Laudatio
Mark J. Smyth

The most difficult part of the medical oncologist's daily practice is telling patients that they suffer from cancer. For almost all patients, this information comes as a shock and they immediately ask, "Why did I get cancer?" The cancer immunologist asks, "Why didn't the immune system recognize and destroy the cancer?" We cannot answer these questions adequately in most cases.

The concept of the immune system constantly surveilling the emergence of new cells in the human body and eliminating the "faulty" or transformed cells is intriguing and was first postulated by Paul Ehrlich at the beginning of the 20th century. The observation that syngeneic mice immunized against a tumor rejected a secondary challenge with the same tumor cells, but did not react against the corresponding non-transformed cells, demonstrated the existence of tumor-specific antigens. This led Burnet and Thomas to their model of *immune surveillance* in which lymphocytes are responsible for eliminating continuously arising, nascent transformed cells.

The model of immune surveillance was challenged in the mid seventies of the last century by data from immune-deficient mice and more mechanistic models that attributed the immune system with the capacity to distinguish between "self" or "non-self" antigens or, later on, between so-called "danger" and "non-danger" signals favored. However, new technologies allowed the engineering of transgenic mouse models with molecularly-defined inactivating defects in innate and/or adaptive immunity have shown that immunodeficient mice do indeed develop more spontaneous and carcinogen-induced tumours than their immunocompetent counterparts. In addition, clinical data obtained from immunosuppressed patients - in the setting of organ transplantation or as a consequence of viral infections - clearly support the immunosurveillance concept and its role in humans.

Dr. Mark Smyth played a key role in the resurrection of immune surveillance model over the last two decades and is spearheading research in this area. During his post-doctoral training in the Laboratory of Experimental Immunology at the US National Cancer Institute (NCI) headed by Drs. John Ortaldo and Howard Young, Dr. Smyth worked on immune effector cells and described a pore-forming protein (later named 'perforin') as a key component of activated T cells and natural killer (NK) cells in their capacity to lyse target cells.

After his return to Australia, Dr. Smyth - together with Dr. Joe Trapani - postulated the granule exocytosis model based on the vectorial secretion of the contents of highly specialized cytoplasmic granules and their pivotal importance in the killing by cytotoxic T cells and NK cells. They purified and cloned multiple members of the serine protease family and described the pivotal importance of perforin and granzymes in the defense against certain virus infections *in vivo*. This model was supported by the identification of a hereditary immunodeficiency due to disordered perforin expression in humans.

Stimulated by his experience in analyzing and controlling the cytotoxic components involved in cell-mediated killing, Dr. Smyth turned to mouse models to analyse more accurately the importance of single effector molecules in tumor immunity. With the improvements in molecular immunology and the development of gene-targeting and transgenic mouse technologies, the contribution of single components could be studied. Published data at that time postulated that perforin-deficient mice were not abnormally prone to malignancy up to 12 months of age, thereby, challenging the concept of immune surveillance. Dr. Smyth repeated these experiments and confirmed that mice up to the age of 12 months did not develop spontaneous tumors. However, he found that soon thereafter, these mice began to succumb to aggressive disseminated lymphomas. In addition, perforin-deficient mice were at least 1,000-fold more susceptible to these lymphomas when transplanted, compared with immunocompetent mice in which tumor rejection was controlled by CD8(+) T lymphocytes. This study was the first to implicate direct cytotoxicity by lymphocytes in regulating lymphomagenesis and confirmed the existence of immune surveillance at least in the mouse model.

Dr. Smyth has spent most of his professional career in Australia and was awarded with the prestigious *Wellcome Trust Senior Research Fellowship in Medical Science* at the age of 30 years. He is currently Co-Program Head of the Cancer Immunology Program at the Peter MacCallum Cancer Centre in Melbourne, Australia.

Charles Rodolphe Brupbacher Foundation

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

Dr. Mark J. Smyth

for his contribution
to the understanding of the concept of
Cancer Immunosurveillance

The President
of the Foundation

Mrs. Frédérique Brupbacher

The President
of the Scientific Board

Dr. med. Erhart H. Brunner

Curriculum vitae
Mark J. Smyth

Date of Birth: April 4, 1963

Place of Birth: Hobart, Tasmania

Citizenship: Australia

Address: Cancer Immunology Program
Peter MacCallum Cancer Centre
St Andrews Place
East Melbourne, 3002, Victoria, Australia
Phone: 61-3-96563728, Fax: 61-3-9656-1411
Email: mark.smyth@petermac.org

Education and Training:

1981 - 1983	B. Sc. University of Melbourne (Biochemistry/Pathology), Melbourne, Victoria
1984	B. Sc. (Hons.) University of Melbourne (Pathology), Melbourne, Victoria
1985 - 1988	Ph. D., Research Centre for Cancer and Transplantation, Department of Pathology, University of Melbourne, Melbourne, Victoria

Fellowships:

1988	Postdoctoral Fellow, Research Centre for Cancer and Transplantation, University of Melbourne, Australia
1989	Visiting Fellow, Fogarty Visiting Program, Frederick Cancer Research and Development Center, NCI, USA
1990 -1991	C. J. Martin Fellow of the National Health and Medical Research Council of Australia, Frederick Cancer Research and Development Center, NCI, USA
1992 - 1993	C. J. Martin Fellow of the National Health and Medical Research Council of Australia, Austin Research Institute, Melbourne, Australia

1993	R. Douglas Wright Research Fellow of the National Health and Medical Research Council of Australia, Austin Research Institute, Melbourne, Australia
1994 - 1998	Wellcome Trust Senior Research Fellow in Medical Science, Austin Research Institute, Melbourne, Australia
1999- 2000	NH&MRC Principal Research Fellow, Austin Research Institute, Melbourne, Australia
2000-2006	NH&MRC Principal Research Fellow, Co-Head (with J. Trapani) Cancer Immunology Program, Peter MacCallum Cancer Centre, Melbourne, Australia
2007- current	NH&MRC Senior Principal Research Fellow, Co-Head Cancer Immunology Program, Peter MacCallum Cancer Centre, Melbourne, Australia

Other Appointments:

1993 - 2000	Senior Associate in the Department of Surgery, Austin and Heidelberg Repatriation Hospitals, University of Melbourne
1996 - 1998	Senior Associate in the Department of Pathology, University of Melbourne
1998 - 2000	Associate Professor, Victoria University of Technology
1998 - 2000	Senior Fellow in the Department of Medicine, Austin and Heidelberg Repatriation Medical Centre
1999 - present	Honorary Associate Professor, University of Melbourne
2000 - present	Honorary Associate Professor, Monash University

Professional Recognition

Appointments:

1998, 2000, 2004-2005	NH&MRC Discipline Panel Member
1998-1999	ACCV National Assigning Panel Member
2004-2005	European Commission Framework Program Grants
2004-2005	NIH Ad Hoc Study Section (TTT, Experimental Immunology)
2004-present	Faculty of 1000 Member (Immunology)

Honors and Awards:

1984-1987	Commonwealth Postgraduate Scholarship, University of Melbourne
1988-1989	NIH Fogarty Visiting Fellowship
1989-1992	NH&MRC C. J. Martin Fellowship
1991	NCI -FCRDC Certificate of Appreciation for Outstanding Performance
1992	Sandoz Young Investigators Award
1993	Australian Life Sciences Research Award
1993	NH&MRC R. Douglas Wright Research Fellowship
1994-1998	Wellcome Trust Senior Research Fellowship in Medical Science
1995	Australian Academy of Science Gottschalk Medal
1998	AMGEN Medical Research Award
1999-2003	NH&MRC Principal Research Fellowship
2004-2008	NH&MRC Principal Research Fellowship
2002	Cancer Research Institute, William B. Coley Award for Distinguished Research in Basic and Tumour Immunology
2003	Commonwealth Health Minister's Award for Excellence in Health and Medical Research – Finalist

Keynote Addresses:

- Second International Workshop on Cytokines, Hilton Head Island, SC, USA, 1989
- First International Symposium on Combination Therapies, Washington D. C., USA, 1991
- EMBO Workshop on Cell-Mediated Cytotoxicity, Neve Ilan, Israel, 1993
- Second Meeting of The Society for Natural Immunity, Taormina, Italy, 1994
- Fifth Meeting of The Society for Natural Immunity, Warrenton, Virginia, USA, 1998
- Inaugural Workshop on NK T cells and CD1-mediated antigen presentation, San Diego, USA, 1999

- International Symposium on Cancer Immunosurveillance, Cancer Research Institute, New York City, NY, USA, 1999
- International Congress in Immunology, Stockholm, Sweden, 2001
- Cancer Research Institute 16th Annual Awards Dinner, New York, NY, USA, 2002
- Cancer Research Institute CVC Symposium, New York, NY, USA, 2002
- The 9th International Congress on the TNF Related Cytokines, San Diego, CA, USA, 2002
- The Second International CD1 and NKT cell Workshop, Woods Hole, USA, 2002
- The Japanese Society for Immunology Annual Meeting, Tokyo, Japan, 2002
- The European Network of Immunology Institutes, Ile des Embiez, France, 2003
- The Annual Meeting of the Korean Cancer Association, Seoul, South Korea, 2003
- Sapporo International Cancer Symposium, Sapporo, Japan, 2003
- The International Society for Interferon and Cytokine Research, Cairns, Australia, 2003
- The International Natural Killer Cell Workshop, Noordwijkerhout, The Netherlands, 2004
- 4th Human Frontiers in Science Program Annual Meeting, Hakone, Japan, 2004
- Genomics, Proteomics and Therapeutics in Cancer Research, Hong Kong, 2004
- The Annual Meeting of the Korean Cancer Association, Seoul, South Korea, 2005
- 1st Crossroads between Innate and Adaptive Immunity Conference, Rhodes, Greece, 2005
- International Symposium on Cancer Vaccines. Barriers, Endpoints, and Opportunities, Cancer Research Institute, New York City, NY, USA, 2005
- 6th International Cytokine Meeting, Vienna, Austria, 2006
- Keystone Symposia Mechanisms Linking Inflammation and Cancer, Santa Fe, NM, USA, 2007

Meeting Organizer

- Australasian Society of Immunology Annual Meeting, Melbourne, 1998, 2005
- Immunology of Victoria Annual Meeting, 2000-2003
- Peter Mac Symposium, Melbourne, 2003
- 3rd International CD1 and NKT cell workshop, Heron Island, 2004
- Apoptosis and Immunology, Palm Cove, 2005
- Advisory Committee, 21st International NK cell workshop, Hawaii, 2005
- 6th International Cytokine Meeting, Vienna – International Advisory Board, 2006

Editorial Boards:

- The Journal of Biological Chemistry, 2005-2010
- Consulting Editor, The Journal of Leukocyte Biology, 1997-2000
- Section Editor, The Journal of Leukocyte Biology, 2004-2008
- Invited Section Editor, Current Opinions In Immunology, 2007

Professional Society Memberships:

1992-present	Australasian Society for Immunology (ASI)
1992-2000	The Transplantation Society of Australia and New Zealand
1995-present	The American Association of Immunologists
1995-present	Immunology Victoria Council Member
1999-present	Natural Society for Immunity ()
1999-present	The Australian Society for Medical Research
2000-2003	ASI State Councillor
2002-present	The International Society for Interferon and Cytokine Research
2004-present	The Society for Leukocyte Biology
2004-present	The American Society for Biochemisty and Molecular Biology

Publications:

Over 250 original publications in international scientific journals, invited reviews and book chapters.

Extrinsic tumor suppression by innate and adaptive immunity

Mark J. Smyth

Introduction

Cancers arise by an evolutionary process during which somatic cells mutate and escape the restraints of regulated expansion, contraction, and apoptosis. A variety of "intrinsic" tumor-suppressive mechanisms exist that trigger apoptosis, repair, or senescence, should proliferation become aberrant (1). Escape from oncogene-induced senescence is a prerequisite for cellular transformation. Generally, both senescence and apoptosis act as stringent barriers to the further evolution of any pre-neoplastic cell. Alternatively, general "extrinsic" mechanisms have been identified by which cells and their adjacent tissues "sense" the presence of cancerous cells. One of these involves the detection and elimination and/or cytostasis of transformed cells by leukocytes of the immune system.

In 1891 William Coley made the remarkable observation that some cancer patients who developed bacterial infections, or were injected cultures of heat-inactivated bacteria, experienced tumor regression, and in 1909 Paul Ehrlich first proposed the notion that the immune system naturally protected the host from cancer. As we now know, "Coley's toxins" (2) contained bacterial products with strong immunomodulatory potential. More than 50 years later, with the development of inbred strains of mice, it was possible to examine whether tumors arising in such mice were immunologically distinguishable from normal tissues in the same strain. The demonstration that syngeneic mice immunized against a tumor rejected a secondary challenge with the same tumor cells but did not react against the corresponding non-transformed cells functionally documented the existence of tumor-specific antigens and thereby showed that tumor-specific immune responses did indeed occur (3,4). Together this work showed that immune cells could detect the presence of transformed tissue either by recognizing specific structures on the tumor cell surface or by responding to soluble molecules secreted by the tumor itself. Based on an emerging understanding of the cellular basis of transplantation and tumor immunity, Burnet and Thomas predicted that lymphocytes were responsible for eliminating continuously arising, nascent transformed cells and thus formally introduced the cancer immune surveillance hypothesis (5, 6). For many years now this hypothesis has been discussed and much of the debate has reflected the inherent difficulties of experimentally determining whether or not natural

immune defense mechanisms could protect the host against the development of cancers of non-viral origin. Over the last two decades, the notion that the natural immune system can indeed detect transformation in the form of abnormal proteins or tumor antigens and eliminate such altered host derived cells, has experienced a new resurgence. New discovered immune cell subsets have been thoroughly dissected and characterized, including professional antigen presenting cells (7), NK cells, and various regulatory T cells (8). Molecularly, the definition of pattern recognition receptors such as toll-like receptors (9) and isolation of families of human tumor antigens (10) have greatly expanded the repertoire of possible adjuvants and cancer vaccines. With the age of molecular biology, has come the development of gene-targeting and transgenic mouse technologies and the capacity to produce highly specific blocking monoclonal antibodies (mAb) to particular immune components. Using these tools we have been able to unequivocally test and prove cancer immune surveillance. My laboratory, the laboratories of Professors Robert Schreiber and Lloyd Old, and other groups worldwide, have now provided a compelling amount of definitive experimental data in mouse models of carcinogenesis that supports immunity as an effective extrinsic tumor suppressor. This, together with increasing clinical data from human cancer patients, has highlighted the important role immunity has to play in cancer development and treatment.

Effector molecules that suppress tumor development

All immune effector cells employ extremely diverse mechanisms to directly or indirectly kill transformed cells. Direct mechanisms include death involving both mitochondrial and cell death receptor pathways. Many cancer vaccine strategies have been based on the premise that specific cytotoxic lymphocytes may eliminate tumor cells. We have validated this assumption using mice that either lack perforin, the key effector molecule of granulated lymphocytes such as NK cells and cytotoxic T lymphocytes (11), or lack tumor necrosis factor related apoptosis-inducing ligand (TRAIL), a molecule that appears to selectively trigger apoptosis in transformed or stressed cells (12, 13). Deficiencies in either of these effector molecules causes enhanced host susceptibility to carcinogenesis and spontaneous tumor development. Interferons secreted by hematopoietic and non-hematopoiteic cells also control tumor

growth and amplify the immune response by a variety of mechanisms. Using a variety of gene-targeted mice for various components of the interferon signaling pathway, Schreiber and colleagues have shown the importance of both type I and type II interferons in cancer immune surveillance (14-16). Our own studies in comparable mouse strains have confirmed these findings (17). NK cells and specialized T cell subsets appear to be the major producers of type II interferon and host and tumor cells are both important targets of IFN-γ (18). Additional work is required to identify the precise cellular targets of type I interferons in the cancer immune surveillance process. Despite many years of clinical use, interferons have many postulated mechanisms of action, yet with little definition of how they function in humans.

Innate and adaptive immunity collectively suppress tumor development

An integrated response involving both the innate and adaptive arms of the immune system is often required to suppress tumor formation. NK cells, dendritic cells, macrophages, $\gamma\delta^+$ T cells and/or NKT cells (19, 20) have shown to be variously important in responding early to transformation. NKT cells recognize glycolipid antigen-CD1 complexes expressed on antigen presenting cells or tumor cells. We provided the first clear evidence that NKT cells naturally participate in cancer immune surveillance by showing that mice that specifically lacked NKT cells developed carcinogen-induced cancers at two to three times higher frequency than wild-type controls (19). While it has not been possible to easily formally test the importance of innate lymphocyte subsets in natural human immunity to cancer, several recent studies in multiple myeloma patients or other patients receiving HLA haplotype mismatch transplants or monoclonal antibodies to human cancers, indicate an important role for NKT cells and NK cells, respectively.

Transformed cells may over express other molecular signposts that can function as recognition targets in the immune surveillance process. The NKG2D-activating receptor expressed on NK cells, $\gamma\delta^+$T cells, and $CD8^+$ T cells, is used by both adaptive and innate immune cells to distinguish distinct stress-induced ligands on cancer cells. We have recently illustrated that cytokines mediate their anti-metastatic activity in part via the NKG2D-NKG2D ligand pathway (21). Others and we have shown that inhibition of

NKG2D in mice increases their sensitivity to carcinogen-induced tumors, directly implicating this pathway in host control of tumor initiation (22, 23). The role of other stress-induced proteins and pattern recognition receptors in regulating tumor development has yet to be described.

Tumor antigens liberated by a variety of cell death pathways and in the context of a milieu of innate immune signals drive the development of tumor-specific adaptive immune responses. Immature dendritic cells that have been recruited to the tumor site become activated either by exposure to the microenvironment created during the ongoing attack on the tumor by innate immunity or by interacting with tumor-infiltrating NK cells. The activated DCs may then acquire tumor antigens, acquire a highly activated mature phenotype and, in response to distinct chemokines and/or cytokines, migrate to the lymph nodes where they induce the activation of naïve T cells. In the last phase, the development of tumor-specific adaptive immunity provides the host with a capacity to completely eliminate the developing tumor. The elimination phase is an ever-ongoing process that must be repeated each time distinct neoplastic cells arise.

Where do we go from here?

Despite strong evidence supporting the existence of a functional cancer immune surveillance process, immunocompetent individuals still develop cancers that are refractory to many treatment approaches. While the design of vaccines that induce strong memory to antigens displayed by the tumor can be a very effective preventative measure (24), cancer vaccines have generally not yet been effective in patients with advanced cancer. Others and we have shown that when the immune system fails to eliminate all tumor cells, tumors with reduced immunogenicity may emerge that are capable of escaping immune recognition and destruction. Schreiber and colleagues have termed this combination of host-protective and tumor-sculpting functions of the immune system throughout tumor development "cancer immunoediting" (18). It is imagined that cancer immune surveillance is a dynamic process comprised of three phases: elimination, equilibrium, and escape. Elimination embodies the classical concept of cancer immune surveillance, equilibrium is the period of immune-mediated dormancy after incomplete tumor destruction, and escape refers to the final

outgrowth of tumors that have evolved beyond immunological and other extrinsic restraints. These latter two phases still require considerable validation and exploration, but may offer new information that results in many new treatment opportunities.

Clearly, immunodeficient humans have a far greater susceptibility to lethal viruses and pathogens than immune compromised mice in pathogen free mouse facilities and therefore the opportunities of observing increased spontaneous tumor formation in people with mutations in specific genes encoding immune effector molecules are rare. Assessment of polymorphisms and mutations in key human immune pathways may provide important clues. Nevertheless, one can draw upon three lines of evidence to suggest that cancer immunosurveillance indeed occurs in humans: (a) immunosuppressed transplant recipients display higher incidences of non-viral cancers than age-matched immunocompetent control populations; (b) cancer patients can develop spontaneous adaptive and innate immune responses to the tumors that they bear, and (c) the presence of lymphocytes within the tumor can be a prognostic indicator of patient survival. It will be important in the future to clarify which particular immune cells are prognostic for each distinct type of cancer. Gene expression profiling and proteomics are going to play a key part in defining the major positive and negative immune indicators in human cancer progression.

We now must begin to understand the immune reaction in context of entire tumor microenvironment. Immune cell interactions with tumor and various stromal cells are possibly numerous and ongoing throughout tumor development. An improved understanding of the immunobiology of cancer surveillance and a molecular definition of how tumors are shaped by this process will undoubtedly bring us closer to a more effective use of immunotherapy to prevent, control and/or eradicate established cancer.

References

1. Lowe, S. W., Cepero, E., and Evan, G. (2004). Intrinsic tumour suppression. *Nature* **432,** 307-15.
2. Coley, W. B. (1991). The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. *Clin Orthop,* 3-11.
3. Old, L. J., and Boyse, E. A. (1964). Immunology of Experimental Tumors. *Annu Rev Med* **15,** 167-86.
4. Klein, G. (1966). Tumor antigens. *Annu Rev Microbiol* **20,** 223-52.
5. Thomas, L. (1959). Discussion. *In* «Cellular and humoral aspects of the hypersensitive states» (H. S. Lawrence, Ed.), pp. 529-532. Hoeber-Harper, New York.
6. Burnet, F. M. (1964). Immunological Factors in the Process of Carcinogenesis. *British Medical Bulletin* **20,** 154-158.
7. Steinman RM, and Nussenzweig MC. (1980). Dendritic cells: features and functions. *Immunol Rev.* **53,**127-47.
8. Sakaguchi S. (2000). Regulatory T cells: key controllers of immunologic self-tolerance. *Cell* **101,** 455-458.
9. Medzhitov R, Preston-Hurlburt P, and Janeway CA Jr. (1997). A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. *Nature* **388,** 394-397.
10. van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, and Boon T. (1991). A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. *Science* **254,** 1643-1647.
11. Smyth, M. J., Thia, K. Y. T., Street, S. E. A., MacGregor, D., Godfrey, D. I., and Trapani, J. A. (2000). Cytotoxic lymphocyte perforin-mediated immune surveillance of spontaneous lymphoma. *J. Exp. Med.* **192,** 755-760.
12. Takeda, K., Hayakawa, Y., Smyth, M. J., Kayagaki, N., Yamaguchi, N., Kakuta, S, Iwakura, Y., Yagita, H., and Okumura, K. (2001). Involvement of tumor necrosis factor-related apoptosis-inducing ligand in surveillance of tumor metastasis by liver NK cells. *Nature Medicine* **7,** 94-100.

13. Smyth, M. J., Cretney, E., Takeda, K., Wiltrout, R. W., Sedger, L., Kayagaki, N., Yagita, H., and Okumura, K. (2001). Tumor necrosis factor related apoptosis-inducing ligand (TRAIL) contributes to IFN-γ-dependent NK cell protection from tumor metastasis. *J. Exp. Med.* **193,** 661-670.
14. Kaplan DH, Shankaran V, Dighe AS, Stockert E, Aguet M, Old LJ, and Schreiber RD. (1998). Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. *Proc Natl Acad Sci USA.* **95,** 7556-7561.
15. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, and Schreiber RD. (2001). IFNγ and lymphocytes prevent primary tumour development and shape tumour immunogenicity. *Nature* 410, 1107-1111.
16. Dunn GP, Bruce AT, Sheehan KC, Shankaran V, Uppaluri R, Bui JD, Diamond MS, Koebel CM, Arthur C, White JM, and Schreiber RD. (2005). A critical function for type I interferons in cancer immunoediting. *Nat Immunol.* 6:722-729.
17. Street, S. E. A., Trapani, J. A., MacGregor, D., and Smyth, M. J. (2002). Suppression of lymphoma and some epithelial malignancies effected by interferon-γ. *J. Exp. Med.* 196, 129-134.
18. Dunn GP, Bruce AT, Ikeda H, Old LJ, and Schreiber RD. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol.* **3,** 991-998.
19. Smyth, M. J., Thia, K. Y. T., Street, S. E. A., Cretney, E., Trapani, J. A., Taniguchi, M., Kawano, T., Pelikan, S., Crowe, N. Y., and Godfrey, D. I. (2000). Differential tumor surveillance by NK and NKT cells. *J. Exp. Med.* 191:661-668.
20. Girardi M, Oppenheim DE, Steele CR, Lewis JM, Glusac E, Filler R, Hobby P, Sutton B, Tigelaar RE, and Hayday AC. (2001). Regulation of cutaneous malignancy by gammadelta T cells. *Science* **294,** 605-609.
21. Smyth, M. J., Swann, J., Kelly, J. M., Cretney, E., Yokoyama, W. M., Diefenbach, A., Sayers, T. J., and Hayakawa, Y. (2004). NKG2D recognition and perforin effector function mediates effective cytokine immunotherapy of cancer. *J. Exp. Med.* **200,** 1325-1335.

22. Smyth, M. J., Swann, J., Cretney, E., Zerafa, N., Yokoyama, W., and Hayakawa, Y. (2005). NKG2D protects the host from tumor initiation. *J. Exp. Med.* **202,** 583-588.
23. Oppenheim DE, Roberts SJ, Clarke SL, Filler R, Lewis JM, Tigelaar RE, Girardi M, Hayday AC. (2005). Sustained localized expression of ligand for the activating NKG2D receptor impairs natural cytotoxicity in vivo and reduces tumor immunosurveillance. *Nat. Immunol.* **6,** 928-937.
24. Lowy DR, Frazer IH. (2003). Chapter 16: Prophylactic human papillomavirus vaccines. *J Natl Cancer Inst Monogr.* **31,** 111-116.