Nobel price in medicine 2008

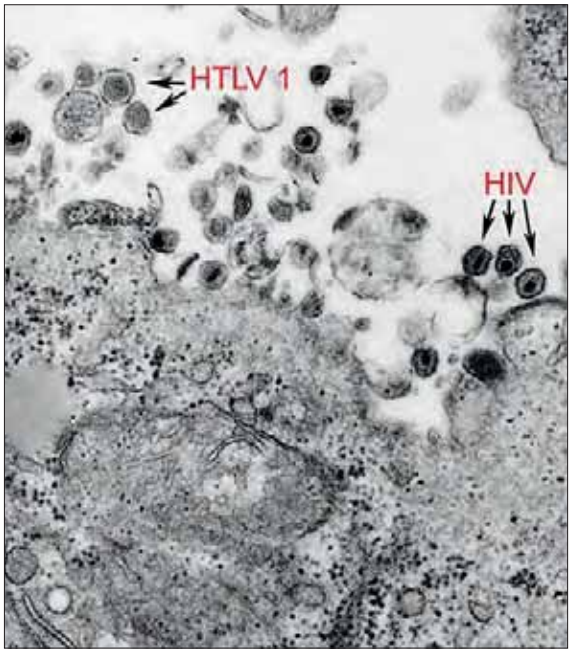
Discovery of HIV

Following medical reports of a novel immunodeficiency syndrome in 1981, the search for a causative agent was on. Françoise Barré-Sinoussi and Luc Montagnier isolated and cultured lymph node cells from patients that had swollen lymph nodes characteristic of the early stage of acquired immune deficiency. They detected activity of the retroviral enzyme reverse transcriptase, a direct sign of retrovirus replication. They also found retroviral particles budding from the infected cells. Isolated virus infected and killed lymphocytes from both diseased and healthy donors, and reacted with antibodies from infected patients. In contrast to previously characterized human oncogenic retroviruses, the novel retrovirus they had discovered, now known as human immunodeficiency virus (HIV) did not induce uncontrolled cell growth.

Instead, the virus required cell activation for replication and mediated cell fusion of T lymphocytes. This partly explained how HIV impairs the immune system since the T cells are essential for immune defense. By 1984, Barré-Sinoussi and Montagnier had obtained several isolates of the novel human retrovirus, which they identified as a lentivirus, from sexually infected individuals, hemophiliacs, mother to infant transmissions and transfused patients. The significance of their achievements should be viewed in the context of a global ubiquitous epidemic affecting close to 1% of the population.

Importance of the HIV discovery

Soon after the discovery of the virus, several groups contributed to the definitive demonstration of HIV as the cause of acquired human immunodeficiency syndrome (AIDS). Barré-Sinoussi and Montagnier's discovery made rapid cloning of the HIV-1 genome possible. This has allowed identification of important details in its replication cycle and how the virus interacts with its host.



The human T-cell leukemia type-1 virus (HTLV-1), and the human immunodeficiency virus (HIV).

Furthermore, it led to development of methods to diagnose infected patients and to screen blood products, which has limited the spread of the pandemic. The unprecedented development of several classes of new antiviral drugs is also a result of knowledge of the details of the viral replication cycle. The combination of prevention and treatment has substantially decreased spread of the disease and dramatically increased life expectancy among treated patients. The cloning of HIV enabled studies of its origin and evolution. The virus was probably passed to humans from chimpanzees in West Africa early in the 20th century, but it is still unclear why the epidemic spread so dramatically from 1970 and onwards.

Françoise Barré-Sinoussi, born 1947 in France, French citizen, PhD in virology, Institut Pasteur, Garches, France. Professor and Director, Regulation of Retroviral Infections Unit, Virology Department, Institut Pasteur, Paris, France.

Luc Montagnier, born 1932 in France, French citizen, PhD in virology, University of Paris, Paris, France. Professor emeritus and Director, World Foundation for AIDS Research and Prevention, Paris, France.

Identification of virus-host interactions has provided information on how HIV evades the host immune system by impairing lymphocyte function, by constantly changing and by hiding its genome in the host lymphocyte DNA, making its eradication in the infected host difficult even after long-term antiviral treatment. Extensive knowledge about this unique viral host interactions has, however, generated results that can provide ideas for future vaccine development as well as for therapeutic approaches targeting viral latency.

HIV has generated a novel pandemic. Never before has science and medicine been so quick to discover, identify the origin, and provide treatment for a new disease entity. Successful antiretroviral therapy results in life expectancies for persons with HIV infection now reaching levels similar to those of uninfected people.

Lazar Popović

Human papillomaviruses as important factor in infected-induced malignancies

On October 6, 2008, the Nobel Prize was divided equally between: **HARALD ZUR HAUSEN** for his discovery of human papilloma viruses causing cervical cancer and: **FRANCOISE BARRE SINOUSSI**, and **LUC MONTAGNIER** for their discovery of human immunodeficiency virus.

Professor zur Hausen was born, on March 11, 1936 in Gelsenkirchen, Germany. He Graduated in Medicine and M.D. University of Düsseldorf, in December 1960. He worked as postdoc at the Institute of Microbiology in Düsseldorf, then as Assistant

Harald zur Hausen

Professor in the Virus Laboratories of the Children's Hospital in Philadelphia, senior scientist at the Institute of Virology of the University of Würzburg, and as Chairman and Professor of Virology at the University of Erlangen-Nürnberg. In 1977, he moved to a similar position to the University of Freiburg. From 1983 until 2003, he was appointed as Scientific Director of the Deutsches Krebsforschungszentrum (German Cancer Research Center) in Heidelberg.

Professor zur Hausen has a special interest in infection-induced malignancies. He showed the role of papillomaviruses in cervical cancer and discovered a larger number of novel virus types.

He received numerous national and international awards, including the Robert-Koch-Prize, the Charles S. Mott Prize of the General Motors Cancer Research Foundation, and the Federation of the European Cancer Societies Clinical Research Award, the William B. Coley Award for Distinguished Research in Basic Immunology of the Cancer Research Institute, the Prince Mahidol-Award, and the Warren Alpert-Prize of the Harvard University.

Harald zur Hausen holds seven Honorary Degrees. He is an elected member of various academies, such as LEOPOLDINA, Academia Europaea, Heidelberg Academy of Sciences, Polish Academy of Sciences, Institute of Medicine of the National Academy of Sciences (USA), and of research organizations including EMBO and HUGO.

HPV

Papillomaviruses are small DNA viruses that infect epithelial tissues. Whether cutaneous or mucosal,

the more than 100 types of HPV described have in common a circular DNA genome of about 8000 base pairs. These small genomes are organized into an early, a late, and a long control region. The products of 2 genes from the early control region, genes *E6* and *E7*, are essential in the HPV-induced processes of cellular transformation and immortalization, and 2 genes from the late control region, genes L1 and L2, encode the viral capsid proteins.

Carcinoma of the uterine cervix is the sixth most common cancer among women worldwide, with very high mortality rates in developing countries. It was observed more than 20 years ago that some types of HPV were more frequent in malignant than in benign lesions, and infection with high-risk types of HPV is now considered the major risk factor for the development of cancer of the uterine cervix. Table 1.

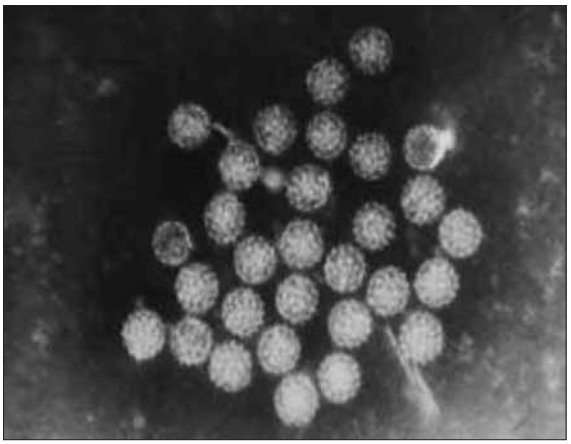


Figure 1.The general organization of a papillomavirus genome and HPV by electrophotomicrography (Thanks to Prof. Dr. M. Janicek).

Table 1. Main low- and high-risk types of HPV

High-risk types:	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Low-risk types:	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108
Potentially high-risk types:	26, 53, 66

REAFERENCES

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Aljoša Mandić

A therapeutic ovarian cancer vaccine – a new approach of preventing ovarian cancer relaps-experimental phase

Starting with first decade of this century, modern biological and immunological science has pointed to important role of an immune system and effect of that system on malignant cells. Developing an immunology many of studies have shown effects of immune system on malignant cells and expressed antigens.

Today around the globe, many studies investigate effect of some therapeutic vaccines in some types of malignant cells.

Study by Kunle Odunsi et al., Roswell Park Cancer Institute, Buffalo, New York, USA, showed effects of vaccine based on NY-ESO-1, a "cancer testis" antigen in preventing the recurrence of ovarian cancer.

NY-ESO-1 is a „cancer-testis" antigen expressed in epithelial ovarian cancer (EOC) and is among the most immunogenic tumor antigens defined to date.

Author's previous study point to the role of presence of intraepithelial $CD8^+$-infiltrating T lymphocytes in tumors that was associated with improved survival of patients with the disease. The NY-ESO-1 peptide epitope, $ESO_{157–170}$, is recognized by HLA-DP4-restricted $CD4^+$ T cells and HLA-A2- and A24-restricted $CD8^+$ T cells. To test whether providing cognate helper $CD4^+$ T cells would enhance the antitumor immune response, Odunsi et al., conducted a phase I clinical trial of immunization with $ESO_{157–170}$ mixed with incomplete Freund's adjuvant (Montanide ISA51) in 18 HLA-$DP4^+$ EOC patients with minimal disease burden. NY-ESO-1-specific Ab responses and/or specific HLA-A2-restricted $CD8^+$ and HLA-DP4-restricted $CD4^+$ T cell responses were induced by a course of at least five vaccinations at three weekly intervals in a high proportion of patients.

Eighteen EOC patients (HLADPB1*0401 or *0402) with NY-ESO-1-expressing tumors who had completed adjuvant chemotherapy for primary or recurrent disease were entered into the trial.

Vaccine-induced $CD8^+$ and $CD4^+$ T cell clones were shown to recognize NY-ESO-1-expressing tumor targets. T cell receptor analysis indicated that tumor-recognizing $CD4^+$ T cell clones were structurally distinct from non-tumor-recognizing clones. Long-lived and functional vaccine-elicited $CD8^+$ and $CD4^+$ T cells were detectable in some patients up to 12 months after immunization.

No major (more than grade II) treatment-related toxicity was observed in any patient. Transient injection site pain was seen in all patients, and systemic hypersensitivity reactions were not observed.

Authors point that these results confirm the paradigm that the provision of cognate $CD4^+$ T cell help is important for **cancer vaccine** design and provides the rationale for a phase II study design using $ESO_{157–170}$ epitope or the full-length NY-ESO-1 protein for immunotherapy in patients with EOC.

The phase I/II study recently reviewed and cleared by the U.S. Food and Drug Administration (FDA) will evaluate the safety and efficacy of the unique ovarian cancer vaccine therapy for up to 42 patients with chemotherapy-resistant, advanced stage ovarian cancer. If they continue to see success, researchers say the vaccine may be on the market in the next five years. Right now, they are only testing it on ovarian cancer, but scientists say it may also show promise in other forms - like prostate, breast and colon cancers as well.

REFERENCE

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Aljoša Mandić

Vitamine C supplement decreased effects of some anti-cancer drugs?

Use of vitamin C during cancer treatment has been controversial. Some studies have suggested that because vitamin C is an antioxidant it might be beneficial to cancer patients. Heaney and his colleagues tested a wide variety of chemotherapy drugs – those that produce reactive oxygen and those that work in other ways – on cancer cells in the laboratory, that were pretreated with dehydroascorbic acid (DHA), the form that ascorbic acid (vitamin C) takes to enter cells.

The therapeutic efficacy of the widely used antineoplastic drugs doxorubicin, cisplatin, vincristine, methotrexate, and imatinib were compared in leukemia (K562) and lymphoma (RL) cell lines with and without pretreatment with dehydroascorbic acid, the commonly transported form of vitamin C. The effect of vitamin C on viability, clonogenicity, apoptosis, P-glycoprotein, reactive oxygen species (ROS), and mitochondrial membrane potential was determined. Pretreatment with vitamin C caused a dose-dependent attenuation of cytotoxicity, as measured by trypan blue exclusion and colony formation after treatment with all antineoplastic agents tested. Vitamin C given before doxorubicin treatment led to a substantial reduction of therapeutic efficacy in mice with RL cell–derived xenogeneic tumors. Vitamin C treatment led to a dose-dependent decrease in apoptosis in cells treated with the antineoplastic agents that was not due to up-regulation of P-glycoprotein or vitamin C retention modulated by antineoplastics. Vitamin C had only modest effects on intracellular ROS and a more general cytoprotective profile than *N*-acetylcysteine, suggesting a mechanism of action that is not mediated by ROS. All antineoplastic agents tested caused mitochondrial membrane depolarization that was inhibited by vitamin C. These findings indicate that vitamin C given before mechanistically dissimilar antineoplastic agents antagonizes therapeutic efficacy in a model of human hematopoietic cancers by preserving mitochondrial membrane potential.

Researchers at Memorial Sloan-Kettering Cancer Center have long been researching the connection between vitamin C and cancer therapy, and these new findings expand on their earlier observation that vitamin C seems to accumulate within cancer cells more than in normal cells.

They found that a DHA as the form of vitamin C that gets into cells, and that the tumor microenvironment allows cancer cells to convert more vitamin C into DHA. DHA is converted back into ascorbic acid inside a tumor cell, and it is trapped there and so is available to safeguard the cell.

As ascorbic acid provides more protection for the mitochondria and extends cell life that, also influence in elimination of the cancer cell.

These results support the hypothesis that vitamin C supplementation during cancer treatment may detrimentally affect therapeutic response.

REFERENCE

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Aljoša Mandić

The 45th Annual Meeting of Oncology Section – Serbian Medical Association and the 22nd Annual Meeting of Oncology Nurses of Republic of Serbia

The 45th Annual Meeting of Oncology Section – Serbian Medical Association and the 22nd Annual Meeting of Oncology Nurses of Republic of Serbia was held in Belgrade, Nov. 13-15, 2008. There were more than 300 participants from all oncology centers in Serbia.

Renowned scientists from Belgium, Greece, and Serbia gave plenary lectures concerning biological markers in breast and colorectal cancer, and increased prevalence of malignant diseases.

The main topic of this meeting was breast cancer. All aspects were discussed – basic research, epidemiology, early breast cancer, locally advanced breast cancer and metastatic disease, and various modalities of therapy. Pregnancy after treatment of early breast cancer was the topic, which attracted the attention of many oncologists. A symposium with cooperation with UMOS was dedicated to the side effect of chemotherapy of this disease.

The Academy of Medical Sciences of the Serbian Medical Association organized a meeting on the same topic; for this occasion, a monograph was published and presented to all attendants.

Two special sessions were organized: ASCO 2008 highlights and Informatics in Biomedicine: E-library and Open Access. Alternative medicine was discussed in Patients forum.

Two new research projects - Promotion of biomedical science and technology aimed at health improvement in Serbia and Molecular biomarkers of the growth invasiveness and metastases of breast cancer – were presented and discussed.

Three Satellite symposiums were held: Nexavar new molecular therapy in kidney and liver carcinoma – (Bayer), Anti-angiogenesis: new concept in metastatic breast cancer (Roche), and OROS technology – future of oral therapy (Janssen-Cilag).

The nurses program included Novelties in Health care, diagnostics and treatment of breast cancer, psychosocial rehabilitation of cancer patients, Experiences of medical nurses/technicians in clinical oncology, and Reports and presentations from scientific meetings.

After scientific program the general Assembly of the Cancerologic Section of the Serbian Medical Association was held, the new president of which was elected (Dr. Svetislav Jelić).

Jasmina Mladenović
Ljiljana Vučković-Dekić