

22nd June 2000

PROPOSAL OF AGREEMENT

for Institutional Scientific Collaboration between the National Institute of Environmental Health Sciences (NIEHS) and the European Foundation of Oncology and Environmental Sciences "B. Ramazzini" (Ramazzini Foundation)

Following:

- 1) scientific meetings between Dr. Kenneth Olden, Director of NIEHS and Professor Cesare Maltoni, Scientific Director of the Ramazzini Foundation, in occasion of Dr. Olden's visit to the Cancer Research Centre of the Ramazzini Foundation in Bentivoglio (Bologna);
- 2) an overview of the Ramazzini Foundation's scientific activity and the future programmes of the NIEHS and Ramazzini Foundation, during Dr. Olden's visit;

Considered that:

- 1) NIEHS and Ramazzini Foundation have many scientific interests and finalities in common;
- 2) more specifically, like the NIEHS, the Ramazzini Foundation is active and interested in:
 - identification of carcinogenic agents and quantification of oncogenic risks by long-term bioassays (to date the Ramazzini Foundation, in more than 30 years of activity, has tested nearly 190 industrial chemical and physical agents);
 - interaction and synergisms between genetic susceptibility and exogenous carcinogenic agents/factors;
 - basic mechanisms of carcinogenesis;
 - statistical evaluation of the significance of the data;
- 3) there are several interesting possibilities of integrating studies, results and materials, made available by NIEHS and the Ramazzini Foundation;

Recognized:

- 1) the expected positive potentialities of a collaboration between NIEHS and the Ramazzini Foundation in the fields of common interest;

all the oversaid taken into account

Dr. Kenneth Olden and Professor Cesare Maltoni agree on the following:

- 1) the establishment of a scientific collaboration between NIEHS and the Ramazzini Foundation in fields of common interest;
- 2) the priorities of such collaboration have been identified as:
 - carcinogenicity bioassays on agents jointly identified;
 - research on the interactions between genetic susceptibility and exogenous carcinogens;
 - biostatistical analysis of results ..
 - molecular biology studies on the basic mechanisms of carcinogenesis;
- 3) a joint scientific commission with representatives of both institutions will specifically identify the research to be performed in the oversaid scientific areas, considering also the know-how and the material made available by both institutions;
- 4) Dr. Olden and Professor Maltoni, as Directors, will appoint their representatives in the scientific commission and will also identify the responsible scientists involved in the various scientific projects;
- 5) the organization, performance and calendar, and the administrative and economical aspects of each project may be specifically agreed in ad hoc documents;
- 6) the results of the above research will be published as a joint NIEHS-Ramazzini Foundation research programme, as a first option in current issues or Supplements of Environmental Health Perspectives, or in a mutually agreed journal. The sequence of the Authors will be established on the basis of their scientific input to the specific studies;
- 7) the present agreement will last 2 years and, based upon the results of this experience, may be renewed for the future.

Approved
Ken Olden



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Director

Telephone: 919-541-3201
Fax: 919-541-2260

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709

July 17, 2000

Professor Cesare Maltoni
Scientific Director, Cancer Research Center
B. Ramazzini Foundation
Castello di Bentivoglio
40010 Bentivoglio
Bologna
ITALY

Dear Professor Maltoni:

The proposal is just fine with NIEHS! I propose that we create the joint scientific commission to identify the collaborative research to be performed.

I have asked Dr. Chris Portier, Director of the Environmental Toxicology Program, to take the lead for us. He will be in touch to work out the details of the composition of the Commission and a proposed work plan.

I look forward to a productive collaboration.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Ken", is written over a horizontal line.

Kenneth Olden, Ph.D.
Director

Enclosure

cc:
Dr. Portier



DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709

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NIEHS

April 29, 2002

Order / Air

CONTINUATION OF AGREEMENT

For Institutional Scientific Collaboration between the National Institute of Environmental Health Sciences (NIEHS) and the European Foundation of Oncology and Environmental Sciences "B. Ramazzini" (Ramazzini Foundation)

Following:

- 1) scientific meetings between Dr. Kenneth Olden, Director of NIEHS and Professor Cesare Maltoni, Scientific Director of the Ramazzini Foundation, in occasion of Dr. Olden's visit to the Cancer Research Centre of the Ramazzini Foundation in Bentivoglio (Bologna);
- 2) and the successful establishment of a series of contacts and scientific collaborations between staff of the Ramazzini Foundation and the NIEHS during the 2-year duration of the initial agreement

Considered that:

- 1) NIEHS and the Ramazzini Foundation continue to have many scientific interests and finalities in common;
- 2) more specifically, like the NIEHS, the Ramazzini Foundation is active and interested in:
 - identification of carcinogenic agents and quantification of oncogenic risks by long-term bioassays (to date the Ramazzini Foundation, in more than 30 years of activity, has tested nearly 190 industrial chemical and physical agents);
 - interaction and synergisms between genetic susceptibility and exogenous carcinogenic agents/factors;
 - basic mechanisms of carcinogenesis;
 - statistical evaluation of the significance of the data;

- 3) and that the first steps have been taken toward integrating studies, results and materials, made available by NIEHS and the Ramazzini Foundation;

Recognized:

- 1) the expected positive potentialities of a continued collaboration between NIEHS and the Ramazzini Foundation in the fields of common interest;

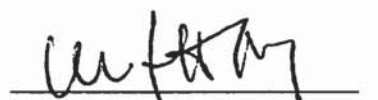
all the oversaid taken into account

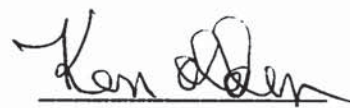
Dr. Kenneth Olden and Dr. Morando Soffritti agree on the following:

- 1) the continuation of the scientific collaboration between NIEHS and the Ramazzini Foundation in fields of common interest;
- 2) the priorities of such collaboration have been identified as:
 - carcinogenicity bioassays on agents jointly identified;
 - research on the interactions between genetic susceptibility and exogenous carcinogens;
 - biostatistical analysis of results and the establishment of common data management tools
 - molecular biology studies on the basic mechanisms of carcinogenesis;
- 3) a joint scientific commission with representatives of both institutions will specifically identify the research to be performed in the oversaid scientific areas, considering also the know-how and the material made available by both institutions;
- 4) Dr. Olden and Dr. Soffritti, as Directors, will appoint their representatives in the scientific commission and will also identify the responsible scientists involved in the various scientific projects;
- 5) the organization, performance and calendar, and the administrative and economical aspects of each project may be specifically agreed in ad hoc documents;

- 6) the results of the above research will be published as a joint NEIHS-Ramazzini Foundation research programme, as a first option in current issues or Supplements of Environmental Health Perspectives, or in a mutually agreed journal. The sequence of the Authors will be established on the basis of their scientific input to the specific studies;

the present agreement will last 2 years and, based upon the results of this experience, may be renewed for the future.


Dr. Morando Soffritti


Dr. Kenneth Olden



NATIONAL TOXICOLOGY PROGRAM

Department of Health and Human Services

NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES
111 T.W. ALEXANDER DRIVE
P.O. BOX 12233
RESEARCH TRIANGLE PARK, NC 27709-2233

April 1, 2004

Continuation of Agreement

For Institutional Scientific Collaboration between the National Institute of Environmental Health Sciences (NIEHS) and the European Foundation of Oncology and Environmental Sciences "B. Ramazzini" (Ramazzini Foundation)

Following:

- 1) the scientific meetings between Dr. Kenneth Olden, Director of NIEHS, and Professor Cesare Maltoni, Scientific Director of the Ramazzini Foundation, on the occasion of Dr. Olden's visit to the Cancer Research Centre of the Ramazzini Foundation in Bentivoglio (Bologna) in 1999 in which for the first time an agreement was formalized between the two institutions;
- 2) renewal of the agreement signed in April 2002 by Dr. Kenneth Olden and Dr. Morando Soffritti, Director of the Ramazzini Foundation, during the international conference held in New York to commemorate the lifework of Cesare Maltoni;
- 3) the successful establishment of a series of scientific collaborations between staff of the Ramazzini Foundation and the NIEHS during the four-year duration of the agreements;

Considering that:

- 1) NIEHS and the Ramazzini Foundation continue to have many scientific interests and aims in common;
- 2) more specifically, like the NIEHS, the Ramazzini Foundation is active and interested in:
 - interaction and synergism between genetic susceptibility and exogenous carcinogenic agents/factors;
 - basic mechanisms of carcinogenesis;
 - statistical evaluation of the significance of data;
 - and that the first steps have been taken towards integrating studies, results and materials made available by NIEHS and the Ramazzini Foundation.

It being recognized that:

- 1) continuing collaboration between the NIEHS and the Ramazzini Foundation in the fields of common interest is likely to be fruitful:

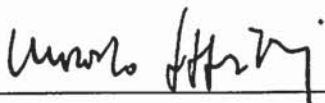
bearing in mind the foregoing

Dr. Kenneth Olden and Dr. Morando Soffritti agree to expand the collaboration and to sign a new contract as follows:

- 1) continuation of the scientific collaboration between the NIEHS and the Ramazzini Foundation in the fields of common interest;
- 2) the priorities of such collaboration have been identified as:
 - promotion of cultural initiatives, such as workshops, conferences, etc. for the improvement of scientific knowledge on the relationships between environment and health, with particular regard to carcinogenic risks;
 - carcinogenicity bioassays on agents jointly identified;
 - publication by the NTP and the Ramazzini Foundation of long-term bioassays performed at the Ramazzini Foundation (and already elaborated) in the format of an NTP Report. The first report will be on the gasoline oxygenated additive ETBE;
 - research on the interactions between genetic susceptibility and exogenous carcinogens;
 - biostatistical analysis of results and the establishment of common data management tools;
 - molecular biology studies on the basic mechanisms of carcinogenesis;
- 3) the invitation of Dr. Morando Soffritti to be an observer at the NTP Board of Scientific Counselors Technical Reports Review Subcommittee;
- 4) appointment to fellowships of young researchers from the Ramazzini staff, to be trained at the NIEHS;
- 5) a joint scientific board with representatives of both institutions will specifically identify the research to be performed in the above-mentioned scientific areas, taking account of the know-how and material made available by both institutions;
- 6) Dr. Olden and Dr. Soffritti, as Directors, confirm Dr. John Bucher and Dr. Fiorella Belpoggi as their representatives on the scientific board and will also identify the scientists responsible for the various scientific projects;
- 7) organization, performance and calendar details, as well as the administrative and economic aspects of each project, may be specifically agreed in *ad hoc* documents;

- 8) the results of the above research will be published as a joint NIEHS-Ramazzini Foundation research programme, as a first option in current issues of Environmental Health Perspectives, or in a mutually agreed journal. The sequence of the authors will be established on the basis of their scientific input to the specific studies;

the present new contract will last three years and, depending on the results of this experience, may be renewed in the future.



Dr. Morando Soffritti



Dr. Kenneth Olden

LETTER OF INTENT
between the
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
and the
EUROPEAN FOUNDATION OF ONCOLOGY AND ENVIRONMENTAL SCIENCES

The National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH) within the United States Department of Health and Human Services (HHS) and the European Foundation of Oncology and Environmental Sciences (Ramazzini Foundation) of Italy [hereinafter referred to as the "Participants"] have shared and continue to share an interest in interaction and synergism between genetic susceptibility and exogenous carcinogenic factors/agents, basic mechanisms of carcinogenesis, statistical evaluation of the significance of data and taking steps to make the reporting of results and study materials more consistent. To these ends, we, the Participants, intend to cooperate in sharing information and continuing and forming new collaborations in fields of common interest, including, but not limited to, the following:

- (1) Scientific initiatives for the improvement of scientific knowledge on the relationships between environment and health, with particular regard to carcinogenic risks;
- (2) Carcinogenicity bioassays on agents jointly identified;
- (3) Research on the interactions between genetic susceptibility and exogenous carcinogens;
- (4) Biostatistical analysis of results and forming common data-management tools; and
- (5) Molecular biology studies on the basic mechanisms of carcinogenesis.

In addition, HHS/NIH/NIEHS is to consider fellowship applications from members of the Ramazzini Foundation staff. Any trainees accepted would be part of the HHS/NIH Visiting Program.

The point of contact for inquiries to HHS/NIH/NIEHS related to the substance of this Letter of Intent is Dr. John Bucher. Dr. Fiorella Belpoggi is the contact for the Ramazzini Foundation.

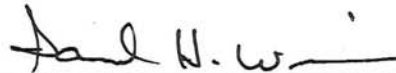
The Participants intend their relationship to be characterized by close cooperation, mutual respect, continuing communication, and compliance with all applicable laws, policies, and processes of each organization. The Participants will characterize and agree to any collaborative projects identified to in separate documents as necessary.

Nothing in this Letter of Intent is intended to be binding under international-law or under the domestic laws that govern the Participants. This Letter of Intent is to be effective for three years from the date of signature, the Participants may renew it .

Signed this 11 day of October 2007.



Morando Soffritti, M.D. Director
Ramazzini Foundation



Samuel H. Wilson, M.D., Acting Director
National Institute of Environmental Health
Sciences and National Toxicology Program
National Institutes of Health
U.S. Department of Health and Human
Services

LETTER OF INTENT
between the
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
and the
BERNARDINO RAMAZZINI NATIONAL INSTITUTE FOR THE STUDY AND CONTROL
OF TUMOURS AND ENVIRONMENTAL DISEASES

Given

- that between the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH) within the United States Department of Health and Human Services (HHS) and the European Foundation of Oncology and Environmental Sciences (Ramazzini Foundation) a collaboration agreement was signed in 2000 by Dr. Kenneth Olden and Professor Cesare Maltoni, respectively Director of the NIEHS and Scientific Director of the Ramazzini Foundation, then confirmed in 2002 and 2004 by their respective directors, and substituted in 2007 with a "Letter of Intent," signed by Dr. Samuel Wilson, Acting Director of the HHS/NIH/NIEHS, and Dr. Morando Soffritti, Scientific Director of the Ramazzini Foundation, on objectives of mutual interest;
- that since 1 January 2009 the Bernardino Ramazzini National Institute for the Study and Control of Tumours and Environmental Diseases (RI) has taken the place of the Ramazzini Foundation in owning and running the Cesare Maltoni Cancer Research Center (CMCRC) and that every agreement previously signed between HHS/NIH/NIEHS and the Ramazzini Foundation is understood to be confirmed by both HHS/NIH/NIEHS and RI [hereinafter referred to as the "Participants"];
- that over the years the aforesaid collaboration has permitted important goals of mutual interest to be attained and;

Considering that

- HHS/NIH/NIEHS and RI share common goals in pursuing interests including, but not limited to:
 - interaction and synergism between genetic susceptibility and exogenous carcinogenic agents/factors;
 - basic mechanisms of carcinogenesis, including the molecular biology of tumors;
 - carcinogenicity bioassays on agents jointly identified.

It being recognized that

1. there exist two major programs in the world that conduct long-term carcinogenic bioassays aimed at identification and quantification of environmental carcinogenic risks, the first being the United States National Toxicology Program (NTP) headquartered at the HHS/NIH/NIEHS, and the second being the RI/CMCRC;

All the aforesaid being taken into account

1. Dr. Linda Birnbaum, Director of the NIEHS and NTP, and Dr. Simone Gamberini, President of the RI, wish to expand their collaboration and sign a new letter of intent between HHS/NIH/NIEHS and RI.
2. The priorities of this collaboration are as follows:
 - to promote initiatives for the improvement of scientific knowledge on the relationships between environmental factors and health, with particular regard to carcinogenic risks;
 - to jointly identify agents to test by long-term bioassays.

To this end the Participants intend to cooperate:

1. to allow the exchange of biological materials for mechanistic studies, identification of markers of exposure, risk, etc.;
 - to allow review and use of histopathology slides of tumour lesions with a view to harmonizing criteria and nomenclature of diagnoses;
 - to promote molecular biology studies focusing on the basic mechanisms of carcinogenesis; likewise research on the interactions between genetic susceptibility and exogenous carcinogens;
 - to promote all useful relations between CMCRC and NTP staff.
2. The HHS/NIH/NIEHS will consider fellowship applications to train young researchers from RI staff at the NIEHS; any trainees accepted would be part of the HHS/NIH Visiting Program.
3. The Participants intend their relationship to be characterized by close cooperation, mutual respect, continuing communication, and compliance with all applicable laws, regulations, policies, and processes pertaining to either Participant. All activities under this Letter of Intent are subject to the availability of personnel, appropriated funds and other resources. Nothing in this Letter of Intent is intended to be binding under international law or under the domestic laws that govern the Participants. The Participants intend to characterize and pursue agreement on any collaborative projects identified through separate documents.

4. The results of the above research, when jointly conducted and subject to the approval of both Participants, may be published in international journals as a joint HHS/NIH/NIEHS-RI research project.
5. The point of contact for inquiries to HHS/NIH/NIEHS relating to the substance of this agreement is Dr. John Bucher. The points of contact for inquiries to RI are Dr. Fiorella Belpoggi for operative issues of this agreement and Dr. Morando Soffritti for the general outline.

John R. Bucher, Ph.D.
Associate Director
National Toxicology Program
National Institute of Environmental Health Sciences
P.O. Box 12233, MD K2-02
Research Triangle Park, NC 27709
USA
Telephone: (919) 541-4532
Email: bucher@niehs.nih.gov

Fiorella Belpoggi, Ph.D., Fellow IATP
Director
Email: belpoggif@ramazzini.it

Morando Soffritti, M.D.
Scientific Director
Email: soffrittim@ramazzini.it

Both
Cesare Maltoni Cancer Research Centre
Ramazzini Institute
Via Saliceto, 3
40010 Bentivoglio
Italy
Telephone: +39 051-6640460

The present agreement will last five (5) years and may be renewed for the future. The agreement may be terminated at any time at the discretion of either Participant, which will endeavour to give 60 days notice to the other.

Signed this 11 day of March, 2011

Signed this 21 day of March, 2011



Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director
National Institute of Environmental Health
Sciences and National Toxicology Program
National Institutes of Health
U.S. Department of Health and Human Services



Simone Gamberini
President
Bernardino Ramazzini National Institute for the
Study and Control of Tumours and
Environmental Diseases

LETTER OF INTENT
between the
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
and the
BERNARDINO RAMAZZINI NATIONAL INSTITUTE FOR THE STUDY AND CONTROL
OF TUMOURS AND ENVIRONMENTAL DISEASES

Given

- that between the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH) within the United States Department of Health and Human Services (HHS) and the European Foundation of Oncology and Environmental Sciences (Ramazzini Foundation) a collaboration agreement was signed in 2000 by Dr. Kenneth Olden and Professor Cesare Maltoni, respectively Director of the NIEHS and Scientific Director of the Ramazzini Foundation, then confirmed in 2002 and 2004 by their respective directors, and substituted in 2007 with a "Letter of Intent," signed by Dr. Samuel Wilson, Acting Director of the HHS/NIH/NIEHS, and Dr. Morando Soffritti, Scientific Director of the Ramazzini Foundation, on objectives of mutual interest, and in 2011 a new "Letter of intent" was signed by Linda Birnbaum, Director of the HHS/NIH/NIEHS and Simone Gamberini, President of the Ramazzini Institute.
- that since 1 January 2009 the Bernardino Ramazzini National Institute for the Study and Control of Tumours and Environmental Diseases (RI) has taken the place of the Ramazzini Foundation in owning and running the Cesare Maltoni Cancer Research Center (CMCRC) and that every agreement previously signed between HHS/NIH/NIEHS and the Ramazzini Foundation is understood to be confirmed by both HHS/NIH/NIEHS and RI [hereinafter referred to as the "Participants"];
- that over the years the aforesaid collaboration has permitted important goals of mutual interest to be attained and;

Considering that

- HHS/NIH/NIEHS and RI share common goals in pursuing interests including, but not limited to:
 - interaction and synergism between genetic susceptibility and exogenous carcinogenic agents/factors;
 - basic mechanisms of carcinogenesis, including the molecular biology of tumors;
 - carcinogenicity bioassays on agents jointly identified.

It being recognized that

1. there exist two major programs in the world that conduct long-term carcinogenic bioassays aimed at identification and quantification of environmental carcinogenic risks, the first being the United States National Toxicology Program (NTP) headquartered at the HHS/NIH/NIEHS, and the second being the RI/CMCRC;

All the aforesaid being taken into account

1. Dr. Linda Birnbaum, Director of the NIEHS and NTP, and Dr. Simone Gamberini, President of the RI, wish to expand their collaboration and sign a new letter of intent between HHS/NIH/NIEHS and RI.
2. The priorities of this collaboration are as follows:
 - to promote initiatives for the improvement of scientific knowledge on the relationships between environmental factors and health, with particular regard to carcinogenic risks, developmental risks, and children's health;
 - to jointly identify agents to test by long-term bioassays and other types of in vivo bioassays.

To this end the Participants intend to cooperate:

1. to allow the exchange of biological materials for mechanistic studies, identification of markers of exposure, risk, etc.;
- to allow review and use of histopathology slides of tumour lesions with a view to harmonizing criteria and nomenclature of diagnoses;
- to promote molecular biology studies focusing on the basic mechanisms of carcinogenesis; likewise research on the interactions between genetic susceptibility and exogenous carcinogens;
- to promote all useful relations between CMCRC and NTP staff.
2. The HHS/NIH/NIEHS will consider fellowship applications to train young researchers from RI staff at the NIEHS; any trainees accepted would be part of the HHS/NIH Visiting Program.
3. The Participants intend their relationship to be characterized by close cooperation, mutual respect, continuing communication, and compliance with all applicable laws, regulations, policies, and processes pertaining to either Participant. All activities under this Letter of Intent are subject to the availability of personnel, appropriated funds and other resources. Nothing in this Letter of Intent is intended to be binding under international law or under the

domestic laws that govern the Participants. The Participants intend to characterize and pursue agreement on any collaborative projects identified through separate documents.

4. The results of the above research, when jointly conducted and subject to the approval of both Participants, may be published in international journals as a joint HHS/NIH/NIEHS-RI research project.
5. The point of contact for inquiries to HHS/NIH/NIEHS relating to the substance of this agreement is Dr. John Bucher. The contact person for RI is Dr. Fiorella Belpoggi.

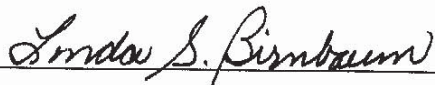
John R. Bucher, Ph.D.
Associate Director
National Toxicology Program
National Institute of Environmental Health Sciences
P.O. Box 12233, MD K2-02
Research Triangle Park, NC 27709
USA
Telephone: (919) 541-4532
Email: bucher@niehs.nih.gov

Fiorella Belpoggi, Ph.D.
Director
Cesare Maltoni Cancer Research Centre
Ramazzini Institute
Via Saliceto, 3
40010 Bentivoglio
Italy
Telephone: +39 051-6640460
Email: belpoggif@ramazzini.it

The present agreement will last five 5 years and may be renewed for the future. The agreement may be terminated at any time at the discretion of either Participant, which will endeavour to give 60 days notice to the other.

Signed this 22 day of October, 2015

Signed this 22 day of October, 2015



Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director
National Institute of Environmental Health
Sciences and National Toxicology Program
National Institutes of Health
U.S. Department of Health and Human Services



Simone Gamberini, Ph.D.
President
Bernardino Ramazzini National Institute for the
Study and Control of Tumours and
Environmental Diseases