezomib in Multiple Myeloma*).

In many cases, against the excellent results produced during the course of clinical trials, these new molecules have multiple action mechanisms which are not very well known. For example, the antiangiogenic effect of Lenalidomide is known, but its immunomodulation activity, which seems to be that mainly responsible for its efficacy in the treatment of multiple myeloma is not quite clear.

The interactions between the tumour cells as well as the inflammatory cells have also been studied. In certain cases, the latter can become pharmacological targets with the aim of negatively conditioning the growth of the neoplastic component (*along the same line the therapeutic experiences with Rituximab in Hodgkin's lymphoma is the preventive use of anti-inflammatory drugs in tumours of the colon-rectum*).

In this regard, in fact, the cells of the immune system can, on the one hand, obstruct the development of tumours while on the other hand they can favour it.

The two apparently opposite functions are actually mainly linked to the polarisation of immune cells towards a pro- or anti-tumoral phenotype, to the modulation of the tumoral microenvironment and to immuno-suppression. For example, in case of macrophages, the cellular polarization has been widely studied and is linked to the variation of the factors which facilitate growth of the tumour and its nourishment by means of angiogenesis. The study of the immune components and their action on the microenvironment will therefore be one of the topics of the investigation.

The study of the immunological pathways of diseases that are exclusively inflammatory, which has for some time been the object of interest of the Laboratory of Immunology, Laboratory of Molecular Biology and Laboratory of Translational Research of the ASMN-IRCCS of Reggio Emilia, may help towards better understanding of the mechanisms of inflammation which support the growth of neoplastic clones.

Another field of study which is included in this line of research is the study of the mechanisms of chemo- and angio-prevention, i.e. the pharmacological prevention of cancer and angiogenesis. The latter, in fact, favours the tumoral growth by providing nourishment to the neoplastic cells.

The identification and evaluation of markers useful for the diagnosis, ongoing monitoring of follow up and the prognostic definition of neoplastic and inflammatory diseases, possibly

through investigations that can be easily replicated in clinical practice are always current issues. Finally, the analysis of the relation between the metabolism and development/progression of the disease and response to treatments has been of great interest in recent times and will therefore be the subject of study.

**Objectives:** Projects and studies

- a) on the role of the components of the microenvironment: leucocytes, lymphocytes, endothelial cells, stromal fibroblasts, proteins and enzymes of the matrix in translation and clinical research studies;
- b) markers derived from the microenvironment;
- c) control of inflammation and angiogenesis, stimulation of the immune system, permeabilization of the stroma to treatment by new drugs and technologies.

Clinical studies on new markers and new drugs in phase I/II and II are included in this program.

**Indicator:**

- Articles in magazines (*position first name and surname; co-authors of publications with other Organisations*).
- Presentations at international congresses.
- Product IF.
- Ability to acquire funds for research.
- Collaboration with other institutions.

**Indicator result:**

- Number of publications per Research Line = 15.
- Medium normalised IF per Line per Year = 5.
- Projects under way funded by external institutions = 1.
- Number of presentations at congresses = 15.
- Collaboration with other institutions = 5.

**Result described:**

The results shall be illustrated by publications and the research projects concerning:

- the study of cellular mechanisms involved in response to active molecules against tumours by means of interactions with the microenvironment of the tumour (*e.g. anti-angiogenic*);
- the identification and study of diagnostic and prognostic markers of inflammatory and tumoral diseases;
- the study of stem cells in tumours and enzymes involved in the formation of the tumour.