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Robert A. Weinberg and The large medal of the Academy of Sciences



Robert A. Weinberg, PhD

Robert Weinberg, 67, professor of biology at Massachusetts Institute of Technology (MIT), is one of the few scientists who have contributed most to the enormous progress made over the last 30 years in our understanding of the origin of cancer. His work has greatly contributed to improve the classification of tumors, diagnosis of cancer and the development of targeted therapies, more effective and less toxic than conventional therapies.

Having demonstrated that the tumor of a malignant cell is included in its genome, Robert Weinberg in 1982 identified the first human oncogene (oncogenes are genes that stimulate the proliferation of tumor cells). By cloning and sequencing the gene, the ras gene, cells from human bladder cancer, he showed the existence in vertebrates of genes, called proto-oncogenes, which can become oncogenic as a result of simple point mutations. He also identified the oncogene neu (ErbB2 or HER2 or) encoding a membrane receptor, now target treatments for some women with breast cancer.

In 1986, Robert Weinberg has cloned the first gene "tumor suppressor" human, the Rb gene, and described the first mutations inactivating this gene in retinoblastoma. He also characterized the human gene for telomerase, an enzyme that maintains the ends of chromosomes, the maintenance of abnormal activity in this enzyme in tumor cells confers the ability to multiply indefinitely.

Pioneer of Molecular and Cellular Oncology, Robert Weinberg in 1999 showed that the tumor transformation of human cells is a multi step process, requiring the disruption of at least five pathways of regulation. At the Whitehead Institute for Biomedical Research, which he co-founded at MIT, he continues research today points to the power of invasive tumor cells and the spread of metastases, with his team, he has already discovered several factors that play a key role in this phase.

Among its many prestigious titles, he received the Doctor Honoris Causa from the Université Paris-Descartes, in December 2008. During his career, Robert Weinberg has trained many researchers and physicians, and he has worked for the understanding of cancer by the general public.

Robert Allan Weinberg¹ (born 11. November 1942) is a Daniel K. Ludwig Professor for Cancer Research at MIT and American Cancer Society Research Professor; his research is in the area of oncogenes and the genetic basis of human cancer. Weinberg is also affiliated with the Broad Institute and is a founding member of the Whitehead Institute for Biomedical Research. He co-teaches 7.012 (introductory biology) with Eric Lander.

He is best known for his discoveries of the first human oncogene *Ras* and the first tumor supressor gene *Rb*, which is partially documented in Natalie Angiers book, *Natural Obsessions* , about her year spent in Weinberg's lab.

He won the National Medal of Science in 1997, and he is a member of the U.S. National Academy of Sciences . In 2007 he received an honorary doctorate degree in commemoration of Linnaeus from Uppsala University . He is a member of the Royal Swedish Academy of Sciences^[1]

He is well known for both his brilliance in cancer research and for his mentorship of many eminent scientists.

He is also the author of the textbook *The Biology of Cancer* published by Garland Science In my research on Cancer² and the pain, I had spoken of Lucien Israel, Professor of Oncology at the University of Paris XIII in his interview with Luicie Soboul, Journalist medical Tfl, insisted like other researchers, on the Biology of Cancer "Before giving an idea of what this cancer, and how it operates and defends itself, it should be a delicacy of the normal functioning of our genes. (I) These units very complex adds Professor Israel "Who are

¹ http://www.kva.se/KVA_Root/eng/contact/searchcontacts/detail.asp?PersonID=1081, Robert Weinberg Professor Member of the Academy Elected as number 1135

² Dr Ali KILIC, Sur le Cancer et Sur la douleur,in www.pen-kurde.org 6 juin 2009

thousands in each of our chromosomes, whose role as a first approximation, to make each of the cell where they are, a protein, and each protéineremplit a particular and specific." (ibid.). Specialists the biology of cancer, insists in a first step on "the normal functioning of the genome" according to them, "one can say that cancers are abnormal functioning of genomes, dukes or inappropriate al'expression of a gene repressor or more, stupid is accidental mutation of a gene and thus its product. The combination of these three mechanisms causing these molecular alterations of certain genes themselves or junctions between molecular certain genes are at the root of all cancers (2). The question that arises is this knowledge, how can we explain change you into the infinite dialectic of genes, in contradiction of the normal operation of the passage has the status of abnormal function in the "genome stability and integrity of the particularly complex genome?

Without addressing methodological issues, Prof. Israel "first studied the biology of cancer and epidemiology, current treatments and resources. But the issue of cancer has not been resolved and it is the task of the whole science. Car this problem is how a normal cell becomes a cancer cell? What is your nature of these cells? How a normal cell becomes cancerous How life gave way to death: Contrary to the idea of Freud, - <Si vis vitam mortem para "if you want to live prepare to die - the science of ways to know the origins of cancer overcome the epistemological obstacles and how lucrétienne and Epicurean. Indeed, ilya a truth in the world is death. At the philosophical and medical approaches to death varied.

In the Preface of the Biology of Cancer 18 new directions in cancer biology, about the epistemology of a tumor and new knowledge has been asked to help "better understand the genesis of certain tumors and to level the molecular part of the inné and aequi: the case of trétnoblastome.

Created in early 2007 on the central site of the Paris Institut Curie Unit Genetics and biology of cancers consists of 6 teams studying aspects of tumor development. Two main strategies are developed within the unit: one is the direct study of human malignant tumors to better understand their pathophysiological mechanisms, the other strategy uses experimental models (cells or animals) to address specific aspects of oncogenesis. The various models and the themes and methods of the various teams allow an integrated approach to study the cellular and genetic origin of tumor development.

The unit Genetics and biology of cancer using a large number of genetic methods including microarray analysis and genotyping to characterize human tumors, as well as molecular biology, cell biology and transgenic approaches to create models and study them.

The large medal, established in 1997, includes 122 foundations of the Academy of Sciences and the Institute de France ³ The medal is a great distinction awarded annually, alternately in the disciplines within each division of the Academy, to a french or foreign scientist who contributed to the development of science in a decisive manner, both the originality of its personal research and by their international influence and the influence it has had challenging by creating a true school of research. The work undertaken will question an important area of basic research and provided a new light and a greater understanding of discipline discussed. This year the large medal is awarded by the Academy of Sciences, Robert A. Weinberg, professor of biology at Massachusetts Institute of Technology (MIT) in Cambridge (United States), for all his work that has revolutionized the understanding of the molecular basis of cancer.⁴ Robert A. Weinberg has made several major discoveries that have

³ Fondations de la Grande Médaille de l'Académie des sciences

Alhumbert (1817) Ancel (1908) Argut (1902) Barbier (1832) Barbier-Muret (1907) Bariot-Faynot (1923) Henri Bazin (1923) Bellion (1881) Aimé Berthé (1895) Bigot de Morogues (1834) Boileau (1882) André-C. Bonnet (1910) Bordin (1835) Charles Bouchard (1917) Jacques Bourcart (1962) Caméré (1904) Carré-Bessault (1951) assé et Fleury (1916) Cesconi (1928) Chaussier (1863) Crépet (1923) Cuvier (1839) Da Gama Machado (1852) Damoiseau (1863) Danton (1903) Debrousse (1899) Delalande-Guérineau (1872) Delesse (1883) Demolombe (1908) Léon Denis (1923) Desmazières (1855) Du Hamel de Breuil (1920) Du Moncel (1880) Eugène et Amélie Dupuis (1930) Dugate (1872) Alfred Dutens (1914) Fanny Emden (1910) Estrade-Delcros (1876) Général Ferrié (1936) Clément Félix (1917) Fonds des laboratoires (1923) Fonds des périodiques Fontannes (1883) Forestier (1914) Fourneyron (1867) Francoeur (1882) Charles Frémont (1931) Lsgot (1885) Paul Gallet (1941) Gas (1895) Gay (1873) Gegner (1868) Henry Giffard (1881) Veuve Gibou (1928) Charles-Adam Girard (1926) Girbal-Barral (1930) Godard (1862) Costantino Gorini (1939-1940) Veuve Guilhot-Driot (1925) Edmond Hébert (1891) François Hébert (1891) Helbronner-Fould (1927) Hély d'Oïssel (1895) Hirn (1889) Hughes (1893) Isbèque (1887) Antoinette Janssen (1921) Baron de Joest (1880) Paul Jousselin (1945) Kastner-Boursault (1880) Joseph Labbé (1908) La Caille (1921) Pierre Lafitte (1924) de La Fons Mélicoq (1864) de Lafontaine de Coincy (1903) Lalande (1802) Lallemand (1852) Lannelongue (1903) Baron Larrey (1896) Aimé Laussedat (1913) Henry Le Chatelier (1922) Leroy-Drouault (1930) Lonchamp (1896) Marquet (1923) Martin-Damourette (1883) Massin (1923) Mège (1869) Millet-Ronssin (1925) Montagne (1862) Charles de Mosenthal (1931) Général Muteau (1927) Ozouff (1913) Amiral Pâris (1889) Parkin (1885) Philipeaux (1888) Pierson-Perrin (1898) Gaston Planté (1889) Ployer (1922) Poirier (1929) Poncelet (1868) . de Pontecoulant (1901) Jérôme Pontü (1879) Pouchard (1924) Pourat (1876) Victor Raulin (1905) Henriette Régnier (1932) Jean Reynaud (1878) Roberge (1913) Rochat-Juliard (1944) Gustave Roux (1911) Jean de Rufz de Lavison (1912) Saintour (1887) Savigny-Letellier (1856) Schutzenberger (1948) Serres (1868) Tchihatchef (1875) Jean Thore (1863) Trappier (1922) Trémont (1847) Vaillant (1872) Benjamin Valz (1874) Henry Wilde (1897)

⁴ Mechanism of activation of a human oncogene Clifford J. Tabin^{*}, Scott M. Bradley^{*}, Cornelia I. Bargmann^{*}, Robert A. Weinberg^{*}, Alex G. Papageorge[†], Edward M. Scolnick[‡], Ravi Dhar[§], Douglas R. Lowy[§] & Esther H. Chang[§]

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2. [†]Merck Laboratories, West Point, Pennsylvania 19486, USA
3. [§]Laboratories of Molecular Virology and Dermatology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205, USA
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Abstract

The oncogene of the human EJ bladder carcinoma cell lines arose via alteration of a cellular proto-oncogene. Experiments are presented that localize the genetic lesion that led to activation of the oncogene. The lesion has no affect on levels of expression of the oncogene. Instead, it affects the structure of the oncogene-encoded protein.

helped to decipher the deregulation of cellular processes that lead to malignant transformation of cells. It showed that chemotherapy-induced carcinogenesis and spontaneous is associated with mutations in genes called proto-oncogenes such as ras gene and tumor⁵ suppressor genes, such as the Rb gene. He developed an experimental protocol for the conversion of several cell types in human tumor cells and thus revealed that the cancerous transformation requires several steps, at least five in humans. One is the continued activity of telomerase, which has isolated the gene in humans. His work can develop new diagnostics and new treatments more targeted, less toxic and more effective. Robert A. Weinberg was also concerned the training of young doctors and researchers and understanding of this disease by the public.⁶

⁵ 5Creation of human tumour cells with defined genetic elements William C. Hahn^{1,2,3}, Christopher M. Counter^{4,3}, Ante S. Lundberg^{1,2}, Roderick L. Beijersbergen¹, Mary W. Brooks¹ & Robert A. Weinberg¹

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4. These authors contributed equally to this work.

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Abstract

During malignant transformation, cancer cells acquire genetic mutations that override the normal mechanisms controlling cellular proliferation. Primary rodent cells are efficiently converted into tumorigenic cells by the coexpression of cooperating oncogenes^{1,2}. However, similar experiments with human cells have consistently failed to yield tumorigenic transformants^{3-4,5}, indicating a fundamental difference in the biology of human and rodent cells. The few reported successes in the creation of human tumour cells have depended on the use of chemical or physical agents to achieve immortalization⁶, the selection of rare, spontaneously arising immortalized cells^{7,8,9,10}, or the use of an entire viral genome¹¹. We show here that the ectopic expression of the telomerase catalytic subunit (*hTERT*)¹² in combination with two oncogenes (the simian virus 40 large-T oncoprotein and an oncogenic allele of *H-ras*) results in direct tumorigenic conversion of normal human epithelial and fibroblast cells. These results demonstrate that disruption of the intracellular pathways regulated by large-T, oncogenic *ras* and telomerase suffices to create a human tumor cell.

⁶ **The Biology of Cancer Robert A. Weinberg**, Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, USA

The Biology of Cancer is a new textbook for undergraduate and graduate biology students as well as medical students studying the molecular and cellular bases of cancer. The book presents the principles of cancer biology in an organized, cogent, and in-depth manner. The clarity of writing and the lucid full-color art program make the book accessible and engaging. The information unfolds through the presentation of key experiments which give readers a sense of discovery and provide insights into the conceptual foundation underlying modern cancer biology.

⁷ Robert A. Weinberg

one of the concerns scientists Robert A Weinberg is research into the biology of cancer. According to the press release of the Academy of Sciences

Great Medal: the highest award of the Academy of Sciences awarded annually

Since its inception in 1997 the Grand Medal of the Academy of Science is awarded annually to a scientist, french or foreign, having contributed to the development of science in a decisive manner, both in the originality of his own research that their radiation international and stimulating influence he has had in creating a true school of research.

The Biology of Cancer synthesizes the findings of three decades of recent cancer research and proposes a conceptual framework from which to teach about these discoveries. It provides the necessary structure, organization, and content for a course on cancer biology for advanced undergraduates and beginning doctoral students. The book is comprehensive and offers many pedagogical features to assist teaching and learning. The book includes many recent and topical references to empower the student to move directly into the primary research literature.

The text is up-to-date and provides current information on topics such as tumor stem cells and recently introduced chemotherapeutics. State-of-the-art techniques are discussed throughout. Modern biomedical research is explored, helping readers to hone their analytical abilities and to assimilate and think clearly about complex biological processes. The Biology of Cancer provides insights into many interfaces between cancer research and the fields of immunology and developmental biology.

The book is extensively illustrated with carefully chosen schematic drawings, micrographs, computer-generated models and graphs. The exceptional full-color art program contains many images from recent research literature. The pieces were chosen to support and clarify the concepts, as well as to supply additional interest.

Besides its value as a textbook, The Biology of Cancer will be a useful reference for individuals working in biomedical laboratories, and for clinicians.

7 Mechanism of activation of a human oncogene Clifford J. Tabin^{*}, Scott M. Bradley^{*}, Cornelia I. Bargmann^{*}, Robert A. Weinberg^{*}, Alex G. Papageorge[†], Edward M. Scolnick[‡], Ravi Dhar[§], Douglas R. Lowy[§] & Esther H. Chang[§]

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The oncogene of the human EJ bladder carcinoma cell lines arose via alteration of a cellular proto-oncogene. Experiments are presented that localize the genetic lesion that led to activation of the oncogene. The lesion has no affect on levels of expression of the oncogene. Instead, it affects the structure of the oncogene-encoded protein.

This medal is awarded alternately in the disciplines of both divisions of the Academy: mathematics and physical sciences, sciences of the universe, and their applications (Division I) on the one hand and chemical sciences, biological and medical and applications (Division II), on the other.

In 2008, the Grand Medal was awarded in Division I to Susan Solomon

Great Medal of the Academy of Sciences will be awarded to Robert Weinberg under the dome of the Institut de France at a ceremony for the awards, on Tuesday 13 October or Tuesday 24 November 2009.

Dr Ali KILIC, Paris le 30 juin 2009

Bibliography

Robert A. Weinberg, PhD

A Founding Member of Whitehead Institute, Robert A. Weinberg is a pioneer in cancer research most widely known for his discoveries of the first human oncogene—a gene that causes normal cells to form tumors—and the first tumor suppressor gene.

His lab now primarily focuses on two areas: the interactions between epithelial and stromal cells (the two major types of cells found in mammalian tissue) that produce carcinomas and the processes by which cancer cells invade and metastasize.

Epithelial and stromal cells. Many mammalian tissues are formed from distinct epithelial and stromal cell layers. Often, a tumor that forms in an epithelial tissue layer must recruit stromal cells in order to become a carcinoma. Weinberg's lab is exploring the molecular process by which this recruitment occurs. In addition, his lab has been investigating a signaling pathway operating within epithelial cells that enables them to release signals that stimulate blood vessel growth in nearby stromal cells.

Invasion and metastasis. Weinberg's lab is focusing on a small group of transcription factors—proteins that control gene expression. These proteins, which are typically involved in embryogenesis, may contribute to cancer cells' ability to disseminate to distant sites in the body where they may form metastases. Weinberg and his team are examining mechanisms by which tumors

can reactivate the properties of these proteins that are active during embryonic development and exploit these transcription factors to execute various steps of the “invasion-metastasis” cascade—the sequence of steps that enables primary tumor cells to disseminate through the body and seed cancer cells. Additionally, the scientists are studying the role of cancer stem cells—the self-renewing, tumor-seeding cells that have been found in a number of solid tumors in the past few years. In 2008, Weinberg lab investigators reported a finding that brings together these two research themes: cancer cells induced to follow one of these embryonic pathways gain many of the properties of adult stem cells.

Weinberg, who received his PhD in biology from Massachusetts Institute of Technology in 1969, has held research positions at the Weizmann Institute and the Salk Institute. In 1982, Weinberg helped found Whitehead Institute, joined the faculty as a professor of biology at MIT, and published his landmark paper "Mechanism of Activation of a Human Oncogene" in the journal *Nature*. In 1999, another major paper, "Creation of Human Tumor Cells with Defined Genetic Elements," was also published in *Nature*.

Selected Publications

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