

15 OCTOBRE 2008

INTERNATIONAL SYMPOSIUM

Stem cells and cancer / Cellules souches et cancer



FONDATION
Singer-Polignac

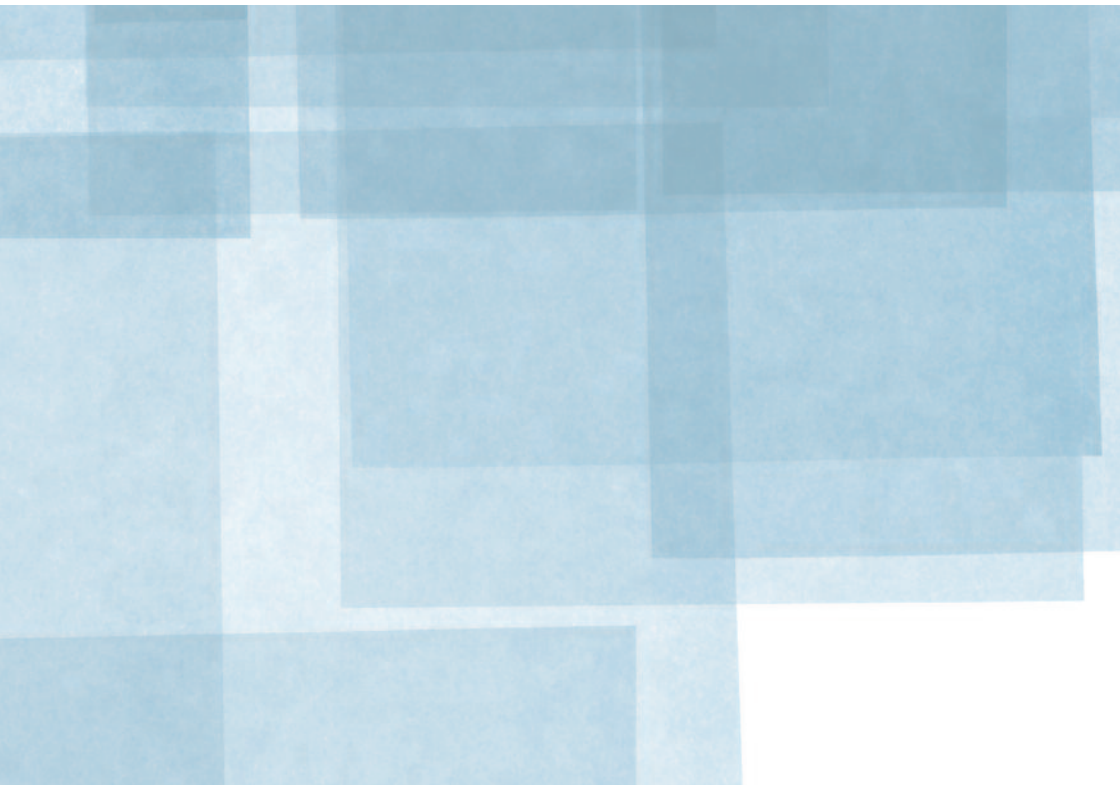


SCIENTIFIC COMMITTEE :

- **Prof. Nicole LE DOUARIN**, Secrétaire Perpétuel de l'Académie des Sciences;
Professeur Honoraire au Collège de France
- **Prof. Fabien CALVO**, Directeur de la Recherche de l'Institut National du Cancer
- **Prof. Daniel LOUVARD**, Membre de l'Académie des Sciences;
Directeur du Centre de Recherche de l'Institut Curie
- Avec le soutien du **Prof. Yves POULIQUEN**, de l'Académie Française et Président
de la Fondation Singer Polignac.

VENUE :

- **Fondation Singer-Polignac**,
43, avenue Georges Mandel
75116 Paris



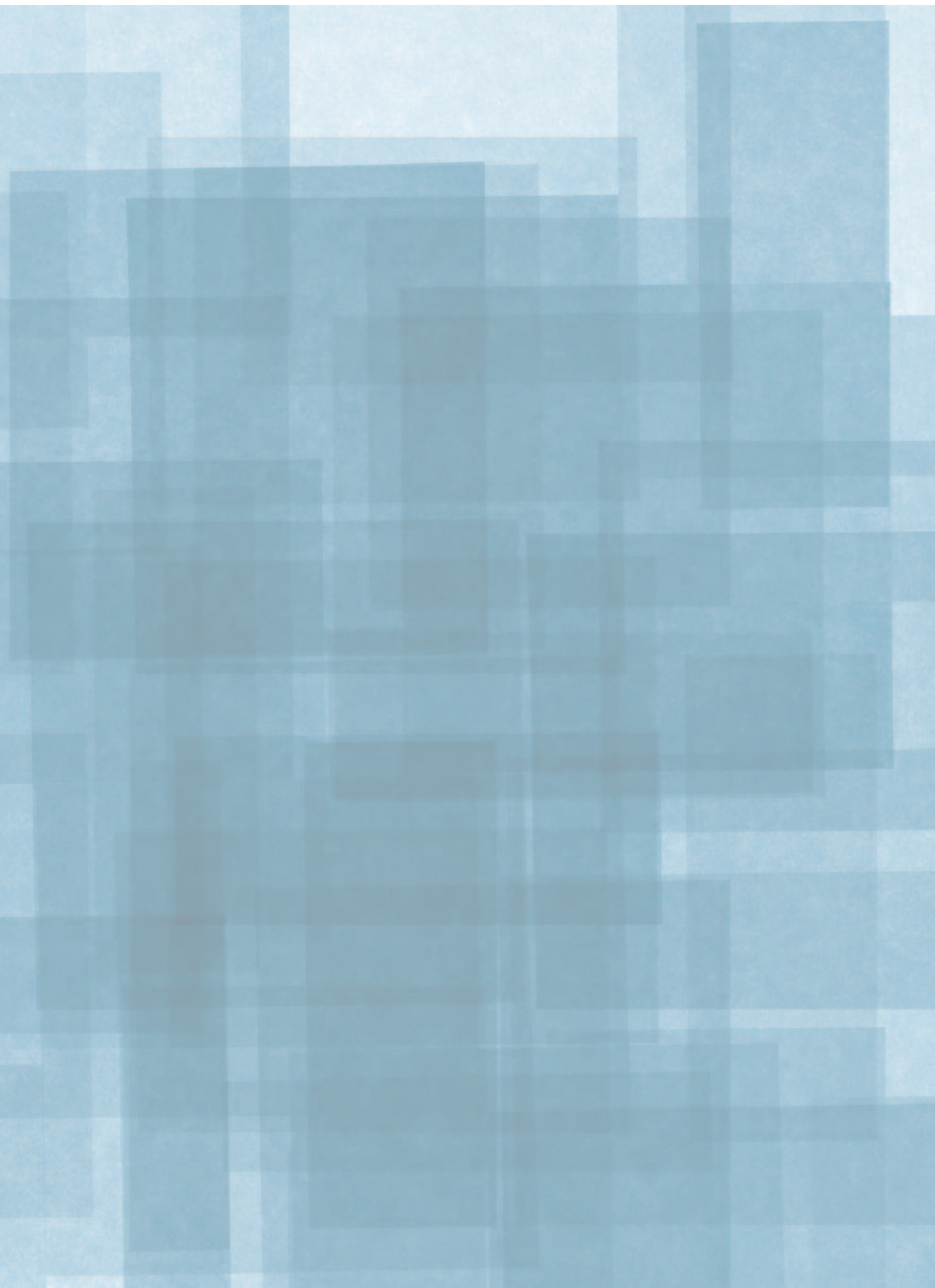
INTRODUCTION

For more than 50 years, few scientists believe that a small population of malignant stem cells can cause cancer. Today the cancer stem cells hypothesis is shared by a growing number of investigators and the study of stem cells is shedding light on cancer research. Firstly isolated from acute myeloid leukaemia and breast carcinoma, cancer stem cells have been reported in tumors of the brain, prostate, colon, pancreas, ovary, lung, bladder, head and neck, melanoma, sarcoma, and various blood cancers. Major characteristics of cancer stem cells are described to be the ability to self-renew and the ability to give rise to a heterogeneous progeny of cancer cells which constitute the tumor. This field of research opens new avenues for treating the cancers since if stem cells are eradica-

ted, the rest of the tumor may die off. Cancer stem cells may potentially account for relapse after years of remission and also be responsible for secondary tumors which may be the result of stem cells escaping from a primary tumor.

The symposium organised today reviews the last discoveries in the field and cancer stem cells research leaders in the world will present their last findings and discuss the future development of cancer stem cell biology.

Prof. Nicole LE DOUARIN,
Prof. Fabien CALVO,
Prof. Daniel LOUVARD



PROGRAMME

9:15 – 9:30	Welcome – Introduction Nicole LE DOUARIN, Fabien CALVO	
9:30 – 10:15	Irving WEISSMAN	06
10:25 – 10:55	Michael CLARKE	08
11:05 – 11:35	Hans CLEVERS	10
11:45 – 12:15	Elaine FUCHS	12
12:30 – 13:30	Lunch break	
14:00 – 14:30	Richard GARDNER	14
14:40 – 15:10	Sean MORRISON	16
15:20 – 15:50	Hervé CHNEIWEISS	18
16:00 – 16:30	William VAINCHENKER	20
16:40 – 17:00	Conclusion Daniel LOUVARD	
17:00 – 19 :00	Cocktail	

IRVING WEISSMAN

STANFORD UNIVERSITY SCHOOL OF MEDICINE
DIRECTOR, INSTITUTE OF STEM CELL BIOLOGY AND REGENERATIVE MEDICINE

Education

1961	Montana State College	B.S.	Pre-Med
1965	Stanford University	M.D.	Medicine

Academic Appointment

Professor in the Departments of Pathology, Developmental Biology, and by courtesy, Biology;

Awards and Honors (Selected)

Member, National Academy of Sciences
Member, Institute of Medicine at the National Academy
Member, American Association of Arts and Sciences
Member, American Academy of Microbiology
President, American Association of Immunologists (1994)

- 2004 Rabbi Shai Shacknai Memorial Prize in Immunology and Cancer Research from the Lautenberg Center for General and Tumor Immunology
New York Academy of Medicine Award for Distinguished Contributions to Biomedical Research
Jessie Stevenson Kovalenko Medal from the National Academy of Sciences Council
Alan Cranston Award from the Alliance for Aging Research
- 2005 “Dare to Dream” award from the Jeffrey Modell Foundation
Linus Pauling Medal for Outstanding Contributions in Science from Stanford University
- 2006 Honorary Doctorate from Columbia University
John Scott Award from the City of Philadelphia
The American Italian Cancer Foundation Prize for Scientific Excellence in Medicine
- 2007 Honorary Doctorate from the Mount Sinai School of Medicine, New York City, New York

Research Interests

Irving L. Weissman's research encompasses the phylogeny and developmental biology of the cells that make up the blood-forming and immune systems. His laboratory identified and isolated the blood-forming stem cell from mice, and has defined, by lineage analysis, the stages of development between the stem cells and mature progeny (granulocytes, macrophages, etc.). This required developing and cloning stromal cells of the hematolymphoid microenvironments—from the bone marrow for myeloid and B cells, and from the thymus for T cells. While the adhesion molecules and factors from these stromal cells proved important as molecules (and the genes that encode them) for myeloid and B cells, the analysis of T cell development required *in vivo* studies of thymic development. In addition, the Weissman laboratory has pioneered the study of the genes and proteins involved in cell adhesion events required for lymphocyte homing to lymphoid organs *in vivo*, either as a normal function or as events involved in malignant leukemic metastases.

The Weissman laboratory also has a small group at Hopkins Marine Station, where they have developed a model organism for laboratory and field study of allorecognition—the invertebrate counterpart of transplantation immunity. Working with the protochordate *Botryllus schlosseri* (which has a chordate larval stage and an invertebrate adult form) they have identified a single major gene locus that governs rapid allorecognition, and 2-3 other loci involved in delayed allorecognition events. They are using this model to study the genes, proteins, and cells that govern protochordate allorecognition, and the effects of these genes on their population dynamics in the field.

KEYNOTE LECTURE NORMAL AND NEOPLASTIC STEM CELLS

IRVING WEISSMAN

ABSTRACT

Following embryonic development, most of our tissues and organs are continuously regenerated from tissue/organ specific stem cells. The principal property that distinguishes such stem cells from their daughter cells is self-renewal; when stem cells divide they give rise to stem cells (by self-renewal) and progenitors (by differentiation).

In most tissues only the primitive stem cells self-renew. Stem cell isolation and transplantation is the basis for regenerative medicine. Self-renewal is dangerous, and therefore strictly regulated. Poorly regulated self-renewal can lead to the genesis of cancer stem cells, the only self-renewing cells in the cancerous tumor.

MICHAEL CLARKE

STANFORD UNIVERSITY SCHOOL OF MEDICINE

ASSOCIATE DIRECTOR, INSTITUTE FOR STEM CELL BIOLOGY AND REGENERATIVE MEDICINE

Education

- 1973 Indiana University B.A.
1977 Indiana University M.D.

Academic Appointment

- 2005 present Professor of Internal Medicine, The Karel and Avice Beekhuis Endowed Professorship in Cancer Biology, Associate Director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine, Stanford, California

Awards and Honors (Selected)

Member, American Society of Hematology
Member, American Society of Clinical Oncology
Member, American Association for Cancer Research
Member, American Society of Gene Therapy
Editorial Board, Cancer Gene Therapy, 2000-2003

- 1996 Elected, American Society of Clinical Investigation
2003 Physician of the Year 2003, Detroit Business Weekly
2005 Elected, Association of American Physicians

Research Interests

In addition to his clinical duties in the division of Oncology, Dr. Clarke maintains a laboratory focused on two areas of research: i) the control of self-renewal of normal stem cells and their malignant counterparts; and ii) the identification and characterization of cancer stem cells. A central issue in stem cell biology is to understand the mechanisms that regulate self-renewal of hematopoietic stem cells, which are required for hematopoiesis to persist for the lifetime of the animal. Until recently, the molecular mechanisms that regulate adult stem cell self-renewal were not known. His laboratory recently found that the proto-oncogene Bmi-1 regulates stem cell self-renewal via an epigenetic mechanism. By investigating the pathways upstream and downstream of Bmi1, the laboratory is actively investigating the molecular pathways that regulate self-renewal.

Cancers arise as a result of a series of genetic mutations. A better understanding of the consequences of these mutations on the underlying biology of the neoplastic cells will help to focus the development of more effective therapies. Solid tumors such as breast cancers contain heterogeneous populations of neoplastic cells. Dr. Clarke's group has developed a technique that allows the isolation and characterization of tumorigenic and non-tumorigenic populations of cancer cells present in human breast, colon and head and neck cancer tumors. Only a small minority of cancer cells had the capacity to form new tumors in a xenograft model. This tumorigenic cell population could be identified prospectively and consistently had definable and identical phenotype. The tumorigenic cells displayed stem cell-like properties in that they were capable of generating new tumors containing additional stem cells as well as regenerating the phenotypically mixed populations of non-tumorigenic cells present in the original tumor. Effective treatment of cancer will require therapeutic strategies that are able to target and eliminate this tumorigenic subset of cells. The laboratory is pursuing the identification of cancer stem cells in other tumors so that they can be studied. Dr. Clarke's laboratory will provide other members of the program with the expertise to identify and isolate cancer stem cells from solid tumors of epithelial origin. Finally, the laboratory is actively pursuing how cancer stem cells self-renew to maintain themselves and escape the genetic constraints on unlimited self-renewal that regulate normal stem cell numbers. Differences in self-renewal pathways between normal and malignant stem cells could be targeted by new therapeutic agents to eliminate cancer stem cells.

WHAT CAN WE LEARN FROM THE PROSPECTIVE ISOLATION OF CANCER STEM CELLS?

MICHAEL CLARKE

ABSTRACT

Most common cancers, such as cancers of the breast and colon, arise in organs such as the breast that contain a small population of stem cells that constantly replenish the mature cells of the tissue. Stem cells are defined by the ability to divide and give rise to a new stem cell (self-renewal), as well as the ability to give rise to the differentiated cells of an organ, and thus are the only long-lived cells in many tissues.

Solid tumors consist of a heterogeneous population of cancer cells which differ in their apparent state of differentiation, suggesting that solid tumors might represent aberrant organs containing a cancer stem cell population that maintains the ability to self-renew. Indeed, using a xenograft model of human breast cancer, a small, phenotypically-distinct subset of the cancer cells (cancer stem cells) has been found to have the exclusive ability to form tumors. The remaining cancer cells, which form the bulk of the tumor, are unable to self-renew or sustain tumorigenesis. Recently, it has become apparent that some oncogenes and tumor suppressor genes also regulate self-renewal, the process by which both normal and malignant stem cells maintain themselves. The process of self-renewal is de-regulated in cancer stem cells resulting in tumor formation. New pathways that regulate normal cancer stem cell self renewal and resistance to conventional cancer therapies will be discussed.

HANS CLEVERS

NETHERLANDS INSTITUTE FOR DEVELOPMENT
DIRECTOR, HUBRECHT INSTITUTE IN UTRECHT

Education

1982	University of Utrecht	M.Sc	Biology
1984	University of Utrecht	M.D.	Biology
1985	University of Utrecht	Ph.D.	Biology

Academic Appointment

- 2002 Professor, Molecular Genetics of The Academic Biomedical Centre, University of Utrecht
- 2002 Honorary professor of Changsha-Hunan, China

Awards and Honors (Selected)

- Member, national top graduation school in biomedical science “Centre for Biomedical Genetics”
- Member, European Molecular Biology Organisation (EMBO)
- Member, Royal Dutch Academy of Sciences
- Member, Scientific Board of the Dutch Cancer Society 2001-2006
- Editorial Board, European Journal of Immunology
- President, board of directors of the International Society of Differentiation 2006-2008

- 2000 Catharijne-prize for medical science
- 2001 European Society for Clinical Investigations Award
Spinoza-award
- 2004 Louis Jeantet Prize
- 2005 Katharine Berkan Judd Award
The Science and Society Prize
French honor of “Chevalier de la Legion d'Honneur”
- 2006 Rabbi Shai Shacknai Memorial Prize for Immunology and Cancer Research

Research Interests

His research focuses on TCF factors, mediators of Wnt signaling in development and cancer. In 1991, they cloned a T cell specific transcription factor termed TCF1. Related genes exist in genomes throughout the animal kingdom. They have shown in frogs, flies and worms that upon Wingless/Wnt signaling, β -catenin associates with nuclear TCFs and contributes a trans-activation domain to the resulting bipartite transcription factor, and designed the widely used pTOPFLASH Wnt reporters. In the absence of Wnt signaling, they found that Tcf factors associate with proteins of the Groucho family of transcriptional repressors to repress target gene transcription. The tumor suppressor protein APC forms the core of a cytoplasmic complex which binds β -catenin and targets it for degradation in the proteasome. In APC-deficient colon carcinoma cells, they demonstrated that β -catenin accumulates and is constitutively complexed with the TCF family member TCF4. In APC-positive colon carcinomas and melanomas, dominant mutations in β -catenin render it indestructable, providing an alternative mechanism to inappropriately activate transcription of TCF target genes.

IDENTIFICATION OF STEM CELLS IN SMALL INTESTINE AND COLON BY A SINGLE MARKER GENE LGR5

HANS CLEVERS

ABSTRACT

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. Current models state that 4-6 crypt stem cells reside at the +4 position immediately above the Paneth cells in the small intestine; colon stem cells remain undefined. *Lgr5/Gpr49* was selected from a panel of intestinal Wnt target genes for its restricted crypt expression. Two knock-in alleles revealed exclusive expression of *Lgr5* in cycling, columnar cells at the crypt base. In addition, *Lgr5* was expressed in rare cells in several other tissues. Using an inducible Cre knock-in allele and the Rosa26-LacZ reporter strain, lineage tracing experiments were performed in adult mice. The *Lgr5*+ve crypt base columnar cell (CBC) generated all epithelial lineages over a 60-day period, implying that it represents the stem cell of the small intestine and colon. The expression pattern of *Lgr5* suggests that it marks stem cells in multiple adult tissues and cancers.

ELAINE FUCHS

NEW YORK, ROCKEFELLER UNIVERSITY
HEAD, LABORATORY OF MAMMALIAN CELL BIOLOGY AND DEVELOPMENT

Education

1972	University of Illinois	B.S.	Chemistry
1977	Princeton University	Ph.D.	Biochemistry

Academic Appointment

1980	University of Chicago, Dept Molecular Genetics & Cell Biology, Assistant Professor ('80-'85), Associate Professor ('85-'88), Professor '88-'02 (Amgen Professor of Basic Sciences)		
1988	Investigator, Howard Hughes Medical Institute		
2002	Rebecca Lancefield Professor, Rockefeller University, Mammalian Cell Bio & Dev. Adjunct Professor, Cornell Medical School, Dept Dermatology.		

Awards and Honors (Selected)

Member, American Academy of Arts and Science
Member, National Academy of Sciences
Member, American Academy of Microbiology
Member, New York Academy of Sciences
Member, Harvey Society
Member, American Philosophical Society
Fellow, American Association of Arts and Sciences
Editorial Board, Genes & Development
Editorial Board, Developmental Cell
Editorial Board, Cell Stem Cell
Editorial Board, Cell

1997	Cell Biology Senior Women's Career Achievement Award
2002	Cartwright Award from Columbia University
2003	Novartis Drew Award in Biomedical Research
2004	Dickson Prize in Medicine
2006	Federation of American Societies for Experimental Biology Award for Scientific Excellence Steven C. Beering Award for Outstanding Achievement in Biomedical Science

Research Interests

Skin is one of the body's major reservoirs of stem cells, as the epidermis must constantly self-renew to repair damage caused by mechanical stress and injuries. Dr. Fuchs is interested in how stem cells located within the skin give rise to the epidermis and to hair follicles, and how molecular mechanisms in adult skin cells cause these cells to differentiate in response to various external cues.

Using a reverse genetic approach, in combination with cell and developmental biology, Dr. Fuchs works to elucidate the genetic basis of a variety of human and mouse disorders, ranging from blistering skin disorders and tumors to a rare form of muscle degeneration and a sensory neurological disorder. Her lab also explores how adult skin cells deal with the constantly changing environment, and how stem cells determine when to divide and what type of cell to develop into. Skin epithelium is one of the few tissues of the body from which human and mouse stem cells can be maintained and propagated in culture. Also, because skin is at the body surface, it is readily accessible for mouse and human genetics, and hence provides an ideal system to study stem cells and dissect their mechanisms of self-renewal and maintenance of an undifferentiated state. Dr. Fuchs's laboratory studies the molecular biology of how skin stem cells behave in vitro, and exploits transgenic and gene knockout technologies in mice to reveal skin protein function in vivo.

STEM CELLS OF THE SKIN: BIOLOGY AND CLINICAL POTENTIAL

ELAINE FUCHS

ABSTRACT

Stem cells can self-renew and differentiate along multiple lineages to generate different tissues. In the embryo, multipotent stem cells respond to various cues to undergo morphogenesis and produce these tissues. The epidermis of the skin is an excellent model to explore how multipotent stem cells are able to respond to different cues to generate three functional tissues: epidermis, sebaceous gland and hair follicles. In the adult, stem cells reside in the epidermal basal layer, at the base of the sebaceous gland and in a niche within the hair follicle known as the bulge. Despite intensive studies, we still know very little about how stem cells and these niches become established and maintained. Genetic marking and molecular approaches stem cells within the bulge typically cycle infrequently. In response to a skin injury, these stem cells can be mobilized to move upward, proliferate and repair epidermal wounds or replenish the sebaceous gland. In normal homeostasis, these stem cells fuel the hair cycle, where they become activated to proliferate and regenerate the hair follicle with each new anagen phase. It has been known for nearly a decade that the transition from dormant to activated follicle stem cells involves changes in signaling by Wnts, BMPs, and other factors but the molecular details of the activation and commitment steps are still unfolding. My laboratory uses a combination of molecular, cellular and genetic approaches to study the molecular mechanisms that underlie the biology of the multipotent stem cells of the skin epithelium. In understanding normal stem cell behavior, we have begun to realize that when sustained through genetic mutations, the pathways involved in stem cell activation lead to tumorigenesis and skin cancers. We have also begun to elucidate features about skin stem cells that have potential for regenerative medicine

RICHARD GARDNER

UNIVERSITY OF OXFORD, DEPARTMENT OF ZOOLOGY
EDWARD PENLEY ABRAHAM RESEARCH PROFESSOR OF THE ROYAL SOCIETY

Education

1971 University of Cambridge Ph.D.

Academic Appointment

1978 Royal Society's Henry Dale Research Professor
2003 Royal Society's Edward Penley Abraham Research Professor
2006 President of the Institute of Biology

Awards and Honors (Selected)

Member, Scientific and Clinical Advances Group of the Human Fertilization and Embryology Authority
Member, Society for Study of Fertility
Member, British Society for Developmental Biology
Fellow, Royal Society
Fellow, European Molecular Biology Organization (EMBO) Heidelberg

1999 March of Dimes International Prize in Developmental Biology
2001 Royal Society's Royal Medal
2004 Albert Brachet Prize of the Belgian Royal Academy

Research Interests

Patterning of the early mammalian embryo with respect to the specification of axes and bilateral asymmetry. Derivation, characterization and exploitation of stem cells from early embryos for transgenesis and for their potential for use in regenerative medicine.

STEM CELLS AND CANCER FROM AN EMBRYOLOGICAL PERSPECTIVE

RICHARD GARDNER

ABSTRACT

There remains much confusion in the literature with stem cells being identified variously with progenitor, founder or precursor cells. The distinction becomes clearer with the recognition that stem cells possess certain attributes which serve to reduce the risk of genomic change that cells incur whenever they replicate their genome.

By the stage at which a malignancy is evident there has usually been ample time for selection to operate and thereby obscure the primary change whereby growth became disregulated. Simply transplanting murine embryonal carcinoma (EC) and embryonic stem (ES) cells into a histocompatible adult rather than early embryonic host can cause them to embark on tumorigenesis. This underlines the importance of an appropriate niche not only for enabling stem cells to retain their 'stemness' but also to ensure that their growth is correctly regulated. That this is likely to be of more general significance is suggested by the relationship of malignancy to disruption of normal tissue architecture and cellular transdifferentiation.

SEAN MORRISON

UNIVERSITY OF MICHIGAN, MEDICAL SCHOOL
DIRECTOR, UNIVERSITY OF MICHIGAN CENTER FOR STEM CELL BIOLOGY

Education

- 1991 Dalhousie University, Halifax BSc Biology and Chemistry
1996 Stanford University Ph.D. Immunology

Academic Appointment

- 2000 Investigator, Howard Hughes Medical Institute
2005 Director, University of Michigan Center for Stem Cell Biology
2005 Henry Sewall Professor of Medicine
2008 Professor, Department of Internal Medicine, University of Michigan
2008 Research Professor, Life Sciences Institute, University of Michigan

Awards and Honors (Selected)

- 2002 Named to TR100 list: MIT Technology Review Magazine's list of 100 young innovators
2003 Presidential Early Career Award for Scientists and Engineers, White House
2004 Dean's Award for Basic Science, University of Michigan Medical School
2006 Detroit News Michiganiaan of the Year
2007 Pfizer Young Michigan Biomedical Investigator of the Year Award
McCulloch and Till Award, International Society for Hematology and Stem Cells
2008 American Association of Anatomists Harland Winfield Mossman Award

Research Interests

Stem cells are self-renewing multipotent progenitors that give rise to all of the other cells in particular tissues. For example, hematopoietic stem cells (HSCs) are the rare cells in bone marrow that give rise to all blood and immune system cells. Neural crest stem cells give rise to a number of different tissues including the peripheral nervous system. Given their seminal roles in development and regeneration, stem cells define the nexus of important questions in both developmental biology and clinical applications. We study stem cell biology using hematopoiesis and neural development as model systems. The next challenge in stem cell biology will be to integrate what we know about stem cells in different tissues in order to understand common mechanisms of regulation and distinctions that permit tissue-appropriate development. Moreover, we study diseases in which stem cell regulatory mechanisms go awry, such as in cancer (where self-renewal mechanisms are inappropriately activated) and birth defects (in which stem cell function can sometimes be disrupted). We have decided to focus on mechanisms that regulate stem cell self-renewal and stem cell aging as well as the ways in which cancer cells coopt stem cell regulatory mechanisms. By studying these mechanisms in stem cells from two different tissues we assess the extent to which different types of stem cells employ similar or different mechanisms to regulate these critical functions.

THE REGULATION OF STEM CELL SELF RENEWAL

SEAN MORRISON

ABSTRACT

Single human melanoma cells efficiently form tumors in a modified xenotransplantation assay

Elsa Quintana, Mark Shackleton, Timothy M. Johnson, and Sean J. Morrison

Howard Hughes Medical Institute, Life Sciences Institute, Department of Internal Medicine, and Center for Stem Cell Biology, University of Michigan

Traditionally, many cancer cells have been considered to have tumorigenic potential even though no assay in any human cancer has ever demonstrated that a high percentage of single cells can form tumors. In contrast, the cancer stem cell model has suggested that only rare (or at least infrequent) cancer cells have tumorigenic potential based on experiments in which human cancer cells have been xenotransplanted into NOD/SCID mice. For example, only one in a million (0.0001%) human melanoma cells is tumorigenic in NOD/SCID mice. Nonetheless, recent studies of mouse hematopoietic malignancies have raised the question of whether NOD/SCID xenotransplantation underestimates the frequency of tumorigenic human cells. Here we show that modified xenograft assay conditions, including the use of more highly immunocompromised NOD/SCID IL2R^{-/-} null mice, can increase the ability to detect tumorigenic human melanoma cells by several orders-of-magnitude. Approximately 25% of unselected melanoma cells from 12 different patients, including both primary and metastatic melanomas obtained directly from patients, formed tumors under these more permissive conditions. A remarkable 27% of single melanoma cells from four different patients formed tumors in NOD/SCID IL2R^{-/-} null mice. Modifications in xenotransplantation assays can therefore increase the detectable frequency of tumorigenic human cells by several orders-of-magnitude, revealing that cells with tumorigenic potential are common in some human cancers, including melanoma.

HERVÉ CHNEIWEISS

UMR-S 894 INSERM- UNIVERSITY PARIS DESCARTES
DIRECTOR OF THE LABORATORY

Education

- 1984** University Pierre and Marie Curie Paris VI MD
- 1988** MD specialized in Neurology
- 1986** University Pierre and Marie Curie Paris VI PhD

Academic Appointment

- 1986-1990** Research associate (CR2) CNRS.
- 1990-1995** Research associate (CR 1) , CNRS.
- 1986-1997** Consultant physician Fédération de Neurologie de l'hôpital de la Salpêtrière
- 1995** Research director (DR2), CNRS.
- 2000-2002** Life Science advisor to the minister for research
- 2002-now** Consultant physician Fédération Mazarin de l'hôpital de la Salpêtrière
- 2006-now** Research director (DR1), CNRS

Awards and Honors (Selected)

- 2002-2006** Member Scientific council Réseau National des Génopoles.
- 2003-now** Member of the Ethic Committee of Inserm ERMES
- 2004-now** Member Scientific council of Parlement Office for Science and Technology
- 2006-now** Chief Editor Médecine/Sciences

Research Interests

A first serie of studies were dedicated to demonstrating the presence and diversity of neurotransmitter receptors on astrocytes. This contributed to evidence astrocytes as communicating cells in the CNS and to demonstrate their heterogeneity. A second step of my scientific carrier was oriented on intracellular signal transduction. I characterized phosphoproteins involved in neuronal signaling, including Stathmin, a small microtubule associated phosphoprotein, modulated by ont-dependent protein kinase, Map kinase and CDK2 kinase, that increase the rate of catastrophies (or instability) of microtubules. Within the last period, I focused the work of my group on phosphoproteins enriched in astrocytes. We characterized PEA-15, a small substrate of PKC and CaMKII, protecting astrocytes from apoptosis. More recently we demonstrated that PEA-15 activates MAP kinase but inhibits entry in the cell cycle. Thus PEA-15 plays as a double key controlling apoptosis, cell proliferation and migration. Inhibitors were characterized, a patented molecule being now developed in the context of diabetes and cancer. This led us to investigate more properly gliomas, with the hypothesis that an unbalance in cell cycling and apoptosis was contributing to tumor progression, and that a subpopulation of astrocytes recognized as neural stem cells might be involved. We recently raised evidence for tumoral stem cells in a new form of malignant brain tumors and now develop high-throughput approaches to discover new therapeutic targets and molecules.

STEM CELLS IN GLIAL TUMOURS

HERVÉ CHNEIWEISS

ABSTRACT

Astrocytes may give rise to gliomas, the most frequent primitive tumours of the central nervous system. TGF α , an EGF family member frequently overexpressed at early steps of human gliomas, is trophic for both astrocytes and glioma cells, but its sole deregulation is insufficient to lead to cancerous transformation of astrocytes. It however triggers their conversion into neural progenitor-like cells capable to give birth to neurons (Sharif et al, *Oncogene*, 2007). Irradiation, a classic mutagen, was used to determine whether astrocytes converted into neural progenitor-like cells are more sensitive than their mature counterpart to cancerous transformation. Mouse astrocyte cultures were maintained 7 days in serum-free medium without (control) or with TGF α (50 ng/ml), prior to be either sham-irradiated or irradiated (¹³⁷Cesium source, 5 Grays once fraction). Irradiation did not modify the life span of control astrocytes, which died within 3 weeks post-irradiation as their sister sham-irradiated counterparts. On the opposite, TGF α -treated astrocytes were immortalized upon irradiation. Their cancerous transformation was ascertained by their ability to form colonies in methylcellulose medium, their karyotype anomalies, and the formation of sub-cutaneous tumours in NOD-SCID mice and high-grade glioblastoma/gliosarcoma-like tumours after grafting into Nude mice CNS. These results demonstrate that an instability of the mature astrocyte phenotype due to a single change in their environment suffices to sensitize them to cancerous transformation. If de novo dedifferentiation-generated neural stem cells are at the origin of brain tumors, is it possible to evidence these tumor-initiating cells in human gliomas? Several groups including our lab characterized from human adult and pediatric gliomas tumoral cells with stem cells characteristics. Our analysis from more than 40 different adult brain tumors identified a subgroup of high grade tumors, malignant glio-neuronal tumors, raising systematically tumoral stem cells with long-term self-renewal capabilities (up to 5 years). We focused on G-protein coupled receptors (GPCRs), which constitute a therapeutic target of choice with regards to their involvement in cell proliferation and migration, and the availability of numerous agonists and antagonists drugs. Quantitative PCR analysis revealed a wide array of GPCR transcripts in CSCs, 178 being expressed by at least one culture, from 350 tested, and revealed a common core of 61. Frizzled, purine and adhesion receptors were the most represented clusters, including also amines, SREBs, secretine/Vip and several orphan receptors. Their levels of expression are modulated according to the proliferative state of the cells. Westernblotting and immunocytochemistry confirmed expression at the protein level whereas gene reporter luciferase assays will allow further intracellular signaling analysis. Functionality was also illustrated by adrenergic β_2 , dopaminergic D2 or muscarinic receptors blockade on cultured CSCs respectively with ICI118551, sulpiride and scopolamine, that resulted in drastic changes in cellular sphere growth related to increased cell proliferation or reduced cell adhesion, respectively. These results reveal for the first time the potentialities of GPCRs as therapeutic targets for glioma treatment.

WILLIAM VAINCHENKER

INSERM U790, INSTITUT GUSTAVE ROUSSY, VILLEJUIF
DIRECTOR OF THE LABORATORY

Education

- | | | |
|------|----------------------|-----|
| 1977 | Université Paris XII | MD |
| 1978 | Université Paris VI | PhD |

Academic Appointment

- | | |
|-----------|--|
| 1981-1983 | Assistant Professor in the Immuno-Hematology department, Hôpital St Louis, Paris |
| 1983 | present Hematology consultant (Hôpital St Louis, Paris) |
| 1983 | Research Director class (DR) (INSERM U91, Director Professor Jean Rosa) |
| 1992 | present Director of an INSERM unit at the Institut Gustave Roussy, Villejuif |

Awards and Honors

- | | |
|------|--|
| 1994 | Prize from the European Haematology Association |
| 1994 | Prize of the Ligue Nationale contre le Cancer |
| 1996 | “Gustave Roussy” prize from the Académie des Sciences |
| 1997 | “Mitjaville” prize from the Académie de Médecine |
| 2000 | Award of the Institut de France/Académie des Sciences |
| 2007 | Dameshek Prize from the American Society of Hematology |
| 2008 | Prize of the foundation AGF – Institut de France |

Research Interests

The hematopoietic system is one of the main cellular model for normal and pathological differentiation. The laboratory is working on both aspects and is specially focusing on stem cell biology and the erythroid and megakaryocytic differentiation. Presently the work on stem cell is focused on the mechanism of hematopoietic stem cell emergence in the embryo and on the role of CXCR4/SCDF1 on the biological properties of normal and leukemic stem cells. Other researches encompass the developmental biology of the megakaryocytic lineages including TPO and its receptors, transcription factors and the mechanisms of megakaryocyte polyploidization and proplatelet formation. Researches on pathologies have included congenital and acquired disorders affecting platelet and red cell production with a specific interest for myeloproliferative disorders

MUTATION JAK2 V617F AND MYELOPROLIFERATIVE SYNDROMES

WILLIAM VAINCHENKER

ABSTRACT

Myeloproliferative disorders (MPDs) are malignant diseases, which arise from the transformation of hematopoietic stem cell. These clonal diseases are characterized by an excess of mature blood cells. The molecular pathogenesis of the classical MPDs including polycythemia vera (PV), essential thrombocythemia (ET) and primitive myelofibrosis (PMF) was unknown until 2005 with the discovery of the JAK2V617F mutation. This acquired gain of function mutation is associated with more than 90% of PV and 50% of ET and PMF. The discovery of this mutation has led to intensive researches on these pathologies, which were nearly orphan before. This has led to the discovery of other mutations in JAK2 in PV and in Mpl, the thrombopoietin receptor in ET and PV.

The role of the JAK2V617F in the pathogenesis of the MPDs has been extremely controversial because this mutation is associated with several disorders. There are increasing evidence that this mutation is really the oncogenic event, which drives the disease. However is it sufficient? and is there the need for other preexisting or secondary genetic events for disease development?

The JAK2V617F mutation really targets a hematopoietic stem cell in all these disorders but does not appear to give a major selective advantage to the mutated stem cells. In contrast JAK2V617F gives a major clonal advantage at the post progenitor level. In some patients or in PMF the clonal advantage takes place at earlier stages of differentiation suggesting that other genetic event (s) have more profoundly modified the hematopoietic stem cell biology. We are presently on the way of identifying one of this genetic event which may precede the JAK2V617F mutation.

Whatever this experimental approach underscores the heterogeneity of MPDs and suggests that MPDs may have a more complex pathogenesis than a tyrosine kinase activation.

A NATIONAL HEALTH AND SCIENCE AGENCY,

THE INSTITUTE:

The French National Cancer Institute was created through the Public Health Act of 9 August 2004, under the Cancer Plan, and implemented in July 2005 to enable a long-lasting, coordinated national policy against cancer. Placed under the tutelage of the Ministry of Health and the Ministry of Research, it brings together all of the players involved in the fight against cancer in France. The Institute is a health and science agency dedicated to oncology.

ITS MISSIONS:

- ➔ To observe and assess the system in place to fight cancer;
- ➔ To define benchmarks for good practices and care in the field of oncology and the criteria for certifying institutions and professionals in the field of oncology;
- ➔ To inform professionals and the public;
- ➔ To participate in the implementation and validation of continuing education for doctors and paramedical personnel;
- ➔ To implement, finance and coordinate research projects in collaboration with the relevant public research organisations and charitable associations;
- ➔ To develop and monitor public/private actions in the areas of prevention, epidemiology, screening, research, education, care and evaluation;
- ➔ To participate in developing European and worldwide actions;
- ➔ To prepare expert reports in oncology and cancer issues at the request of the relevant ministries.

A PUBLIC EXPERTISE AGENCY:

The Institute is a **public expertise agency** whose means of actions are the implementation of partnerships with and through the existing public and/or private structures of Care, Public Health and Research, and calls for proposals. The Institute covers the whole spectrum of the fight against cancer and has four main areas of interventions (below); the Institute's budget in 2007 was about 100 millions € dedicated to actions related to health, research, treatment and information

4 ACTION DOMAINS:

- ➔ **PUBLIC HEALTH:** Implement a better cancer prevention strategy and diagnose cancer earlier;
- ➔ **CARE:** Guarantee access to top-quality care for all, in line with the principle of equity;
- ➔ **RESEARCH:** Make innovation and progress more accessible;
- ➔ **INFORMATION:** population, patients and health care professionals.

THE GOVERNANCE:

The National Cancer Institute is governed by a board of directors, which defines the overall strategy, and is made of public, private and associative stakeholders in the fight against cancer. An independent international scientific advisory board ensures the cohesion of scientific and medical policies. A committee of patients and a committee of health professionals are consulted on a regular basis, they advise on all actions of the Institute and actively participate to working groups on specific issues.

DEDICATED TO CANCEROLOGY

CANCER RESEARCH ORGANISATION:

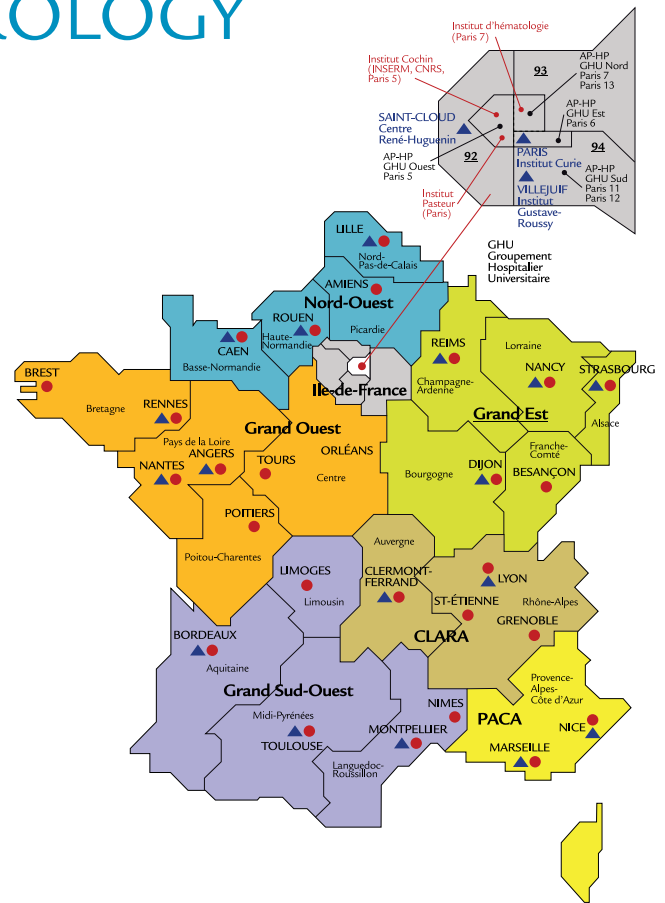
In 2003, 7 comprehensive cancer regions called “canceropôles” were created. These regional structures bring together the research units of scientific organisations, university hospitals with the aim of strengthening the coordination of research.

Research networks concentrated over 950 cancer research teams spread over France.

FUNDING OF RESEARCH:

To ensure the care-research continuum, translational research is strongly supported by the Institute. From 2005 to 2007, 65.6 millions € were allocated to 211 projects which included an objective of translation; these projects represent more than 50% of the projects funded by the Institute. Since 2005, there is a constant increase in the funding of translational research projects;

- ➔ 2005: 50 projects, 16.7 M €;
- ➔ 2006: 60 projects, 19.5 M €;
- ➔ 2007: 78 projects, 29.4 M €.
- ➔ From 2008, a specific complementary programme will be dedicated to translational research.



Clinical research is supported by a yearly highly competitive cancer research programme sponsored by the Ministry of Health (16 millions €) and managed by INCa: 338 projects (clinical trials, epidemiological and clinical practice surveys, etc) were sponsored between 2003 and 2008. In addition, support is provided to 10 data management centres dedicated to cancer and to 140 clinical research nurses in cancer to help in collecting data and including patients into clinical trials.

Integrated research programmes covering all research areas from biology to clinical and social sciences are developed in specific types of cancer. In the last two years, two such specific research programmes were focused on early stages of colorectal cancer (5 M €) and lymphomas (5 M €). Hepatocarcinoma will be the next cancer type targeted in a 2009 call.

Cancer genomics is strongly supported, not only through specific calls but also through strengthening of networks, biological platforms and biobanks. The Institute is the French member of the **ICGC International Cancer Genome Consortium** which plans to sequence and analyse the genome of 50 different tumour types in the next five years.

LA FONDATION



FONDATION Singer-Polignac

C'est en 1928 que Winnaretta Singer, princesse Edmond de Polignac, donna une forme juridique à l'activité de mécénat qu'elle menait depuis longtemps en faveur des arts, des lettres et des sciences. La loi du 25 mars 1928 ratifia la création de l'établissement public dénommé Fondation Singer-Polignac et le décret du 17 octobre 1928 approuva la dotation de Winnaretta à l'État français en vue de cette création, le revenu de ce capital étant destiné aux activités définies par les statuts de la Fondation. Raymond Poincaré en fut le premier président.

À la mort de la princesse, la Fondation reçut en legs son hôtel particulier de l'avenue Georges Mandel et s'y installa en 1945.

Le fonctionnement de la Fondation repose sur la gestion de produits financiers. La Fondation ne reçoit aucune subvention ni dotation de l'État.

La Fondation Singer-Polignac se consacre à des activités de mécénat culturel. Elle accueille les chercheurs, penseurs, témoins, lors de rencontres sur les sujets les plus divers. Elle apporte également son aide aux musiciens à travers de nombreuses activités : musiciens en résidence, concerts, répétitions publiques, enregistrements, causes musicales... Elle accorde des bourses ou des aides aux étudiants en post-doctorat dans le domaine des lettres, des sciences et des arts. Le Conseil d'administration

soutient la protection et la sauvegarde du patrimoine ainsi que le rayonnement de la culture française.

L'ESPRIT D'UN MÉCÉNAT EXCEPTIONNEL

Les plus remarquables œuvres humaines nous font nous interroger sur les raisons qui firent qu'un jour elles devinrent ce qu'elles sont et que nous puissions en être les heureux bénéficiaires. La Fondation Singer-Polignac fait partie de celles-là. À l'évidence, c'est la décision de Winnaretta Singer, princesse Edmond de Polignac, de donner une forme juridique à l'action de mécénat qu'elle entretenait depuis très longtemps, qui en marqua, en 1928, définitivement la naissance, mais il est plus juste d'y retrouver l'ultime conséquence de la passion que la princesse entretenait depuis son adolescence avec la peinture et la musique. Elle y exprimait de beaux talents dont témoignent les toiles qu'elle nous a laissées et la voûte de la salle de musique construite autour de son orgue, qui vibre encore des harmonies qu'elle y composait. Mais il y eut aussi l'attrait de Paris, d'où sa mère était originaire et où il n'était guère possible d'être célèbre, pour un artiste, sans y être reçu en ses salons. Il y eut enfin la rencontre avec le prince Edmond de Polignac, ce fin compositeur avec lequel elle partagea, tant qu'il vécut, le goût immodéré qu'elle avait pour la musique. Il y eut enfin ce désir de construire ce bel hôtel particulier, sur les traces de l'ancien, afin qu'il devînt l'un des lieux les plus attrayants de la capitale. Il le

fut au-delà de ce qu'elle espérait, pour les musiciens tout d'abord, qui y exprimèrent souvent en première audition des œuvres que la princesse leur avait commandées. Fauré, Chabrier, Ravel, Satie, de Falla et Stravinski en sont les plus connus. Pour les amis de la princesse, en second lieu, qui les conviait à ces concerts dont la presse faisait écho, parmi lesquels Marcel Proust, Colette, etc. ne furent pas les moins célèbres. Mais il fut aussi le lieu de rencontre que Winnaretta Singer-Polignac offrit à tous ceux qui pensaient qu'elle pourrait les aider dans leur vocation ou leur mission, sculpteurs, peintres, hommes de sciences, architectes ou responsables d'œuvres charitables. Ainsi se définissait l'étendue du domaine solidaire qu'elle avait créé, enclos en cet écrin superbe, ce magnifique hôtel qu'à sa mort à Londres, en novembre 1943, elle nous laisserait afin que survive la mission qu'elle avait de sa seule initiative créée. Son héritage nous impose d'en conserver l'esprit, avec la rigueur mais aussi l'extraordinaire ouverture d'esprit qu'elle entretenait à l'égard de la création artistique, qu'elle fût musicale ou plastique, mais aussi de la pensée scientifique, sans pour autant négliger ce que son cœur, parfois, jugeait utile d'accomplir. C'est le devoir dont furent chargés ses héritiers successifs et c'est celui que son président et le conseil d'administration s'engagent à honorer avec le sentiment qu'il leur est confié l'incomparable possibilité de servir les arts et les sciences à la manière de l'inoubliable mécène que fut la princesse de Polignac.

Professeur Yves POULIQUEN,
de l'Académie française, président de la Fondation

AUJOURD'HUI

La Fondation Singer-Polignac accueille les chercheurs, penseurs, témoins, lors de rencontres sur les sujets les plus divers. La Fondation apporte également de toutes les manières souhaitables son aide aux musiciens. Elle accorde des bourses ou des aides aux étudiants, en post-doctorat, dans le domaine des lettres, des sciences et des arts. Le Conseil d'administration soutient la protection et la sauvegarde du patrimoine ainsi que le rayonnement de la culture française.

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www.e-cancer.fr