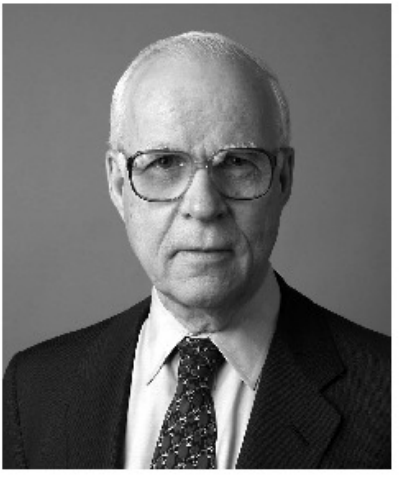
Laudatio
Lloyd J. Old, M. D.

Dr. Lloyd J. Old is internationally recognized as one of the founders and standard-bearers of the field of tumor immunology. When Dr. Old began his career in 1958, tumor immunology was in its infancy. However, pioneering and systematic research has built the field to a point where there is now an understanding of tumor immunology at the cellular and molecular level, and cancer immunotherapies are emerging as potentially the most significant

advances in cancer therapy since the development of the first chemotherapies. Many of the seminal findings in this field have been contributed by Dr. Old, his colleagues and his students.

His research over a period of nearly fifty years - from demonstrating that cancers in mice and humans are recognized by the immune system, to defining the antigenic targets that elicit this recognition - has directly enabled the rational design and development of tumor-specific vaccines and targeted antibodies. He has shown tireless dedication to developing a field rather than pursuing a single avenue of research, and he has been a devoted and selfless mentor to hundreds of young researchers for over four decades. Most importantly for the benefit of mankind, his vision and leadership have brought basic and clinical investigators together, across institutional and international borders, to take tumor immunology from animal models into clinical research and the development of promising new cancer therapies.

Dr. Old's contributions to science extend far beyond his own research interests. As Director of the international Ludwig Institute for Cancer Research for 17 years, Scientific Director of the Cancer Research Institute (CRI) for 30 years, and his previous appointment as Associate Director of Research at Memorial Sloan-Kettering Cancer Center for 10 years, Dr. Old has guided the scientific vision of several institutions and the training and development of generations of young scientists in many fields. In particular, in his role as Scientific Director of CRI, he was the driving force behind establishing research fellowships for young investigators studying the fundamentals of tumor immunology, and developing the internationally acclaimed CRI Symposium Series. Dr. Old also forged the unique partnership between the Ludwig Institute and the CRI to create the Cancer Vaccine Collaborative (CVC), a global effort to construct effective cancer vaccines. Dr. Old is a member of multiple scientific and medical societies, including the National Academy of Sciences, the Institute of Medicine, and the American Academy of Arts and Sciences. He has been the recipient of many honors and awards, including the Robert Koch Prize, the New York Academy of Medicine Medal, the President's Medal of Johns Hopkins University, the Harvey Lecture, the G.H.A. Clowes Memorial Lecture, and Honorary Degrees from the Karolinska Institute, University of Lausanne, and University College London.



Charles Rodolphe Brupbacher Foundation

The
Charles Rodolphe Brupbacher Prize
for Cancer Research 2007
is awarded to

Dr. Lloyd J. Old

for his lifetime contributions
to the field of
Cancer Immunology

The President
of the Foundation

Mrs. Frédérique Brupbacher

The President
of the Scientific Board

Dr. med. Erhart H. Brunner

Curriculum vitae
Lloyd John Old

Date of Birth: September 23, 1933

Place of Birth: San Francisco, CA

Nationality: United States of America

Office Address: Ludwig Institute for Cancer Research
605 Third Avenue
New York, NY 10158
Telephone: (212) 450-1510
Facsimile: (212) 450-1515
E-mail: lold@licr.org

Education:

1955 B. A. (Biology)
University of California
Berkeley, CA

1958 M. D.
University of California School of Medicine,
San Francisco, CA

Postdoctoral Training:

1958-59 Sloan-Kettering Institute for Cancer Research
Research Fellow

Positions and Appointments:

	Cornell University Graduate School of Medical Sciences
1960-62	Research Associate in Biology
1962-65	Assistant Professor of Biology
1966-69	Associate Professor of Biology
1969-81	Professor of Biology
1981-present	Professor of Immunology
	Sloan-Kettering Institute for Cancer Research
1959-60	Research Associate
1960-64	Associate
1964-67	Associate Member
1967-present	Member
	Memorial Hospital for Cancer and Allied Diseases
1973-83	Associate Director of Research
1984-95	Attending Immunologist
1972	Acting Associate Director for Research Planning
1973-76	Vice-President and Associate Director
1976-83	Vice-President and Associate Director for Scientific Development
	Memorial Sloan-Kettering Cancer Center
1973-83	Associate Director of Research,
1983-present	Member and Incumbent, William E. Snee Chair of Cancer Immunology

	Ludwig Institute for Cancer Research, Inc.
1971-86	Member and Scientific Director, Emeritus Scientific Committee
1988-present	Member and Chairman, Scientific Committee
1988-2005	Director
1989-present	Member, Board of Directors
1995-2004	Chief Executive Officer
2001 - present	Trustee, LICR Charitable Trust
2001 – present	Trustee, Virginia & D.K. Ludwig Fund for Cancer Research
2005	Vice Chairman, Board of Directors
2006-present	Chairman, Board of Directors
	Ludwig Institute for Cancer Research, New York Branch at Memorial Sloan-Kettering Cancer Center
1990-present	Director
	Columbia University, New York
2004	Adjunct Professor of Medicine
	New York University, New York
2004	Adjunct Professor of Medicine

Scientific and Medical Societies:

1962 American Association for Cancer Research
1962 New York Academy of Sciences
1963 Reticuloendothelial Society
1963 Society of Experimental Biology and Medicine
1969 American Association for the Advancement of Science
1971 American Association of Immunologists

Honors and Awards:

1955 Phi Beta Kappa
1955 Sigma Xi
1957 Roche Award
1958 Alpha Omega Alpha
1962 Alfred P. Sloan Award in Cancer Research
1970 Lucy Wortham James Award, James Ewing Society
1972 Lecturer, Harvey Society
1972 Louis Gross Award
1974 Member, Institute of Medicine, National Academy of Sciences
1975 Founder of Tumor Immunology Award, Cancer Research Institute
1976 Member, American Academy of Arts and Sciences
1976 Rabbi Shai Shacknai Memorial Award
1978 Member, National Academy of Sciences
1978 Research Recognition Award, Noble Foundation
1980 G.H.A. Clowes Memorial Lecturer
1981 Robert Roesler de Villiers Award
1985 New York Academy of Medicine Medal
1986 Honorary member, Japanese Cancer Association
1990 Robert Koch Prize, Robert Koch Foundation
1994 Honorary Doctor of Medicine, Karolinska Institute
1995 Honorary Doctor of Medicine, University of Lausanne
1997 Honorary Doctor of Science (Medicine),
University College London,
2004 President's Medal, Johns Hopkins University
2004 Dean's Award, Stanford University School of Medicine

Other Activities:

- General Motors Cancer Research Foundation Visiting Professor of Clinical Investigation, Dana-Farber Cancer Institute, and Visiting Professor of Pathology, Harvard Medical School, 1986
- Foreign Adjunct Professor, Faculty of Medicine, Karolinska Institute, 1994-present
- National Cancer Institute, National Institutes of Health Consultant, 1967-70
- Member, Developmental Research Working Group, 1969
- Member, Special Virus Cancer Program, Immunology Group, 1970
- Member, Virus Cancer Program Advisory Committee, 1975-78
- Member, Board of Scientific Counselors, Division of Cancer Cause and Prevention, 1978-81

	Cancer Research Institute
1970	Associate Medical Director
1971-74	Medical Director
1974-present	Director, Scientific Advisory Council
	Leukemia Society of America
1970-73	Member, Board of Trustees,
1970-73	Member, Medical and Scientific Advisory Board,
	Jane Coffin Childs Memorial Fund for Medical Research
1970-75	Member, Scientific Advisory Board,
	Public Health Research Institute of the City of New York
1977-80	Member, Research Council,
1979-89	Member, Board of Directors, ;
1984-89	Vice-Chairman, Executive Committee,
	American Association for Cancer Research
1980-83	Member, Board of Directors

Editorial Activities

- Editorial Advisory Board, Cancer Research, 1967-70
- Editorial Advisory Board, Cancer, 1968-71
- Advisory Editor, The Journal of Experimental Medicine, 1971-76; 1990-95
- Editorial Board, Recent Results in Cancer Research, 1972
- Advisory Editor, Progress in Surface and Membrane Science, 1972-74
- Associate Editor, Virology, 1972-74
- Editor, Immunobiology, 1987-present
- Section Editor, Current Opinion in Immunology, 1991-present
- Editorial Advisory Board, Oncology Research, 1992-present
- Editor, Cancer Immunity, 2001 - present

Contributions to the Field of Cancer Immunology

Lloyd J. Old, M.D.

Lloyd Old's first publication in Nature in 1959 with Baruj Benaceraaf introduced BCG, the tuberculosis vaccine, into experimental cancer research as a way to stimulate resistance to tumor growth (1). BCG today is a first line treatment for in-situ bladder cancer. This early work inaugurated a 5 decade focus by Dr. Old and his colleagues on the three dominant questions of cancer immunology – 1. Does cancer elicit immune recognition in the host of origin? 2. If so, what are the antigenic targets of the immune response and, 3. How can immune resistance to cancer be strengthened. In addition to pursuing the basis for the BCG-mediated anti-tumor response, Old chose 2 experimental systems in the mouse for detailed immunological analysis – chemically-induced sarcomas and mouse leukemia. The discoveries coming from these early studies in the 1960's and 1970's helped set the subsequent course of the field of tumor immunology and established many of its principles and practices.

The demonstration of tumor-specific rejection antigens in methylcholanthrene (MC)-induced sarcomas by Gross, Foley and Prehn and Mann in the 1950's must be considered the foundation stone for contemporary cancer immunology (2) , and Old and his long term collaborators E. A. Boyse, E. Carswell and E. Stockert initiated a broad survey of the immunogenicity of these tumors, confirming the striking antigenic individuality of each tumor, showing that lymphocytes (not serum) could transfer transplantation resistance, and discovering the aberrant expression of mouse leukemia viruses (MuLV) and their antigens in sarcomas, even in those arising in strains lacking evidence for MuLV (3-5). The first demonstration of p53 and its association with cancer was found by analyzing the serum from mice immunized with MC-induced sarcomas (6), and efforts to characterize the transplantation rejection antigens of MC-induced sarcomas by P. Srivastava led to the discovery that these antigens were carried by gp96, a heat-shock protein (HSP), opening up an understanding of the role of HSPs in immune responses (7). The first cloning of a transplantation rejection antigen of MC-induced sarcomas by H. Shiku and his colleagues showed it to be a mutant form of a signaling molecule (8).

The comprehensive serological analysis of mouse leukemia by Old, Boyse, and Stockert, led to discoveries with impact far beyond tumor immunology. In their work, the cytotoxic assay developed by Peter Gorer coupled with

absorption analysis became a powerful analytical tool for dissecting the antigenic structure of the cell surface. Application of this approach to normal and malignant mouse lymphoid cells led to the discovery of a range of cell surface antigens, including lymphocyte-specific antigens (Ly-2/CD8), leukemia-specific antigens (TL), and MuLV-related antigens (GCSA/GIX), and to the recognition that the cell surface was a highly differentiated structure, far more complex than originally envisioned (9-14). These findings gave rise to the concept of cell surface differentiation antigens, and the reagents generated in these studies inaugurated the era of distinguishing cells by their surface phenotype. With the introduction of the hybridoma technology for generating monoclonal antibodies and the power of flow cytometric techniques, the use of cell surface phenotyping has had a revolutionary impact in the laboratory and clinic, from distinguishing cells by lineage, stage, and functional surface markers, to classifying hematopoietic and other malignancies, to identifying targets for antibody therapy.

These early studies of mouse leukemia also led to another finding with implications far beyond this experimental system. Gorer, the founder of the MHC field and Boyse's mentor, had observed that inbred strains with a high incidence of leukemia shared a common H-2 (now referred to as MHC) type, and this prompted F. Lilly, Boyse and Old to investigate this association in a formal genetic analysis and to discover the first linkage of MHC to a disease state – mouse leukemia (15), a finding that sparked the intense focus of subsequent work on the central role of the MHC in immune responses, in susceptibility to neoplastic and non-neoplastic diseases, and in other physiological process such as olfaction.

The discovery of tumor necrosis factor (TNF) by Old, Carswell and their colleagues in the 1970's came about during their continuing study of the antitumor activity of BCG (16-17). The two cardinal characteristics of TNF – hemorrhagic necrosis of mouse tumors and specific cytotoxic action on transformed cells – provided insight into two well known phenomena in the history of cancer research; the induction of tumor hemorrhage by bacterial liposaccharides, and the beneficial effect of bacterial infection on the course of cancer, which William B. Coley developed into a therapeutic approach with bacterial vaccines (Coley's Toxins). The TNF discovery also added to the growing

realization that many of the body's reactions to infectious agents were mediated by a family of endogenous factors – cytokines and chemokines - that we now know orchestrate the complex events involved in inflammation and immunity. Although the current beneficiaries of therapies targeted at TNF are patients with inflammatory diseases, such as rheumatoid arthritis rather than patients with cancer, there is still hope that TNF or its inhibitors can be fashioned into effective cancer therapies.

One of the most persistent ideas in cancer research is that the immune system protects the body against emergence of mutant cells with the potential of becoming a cancer. Paul Ehrlich argued that cancers would be far more frequent if this were not the case, and L. Thomas and MF and Burnett in the 1950's developed this idea into the cancer immunosurveillance hypothesis. Although very popular for a period, O. Stutman in an extensive series of experiments with immunocompromised nu/nu mice found no evidence to support the hypothesis. As a consequence, the idea of cancer immunosurveillance was essentially abandoned. In experiments carried out to establish the role of TNF in LPS-induced tumor hemorrhagic necrosis, Old and R. Schreiber unexpectedly found that antibody against interferon-γ (IFN-γ) completely abolished tumor regressions following LPS treatment. This led them to examine the basis for this action of IFN-γ on transplantable tumors and then to the role of IFN-γ in the induction of MC-induced tumors. The results with IFN-γ receptor knock-out mice gave clear evidence for the existence of an IFN-γ-dependent surveillance system that protected mice against primary tumor development (18). Extending these studies to RAG mice which lack functional T and B cells, led to the same conclusion – mice with compromised immunity are more susceptible to tumor induction (19). In addition, tumors arising in immune deficient mice are more immunogenic than wild-type tumors, indicating that the immune system edits out the more antigenic tumor cells during tumorogenesis (immunoediting) (20). These results and comparable findings by M. Smyth and his colleagues resurrected the immunosurveillance hypothesis, providing a firm foundation for the field of tumor immunology and for therapies based on immunological principles.

The first attempts by Old and his colleagues to extend their work to human cancer was based on their extensive analysis of mouse leukemia viruses

and mouse mammary tumor viruses and their definition of cell surface antigens and structural components (envelope and group specific antigens) coded for by these viruses. (21) Applying similar serological approaches to the analysis of the Epstein-Barr virus that had been linked to Burkitt's lymphoma led to the unexpected finding that EBV was associated with nasopharyngeal carcinoma, a cancer common in China and areas of Africa. (22)

Old, and his other long-term collaborators, H. F. Oettgen, T. Takahashi, and H. Shiku initiated their major commitment to the study of human cancer in the early 1970's, and because of the experience gained from analyzing cell surface antigens of the mouse, it was logical that the cell surface would be the focus of their search for tumor-specific antigens in humans. Without the benefit of inbred strains, Old and his group had to develop a test system that would exclude alloantibodies and other naturally occurring antibodies that could obscure the definition of tumor specificity. To do so, a system known as autologous typing was established in which the initial serological analysis focused on tumor cells, serum, lymphocytes and normal cells (mainly fibroblasts) obtained from the same patient. In this way, the genetic identity of normal and tumor cells from each patient made possible a test system in humans that reproduced as closely as possible the in vitro systems in inbred mice that permitted tumor specificity analysis. Establishing tumor cell lines was the first challenge, and this restricted the analysis to tumor types that could be relatively easily adapted to growth in vitro – melanoma, renal cancer and glioblastoma. As a consequence of this effort, hundreds of tumor lines were established in Old's laboratory and these have found wide use in cancer research. The serological assays used in this search for tumor-specific antigens were mixed hemadsorption and immune adherence, two powerful and underutilized techniques for the analysis of surface antigens of cells that grow attached to a substrate. Absorption analysis with normal and malignant autologous and allogeneic cells provided exquisite specificity confirmation. A large series of patients were analyzed by autologous typing over a period of 10 years (1972-1982), and three categories of cell surface antigens of human tumors were defined: Class I unique to the autologous tumor, Class II shared with allogeneic tumors, and Class III expressed by both normal and malignant autologous and allogeneic cells (23). Although biochemical characterization of these antigens was limited, a num-

ber of Class II antigens were subsequently identified as gangliosides. Of most importance, this serological analysis provided the most compelling evidence at the time for tumor-specific recognition of human cancers. With the discovery of IL-2 and its use for growing human T cells in vitro, Knuth began to apply the principles of autologous typing and the bank of reagents that had been collected for this purpose to the analysis of T cell recognition of human cancer. In the initial analysis of 14 melanoma patients, 2 patients were found with specific reactivity for autologous tumor cells, one of whom (AV) had an unusually favorable course with metastatic melanoma (24). After Knuth returned to Germany, he established the autologous typing system in his laboratory and continued to search for the rare patient with specific T cell reactivity for autologous tumor. He found one melanoma patient (MZ2) with advanced disease with exceptionally strong tumor-specific reactivity who had experienced tumor regression after immunization with autologous irradiated tumor cells. The next step was to identify the targets recognized by AV and MZ2 T cells, and Old suggested that Knuth contact T. Boon at the Brussels Branch of the Ludwig Institute for Cancer Research. Boon and his group had developed molecular cloning techniques to identify the antigenic targets of T cells in mouse tumor systems, and were beginning to apply these techniques to the identification of human tumor antigens. The collaboration of Boon and Knuth led to the cloning and identification of the first T cell recognized tumor antigens in humans, representing a major landmark in tumor immunology (25,26), and a notable achievement for the autologous typing approach. Cloning of the antigens was facilitated by a technique (TNF release assay) developed by Old and N. Ohta for mouse systems in which release of TNF by T cells could be used to assess specific T cell recognition.

Because many tumors could not be grown in vitro, autologous typing for antibody and T cell reactivity was limited to a very restricted set of tumors. To overcome this and also provide structural information about antigens detected in autologous typing, Pfreundschuh, who had previously worked on autologous typing with Old in New York, developed an approach called SEREX that involved the serological screening of recombinant DNA libraries of human tumors with autologous sera (27). The method proved to be an enormously powerful serological tool to define the specificity of human antibodies to intra-

cellular antigens, a previously impenetrable forest for the cancer serologist. The broad application of SEREX to human cancer, first by Pfreundschuh and his group and then by Old and his colleagues Y. Chen, M. Scanlan, and Y. Obata gave rise to knowledge about a rich array of antigens recognized by the humoral immune system of cancer patients and to a classification system for SEREX defined antigens (28-31). To deal with the avalanche of information coming from SEREX analysis by groups around the world, Old and his colleague V. Jongeneel developed the SEREX databank as a central repository to collect information about SEREX defined antigens, their sequences, their tumor and normal tissue expression, and their immunogenicity (www.cancerimmunity.org/SEREX/).

Several categories of tumor antigens have been recognized by SEREX analysis, including differentiation antigens, mutational antigens, viral antigens, overexpressed antigens, and cancer-testis (CT) antigens (32). Among these, the CT antigens have attracted the most interest because of their highly restricted expression pattern in normal tissues - spermatogonia, oogonia and trophoblast cells- and their frequent expression in a broad array of cancers, as extensively analyzed by A. Jungbluth (33-35). The first CT antigens (MAGE, BAGE, and GAGE) were discovered by Boon and his colleagues as targets of T cells from Knuth's single remarkable patient MZ2. Pfreundschuh and his colleagues discovered SSX-2, and SCP-1, and Chen, Scanlan, and A. Gure discovered NY-ESO-1, CT7, CT10, SSX-1 and 4, among others. A CT database was created by Scanlan (36),and the list of CT antigens continues to grow, currently numbering 87 genes or gene families.

The aberrant expression of gene products normally found only in germ cells and trophoblasts raises the question of what role CT antigens play in cancer cells. In addition to shared expression of CT antigens, cancer cells and gametic cells have many other characteristics in common, including immortality, invasiveness, migratory behavior, immune evasion, and inducing angiogenesis. Old has proposed that cancers acquire many of their malignant traits, including the ability to metastasize, by reactivating the normally silent gametogenic program (37), and Simpson, Old and their colleagues are developing this idea that CT gene products play a central role in tumorgenesis and that they are promising targets for therapeutic intervention (38).

Because of their high degree of specificity for cancer, CT antigens represent ideal targets for cancer vaccine development. NY-ESO-1, the most immunogenic CT antigen found to date (39-42), has been the focus of a major vaccine effort organized and directed by Old as a partnership between the Ludwig Institute for Cancer Research and the Cancer Research Institute – the Cancer Vaccine Collaborative (CVC). The CVC represents a coordinated network of laboratory and clinical scientists at 14 different academic centers around the world with the objective of constructing maximally immunogenic NY-ESO-1 vaccines (43). Phase I trials of NY-ESO-1 peptides (44, 45), protein (46), DNA, viral (47) and bacterial NY-ESO-1 vaccines are being conducted and analyzed at the different sites in Australia, Japan, USA, England, Germany, Switzerland, France and China using standardized immunological monitoring methodologies to assess the comparative immunogenicity of these different vaccines (48). Once immunogenicity has been established, therapeutic endpoints can be rationally assessed, reflecting Old's mantra that "to vaccinate you need to know how to immunize, and to immunize you need to know how to monitor." Prime-boost strategies, polyvalent CT vaccines, and the use of CTLA-4 antibody and other ways to modulate immune regulatory systems that limit tumor immunity are being incorporated into future CVC activities.

With the advent of hybridoma technology and the generation of monoclonal antibodies, the cancer serologist was given a grand opportunity to explore the surface antigenic structure of cancer cells. Old took full advantage of this new technology, and he and his many colleagues conducted the most extensive dissection to date of the cell surface of human cancer with the objective of finding antigens with sufficient tumor specificity to serve as targets for antibody-based therapies. Detailed analysis of the thousands of antibodies generated in their studies led to the discovery of a vast array of new surface antigens expressed by human cancer cells, as well as to antigens selectively expressed on tumor stromal fibroblasts and tumor endothelium. However, even antigens with the greatest specificity for cancer were found to be expressed on a subset of normal cells (differentiation antigens) (49). The most tumor specific of all the antibodies, 806, was directed against an epitope on the EGF receptor that is exposed when the antigen is overexpressed (50, 51). From the large collection of antibodies generated by Old's group, a panel of antibodies with the

greatest cancer restricted specificity were purified for clinical testing, first in a production facility Old established at Memorial Sloan-Kettering Institute and then in a GMP facility established by A. Scott at the Ludwig Institute Branch in Melbourne. The initial aim of these clinical trials was to define the in vivo specificity of trace-labeled antibody, i.e. comparing uptake in tumor and normal tissues and to assess antibody pharmacokinetics and immunogenicity. Six antibodies have now been analyzed in this way by S. Welt, C. Divgi, A. Houghton, D. Scheinberg, E. Oosterwijk, S. Larson, K. Lloyd, G. Ritter, A. Scott and their colleagues (52-60), and the information from these academic-sponsored trials forms a secure and rational basis for the development of antibody-based therapies, either with antibodies alone or using antibodies as a delivery system for cytotoxic agents. The Ludwig Institute's antibody program developed by Old represents the largest academic effort directed at developing antibody-based therapies for cancer.

In a career spanning nearly five decades, Old has contributed to virtually every aspect of cancer immunology. With his many colleagues around the world, Old has created a school of tumor immunology that has answered some of the key questions of the field. In doing so, he has laid a firm foundation for the century-long aspiration of tumor immunologists – controlling cancer by harnessing the power of the immune system.

Selected References from 650 publications by Lloyd J. Old and his Colleagues

1. Old LJ, Clarke DA, Benacerraf B. Effect of Bacillus Calmette Guerin infection on transplanted tumors in the mouse. Nature 1959; 184:291 292.
2. Old LJ, Boyse EA. Immunology of experimental tumors. Ann Rev Med 1964; 15:167-186.
3. Old LJ, Boyse EA, Clarke DA, Carswell EA. Antigenic properties of chemically induced tumors. Ann NY Acad Sci 1962; 101:80-106.
4. Nowinski RC, Old LJ, Boyse EA, de Harven E, Geering G. Group spe-

cific viral antigens in the milk and tissues of mice naturally infected with mammary tumor virus or Gross leukemia virus.
Virology 1968; 34:617- 629.

5. DeLeo AB, Shiku H, Takahashi T, John M, Old LJ. Cell surface antigens of chemically induced sarcomas of the mouse. I. MuLV related antigens and alloantigens on cultured fibroblasts and sarcoma cells. Description of a unique antigen on transplanted Meth A sarcoma.
J Exp Med 1977; 146:720-734.
6. DeLeo AB, Jay G, Appella E, Dubois GC, Law LW, Old LJ. Detection of a transformation related antigen in chemically induced sarcomas and other transformed cells of the mouse.
Proc Natl Acad Sci USA 1979; 76:2420-2424.
7. Srivastava PK, DeLeo AB, Old LJ. Tumor rejection antigens of chemically induced sarcomas of inbred mice.
Proc Natl Acad Sci USA 1986; 83:3407- 3411
8. Ikeda H, Ohta N, Furukawa K, Miyazaki H, Wang L, Furukawa K, Kuribayashi K, Old LJ, Shiku H. Mutated mitogen-activated protein-kinase: A tumor rejection antigen of mouse sarcoma.
Proc Natl Acad Sci USA 1997; 94:6375-6379.
9. Old LJ, Boyse EA, Stockert E. Antigenic properties of experimental leukemias. I. Serological studies in vitro with spontaneous and radiation induced leukemias. J Natl Cancer Inst 1963; 31:977-986.
10. Boyse EA, Miyazawa M, Aoki T, Old LJ. Ly A and Ly B: two systems of lymphocyte isoantigens in the mouse.
Proc Royal Soc Brit 1968; 170:175- 193.
11. Boyse EA, Old LJ. Some aspects of normal and abnormal cell surface genetics. Ann Rev Genet 1969; 3:269-290.
12. Old LJ, Boyse EA. Current enigmas in cancer research.
Harvey Lect 1973; 67:273-315
13. Old LJ, Stockert E. Immunogenetics of cell surface antigens of mouse leukemia. Ann Rev Genet 1977; 11:127-160.
14. Shiku H, Kisielow P, Bean MA, Takahashi T, Boyse EA, Oettgen HF, Old LJ. Expression of T cell differentiation antigens on effector cells in cell mediated cytotoxicity in vitro. J Exp Med 1975; 141:227-241.

15. Lilly F, Boyse EA, Old LJ. Genetic basis of susceptibility to viral leukemogenesis. Lancet 1965; :1207-1209.
16. Carswell EA, Old LJ, Kassel RL, Green S, Fiore NC, Williamson BD. An endotoxin induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci USA 1975; 72:3666-3670.
17. Old LJ. Tumor necrosis factor (TNF). Science 1985; 230:630-632.
18. Kaplan DH, Shankaran V, Dighe AS, Stockert E, Aguet M, Old LJ, Schreiber RD. Demonstration of an IFNÁ-dependent tumor surveillance system in immunocompetent mice. Proc Natl Acad Sci USA 1998; 95:7556-7561
19. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, Schreiber RD. INF-Á and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature 2001; 410:1107-1111.
20. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002 3:991-998.
21. Old LJ, Boyse EA, Geering G, Oettgen HF. Serologic approaches to the study of cancer in animals and in man. Cancer Res 1968; 28:1288-1299.
22. Old LJ, Boyse EA, Oettgen HF, de Harven E, Geering G, Williamson BD, Clifford P. Precipitating antibody in human serum to an antigen present in cultured Burkitt's lymphoma cells. Proc Natl Acad Sci USA 1966; 56:1699-1704.
23. Old LJ. Cancer immunology: The search for specificity. The G.H.A. Clowes Memorial Lecture. Cancer Res 1981; 41:361-375.
24. Knuth A, Danowski B, Oettgen HF, Old LJ. T cell mediated cytotoxicity against malignant melanoma: Analysis with IL 2 dependent T cell cultures. Proc Natl Acad Sci USA 1984; 81:3511-3515.
25. Traversari C, van der Bruggen P, van den Eynde B, Hainaut P, Lemoine C, Ohta N, Old LJ, Boon T. Transfection and expression of a gene coding for a human melanoma antigen recognized by autologous cytolytic T lymphocytes. Immunogenetics 1992; 35:145-152.

26. van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, Boon T. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science. 1991;254:1643-1647.
27. Sahin U, Tureci O, Schmitt H, Cochlovius B, Johannes T, Schmits R, Stenner F, Luo G, Schobert I, Pfreundschuh M. Human neoplasms elicit multiple specific immune responses in the autologous host. Proc Natl Acad Sci U S A. 1995;92:11810-11813.
28. Chen Y-T, Scanlan MJ, Sahin U, Türeci Ö, Gure AO, Tsang S, Williamson B, Stockert E, Pfreundschuh M, Old LJ. A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. Proc Natl Acad Sci USA 1997; 94:1914-1918.
29. Scanlan MJ, Chen Y-T, Williamson B, Gure AO, Stockert E, Gordan JD, Türeci Ö, Sahin U, Pfreundschuh M, Old LJ. Characterization of human colon cancer antigens recognized by autologous antibodies. Int J Cancer 1998; 76:652-658.
30. Scanlan MJ, Gout I, Gordon CM, Williamson B, Stockert E, Güre AO, Jäger D, Chen Y-T, Mackay A, O'Hare MJ, Old LJ. Humoral immunity to human breast cancer: antigen definition and quantitative analysis of mRNA expression. Cancer Immunity 2001; 1:4.
31. Lee SY, Obata Y, Yoshida M, Stockert E, Williamson B, Jungbluth AA, Chen YT, Old LJ, Scanlan MJ. Immunomic analysis of human sarcoma. Proc Natl Acad Sci U S A. 2003;100:2651-2656.
32. Old LJ, Chen Y-T. New paths in human cancer serology. J Exp Med 1998; 187:1163-1167.
33. Jungbluth AA, Busam KJ, Kolb D, Iversen K, Coplan K, Chen Y-T, Spagnoli GC, Old .LJ. Expression of MAGE-antigens in normal tissues and cancer. Int J Cancer 2000; 85:460-465.
34. Jungbluth AA, Chen Y-T, Stockert E, Busam KJ, Kolb D, Iversen K, Coplan K, Williamson B, Altorki N, Old LJ. Immunohistochemical analysis of NY-ESO-1 antigen expression in normal and malignant human tissues. Int J Cancer 2001; 92:856-860.
35. Jungbluth A, Chen Y-T, Busam K, Coplan K, Kolb D, Iversen K, Williamson B, van Landeghem F, Stockert E, Old LJ. CT7 (MAGE-

C1) antigen expression in normal and neoplastic tissues.
Int J Cancer 2002:99:839-845.

36. Scanlan MJ, Simpson AJ, Old LJ. The cancer/testis genes: review, standardization, and commentary.Cancer Immun. 2004 ;4:1.
37. Old LJ. Cancer/Testis (CT) antigens – a new link between gametogenesis and cancer. Cancer Immunity 2004; 4:1.
38. Simpson AJ, Caballero OL, Jungbluth A, Chen YT, Old LJ.
Cancer/testis antigens, gametogenesis and cancer.
Nat Rev Cancer. 2005 Aug;5(8):615-625.
39. Jäger E, Chen Y-T, Drijfhout JW, Karbach J, Ringhoffer M, Jäger D, Arand M, Wada H, Noguchi Y, Stockert E, Old LJ, Knuth A. Simultaneous humoral and cellular immune response against «cancer-testis» antigen NY-ESO-1: definition of HLA-A2 binding peptides epitopes. J Exp Med 1998; 187:265-270.
40. Stockert E, Jaeger E, Chen Y-T, Scanlan MJ, Gout I, Karbach J, Knuth A, Old LJ. A survey of the humoral immune response of cancer patients to a panel of human tumor antigens. J Exp Med 1998; 187:1349-1354.
41. Jäger E, Nagata Y, Gnjatic S, Wada H, Stockert E, Karbach J, Dunbar PR, Lee SY, Jungbluth A, Jäger D, Arand M, Ritter G, Cerundolo V, Dupont B, Chen Y-T, Old LJ, Knuth A. Monitoring CD8 T cell responses to NY-ESO-1: Correlation of humoral and cellular immune responses. Proc Natl Acad Sci USA 2000; 97:4760-4765.
42. Gnjatic S, Atanackovic D, Jager E, Matsuo M, Selvakumar A, Altorki NK, Maki RG, Dupont B, Ritter G, Chen YT, Knuth A, Old LJ. Survey of naturally occurring CD4+ T cell responses against NY-ESO-1 in cancer patients: correlation with antibody responses.
Proc Natl Acad Sci U S A. 2003;100:8862-8867.
43. Old LJ; Cancer Vaccine Collaborative 2002.
Cancer Immunity. 2003; 1:1.
44. Jäger E, Gnjatic S, Nagata Y, Stockert E, Jäger D, Karbach J, Neumann A, Rieckenberg J, Chen Y-T, Ritter G, Hoffman E, Arand M, Old LJ, Knuth A. Induction of primary NY-ESO-1 immunity: CD8+ T lymphocyte and antibody responses in peptide-vaccinated patients with NY-ESO-1+ cancers. Proc Natl Acad Sci USA 2000; 97:12198-12203.

45. Nishikawa H, Qian F, Tsuji T, Ritter G, Old LJ, Gnjatic S, Odunsi K. Influence of CD4+CD25+ regulatory T cells on low/high-avidity CD4+ T cells following peptide vaccination.J Immunol. 2006 ;176:6340-6.
46. Davis ID, Chen W, Jackson H, Parente P, Shackleton M, Hopkins W, Chen Q, Dimopoulos N, Luke T, Murphy R, Scott AM, Maraskovsky E, McArthur G, MacGregor D, Sturrock S, Tai TY, Green S, Cuthbertson A, Maher D, Miloradovic L, Mitchell SV, Ritter G, Jungbluth AA, Chen YT, Gnjatic S, Hoffman EW, Old LJ, Cebon JS. Recombinant NY-ESO-1 protein with ISCOMATRIX adjuvant induces broad integrated antibody and CD4+ and CD8+ T cell responses in humans. Proc Natl Acad Sci U S A. 2004; 101:10697-10702.
47. Jäger E, Karbach J, Gnjatic S, Neumann A, Bender A, Valmori D, Ayyoub M, Ritter E, Ritter G, Jäger D, Panicali D, Hoffman E, Pan L, Oettgen H, Old LJ, Knuth A. Recombinant vaccinia/fowlpox NY-ESO-1 vaccines induce both humoral and cellular NY-ESO-1-specific immune responses in cancer patients. Proc Natl Acad Sci U S A. 2006 ;103:14453-14458.
48. Gnjatic S, Nishikawa H, Jungbluth AA, Gure AO, Ritter G, Jäger E, Knuth A, Chen YT, Old LJ. NY-ESO-1: Review of an Immunogenic Tumor Antigen. Adv Cancer Res. 2006;95:1-30.
49. Rettig WJ, Old LJ. Immunogenetics of human cell surface differentiation. Ann Rev Immunol 1989; 7:481-511.
50. Jungbluth AA, Stockert E, Huang HJ, Colins VP, Coplan K, Iversen K, Kolb D, Johns TJ, Scott AM, Gullick WJ, Ritter G, Cohen L, Scanlan MJ, Cavenee WK, Old LJ. A monoclonal antibody recognizing human cancers with amplification/overexpression of the human epidermal growth factor receptor. Prof Natl Acad Sci USA. 2003 :100:639-644.
51. Johns TG, Adams TE, Cochran JR, Hall NE, Hoyne PA, Olsen MJ, Kim YS, Rothacker J, Nice EC, Walker F, Ritter G, Jungbluth AA, Old LJ, Ward CW, Burgess AW, Wittrup KD, Scott AM. Identification of the epitope for the Epidermal Growth Factor Receptor-specific monoclonal antibody 806 reveals that it preferentially recognizes an untethered form of the receptor. J Biol Chem. 2004 ;279:30375-30384.

52. Welt S, Divgi CR, Real FX, Yeh SD, Garin-Chesa P, Finstad CL, Sakamoto J, Cohen A, Sigurdson ER, Kemeny N, Carswell EA, Oettgen, HF, Old, LJ. Quantitative analysis of antibody locatization in human metastatic colon cancer: A Phase I Study with Monoclonal Antibody A33. J Clin Oncol 1990; 8:1894-1906.
53. Scott AM, Lee FT, Jones R, Hopkins W, MacGregor D, Cebon JS, Hannah A, Chong G,UP, Paperfuss A, Rigopoulos A, Sturrock S, Murphy R, Wirth V, Murone C, Smyth FE, Knight S, Welt S, Ritter G, Richards E, Nice EC, Burgess AW, Old LJ. A phase I trial of humanized monoclonal antibody A33 in patients with colorectal carcinoma: biodistribution, pharmacokinetics, and quanititative tumor uptake.
Clin Cancer Res. 2005 : 11: 4810-4817.
54. Scheinberg DA, Lovett D, Divgi CR, Graham MC, Berman E, Pentlow K. Feirt N. Finn RD., Clarkson BD, Gee TS, Larson SM, Oettgen HF, Old LJ. A phase I tral of mAb M195 in acute myelogenous leukemia: specific bone marrow target and internalization of radionuclide.
J Clin Oncol 1991; 9:78-490.
55. Oosterwijk E, Bander NH, Divgi CR, Welt S, Wakka JC, Finn R, Carswell EC, Larson SM, Warnaar SO, Fleuren GJ, Oettgen HF, Old LJ. Antibody localization in human renal cell carcinoma : a phase I study of monoclonal antibody G250.
J Clin Oncol 1993; 53:3327-3335.
56. Divgi CR, Bander NH, Scott AM, O'Donoghue JA, Sgouros G, Welt S, Finn RD, Morrissey F, Capitelli P, Williams JM, Deland D. Nakhre A, Oosterwijk E, Gulec S. Graham MC, Larson SM, Old LJ. Phase I/II radioimmunotherapy trial with iodine 131-labeled monoclonal antibody G250 in metastatic renal cell carcinoma.
Clin Cancer Res 1998; 4:2727-2739.
57. Welt S, Divgi CR, Scott AM, Garin-Chesa P, Finn RD, Graham M, Carsell EA, Cohen A, Larson SM, Old LJ, Rettig WJ. Antibody targeting in metastatic colon cancer: A phase I study of monoclonal antibody F19 against a cell surface protein of reactive tumor stromal firbroblasts.
J Clin Oncol 1994; 12:1193-1203.

58. Scott AM, Wiseman G, Welt S. Adjei A, Lee FT, Hopkins W, Divgi CR, Hanson LH, Mitchell P, Gansen DN, Larson SM, Ingle JN, Hoffman EW, Tanswell P, Ritter G, Cohen LS, Bette P, ARvay L, Amelsberg A, Vlock D, Rettig WJ, Old LJ. A phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer.
Clin Cancer Res. 2003 May 9; (5):1639-1647.

59. Houghton AN, Mintzer D, Cordon-Cardo C, Welt S, Fliegel B, Vadhan S, Carswell E, Melamed MR, Oettgen HF, Old LJ. Mouse monoclonal IgG3 antibody detecting GD3 ganglioside: a phase I trial in patients with malignant melanoma.
Proc Natl Acad Sci U S A. 1985 ;82:1242-6.

60. Scott AM, Lee F-T, Hopkins W, Cebon JS, Wheatley JM, Liu Z, Smyth FE, Murone C, Sturrock S, MacGregor D, Hanai N, Inoue K, Yamasaki M, Brechbiel MW, Davis ID, Murphy R, Hannah A, Lim-Joon M, Chan T, Chong G, Ritter G, Hoffman EW, Burgess AW, Old LJ. Specific targeting, biodistribution and lack of immunogenicity of chimeric anti-GD3 monoclonal antibody KM871 in patients with metastatic melanoma – results of a phase I trial.
J Clin Oncol 2001; 1:3976-87.