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They can cause harm. However, when cancer develops, for malfunctioning cells in order to eliminate them before other diseases. This process is termed immunosurveillance, in order to safeguard against the development of cancer and place to alert the immune system to these dangerous self cells are dangerous to the host. There are several mechanisms in remove foreign agents such as bacteria and viruses, and “self agents” such as cellular debris and malfunctioning cells that are dangerous to the host. There are several mechanisms in place to alert the immune system to these dangerous self cells in order to safeguard against the development of cancer and other diseases. This process is termed immunosurveillance, and it allows for constant screening by the immune system for malfunctioning cells in order to eliminate them before they can cause harm. However, when cancer develops, immunosurveillance mechanisms have been averted and the harmful cells are allowed to survive. Furthermore, cancer cells no longer respond to appropriate growth controls and therefore multiply without constraint and become dangerous to the host. Therefore, the coordinate failure of cells to respond to growth control signals and the failure of the effective immunosurveillance mechanisms to alert the immune system to destroy aberrant cells can lead to malignant disease.

Cancer poses a particularly difficult problem to the immune system, as these cells have overcome immunosurveillance mechanisms and are recognised as self and therefore do not illicit an immune response. Cancer cells can alter their behaviour in many ways to avoid detection and deletion. Firstly, they can overcome programmed cell death (apoptosis) mechanisms that cause cells to die when they have acquired mutations that inappropriately signal the cell to cycle and proliferate. Furthermore, many chemotherapy agents work by triggering apoptotic pathways in cycling cells and thus some cancers are resistant to these types of chemotherapeutic agents due to alterations in their apoptotic machinery. Secondly, cancer cells can evade detection of the immune system by altering the expression of cell surface molecules. MHC molecule expression is essential to trigger an immune response by activating T lymphocytes through the T cell receptor (TCR). Therefore, it is common for cancer cells to down-regulate expression of its MHC molecules. Finally, cells can secrete immunosuppressive soluble cytokines such as IL-10 and TGF-β that can down-regulate the immune response. Generally, these cytokines act as brakes on the immune system to control the immune response in order to prevent damage that can be caused by the immune system when unregulated. Therefore, when immunosuppressive cytokines are inappropriately expressed, it can dampen immune responses and allow for cancer cells to avoid attack by the immune system.

Malignant cells can also up-regulate the expression of certain cell surface molecules that may not be innately antigenic but may be useful as tumour associated antigens (TAA) in future therapies such as prostate specific antigen (PSA). An example of well-studied tumour-associated antigens is the MAGE and GAGE families of genes. While these antigens were initially described in melanoma, they have been demonstrated to be present in a variety of tumour types including lung and bladder carcinoma, sarcomas, and head and neck tumours. They are, however, non-detectable in a large range of normal tissues, including brain, bone marrow and peripheral blood. Therefore, they may be used as potential targets for future therapies.

Types of immunotherapy

The aim of immunotherapy approaches is to prime the immune system to target these cancer cells specifically and without creating an autoimmune response. Immunotherapy can refer to any method in which the immune system is being altered creating an autoimmune response. Immunotherapy can refer to any method in which the immune system is being altered to become more effective. Generally, there are three modes of immunotherapy that are currently being utilised – antibodies, cytokines and cellular immunotherapy.

Antibodies have been used in a variety of ways to affect cellular behaviour. They can be administered to replace naturally-occurring ligating events. When antibodies bind to cell surface molecules they can have activating, inhibiting or null effects on cell signalling. It is possible to use activating antibodies to ligate death receptors on cancer cells in order to cause these cells to die (ie Fas). It is also possible to ligate lymphocyte cell surface receptors in order to induce lymphocytes to expand and activate an immune response (B7.1, LFA-3, ICAM-1). In addition, blocking antibodies can be used to interfere with naturally-occurring ligation events that are activating. Using a blocking antibody to the epidermal growth factor receptor (EGF-R) has been effective in reducing the growth of several tumour types that have amplified EGF receptor expression. Further, as described in this paper by Dr Frazer, anti-viral vaccines can be administered to produce neutralising antibodies against the papilloma virus, which is responsible...
FORUM

express MHC I molecules. This dynamic arrangement allows and glycolipid antigens within the context of CD1a expressed via granzymes when activated after ligation with MHC I and natural killer T cells (NKT) cells. DCs engage and activate cells and the innate response facilitated by natural killer (NK) immune cells ex vivo, which are then administered to the human body (less than 1.0% of mononuclear cells14,15) and the enormous potential for exploiting DC for immunotherapy has been hindered until recently by the rarity of this cell type in the ways of isolating and preparing DC: separation of CD34+ cells from mobilised peripheral blood mononuclear cell (PBMC) harvests; or isolation of monocytes from PBMC by adherence to plastic. Both cell subsets are then stimulated to develop into DC via GM-CSF, TNF-α, SCF or IL-416,17. The fundamental role of DC in orchestrating the different immune cells ex vivo, which are then administered to the patient to produce a specific anti-tumour effect. Current models are focusing on the use of dendritic cells (DC), which are the most potent antigen-presenting cells and therefore the best candidates to introduce tumour-specific antigens. The enormous potential for exploiting DC for immunotherapy has been hindered until recently by the rarity of this cell type in the human body (less than 1.0% of mononuclear cells14,15) and the lack of methods to generate DC in vitro. There are two major

immunocompetence of cancer patients


Monoclonal antibodies for cancer therapy

A large number of monoclonal antibodies (mAbs) are currently under investigation for the treatment of malignant diseases. To date, a significant amount of experimental and clinical research has been conducted which has furthered our understanding of the potential clinical applications of mAbs. Present, five monoclonal antibodies based on antibodies produced in the United States Food and Drug Administration (FDA) for cancer therapy. Further advances will occur in key areas such as identification of optimal treatment regimens, and the development of new mab targets that produce the best clinical outcomes with the fewest possible side effects.

Introduction

The development of monoclonal antibody technology by Köhler and Milstein 27 years ago has provided the potential for the diagnosis and treatment of a range of disorders. However, until recently, little progress had been achieved in the area of immunotherapy of human disease since induction of strong human anti-mouse antibody (HAMA) responses in patients to murine mAbs has limited the use of murine mAbs to very few invasive applications in oncology biology and protein engineering technologies for creating and producing better-tolerated antibodies have led to a renewed

References


Dendritic cells in cancer immunotherapy

Immunisations using autologous dendritic cells loaded with tumour antigens should overcome two of the major issues in cancer therapy today—donor suitability and engagament of complications (attaining suitable donors, graft rejections and graft versus host disease), and the specificity of action of the therapeutic agent against the tumour alone. Several successful studies in murine models of malignancy have increased the potential of DC vaccination as a possible form of therapy in human cancer. These studies have demonstrated that DC pulsed with specific antigens induces both protective and therapeutic tumour immunity in immunocompetent mice (A Pogador and A Gilboa 1995, C. Celluzzi, et al, 1996, P. Paglia, et al, 1996). Various methods have been used to load DC with antigen that result in anti-tumour immunity. Tumour material in the form of peptides24,25, cell lines26 and RNA27,28 have all been used in an effort to mount a specific anti-tumour response by the immune system.

Preliminary studies in humans using DC alone or DC loaded with antigen have been conducted in patients with advanced malignant disease. A feasibility and toxicity study was performed using monocytes isolated from patients with melanoma. Both cell subsets were demonstrated to have sufficient numbers of MoDC could be generated in vitro to fulfil dose requirements. Cryopreserved MoDC were then administered to patients without any adverse effects.29 This study paved the way for further DC studies where DCs loaded with tumour lysate were injected into patients and anti-tumour immunity was shown to be tumour-specific, T cell activation and IgM/IgG antibody production30,31. Taken together, these studies demonstrate the potential beneficial use of DC-based vaccines. The results of recent clinical trials and recent advances in DC vaccination are further discussed by Dr Hart and his group below.

Conclusion

There have been many advances recently in the field of cancer immunotherapeutics for Cancer Research. Australian National Health and Medical Research Council, Canberra, ACT, 2601, Australia

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Cancer Forum  n Volume 26 Number 2  n July 2002

n cell surface differentiation antigens, including glycoproteins
n hematopoietic differentiation antigens – glycoproteins of malignancies, and include:
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surface antigens in solid tumours) are poorly defined. They and tumours2. It is often the case that molecular nature and
Identification and characterisation of TAA reactive to mAbs
also by at least one subset of normal adult cells. However,
treatment of cancer, and a growing number of mAbs are being made possible with the advent of phage display technology, originally described in 1985. Phage display allows selection of proteins, such as antibodies and antibody fragments, with specific or novel functions. Most antibody display libraries are constructed by cloning the antibody repertoire either from immune or naïve sources into phage display vectors, resulting in antibody fragments being expressed as fusions with coat proteins of bacteriophage, while the DNA encoding the fusion resides within the virion. Important advances in phage display technology include development of libraries with synthetic complementarity-determining regions, and affinity maturation of conventional antibodies. Production of fully human mAb in immunised transgenic mice has also emerged as an important technology that is currently in early phase clinical trials. Engineered bispecific antibody fragments, designed to mimic the activity of the natural trispecific antibody, mabthera (CAMPATH-1H, a humanised version of rat anti-CD52 mAb, which is licensed for treatment of refractory chronic lymphatic leukemia in the USA, had been shown to be a potent recruiter of effector cells in vitro, and is thought to operate via this mechanism in cancer patients16.

Receptor binding and signalling inhibition
The binding of mAb to growth factor receptors expressed on tumour cells may result in blocking of ligand binding to the receptor, and subsequent inhibition of receptor protein tyrosine kinase phosphorylation. A downstream activation of ERKs, p38, JNKs, and caspase cascades, including glycoproteins (such as carcinoembryonic antigen (CEA), sialic T antigen (TAG-72), polymorphic epithelial mucin (FEM), epithelial cell adhesion molecule (E cad), biliary proteins, prostate-specific membrane antigen (PSMA) and prostate-specific antigen (PSA)), glycolipids (such as gangliosides, gd2, GD2, GM2) and carbohydrates (such as blood group-related antigens, alpha and beta chains).

Receptor binding and signalling inhibition
The development of genetic engineering has been central to the clinical use of antibodies. This classic version of chimeric mAbs (constructed from variable regions derived from murine Ab, and constant regions derived from human Ab) and humanised antibodies (mAbs constructed with only the complementarity-determining regions from a mouse, and the remainder of the variable and constant regions derived from a human source). In addition, primatised mAbs, which are constructed from variable regions derived from Cynomolgus macaque complement regions from a human source, have also been described. Production of fully human antibodies and antibody fragments in vitro has been made possible with the advent of phage display technology, originally described in 1985. Phage display allows selection of proteins, such as antibodies and antibody fragments, with specific or novel functions. Most antibody display libraries are constructed by cloning the antibody repertoire either from immune or naïve sources into phage display vectors, resulting in antibody fragments being expressed as fusions with coat proteins of bacteriophage, while the DNA encoding the fusion resides within the virion. Important advances in phage display technology include development of libraries with synthetic complementarity-determining regions, and affinity maturation of conventional antibodies. Production of fully human mAb in immunised transgenic mice has also emerged as an important technology that is currently in early phase clinical trials. Engineered bispecific antibody fragments, designed to mimic the activity of the natural trispecific antibody, mabthera (CAMPATH-1H, a humanised version of rat anti-CD52 mAb, which is licensed for treatment of refractory chronic lymphatic leukemia in the USA, had been shown to be a potent recruiter of effector cells in vitro, and is thought to operate via this mechanism in cancer patients16.

Mechanisms of action of unconjugated antibodies

Unconjugated mAbs may induce therapeutic effect by a variety of mechanisms, including immune adjuvant activity, cytokine-mediated effector mechanisms, and direct cytotoxic mechanisms, including complement-mediated cytotoxicity (CMTC). Other mechanisms that contribute to tumour-specific toxicity include: the ability of antibodies to recruit activated T lymphocytes and natural killer cells, which can mediate effector cell mechanisms involving NK cell and macrophage cytotoxicity; the ability of antibodies to recruit activated B cells; and the ability of antibodies to recruit activated T cells, which can mediate effector cell mechanisms involving T cell cytotoxicity, such as the ability of antibodies to recruit activated T cells.

Mechanisms of action of unconjugated antibodies

Hematopoietic differentiation antigens
B lymphocytes and plasmacytoid dendritic cells are the major source of antibodies. The main function of these cells is to secrete antibodies, which are a class of immunoglobulin (Ig) molecules that can bind to and neutralize a wide range of pathogens, including bacteria, viruses, fungi, and parasites. Antibodies are composed of four polypeptide chains (two heavy chains and two light chains) that are linked by disulfide bonds, forming an antigen-binding site.

Mechanisms of action of unconjugated antibodies

Bone marrow transplantation
Bone marrow transplantation (BMT) is a medical procedure in which stem cells from a donor are used to replace damaged or destroyed bone marrow. The aim of BMT is to provide a normal immune system or a type of therapy approach is currently under investigation in clinical trials.

Engineered antibody fragments
Smaller forms of antibodies have been made in an attempt to improve penetrability into avascular tumours. Engineered antibody fragments include bispecific antibodies that can target two independent targets, bispecific T-cell engagers (BiTEs) and tumour necrosis factor (TNF) receptors. Monoclonal antibodies can also serve as immunogens for cancer vaccines through the use of peptide libraries or phage display technology.

Mechanisms of action of unconjugated antibodies

Recombinant antibodies as targeting systems
Conjugated monoclonal antibodies
Some antibodies, which target neoplastic cells, do not induce cell death by themselves. Instead, they deliver natural toxins, radioisotopes, chemotherapies, cytokines, or cytokine receptors directed against the target cell. The mAbs may induce antibody-dependent cellular cytotoxicity (ADCC), which is mediated by the interaction of the Fc receptor on the effector cells with the Fc region of the antibody. Alternatively, the mAbs may induce apoptosis of the target cells through the Fas ligand (CD95L) pathway.

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Chimerisation and humanisation of antibodies
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Antigen-presentation network cascade
Monoclonal antibodies can also serve as immunogens for cancer vaccines through the use of peptide libraries or phage display technology. Anti-tumour antibody fragments conjugate to antibody-binding antigenic epitopes, which select for the appropriate complementary determinant region (CDR) of the antibody in the CDR of the antibody.

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Monoclonal antibodies in combination with other treatment modalities

The combination of monoclonal antibody therapy with other treatments, particularly chemotherapy and radiotherapy, has been shown in in vivo models and in clinical trials to have potential additive or synergistic effects. The mechanisms of this effect are complex, and related to the interactions between conventional therapy mechanisms of action, and the effect of FC function or signaling inhibition on tumor cell proliferation and repair mechanisms. The majority of data comes from combining mAb-based therapy with chemotherapy. The combination of radiotherapy with EGFR-targeted mAbs, and chemotherapy with immunotherapy, has also been shown in in vivo models – and in early phase clinical trials - to have synergistic effects. This approach of combination therapy will have increasing importance in the development of mAbs as therapeutics, particularly in solid tumours.

Summary and future directions

It is now apparent that the choice of target antigen, immunogenicity of antibodies, extent of antibody half-life, potential of antibodies to recruit immune effectors, decisions on conjugation partners and mAbs manufacturing processes are critical in the development of monoclonal antibodies for cancer therapy. Advances in hybridoma technology, and more recently developments in antibody engineering, have been essential for progress in immunoconjugates. Optimisation of monoclonal antibody therapeutics will be directed towards design of better antibodies and immunoconjugates, enhancement of tumour-specific cytotoxicity, and the development of more effective combinatorial therapy approaches. Consequently, the full potential of mAb-based immunotherapy is yet to be reached.

References

[3] A S A Im, C Gomez-Manzano, J Fueyo, T J Liu, et al. “Antiangiogenesis effective combination therapy approaches. Clearly, the full potential of antibodies to recruit immune effectors, decisions on conjugation partners and mAbs manufacturing processes are critical in the development of monoclonal antibodies for cancer therapy. Advances in hybridoma technology, and more recently developments in antibody engineering, have been essential for progress in immunoconjugates. Optimisation of monoclonal antibody therapeutics will be directed towards design of better antibodies and immunoconjugates, enhancement of tumour-specific cytotoxicity, and the development of more effective combinatorial therapy approaches. Consequently, the full potential of mAb-based immunotherapy is yet to be reached.

Table 1: Selected examples of monoclonal antibodies currently in clinical use and development

<table>
<thead>
<tr>
<th>Antigen Target</th>
<th>Cancer</th>
<th>Antibody</th>
<th>Antibody Type</th>
<th>Company / Institute</th>
<th>Trial Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2/neu (ErbB-2)</td>
<td>Breast, Colon, NSCLC</td>
<td>Herceptin (Trastuzumab)</td>
<td>Humanised</td>
<td>Genentech</td>
<td>FDA approval 1998 (breast cancer)</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Solid Tumours</td>
<td>Cemiplimab</td>
<td>Humanised</td>
<td>Moderna</td>
<td>FDA approval 2020 (solid tumors)</td>
</tr>
<tr>
<td>EGFR</td>
<td>Head and Neck, NSCLC, Colon</td>
<td>IMC-C225 (Eributin)</td>
<td>Chimeric</td>
<td>Immunomedics</td>
<td>FDA approval 2010 (ESMO)</td>
</tr>
<tr>
<td>VEGF</td>
<td>Solid Tumours</td>
<td>Bevacizumab</td>
<td>Humanised</td>
<td>Genentech</td>
<td>FDA approval 2004 (solid tumors)</td>
</tr>
<tr>
<td>VEGFR-2</td>
<td>Solid Tumours</td>
<td>IMC-1C1</td>
<td>Chimeric</td>
<td>Immunomedics</td>
<td>FDA approval 2015 (ESMO)</td>
</tr>
<tr>
<td>A33</td>
<td>Colorectal</td>
<td>huA33</td>
<td>Humanised</td>
<td>LIGC</td>
<td>FDA approval 2016 (ESMO)</td>
</tr>
<tr>
<td>Lewis-</td>
<td>Solid Tumours</td>
<td>SGN-15 hu3S193</td>
<td>Chimeric</td>
<td>Seattle Genetics</td>
<td>FDA approval 2015 (ESMO)</td>
</tr>
<tr>
<td>GD3</td>
<td>Melanoma</td>
<td>KW-2871</td>
<td>Humanised</td>
<td>Kyowa Hakko Kogyo</td>
<td>FDA approval 2015 (ESMO)</td>
</tr>
<tr>
<td>M20/GN</td>
<td>Renal, Biliary</td>
<td>cG250</td>
<td>Chimeric</td>
<td>LIGC</td>
<td>FDA approval 2016 (ESMO)</td>
</tr>
<tr>
<td>PSMA</td>
<td>Prostate</td>
<td>PSMA0691</td>
<td>Humanised</td>
<td>Millennium</td>
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</tr>
<tr>
<td>CTLA-4</td>
<td>Prostate, Melanoma</td>
<td>MxD010</td>
<td>Humanised</td>
<td>Medarex</td>
<td>FDA approval 2016 (ESMO)</td>
</tr>
</tbody>
</table>

Introduction

The dendritic cell (DC), an uncommon type of bone marrow-derived leukocyte, is widely acknowledged as the most effective antigen presenting cell (APC) and has the unique capacity to initiate and control immune responses against naive and tumour antigens. These cells have generated immense interest in the scientific community because of their potential use as "autologous adjuvants" in cancer vaccination.

DC biology

DC differentiate from early myeloid and lymphoid progenitors. In at least two biological subpopulations are described – the DC1/CD123+ "myeloid" DC and the CD11c+CD123+ "lymphoid" DC. They have different properties. Current suggestions are that the surface marker profile is not only involved in negative and positive signalling and migration to regional lymph nodes through the afferent lymph. The CD11c+CD123- DC migrate directly to the lymph node from the blood stream via high endothelial venules. Monocytes may contribute directly to both populations.

DC integrate signals from the environment to link the innate and adaptive immune systems.

DC in cancer

Abnormalities in cancer

An effective immunologic response to tumour is reliant on a coordinated immune response, a major component of which is the tumouricidal role played by CD8+ cytotoxic T lymphocytes (CTLs). In a normal individual, tumour antigen from transformed cells is taken up by DC, processed, and presented to T and B lymphocytes in secondary lymphoid tissues. The ensuing interaction between DC and an antigen-specific naive CD8+ T cell results in clonal proliferation and expansion of CD8+ effector and memory T cells. Effector CTL are then able to recognise and kill antigen-bearing tumour cells in the periphery, preventing the spread of the tumour.

Once a malignancy becomes established, it is clear that DC, along with the immune system, have failed in their role of immunosurveillance. There is a multitude of reasons for this to have occurred. Abnormal DC numbers have been described in some cancer patients and abnormal DC function has been noted in breast adenocarcinoma, renal cell carcinoma, prostatic adenocarcinoma, basal cell carcinoma, multiple myeloma, melanoma and transitional cell carcinoma of the kidney and bladder.

DC function can be suppressed by the release of tumour-derived inhibitory factors. Interleukin-6 (IL-6) from melanoma, multiple myeloma and bronchogenic carcinoma can impair DC function. IL-6 and macrophage colony stimulating factor (M-CSF) released by renal cell carcinoma inhibited the differentiation of CD14-expressed DC from CD34+ progenitors. Vascular endothelial growth factor (VEGF) release from human tumours can alter dendritic cell maturation, and high serum levels of VEGF have been associated with a decreased stage of immature myeloid cells in the blood, which in turn were closely correlated with the stage and duration of clinical neoplastic disease.

In multiple myeloma, DC numbers are relatively normal but CD86 induction is decreased. In breast cancer, there was a low or absent expression of the costimulatory molecules CD80 and CD86 on DC obtained from the tumour site. In addition, data from analysis of tumour cells from patients with transitional cell carcinoma and prostatic adenocarcinoma have revealed that DC are not effectively recruited and activated in tumour tissue. In melanoma, DC appear to be able to present tumour antigen to T cells, however they are not able to induce the CD8 T cell receptors when it is presented in conjunction with the I and II molecules and transported to the cell surface. Peptide from the tissues. Exogenous and endogenous protein antigen associated with the presentation of the tumour antigen to T cells, however they are not able to induce antigen processing and vaccination.

The use of DC in cancer immunotherapy is based on two main principles. The first is that cancers express either unique tumour-specific antigens or self-antigens that are abnormal in quantity or quality. These antigens are processed by the tumour cell and expressed in conjugation with self-MHC molecules, providing the immune system with a recognisable therapeutic target. The second is that DC function is abnormal in vivo and can be normalised in an ex vivo setting, free from the negative influences of the tumour. The appeal of laboratory-based, in vitro expansion of DC is that, in contrast to direct in vivo peptide vaccination, the process can be performed in a defined manner with specific control over such factors as DC activation and antigen loading.

DC preparations

There are three main preparations currently in use for DC immunotherapy.

The most commonly used preparation is the monocyte-derived DC (MoDC). Large numbers of these DC-like cells can be generated from peripheral blood mononuclear cells and used in vaccination studies, but are extremely cumbersome to produce and are sometimes expensive.

Blood DC precursors (BDC), obtained by immunomagnetic selection from leucopheresis products, are the focus of increasing attention. This protocol requires a long period of culture, ex vivo peptide vaccination, the process can be performed in a defined manner with specific control over such factors as DC activation and antigen loading.

CD34 cells can be differentiated into DC in vitro and have been used in vaccination studies, but are extremely cumbersome to produce and are sometimes expensive.

Tumour antigens

In addition to the choice of DC preparation for vaccination, the selection of tumour antigen for vaccination is of great importance. The ideal tumour antigen for vaccination is one that is highly specific for tumour tissue and not expressed on normal tissues. It should be processed by the tumour cell and contain immunogenic epitopes that are presented in conjunction with MHC molecules. It should be stable and not susceptible to degradation. Although not entirely necessary, targeting a tumour antigen that is of vital functional importance to the tumour would be a considerable advantage.

Unfortunately, at our current level of knowledge, we are only able to identify tumour antigens that fulfil some of these ideals.

The form of antigen presentation is also of vital importance. There is a spectrum of options from peptide antigen encoding a single MHC restricted epitope to various forms of whole tumour antigen, which encompasses a range of epitopes specific for multiple different MHC alleles. As the range of antigen and epitope coverage increases, so does the likelihood of autoreactive T cells. Despite the theoretical risks, there is relatively little evidence to suggest that autoreactivity will pose a major impediment to anti-tumour vaccination.

Clinical trials

Since the first clinical trial of DC immunotherapy was published in 1996, a large number of trials in many different diseases has been undertaken. Virtually all of these trials have been phase I trials and only recently have phase II trials commenced (for a review of current clinical trials see reference 3). Perhaps the most common malignancy to be examined thus far is melanoma. Although comparatively few of these studies have been formally published, trials using MoDC and CD34DC have generated encouraging results with objective clinical responses in 20-30% of patients with late stage disease. Some of these responses have been complete and long-lasting. Associations have been noted between the clinical response (including cutaneous vitiligo) and immunologic response. In one trial, in which subjects were vaccinated with CD34DC pulsed with four melanoma-derived peptides, clinical responses (albeit in an early stage follow-up) were correlated with the number of peptide-specific immunologic responses. The clinical response rate of DC trials in melanoma certainly seems encouraging and warrants further investigation by randomised controlled trial, particularly in early stage disease.

Another tumour in which promising results has been seen is renal cell carcinoma. This tumour has been historically associated with responses to non-specific immunotherapies such as IL-2 and lymphokine activated killer cells (LAK). Excellent results were achieved (4/17 attained complete remission) in renal cell carcinoma patients through vaccination with allogeneic DC.

Multiple myeloma and non-Hodgkin's lymphoma are promising candidates for immunotherapy, particularly in the setting of minimal residual disease post-autologous transplant. A recent controlled trial of non-Hodgkin's lymphoma patients showed impressive results after vaccination with idiotypic protein pulsed DC. Even more impressive than the 20% complete response rate after one dose was that patients with disease progression after the first vaccination subsequently responded to further treatments. The identification of more broadly applicable tumour antigens than immunoglobulin idiotype will provide increased impetus to study DC vaccination in these diseases.

Prostate carcinoma has been evaluated in a number of trials but clinical responses are inconsistent, mainly being restricted to stabilization of tumour marker levels. CTL responses after vaccination with MoDC have been noted in vivo in breast, ovarian and colon adenocarcinoma amongst others, demonstrating the feasibility of this approach.

Vaccination protocols

One of the problems with assessment of the accrued data is that many of the reported trials have studied small numbers of patients treated with multiple different vaccination protocols. As a consequence, a consensus on the optimal choice of DC preparation is not yet apparent. Available evidence suggests that immature MoDC may be more effective than mature DC in terms of vaccine and timing of antigen loading has not been reached. One of the reasons for this is that direct correlations between clinical responses and peripheral blood immunologic responses have not been forthcoming, although the vast majority of clinical responses occur in patients who have an immunologic response. This may be due to the fact that the immune response in the tumour does not always reflect that seen in the local tumour environment.

Some tentative conclusions regarding DC preparation can be made. It appears that BDC, MoDC and CD34DC are all feasible alternatives for an immunotherapy program. No head-to-head comparisons have been made in an in vivo setting and there is only limited in vitro data to support one preparation over another. Available evidence suggests that immature MoDC may not be as efficient as mature MoDC. Human vaccination studies have suggested that the use of immature MoDC may lead to antigen-specific tolerance, clearly an undesirable outcome for tumour immunotherapy. Certainly,
patients with metastatic melanoma (F O Nestle – unpublished vaccination. This appears to be less commonly seen than intuitively As most tumour antigens are self-antigens, there is always
of DC under ultrasound guidance have also shown clinical and
Techniques such as the 51chromium release cytotoxicity assay
is also being used to define the nature of a response at the
most accessible tissue for monitoring is obviously the peripheral
Efforts are also underway to define immunologic “surrogate”
Complications
To date, relatively few complications have been seen with DC
immunotherapy. But for the majority of patients, the only complication is fever or the occurrence of a local injection site reaction. Biopsy-
To date, relatively few complications have been seen with DC
Complications

Future directions
Paradoxically, the future of DC immunotherapy requires some backtracking in the laboratory. A plethora of clinical trials have been completed with great initial enthusiasm, however it is now becoming apparent that use of immature DC preparations may be quite detrimental. Clearer characterisation of the in vitro conditions required to break tolerance to self-antigen is critical. This includes careful monitoring of the immune response profile early in any clinical trial. Future directions include targeting antigen to various cellular compartments, including helper epilopes or constructs, improving activation of the upstream signaling pathway to improve in vivo induction of immune responses. The promising indications that the effort expended in the many aspects involved may yield great dividends.

References
Vaccines to prevent and treat cervical cancer

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Many epidemiologic studies now support a hypothesis, formulated 20 years ago by Gissmann and Zur Hausen, that papillomaviruses (PVs) are a major cause of cervical cancer and other anogenital malignancies. PVs come in many varieties or genotypes. Persistently infected with one of a high risk of developing cervical cancer. Following persistent infection with a high risk HPV type, the World Health Organization has determined that high risk HPV infections are a "necessary" factor for development of cervical cancer, and the contribution of other identifiable genetic and environmental factors appears to be relatively small. Thus, prevention and control of cervical cancer might best be achieved through vaccine-mediated prevention of HPV infection, and/or elimination of persistent infection at a high risk of developing squamous malignancy. Initial work on therapeutic vaccines for cervical cancer allowed observations on production of PV virions which became the basis of current vaccines designed to prevent infection with HPV.

Natural immune responses to HPV infection
Point the way to a vaccine

Generally, effective viral vaccine work through generation of neutralising antibody. Protection is proportional to the amount of antibody available at the virus entry site, and lasts as long as neutralising antibody persists. Larger scale longitudinal studies of papillomavirus seroepidemiology are available only for a limited subset of genital PV genotypes. These demonstrated that papillomavirus infection naturally induces relatively low titres of neutralising antibody, and that the antibody may be seemingly acquit and clear infection without ever developing measurable antibody. Thus, serology would appear to have little role to play in screening for risk of cervical cancer. Following natural infection, serum antibodies against PV antigens are detectable in immunological assays depicted on the outer aspect of the virus capsid, and directed to the major capsid protein L1. Such antibodies are genotype specific, and mostly of IgG type, and are present only in low titre in mucosal secretions. The limited epidemiological evidence available to date suggests that prior infection with a particular PV genotype is host protective against further infection with that genotype, though not with other types. Thus, vaccines to prevent PV infection will likely be designed to induce antibodies directed to conformational epitopes of the L1 capsid protein, and would be predicted to be type specific. Papillomavirus cannot be grown in tissue culture or purified in bulk from infected tissues, and these problems have slowed the development of a vaccine for this virus. We were fortunate to observe in 1990 that the L1 capsid protein of HPV16, when expressed in eukaryotic cells using recombinant baculovirus technology, assembled into virus-like particles (VLP), and these VLPs have the basis of the current efforts in HPV vaccine development.

Vaccines to prevent PV infection and cervical cancer

VLP-based vaccines to prevent HPV infection are now in late phase clinical trials. One study, an international meeting included a post-hoc analysis of the results of a number of phase I and II studies of HPV16 specific VLP vaccines based on recombinant L1 virus-like particles. While post-hoc analysis can be deceptive, the results, taken together, suggest that VLPs can elicit absolute protection against new HPV infections of type 16 among individuals vaccinated with a range of doses and formulations of HPV16 VLPs (3 doses in 6 subjects), and several incident cases (nine in 129 subjects) amongst those given placebo vaccine. Similar numbers of incident cases of HPV infection with other genotypes in both groups confirmed that a dose-unrelated effect of placebocontrolled studies and the type specificity of vaccine-induced host protection. Several reported studies in human volunteers of VLP-based HPV16 VLPs (16) show seroconversion with safety profiles and almost universal induction of high titres of virus-specific antibody, suggesting strongly that PV vaccines are likely to be at least partially effective in prevention of new infection with the high risk HPV genotypes. Modelling the decline antibody titre following vaccination in the early phase human studies suggests that protection against infection will persist, like the protection following immunisation with the particle-based vaccine for Hepatitis B, for several years if not decades. Animal and human studies suggest that it should be possible to induce simultaneous protection against many types of PV with multivalent vaccines, to levels which have yet to be tested, and priming through past infection with one genotype may limit the ability of the immune system to respond adequately to other types incorporates into a multivalent vaccine, an issue not easily resolved. Mucosal antibody seems to be induced by systemic delivery of VLPs and can also be induced or boosted by mucosal delivery. This mode of delivery also allows study of the concept of be of comparable duration and protection as systemic delivery before it could be considered a preferred delivery route for vaccines in developing countries. Confidence that VLP-based vaccines have the potential to prevent PV infection has focused on both the cost-effectiveness and the feasibility of how these vaccines could be delivered to the developing world to have an impact in preventing cervical cancer. A potential advantage to local, cheap and simple production of VLPs has led to exploration of production of VLPs in plants and other simple expression systems.

Other means of inducing protection against PV infection have been tried in animals, and vaccine candidates are cheap to produce and heat stable, and may overcome some of the difficulties of delivering VLP vaccines to the developing world – where currently no vaccine program accepts women for HPV vaccination and are likely to be inadequate for the large scale production of PV vaccines. DNA vaccination, in which recombinant DNA technology, assembled into virus-like particles (VLP), and these VLPs have the basis of the current efforts in PV vaccine development.

References
2 J J Carter, J A Koutsky, J P Hughes, S K Lee, J Sayers, K Napot, D A Galloway. "Comparison of human papillomavirus types, 16, 18, and 6 infection in the squamous epithelium of vulvar and vaginal skin lesions, which lack inflammation necessary to recruit innate immune responses. Against this background, what has been achieved so far by ourselves and others – recently reviewed by Bredt – is to demonstrate firstly that the PV-structured proteins are not only immunogenic, but vaccines which can be used to prevent the grafting of transplantable tumours expressing these antigens, and in some cases to cause partial regression of existing tumours. For cotillion rabbit papillomavirus virus, which is not a major cause of cervical infection has also been demonstrated. The optimal choice of antigen, means of production, dose, route of delivery, and frequency of immunisation have all been established, though many such delivery systems have been proposed and have shown to be of benefit in at least one animal model. Patients with cervical or other HPV-associated cancer or pre-cancer have been immunised with E6 and E7, and these studies have demonstrated that these proteins are immunogenic, and that there are hints of potential efficacy for cervical cancer. The next steps undertaken by the centre demonstrated immunogenicity of HPV6 VLPs without adjuvant in patients with existing warts, and hinted at possible therapeutic efficacy.

A major effort will be needed to develop laboratory assays that predict vaccine efficacy that might be used to allow cost-effective dose-finding, and therapeutic vaccines in man. There is therefore great interest in the epidemiological studies currently being undertaken, to evaluate whether viral load is predictive of clinical outcome for PV, which has not been the case for other viruses. Similarly, studies of cellular immune responses to vaccines in man are being undertaken, though the constraint of only being able to access blood, and in limited quantities, creates practical problems which even the newer techniques of tetramer technology, ELISPOT, and intracellular cytokine staining have not yet overcome.

Conclusions
Vaccines to prevent papillomavirus infection, using papillomavirus virus-like particles to induce neutralising antibody, are in clinical trial and show all the characteristics likely to be associated with success. Results warrant global planning for the deployment of these vaccines within a decade, as part of a program to prevent cervical cancer.

Vaccines designed to treat existing papillomavirus infection, by inducing therapeutic cellular immunity targeted to viral proteins, are at a much earlier stage of development. The wide choice of potential and proposed antigens, routes and mechanisms of delivery, and possible treatment regimens suggest that to move the field forward, surrogate assays for the relative efficacy of different vaccine approaches are required. These assays might be based on reduction in the load of virus infection following immunisation, and need to be validated in animal models and in man.

Immunotherapy of melanoma

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Why?

Melanoma is a cruel disease. The most recent Australian figures indicate that over 8000 cases of melanoma were reported in 1997 and that approximately 900 people died of the disease that year. Overall, because most melanomas are diagnosed early, the five-year survival for melanoma is more than 90% and Australia in fact leads the world in this respect. However, for those with advanced disease or metastatic disease or metastatic disease, the outlook is very poor. The one-year survival of metastatic melanoma is 41-59% and the median survival is approximately 7.5 months, although this varies according to the site of metastasis. No intervention has been shown to improve the outcome of patients with metastatic disease. Clearly, better treatment approaches are required.

Tantalising evidence that immune responses may alter the outcome of patients with melanoma. Many of these patients have circulating antibodies or T cells specific for particular tumour antigens. This does not prove a cause and effect relationship, since a cell population can have identical melanomas and that the immune response is an epiphenomenon. However, it is a consistent observation and the hypothesis that immune responses help to control some cancers is reasonable.

Interleukin-2 (IL-2) is approved for use for patients with metastatic melanoma in the USA but not in Australia. Although responses are infrequent and toxicity is high, the small proportion (about 5%) of patients who have achieved a complete response to IL-2 have a high probability of long term complete remission and presumed cure. This is very rare in conventional chemotherapy and indicates a substantial difference in the mechanism of action of this agent – induction of immune memory. Many of these patients develop viltige due to T cell mediated killing of normal melanocytes, indicating that the immune response is specific for antigens in the cells of the melanocyte lineage. The development of viltige in these patients indicates a higher probability of a therapeutic response to dose IL-2 is both expensive and very toxic. Current work is concentrating on approaches that may be less toxic, more effective and based on known antigens specific for particular tumour types. Taken together, these observations indicate that melanoma is capable of being controlled by immunological responses. The best way of eliciting these responses is not yet known.

What?

Many approaches have been used for immunotherapy of melanoma. This very much is a strong indicator that none of these approaches have been particularly successful thus far. Initial work concentrated on using non-specific immunostimulants such as BCG or sources of undefined antigens such as tumour cell extracts or lysates. Since the first human cancer antigens that could be recognised by T cells were defined, the field has advanced rapidly. Numerous potential vaccine targets are now available, and there are also many new adjuvants that can predispose towards a T cell response and are required to kill cells expressing these intracellular antigens.

In the case of melanoma, most work involving defined melanoma antigens has used either antigens specific for cells of the melanocyte lineage (and therefore expressed also in normal melanocytes), or antigens that are relatively specific for cancer cells and not present on normal melanocytes (or CT antigens). The latter group is particularly appealing since the proteins in this family are expressed by a broad range of cancers. Expression in normal tissues is restricted to cells such as spermatorrheas, which do not express HLA class I molecules and are not subject to T cell killing.

One antigen of particular interest is the CT antigen NY-ESO-1, initially identified from a patient with oesophageal cancer who had circulating antibodies specific for this protein. NY-ESO-1 is expressed in a wide variety of cancers and is very immunogenic: spontaneous immune responses to NY-ESO-1 occur in 50% of patients whose tumours express this antigen. Both antibody and T cell responses are seen de novo, and patients treated with NY-ESO-1 peptides commonly develop T cell responses. Our group and others are investigating various ways of using NY-ESO-1, including peptide-based approaches as well as using the recombinant protein.

In view of the fact that immune responses may take several months to become apparent, it was logical to combine immunological approaches with conventional cytotoxic chemotherapy in order to achieve a synergistic effect to subdue a longer term immunological effect. Although there is a general belief that chemotherapy impairs immune responses, the immunosuppression seen after most cytotoxic treatments is primarily related to neutropenia. There is little evidence that memory responses to viral antigens are impaired unless immunosuppression accompanies chemotherapy. Various regimens combining chemotherapy and immunotherapy (“biochemotherapy”) have been tried and these have been reviewed recently. Single arm studies indicated good responses, but this was schedule dependent – ie responses when the two modalities were given concurrently were superior to those in which the chemotherapy preceded the immunotherapy. Perhaps the cell death induced by the cytotoxic agents then provides a larger pool of antigens that can then stimulate a subsequent immune response that is more effective.

A recent phase III trial comparing chemotherapy with conventional chemotherapy was disappointing. Although the experimental arm had an improved response rate and a significant although minor benefit in terms of progression-free survival, overall survival was not significantly prolonged. The highly selected study population had substantial toxicity in the experimental arm. However, long term responders have been described and this regimen can act as a basis for future work, having proven the principle.

How?

Much of the work to date in melanoma immunotherapy has been empirical. Observations made in vitro or in animal models, have been turned to humans, and high hopes have been held for useful anti-tumour responses. However, with few exceptions, the results of these approaches have been disappointing. Obviously, the immune system is capable of controlling large, or even metastatic tumours (ie in the bone of the transplanted kidney). The difficulty is that cancers arise from the cells of the host and are not allogeneic. Although they are not normal cells, they are insufficiently abnormal to trigger a potent anti-tumour response, and such responses that must be addressed if these approaches are to be successful.

Tumours have evolved to down-regulate or evade immune responses, but this can be overcome. If it is possible to elicit an immune response against a cancer, anti-tumour responses can often be observed. This is probably the mechanism of action of BCG in bladder tumours. Similar effects have been seen in melanoma, which will often regress when injected with cytotoxic drugs, particularly if the case of high dose IL-2. It is possible that its pharmacological toxicity may be an important part of its effect, rather than direct effects on cells of the immune system, since interventions to decrease the toxicity of IL-2 also abrogate its efficacy.

It is logical to assume that a vaccine delivered in such a fashion as to cause an appropriate “danger” signal is the one most likely to elicit a useful immune response. Such signals might be provided either by the vaccine itself or associated cellular effectors such as T cells or DC might be manipulated ex vivo so as to allow optimisation of both antigen presentation and of functional activation. The area of DC biology is reviewed elsewhere in this issue.

Where and when?

So far, most work in cancer immunotherapy has involved patients with advanced disease. Although these patients offer the pool of antigens that can then stimulate a subsequent immune response if they can be induced, they are probably the worst group to study if the aim is to optimise the vaccination approach. Patients with advanced cancer are often inherently immunosuppressed due to their disease, their poor nutrition or in some cases their treatment. Their cancers are usually progressive, sometimes rapidly. Because an immune response can take weeks to months to become apparent it will become apparent – a risky assumption, it is likely that these patients will encounter problems due to their progressing cancers before an immune response has a chance to develop. In patients with metastatic melanoma means that if a course of vaccination lasts for three months, many patients will not be able to complete it. In one sense, it is surprising that clinical effects of immunotherapy have ever been seen in this population.

Early immunotherapy studies in melanoma used approaches that were thought to be good ideas but had not been validated in humans. Clinical responses were rare, but significant toxicity was recorded. Because of the infrequency and unpredictability of clinical responses to treatment, valid immunological surrogate endpoints were required. Until recently these assays were not available. Newer assays are now available that are more reproducible and sensitive (reviewed in reference 16). For the first time, immunological responses can now be characterised and measured, finally raising the possibility of optimisation of vaccine protocols.

For this reason, several investigators including our group are performing a series of small studies involving patients who have had cancers that express the antigen of interest but which have not been removed. These patients are thought to have a risk of relapse of at least 25% over five years. For melanoma, this means patients with a primary melanoma of 1.5-5.5 mm and those with nodal disease or resected distant metastases have a higher risk of recurrence and are also eligible. Depending on the nature of the study, it is sometimes necessary to limit eligibility to patients of a particular HLA type. Patients in these studies are usually able to finish a three-month course of vaccination without a significant risk of relapse of their melanoma. This then provides the opportunity to determine whether a vaccination strategy that seemed a good idea on paper in fact able to elicit measurable immunological responses. The underlying assumption is that only if an immune response is measurable will it be able to be translated into a clinical response. This assumption has never been proven, but it provides a reasonable starting point.

Where to now?

As a result of these observations at both the preclinical and clinical level, it is possible to conceive of a strategy that is most likely to be effective. It is important to identify antigens that are widely expressed and are important to the malignant phenotype so that tumours are not easily able to down regulate their expression. These antigens then need to be delivered in such a way that they may be effective in a population and a vigorous immunological response can be elicited. Our understanding of the basic biology of the process suggests that this will best be done in a context that provides an inflammatory environment in the presence of the antigen. Once an immune response is elicited, it will then be important to sustain it so that effector T cells continue to traffic through the tumour and recognise and killing any residual or recurrent tumour cells. At the same time, consideration must also be given to non-T cell approaches so as to capture the inevitable “escape” mutants.

These approaches may also need to be considered in the context of other treatments such as surgery, radiotherapy, or in combination with newer biological agents such as inhibitors of tumour angiogenesis, receptor tyrosine kinase inhibitors, or cell cycle inhibitors. Once an optimal vaccination strategy has been identified and validated using immunological surrogate measures, it will then be important to test these approaches once again in patients with advanced disease. For patients whose disease is progressing rapidly, it will probably be necessary to combine these treatments with some other intervention in order to change the kinetics of the tumour growth so as to allow time for an immune response to develop. However, it is also likely that one of the most useful applications of immunotherapy will be in the adjuvant setting, when the burden of disease is at its lowest. Trials in this setting can only be justified once the optimal method of vaccination has been determined.

References
Breast cancer and pregnancy: What we know and where we go

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Abstract

While breast cancer is a high profile disease, its association with pregnancy is less often reported. Pregnancy-associated breast cancer or gestational breast cancer (GBC) is defined as breast cancer diagnosed during pregnancy or in the 12 months post-partum. GBC is uncommon, but likely to become more common as women delay pregnancy until they are in their thirties and forties when the chance of developing breast cancer begins to rise. Delays in diagnosis mean that the prognosis for GBC is often poor. Women who become pregnant later in life also run the risk of developing breast cancer before they conceive. These breast cancer survivors then have difficult choices to make about conception.

Research in these areas is based mainly on reports from single institutions. Further research is needed, and in Western Australia a population-based study to evaluate the epidemiology and management of breast cancer and pregnancy is underway. This work will provide fresh evidence on which to base future practice recommendations, and will enable further research to be conducted about the pathological, biological and imaging characteristics of the malignancies in the pregnant and lactating breast.

Introduction

Because of the high incidence and mortality of breast cancer in the developed world, research in this area has been given a high priority and been widely reported to the general community. Breast cancer's association with pregnancy, while uncommon, has been less often reported. More women are choosing to delay pregnancy until their thirties and forties, when the incidence of breast cancer rises. This is likely to lead to an increased risk of pregnancy-associated breast cancer, and more women are likely to develop breast cancer before they conceive. This has major implications for both women and the healthcare system.

At present, the association between breast cancer and pregnancy is uncommon, with estimates of it affecting between one in 3,000 and one in 10,000 pregnancies. Historically breast cancer concurrent with pregnancy, also known as gestational breast cancer (GBC), was thought to carry a poor prognosis. This adverse outlook, and the fact that most clinicians' experience and knowledge of GBC is limited, has continued to impact on the medical psyche. It has also meant that subsequent pregnancy in breast cancer survivors has not been widely recommended. In this paper we will discuss the evidence available, on which clinicians can base their management of women with GBC and breast cancer survivors who may want to conceive. We will also report on a population-based study of these two groups of women, recently commenced in Western Australia.

Gestational breast cancer (GBC)

GBC is defined as breast cancer diagnosed during or in the 12 months post-partum (including lactation). The reported incidence of GBC, based on mainly single institution reports, ranges from 0.76 – 3.8% of all diagnosed breast cancers. Overall, the incidence appears low, but in premenopausal women, incidence of GBC is reported to be between 7-14‰. Pregnancy-associated breast cancers have been reported to have a worse prognosis and are commonly more advanced at presentation (larger tumours and lymph node positive) than non-pregnancy associated breast cancers. However, when matched for age and stage at diagnosis, there is no difference in survival between pregnancy-associated and non-pregnancy associated breast cancers. Ezzat reports on a seven-year survival...
The rarity of GBC means that a randomised controlled trial is not an appropriate method to investigate the clinical epidemiology and outcomes of the disease. In general, most studies published to date relating to breast cancer and pregnancy have been descriptive, consisting of retrospective, single institution series, where over a long period of time only small numbers of women have been recruited. There are only four published series involving more than 100 women. The results of these studies have given us a greater appreciation of how pregnancy may influence the outcome of breast cancer, but have also led to conflicting and confusing information.

The Gestational Breast Cancer Project that commenced in Western Australia (WA) will be the first to use a population-based data set to investigate breast cancer and pregnancy. The project involves collaboration between the WA Safety and Quality of Surgical Care Project and the WA Breast Cancer Research Alliance. Initially this study is retrospective, and has used the WA Record Linkage Project to identify women who were diagnosed with GBC or have survived breast cancer and subsequently conceived since 1982. The WA Record Linkage Project brings together data from a variety of population-based hospital morbidity data, birth and death records, mental health services data, cancer registrations and midwives’ notifications, linked back to 1990. This linkage system is one of the largest in the world.

The use of population-linked health data enables us to explore community outcomes and provides additional information for the knowledge base required for evidence-based practice, in areas where it is difficult to gain such data from randomised clinical trials. We expect to identify about 300 cases of population-based breast cancer (10% GBC and seven subsequent pregnancies per year). The information obtained will be supplemented with data from patient medical records and cancer registry data to provide information on diagnosis, treatment and outcomes of the breast cancer and pregnancy. The project has approval to access named data from the WA Department of Health, and ethics approval from the University of WA and all relevant ethics committees.

Acknowledgements

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References

Living with cancer in Australia

Report of a conference held in Canberra on 4 February 2002

K Kirke AM
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The Charter of Paris Against Cancer is a global call to action against cancer. Its purpose is to foster improved cancer treatment and research worldwide. The Charter was signed on 4 February 2000 by representatives of many nations, including Australia. The preamble to the Charter sets out its purpose.

PREAMBLE

- Deeply troubled by the professional and universal impact of cancer on human life, human suffering, and on the productivity of nations,
- Committed to the humanitarian treatment and equal partnership of people with cancer in the ongoing effort against this disease,
- Anticipating the rapidly rising tide of cancer incidence throughout the globe, in developed and developing nations alike,
- Recognising the need for intensified innovation in all avenues of cancer research, prevention and healthcare delivery,
- Believing that quality healthcare is a basic human right,
- Acknowledging that currently achievable improvements in cancer survival remain unrealised, due to inadequate emphasis on prevention, inadequate funding and unequal access to quality cancer care,
- Certain that lives can and will be saved by increasing access to existing technologies,
- Aspiring to nothing less than an invincible alliance – between researchers, healthcare professionals, patients, government, industry and media – to fight cancer and its greatest allies, which are fear, ignorance and complacency

On the first anniversary of the signing, an inter-faith event was hosted by The Cancer Council Australia (TCCA) in the Great Hall of the University of Sydney.

With the Charter as its lodestar, the Patient Support Committee of TCCA, through its national network of Cancer Councils, organised regional seminars for people living with cancer and their supporters, to explore, discuss and document their expectations and experiences with the healthcare system. In 2001, 42 urban and rural seminars were held, attended by over 900 people in all. From these, 129 priority issues were identified. The themes were grouped in categories as:

- Access to information and support
- Practical issues
- Communication
- Coordination and multidisciplinary care
- Service development
- Community education
- Equity
- Survivorship

With information gathered through this process, a national conference was convened in Canberra on the third anniversary of the signing of the Charter. Called ‘Living With Cancer’, the meeting brought together consumers and health professionals to discuss the issues raised, seek consensus and develop an action plan.

The conference keynote address on ‘Survivorship’ was delivered by Professor Miles Little, from the University of Sydney. The conference then broke into workshops to tackle the priority issues identified at regional seminars by affirming their importance and proposing ways in which deficiencies might be addressed. These were brought back to a plenary session for general scrutiny and endorsement.

The draft report of the conference identified nine areas for attention, and within each area checkpoints for detailed action (Table 1).

The draft report was circulated for comment/sign off by all participants and is now the blueprint for Cancer Councils and consumer groups in initiating action collectively and independently to ensure that all cancer patients in Australia, irrespective of where they live, have access to an acceptable level of advice and support. In this way the aims of the Charter of Paris will be realised in Australia.

Prof Miles Little addressing the Living with Cancer conference

Table 1 – Action points

1. Coordinators of cancer care
   - Specially trained, defined role, funded, qualification
   - Based in treatment centres and regional areas
   - Members of multidisciplinary team/liaison
   - Networked, informed, relieved, supported

2. Education
   (i) Healthcare professionals
      - “The ideal oncology curriculum”
      - Early involvement of palliative and supportive experts
      - Better communicators
      - Understand survivorship
   (ii) Community
      - Cancer as chronic, controllable disease
      - Reduce stigma and discrimination
      - Peculiar needs of people living with cancer

3. Information (and helpful advice)
   - National Cancer Information Service (13 11 20)
   - Quality assurance, accessibility, availability
   - Public and professional awareness of the CIS Business cards with 13 11 20 and “tips”
   - GP referral point

4. Infrastructure (and practical matters)
   - Review of patient, accommodation and transport scheme (PATS) and isolated patient, transport and accommodation scheme (IPTAAS)
   - Accommodation near treatment centres
   - Parking near treatment centres
   - Schedule appointments conveniently
   - Financial relief and respite care

5. Empowerment (patients and carers)
   - Information about options
   - Explanation about possible implications
   - Help with formulating questions

6. Support (for support groups)
   - Guidelines and “tipsheets”
   - Evidence-based guidelines eg narrative therapy
   - Support for informal carers
   - Practical help at community level

7. Standards for care
   - Minimum national standards defined
   - Routine best practice
   - Take luck out of process

8. Research
   - Option to participate in clinical trials
   - Encourage translational, psychosocial, behavioural and epidemiological research to inform Cancer Councils
   - Evaluate existing programs
   - What works and what does not
   - Monitoring quality of life indicators

9. Prevention and early detection
   - Participation rates in screening programs
   - Advocacy for application of current knowledge

Actions/targeted outcomes

Some examples are:

- National review of PATS/IPTAAS by end of 2002
- Increase number of medical schools using the Ideal Oncology Curriculum (all by 2005)
- Training program for cancer care coordinators by 2004
- Increase GP referrals to the CIS by 10% per annum

A copy of the proceedings of the Living with Cancer conference is available on request from The Cancer Council Australia.
In February, Australia’s cancer researchers meet at Erskine House, Dunedin, New Zealand, to review the 14th Lorne Cancer Conference. Over 350 delegates listened to a selection of national and international speakers present their latest data. As usual, the talks covered a wide range of topics, including signal transduction, tumour suppressor genes, immunology, apoptosis and animal models of human cancers. However, a recurrent theme throughout the meeting was the role of the p53 tumour suppressor pathway.

From p53 to therapy

The plenary lecture was delivered by Sir David Lane from the University of Dundee and Cyclacell Ltd, Dundee, Scotland, who discussed the pathway as a target for anti-cancer therapy. p53 is a tumour suppressor protein with potential cell cycle arrest and apoptotic functions. In normal cells, the wild type p53 protein is believed to be maintained in a latent state. Upon exposure to a wide variety of stress signals, this latent wild type p53 becomes activated. The p53 pathway is inactivated in most cancers (including breast, lung, stomach and colorectal) and provides an appropriate target for clinical trials. Lane discussed potential therapeutic strategies based around the p53 pathway, a key regulator of p53, Mdm2, which binds to p53 and directs its degradation via the proteasome. In tumours in which the p53 gene is intact but its function is compromised by loss of upstream signalling pathways, small peptides can be used to target p53 activity. Inactivation can occur through a variety of phosphorylation events that contribute to the regulation of Mdm2 activity. In addition to phosphorylation events that inhibit Mdm2, there are also situations where Mdm2 is actually activated by phosphorylation. This is the case for the Akt kinase. Oren showed that Akt, a well-characterised downstream effector of phosphoinositide 3-kinase, is able to directly phosphorylate Mdm2, leading to its activation and subsequent inhibition of p53.

Selectivity of oncolytic adenoviruses questioned

Oncolytic adenoviruses that have been touted as potential new anti-cancer therapeutics. Most anti-cancer therapies suffer from a lack of selectivity. Not only do they kill the tumour cells, but they often also kill normal cells – resulting in unwanted side effects and morbidity. However, a number of groups have suggested that mutant adenoviruses may be used to selectively target cells. Such viruses have evolved proteins (encoded by the E1a and E1b genes) that are used to deregulate the cell cycle of the host cell to provide an environment conducive to viral replication. Since cancer cells already have deregulated signalling and can be engineered to remove the E1 proteins, the virus should be able to replicate in cancer cells but will be unable to replicate in normal cells. Such E1-deficient adenoviruses should, in theory, eventually cause the loss of tumour cells while leaving normal cells intact.

However, Antony Brarthwaite from the University of Otago in Dunedin, New Zealand, is not convinced that such viruses can cause cancer-specific. He has been testing some of the predictions concerning cancer cell selectivity of adenoviruses using the ONYX-015 virus that is currently in phase III clinical trials. This virus has the E1b-55kV protein deleted, which should it can only replicate in cells with a mutant p53 protein. Brarthwaite presented data showing that the ability of this virus to cause cell death was not restricted by the status of the p53 pathway. Indeed, he found that ONYX-015 killed p33 wild type cells with similar efficacy to the p53 mutant cells. His results thus do not support a case for the ONYX-015 virus being cancer cell selective. He concluded that the therapeutic benefit of ONYX-015 might be due with viral interaction with cellular stress response pathways and not due to the original premise of tumour-specific viral replication.

Complex roles for MMPs in tumour progression

Lynn Matrisian from Vanderbilt University in Nashville presented an excellent overview of the role of the matrix metalloproteinase (MMP) family of extracellular proteases in tumour progression. The concept that tumour-produced MMPs contribute to invasion and metastasis by virtue of their ability to degrade extracellular matrix has been widely accepted for many years. However, Matrisian argued that the role of MMPs is much more complex, and discussed data which challenges some of the early assumptions of how MMPs are involved in tumour progression. Firstly, Matrisian pointed out that MMPs are not, as previously thought, produced by the tumour cells – rather it is the stromal cells that produce the MMPs in response to tumour cells. Matrisian then went on to question the assumption that the primary role with MMPs is to mediate the invasion of the tumour through tissues. Recently, she has indicated that MMPs are involved in the growth of primary tumours, including benign tumours such as colon polyps. The assumption that MMPs act by degrading extracellular matrix also came under scrutiny. While there is little doubt that MMPs do degrade matrix, an increasing number of non-matrix substrates are being described. These include proteins such as tumour necrosis factor α, E-cadherin, CD44 and many more. In fact, the potential for MMPs to have a much broader influence on the tumouring process. All this raises the question as to whether or not MMPs really are appropriate targets for anti-cancer therapies. Certainly the concept that inhibition of MMPs will have clinical efficacy by stopping cells migrating into the vasculature and out into the tissues would seem a very narrow and simplistic view. Indeed, Matrisian noted that non-collagenous type MMP inhibitors have so far been disappointing, although there is some indication of efficacy in early stage cancer. This was somewhat surprising in that there is a large amount of preclinical data suggesting that MMP inhibitors should have clinical efficacy. Matrisian put this down to differences in the way that preclinical and clinical data is obtained. She pointed out that preclinical experimentation is driven primarily by the availability of small-molecule inhibitors. However, clinical trials are more likely to be driven by clinical and/or financial considerations. Furthermore, clinical trials are often carried out on late stage disease, whereas preclinical models can more easily test the benefit of early intervention.

Matrisian concluded by stressing the need for cooperation between basic scientists, clinicians, academics and the pharmaceutical industry to close the gap between preclinical experimentation and clinical trials.

Time to pass the baton

Ashley Dunn, who has been the driving force guiding the Lorne Cancer Conferences since their inception in 1989, announced at the conference that he would step down as chairman of the organising committee. Dunn said that while he had “enjoyed immensely” his association with the conference, he felt it was “time to pass the baton” to the younger generation. He indicated he was confident that the conference was in good hands with Doug Hilton and Warren Alexander taking over the reins.

The surgical management of ductal carcinoma in situ in Australia in 1995

Data on surgical management of ductal carcinoma in situ (DCIS) of the breast in females were collected as part of the National Survey of the Management of Breast Cancer in Australia. The data is comparable to other registries as having treated a new diagnosis of DCIS between 1 April and 30 September 1995. The survey was conducted by a national review team and funded by the National Breast Cancer Centre. The report was prepared by Victoria White and Myee Pruden from the Centre for Behavioural Research in Cancer (CBRC) in collaboration with Dace Shugg from the Menzies Centre for Population Health Tasmania and Melbourne surgeons Paul Kitchen and John Collins.

Two hundred and five surgeons supplied treatment details on 418 DCIS tumours in 415 women. Half of all tumours were detected at BreastScreen clinics, and a further 25% were prepared by Victoria White and Myee Pruden from the CBRC.
The commencement of the new year often presents as a time when people make resolutions for the year ahead. Anti-smoking groups have often used the media during this period to encourage smokers to quit. While anecdotal information suggests that such an approach may be worthwhile, until now there have been no published Australian data to support this strategy. Recently, Dr Raoul Walsh and colleagues published their results from a study which examined current and former smokers’ perspectives on this issue. Current smokers – who were also smoking at the time of the survey (n=251) – and former smokers (n=400) were asked about the influence of both new year and birthday resolutions on their longest period of abstinence or successful cessation attempt. While both new year and birthdays had an impact, new year resolutions were shown to have a small, but significant impact on successful quit attempts. For example, about one in 20 former smokers said his or her successful cessations were associated with a new year resolution. Importantly, the data were collected when there was no funded new year-related quit campaign running, which indicates that expenditure on such campaigns may increase the proportion of smokers who make a serious quit resolution at this key time of the year. This may also be of significance to health providers as additional stimulus for patients to quit.

Cancer Education Research Program (CERP), NSW

Community attitudes and practices in relation to environmental tobacco smoke

Environmental tobacco smoke (ETS) has been identified as a serious cause of acute and chronic health problems in both adults and children. Given recent legislative changes in NSW to introduce smoking enforces it is important that the current views of the community regarding ETS are measured. As part of a larger community survey, Dr Raoul Walsh and colleagues examined the perspectives of the skin and lip cancers. Results are encouraging, of a larger community survey, Dr Raoul Walsh and colleagues measured the views of the community regarding ETS are measured. As part to smoking in enclosed spaces, it is important that the current serious cause of acute and chronic health problems in both environmental tobacco smoke

Breast care: Improving women’s access to a quality breast prostheses service. A research study to inform policy development

An intervention study led by Trish Livingston was undertaken to evaluate prosthesis use among 102 women who had a mastectomy. Women were recruited through 13 major public hospitals in metropolitan Melbourne. The 64 women in the intervention group received full funding for the prosthesis of their choice ($90), while the 34 women in the control group received their hospital's usual funding ($150-$395). An evaluation of the quality of women’s experiences in relation to their first prosthesis was conducted, with the women being interviewed shortly after receiving their prosthesis and then again three and six months later.

Over 80% of women found the administrative procedures to be extremely easy. Compared to women in the intervention group, women in the control group reported that cost was an important influence on their choice of prosthesis. Women in the intervention group rated the hospitals’ usual funding level significantly higher (86%) than women in the control group (50%). The most important features for women choosing a prosthesis were the shape of the prosthesis, whether it looked natural and how comfortable it was.

The results of this research, which was funded by the Department of Human Services and BreastCare Victoria, will inform recommendations on policy development and administrative arrangements in order to improve equity and satisfaction for women who purchase breast prostheses.

Cancer statistics monograph series

In February 2002, the centre released the second publication in its cancer statistics monograph series, entitled Sun-related cancers of the skin and lip. Each year, approximately 23,400 South Australians are diagnosed with melanocytic and non-melanocytic cancers of the skin and lip. About 90 people die from these cancers each year – 22 of them in their fifties or younger. The monograph shows time trends in incidence, prevalence and survival, and indicates those sectors of the population at special risk where prevention through sun protection is a priority and where the promotion of earlier detection warrants emphasis.

The third publication in this monograph series, entitled Cancers of the breast and female genital organs, was released around the end of May. From the scientific literature, it is estimated that elimination of use of (and exposure to) tobacco smoke, plus a reduction in excess alcohol consumption, would be predictive; to identify the impact by about 80% in breast cancer. Collectively, these cancers account for approximately 890 cancer diagnoses and 710 deaths each year in South Australia.

The monograph shows the comparative incidence of these cancers in South Australia in the context of rates for Australia and New Zealand, and more generally in the context of the world. Lung cancer incidence is continuing to decline in South Australian males, whereas there is an indication of a plateau in women, following an approximate 60% increase during 1971-91. With continuing anti-smoking initiatives, it is expected that females – like males – will show a decreasing incidence of lung cancer. The monograph shows socio-demographic components of the South Australian population at an elevated risk of cancers at these sites. This information is relevant for the planning of preventative initiatives, including initiatives targeted at toxic exposures, such as reducing excess alcohol consumption, dietary improvements, and maintaining good workplace practices and environments.

The fourth in this monograph series, entitled Cancers of the female breast and gynaecological organs, has been drafted. As with the earlier monographs, it is aimed at providing the public, as well as secondary school and tertiary students with a range of information on cancer trends in South Australia, and opportunities for prevention initiatives.

A monograph supplement was also prepared – at the request of staff of the Foundation and South Australian screening services – on risks of cancers of the breast, cervix, and skin (melanomas), and stages of progression of these cancers at diagnosis, by country of birth. This is also being used to evaluate primary and secondary preventative initiatives and to plan future services.

Community support for smoking bans in bar and gaming venues over time

Passive smoking has many known negative health effects, including lung cancer. The only way to fully protect staff and patrons in bar and gaming venues from exposure to second-hand smoke is by implementing complete smoking bans in these venues. Evidence of community support for smoking bans is important in reassuring governments who are considering implementing smoking bans, and also to counter hostility indirectly generated by reduced prevalence of smoking.

The Tobacco Control Research and Evaluation Program conducted representative surveys of approximately 2000 adults throughout South Australia in July 2000 and October 2001, to measure changes in community perceptions of smoking bans. Significant increases in community support for smoking bans in both bar and gaming venues over this period. Support for bans in bars did increase significantly between these surveys. The overall, and the largest increase in support was seen among smokers. Support for bans in gaming venues similarly increased (significantly) to 73%, with the largest increase again observed among smokers. Regular patrons showed high levels of support for bans in both types of venue.

Intramural studies

Research in the Pipeline

n CBRC

Referral of men newly diagnosed with prostate or colorectal cancer to a telephone-based support program

The compelling evidence that providing information, education, and counselling services is beneficial to cancer patients adapting to their illness has led to the development of a strategy to link cancer support resources to cancer patients via their specialists. Trish Livingston and her team have been awarded a seeding grant from the Australian Health Management Group to start a telephone-based support service for newly-diagnosed prostate and male colorectal cancer patients to a telephone outcall service provided by The Cancer Council...
Victoria’s Cancer Information Support Service (CISS). The research aims to determine whether the strategy of having cancer specialists actively refer newly-diagnosed patients to an outcall program starting shortly after diagnosis, leads to improved psychological adjustment to cancer diagnosis and treatment.

The three research arms of the block-randomised control trial comprised:

- specialist referral with CISS outcalls within one week of diagnosis and again at six weeks, three months and six months post-diagnosis;
- specialist referral with one CISS outcall; and
- specialist referral to CISS with contact to be initiated by the patient.

The CISS outcall program will be conducted by nurse counsellors who will follow a standardised agenda to capture the range of issues and needs facing newly-diagnosed cancer patients. To assess the effectiveness of active and passive referrals, patients will be interviewed by telephone at four, seven and 12 months after diagnosis. Specialists’ experience and acceptance of the referral procedure will be assessed, as will the impact of the outcall program on CISS staff and resources.

**CERP**

Coordinated care for advanced cancer: evaluation of two models

Patients with advanced cancer often have long-term complex health needs and complicated treatment regimes. To ensure patient care is optimised, the coordination of cancer care services must be a priority. Afaf Girgis, Sibilah Breen and colleagues are undertaking a study of the effectiveness of two models of coordinated care for advanced cancer (an oncologist/GP model and a telephone caseworker) against current “usual care”. Newly-diagnosed patients with advanced (non-localised) cancer will be recruited from across NSW via the NSW Central Cancer Registry and randomly allocated to one of the three groups. Data will be collected by computer-assisted telephone interview (CATI) at three and six months, and will be used to provide feedback to appropriate care coordinators on issues of concern and recommended strategies for addressing these. In the oncologist/GP model, tailored feedback will be sent directly to clinicians about patient outcomes, for use during routine visits by that patient. In the telephone caseworker model, feedback will be sent to the patient’s nominated caseworker, who will proactively phone the patient at six-weekly intervals (including at the three and six month data collection points). The focus of the call will be to provide phone support to patients and to link them to local support strategies and community services via a cancer services directory. Patients can call their caseworker at any time, with a 24-hour answering machine available to leave messages if a call is made after hours. Patient-oriented outcomes including quality of life, prevalence and severity of symptoms and unmet needs, will be the focus for assessing the efficacy of the interventions. Patients in all three groups will receive a hand-held Cancer Care Record to assess referral to and utilisation of services and resources. An incremental cost-effectiveness ratio will also be calculated for each model compared to usual care. If found to be effective in improving patient outcomes compared to usual care, it is anticipated that the two models will be particularly useful in rural areas (especially the caseworker model) and should easily be implemented on a national level in conjunction with existing mechanisms in a cost-effective manner.

**CCCR & TCRE**

Enhancing the multidisciplinary care of women with breast cancer (Breast Cancer Project)

It is well-recognised that best practice in the management of breast cancer involves a multidisciplinary approach to care. This approach has been found to have a positive influence on the psychosocial well-being and survival of women with breast cancer. GPs would like to be more involved in the continuing care of their breast cancer patients, and play a key role in the multidisciplinary team. In the primary care setting, GPs are uniquely placed to provide to the breast cancer patient appropriate information, referral, treatment options, patient support, and follow-up. This 18-month project was initiated by Queensland Health in conjunction with the Brisbane North Division of General Practice and the Centre for Health Promotion and Cancer Prevention Research at the University of Queensland. The project aims to explore ways to enhance the current role of the GP in the care of women with breast cancer.

Analysis of hysterectomy rates in South Australia

Using hospital separation data, the prevalence of a hysterectomy status among South Australian women has been estimated across different age groups and regions. These data will be used to assess cervical screening coverage, adjusting for differences in hysterectomy rates by area and age group.

Follow-up survey of local governments in relation to sun protective policies and practices

This survey follows one undertaken in 1999 to assess sun protection activities of councils from the perspectives of shade provision at outdoor facilities/parks and gardens, and building and planning approvals to incorporate shade requirements to protect the public as well as occupational health and safety of council workers. Data have been collected for 2002 and will be compared with results from 1999 to determine progress in the Local Government sun protection program.

Support needs of people at risk of genetically inherited cancers (clients of the Familial Cancer Service)

A study is being planned to assess the support needs of familial cancer registry clients and their preferences for various modes of support services. Results from this survey will be used to inform the development of a support program for these people, who are not currently able to access many support services because they don’t have cancer.

Quitting smoking and physical activity

Previous research has suggested a relationship between quitting smoking and engaging in increased levels of physical activity. Physical activity has been viewed as a potential quitting aid, a way to counter weight gain associated with quitting, or a natural consequence of quitting smoking and beginning to feel more fit and healthy.

The Tobacco Control Research and Evaluation Program is investigating this relationship amongst a cohort of callers to the Quitline, through a follow-up survey conducted 12 months after the initial call to the Quitline. Some population survey data may also be used to investigate this relationship.

**News**

- CERP

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- CCCR & TCRE
The Editor  
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Sir

Falling between the Stools?

A consumer-initiated survey of cancer patients’ experiences

Cancer consumers are increasingly trying to influence the cancer research agenda, urging the investigation of those aspects of cancer prevention and treatment which are of most interest to them. Sometimes this is pursued through influencing the usual channels of scientific and behavioural inquiry and sometimes by undertaking a study themselves. We think Cancer Forum readers will be interested to hear about an example of the latter, which we believe to be the first of its kind in Australia.

Last year the Breast Cancer Action Group NSW, in order to more formally assess gaps and problem areas in the health care system for women with breast cancer, designed and circulated a questionnaire to its members. The principal aim of the survey was to ask for members’ qualitative views on the most positive and negative aspects of their cancer journeys. Some quantitative information was also sought. Although the respondents were not randomly selected, being BCAG members, their views were considered and informed.

The results, analysed and reported by Julie Billitt, Policy Officer at The Cancer Council NSW, highlight common deficiencies and gaps in the breast cancer journey, and the areas most frequently seen as well served. Amongst the key service improvements that consumers wanted to see were:

- Patient communication and information – need for more accessible, timely and authoritative information tailored to women’s needs, and communication skills training for health professionals.
- Integrated, multi-disciplinary, specialist care spanning the treatment pathway – need for a stronger multi-disciplinary approach to care, provided by a team of clinicians with specialist training in breast cancer care including breast nurses.
- Supportive care – need improved services and support mechanisms to address women’s psycho-social, practical and information needs.
- Accessible services for all patients – need for improved links and coordination between referral centres and local services to ensure seamless, accessible care for all women, backed up by practical support to meet the particular needs of remote and rural women.

The impetus for the survey came from BCAG’s participation in The Cancer Council NSW’s Breast Cancer Services Development Group, in turn set up at the request of consumers. The Cancer Council’s willingness to assist with the analysis and write up of the survey’s findings was much appreciated and shows the synergy that can be generated through partnerships with consumer groups. Very cost-effective too.

Consumer initiated and designed research can contribute valuable insight into the treatment experiences of people living with cancer. These insights in turn provide consumer groups with an evidence-based platform for their advocacy and lobbying activities.

We intend to present the results to cancer conferences such as COSA. A copy of the report is available from either The Cancer Council NSW or from BCAG NSW.

Yours faithfully

Sally Crossing
Chair

4 April 2002

Eat & Run nutrition conference

The first Australasian Nutrition, Physical Activity & Cancer Conference was held in Sydney between 24–26 June 2002. Attended by around 250 people, the Eat & Run conference was convened by The Cancer Council Australia and the New Zealand Cancer Society and hosted by The Cancer Council New South Wales. The conference helped guide and influence what cancer societies can do about nutrition, physical activity and obesity. The forum addressed the epidemiology of nutrition, physical activity and cancer, the efficacy of nutrition and physical activity interventions and the potential role of policy and advocacy.

Australia’s Biggest Morning Tea

Australia’s Biggest Morning Tea (ABMT) is The Cancer Council Australia’s second largest fundraising event. The event provides an opportunity for communities to build awareness of cancer while raising funds to help fight this disease.

Throughout May, more than 37,000 hosts nationwide held morning teas and had a cuppa for cancer research with their friends or co-workers. At the time of publication, ABMT had already raised more than $5.1 million, and TCCA is confident of reaching this year’s national target of $5.5 million.

Thank you to the event’s national sponsor, Bushells, whose backing means that money raised by the community goes directly to support vital cancer research programs.
Jennifer replaces Lisa-Maree Aged Care.

she was PR and media officer cancer organisations. Previously on oncologists and patient-focused communications agency in The Cancer Council Australia Cancer Network (ACN).

Oncological Society of Australia (COSA) and the Australian The Cancer Forum  n Volume 26 Number 2 n July 2002 take place in mid-September 2002, will also involve the Clinical Foundation Building in Camperdown. The move, anticipated to TCCA moving Australia. Jennifer comes to Manager of The Cancer Council appointed Communications.

John Fahey and friends support The Cancer Council Australia

The proceeds of a special tribute dinner for former Commonwealth Finance Minister and NSW Premier the Hon John Fahey, who retired from Federal Parliament last year, have been donated to The Cancer Council Australia. The dinner was hosted by NSW Senator Marise Payne and NSW Opposition Leader John Brogden.

Mr Fahey decided to retire from politics after being diagnosed with lung cancer. In presenting the $10,000 cheque to The Cancer Council Australia Chief Executive Officer Professor Alan Coates last month, he said: “When you’re directly affected by cancer, the importance of quality information and support – and the need for ongoing research – really hits home. I, and all my friends who attended the dinner, are very pleased to be able to make a contribution to reducing the impact of cancer through this donation to the TCCA.”

New TCCA Communications Manager

Jennifer Denholm has been appointed Communications Manager of The Cancer Council Australia. Jennifer comes to The Cancer Council Australia from a specialist healthcare communications agency in London, where much of her time was spent working with oncologists and patient-focused cancer organisations. Previously she was PR and media officer for the pharmaceutically benefits branch of the Commonwealth Department of Health and Aged Care.

Jennifer replaces Lisa-Maree Herron who is currently on maternity leave.

TCCA moving

The Cancer Council Australia is moving from its current William Street address to the University of Sydney’s Medical Foundation Building in Camperdown. The move, anticipated to take place in mid-September 2002, will also involve the Clinical Oncological Society of Australia (COSA) and the Australian Cancer Network (ACN).

Who will you buy a daffodil for?

Daffodil Day

FRIDAY 23 AUGUST

www.daffodilday.com.au

Who will you buy a daffodil for?

Anticancer drug development

Baguley and Kerr (ed)

Published by Academic Press (2001)

Distributed by Harcourt Australia Customer Service

ISBN 0120726513. 384 pages plus Index

RRP: $A243.10

This book gives an overview of the stages of drug development. The first four chapters deal with underlying mechanisms of tumour development and how basic information about the cell cycle, cell signalling and death pathways can provide targets for therapeutic attack. The next section is mainly about approaches to block tumour progression and includes a useful summary of tumour antigens, an area with which tumour biologists and drug designers should become more familiar. This first half of the book together with the three chapters on drug screening should be of wide interest to chemists, biomedical researchers and oncologists because of the concise, comprehensive descriptions of pathways, with clear diagrams. The results given for some of the lead compounds highlight the complexities of signalling pathways and the importance of context, but at the same time provide a framework for further development. The inclusion of chemical structures, often omitted in such reviews, is welcome. The chapters on drug design, bryostatins and peptide libraries are more specialised in appeal.

The areas of toxicity and clinical trials highlight strategies important to the eventual clinical testing of an anticancer drug. Given the expectations of funding sources, researchers need to recognise and cope with issues of drug development beyond their own specialty, for example pharmacology, surrogate markers for efficacy and toxicology, and trial design. There is little mention of the rapidly expanding use of genomics and proteomics to address some of these problems. However, the book will be a starting point for unravelling the molecular correlations emerging from gene expression profiling of tumours, and for designing tests for functional validation.

Well-referenced and indexed, with some colour plates, this text would be a useful addition to the clinic, research laboratory and institution library.

P Parsons

Queensland Institute of Medical Research

Herston, Qld

Book reviews

ADVANCES IN CANCER RESEARCH, VOLUME 79

G F Vande Woude and G Klein (eds)

Published by Academic Press (2000)

ISBN 0 12006879 3. 276 pages plus index

RRP: $A257 40

The first three chapters of this volume continue the theme of the series by focussing on important and topical areas of wide interest within the cancer field.

Anti-angiogenic therapy is one of the hottest areas in cancer research, so a review in this series is most appropriate. Cherrington, Shaw and Shaver, from the US biotechnology company Sugen Inc., naturally devote much of their attention to angiogenic factors and their cognate receptor tyrosine kinases. They first review the receptors themselves, then discuss several inhibitors that are under clinical development. Of course, the date of this volume requires the reader who wants current information to follow up from other sources. The authors then move on to discuss the matrix metalloproteinases, a class of proteases that are involved both in angiogenesis and tumour invasion. These too have become a popular drug target, with several inhibitors already in clinical trial.

The next chapter by van der Voort et al. from the University of Amsterdam is a very comprehensive review of hepatocyte growth factor (HGF) and its receptor, Met. HGF interacts with extracellular heparan sulphate proteoglycans, which function as co-regulators of Met signalling. While discussing the multiple roles of HGF/Met in development, the authors point out the strong connection between this pathway and branching morphogenesis in a number of epithelial systems such as lung, pancreas and mammary gland. They then go on to examine the biochemical events triggered by Met, such as activation of the Ras-MAPK pathway, the PI3K pathway and the Rho-family GTPases. Finally, the authors review the role of Met in cancer focusing on its roles in invasion and metastasis, and then its possible role in B-cell development and neoplasia.

Chambers et al from Ontario contribute another very topical review to this volume, which has as its subject anti-metastasis therapy. After examining new methods for studying metastasis, the authors explore the requirements for metastasis to a particular site. This is done in terms of the ‘seed and soil’ analogy – that is, by considering the roles of cancer cell spread and ability to grow in a given secondary site. They conclude with the notion that the most promising steps for therapeutic intervention are the initiation of growth in the secondary site and its progression, rather than the steps leading to tumour spread in the first place.

The fourth chapter by Bardeesy et al from the Harvard Medical School is entitled ‘Animal Models of Melanoma’. In reviewing this area it actually covers the role of two major tumour suppressor pathways – p53/ARF and p16INK4 in this disease also. Another section is devoted to the roles of receptor tyrosine kinases and their corresponding growth factors.

The remaining chapters of this volume each deal with areas that are of somewhat less general interest, though of course between them, these are important to many researchers and clinicians. The topics reviewed are: the role of B-cell microenvironment in low-grade B-cell tumours (Olia and Calgaris-Cappio, Turin); EBV latency (Longnecker, Chicago); Mucin-associated antigens in GI tract cancer (Baldus and Hanisch, Cologne); and Polyoma virus persistence (Berke and Dalanis, Karolinska Institute, Sweden).

Book reviews

Thebarton, SA

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P Parsons

Queensland Institute of Medical Research

Herston, Qld
APPLIED RADIOBIOLOGY AND BIO-EFFECT PLANNING

D Wigg
Published by Medical Physics (USA) (2001)
RPP: US$180.00

This erudite volume is a tribute to the intellect and scholarship of its author, David Wigg. Although he has never worked directly with experimental radiobiologists, he displays a mastery of the subject that is acknowledged in one of the forewords by no lesser luminary than Professor Jack Fowler, who states: "This book provides the most comprehensive source of both methods and data available anywhere..."

In his opus magnum, Dr Wigg reviews existing models of bio-effect to discuss the generation and volume effects and explains how, with all the caveats surrounding the imperfections of the models and the uncertainties of the parameters applied to them, such models can be clinically useful.

The book is not for the mathematical faint-hearted, and it is unfortunately probable that most clinicians will be put off by the complex equations that punctuate the text and clutter the figures. If, however, like me, they assume the equations to be valid and just concentrate on the text, there is a wealth of information of value to clinicians to be found. The book consists of 10 chapters followed by two appendices of published work. In the first six chapters, Dr Wigg reviews existing bio-effect models and develops methods for extending them to brachytherapy and chemoradiotherapy. Chapter seven is potentially the most controversial of the book in challenging current dogma. In it, he argues that, based on a derived O/IR ratio of 10 Gy or more for obliteration of arterio-venous malformations, a dose stereotactic radiosurgery may not be the optimal way to treat AVMs, especially those located in critical areas of the central nervous system.

I personally found the last three chapters of the book to be the most rewarding. Chapter eight summarises the most plausible parameter values for normal tissues and tumours for application in planning of dose-bio-effect planning. Chapter nine describes the use of such models to predict tumour control probability and late effects risk for a variety of established malignant disease, radiotherapy and the principles of systemic therapy and adjuvant systemic therapy.

The line drawings, tables, graphs or photographs or pathological specimens and clinical material are well chosen and superbly executed. The text accompanying the illustrations is clear and concise, appropriate to the illustration, and to the point.

The second edition has appeared five years after the first edition and is updated in almost all chapters. It demonstrates the quite significant changes that have occurred in the field of breast cancer research in that time.

The prevention chapter includes most of the recent data relating to breast cancer prevention and although not clinically orientated, describes well the current situation regarding prevention strategies.

The breast imaging chapter is comprehensive and in particular the mammography is beautifully illustrated. The chapter describes the limitations of imaging techniques, and in particular it introduces the new imaging techniques – such as MRI – and describes the advances in the field.

The surgical section is comprehensive and includes diagnostic techniques and well-illustrated pictures of the basic surgical techniques in the early treatment of breast cancer, utilising both mastectomy and breast conservation. The principles of early breast reconstruction including tissue expansion and flap reconstruction are well illustrated.

A brief pictorial chapter on the pathology of benign and malignant disease is a little short of detail but clear and to the point.

The chapter on breast radiotherapy is quite comprehensive for a book of its size, and it is very useful. The final chapters on the principles and applications of systemic adjuvant therapy are clear and informative.

The quality of the presentation of this book, including the beautiful colour photographs and diagrams, make it a suitable textbook for medical students and residents working in breast units and for breast cancer nurses. It is well-structured and clearly demonstrates the multidisciplinary nature of the management of breast cancer – although it does not actually state this. I think this book should find a place on the bookshelf of every breast unit and would be excellent reading for all members of the multidisciplinary team.

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BREAST CANCER: A PRACTICAL GUIDE

O E Silva and S Zurrida (eds)
Published by Elsevier (2000)
RPP: US$54.95

This handbook provides a very comprehensive summary of key information and data supported by references to current literature, major trials and landmark articles. The information contained covers all aspects of breast cancer including sections about screening and diagnosis, mastectomy, breast reconstruction, psychosocial sequelae, palliative care, breast cancer quality and much more. In addition, although the book is primarily about breast cancer, the first chapter is a summary of definitions, clinical features and treatment of benign breast disease.

The book is written in an outline format, somewhat like having access to someone’s very good lecture notes, supported by summaries of recent trial data including features of the trials – such as whether or not randomised, number of subjects, median follow-up and relevant reference details provided in the text. There is also an expanded table of contents in which key references are appended to sections and topics. Such a handbook provides clinicians of all disciplines involved in breast cancer care, with a very useful, comprehensive reference of current information in a handy, concise form and easy-to-read format. Such information in paper-based format will, of course, require regular updates, and this is acknowledged by the editors. This 2000 edition represents an updated and revised version of the first edition, in 1999. This is an issue for all guidelines and information sources which aim to maintain currency and must be borne in mind by the readers.

Although this handbook is written for an American audience and contains information which is specific to the American health care system, it is a now widely used book in the UK and Western Europe. The book is also clear and concise, appropriate to the illustration, and to the point.

The second edition has appeared five years after the first edition and is updated in almost all chapters. It demonstrates the quite significant changes that have occurred in the field of breast cancer research in that time.

The prevention chapter includes most of the recent data relating to breast cancer prevention and although not clinically orientated, describes well the current situation regarding prevention strategies.

The breast imaging chapter is comprehensive and in particular the mammography is beautifully illustrated. The chapter describes the limitations of imaging techniques, and in particular it introduces the new imaging techniques – such as MRI – and describes the advances in the field.

The surgical section is comprehensive and includes diagnostic techniques and well-illustrated pictures of the basic surgical techniques in the early treatment of breast cancer, utilising both mastectomy and breast conservation. The principles of early breast reconstruction including tissue expansion and flap reconstruction are well illustrated.

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The quality of the presentation of this book, including the beautiful colour photographs and diagrams, make it a suitable textbook for medical students and residents working in breast units and for breast cancer nurses. It is well-structured and clearly demonstrates the multidisciplinary nature of the management of breast cancer – although it does not actually
The initial four chapters are about generic disciplines in the field, covering agent identification and preclinical testing, intermediate biomarkers; tissue microdissection and processing; and basic pharmacokinetics and pharmacodynamic principles. The first of these chapters, by Jim Crowell at the National Cancer Institute (NCI), is a striking account of the systematic approach taken by the Division of Cancer Prevention in its Chemopreventive Agent Development Research Group. First there is a careful scouring of the literature and, quite admiringly, noting what common threads run across the world, for clues about agents whose scientific basis may be a lot more than folklore. This approach has the benefit of ready-made “post marketing” experience, as there may well be centuries of human exposure information, though not well compared through observational epidemiology on humans. For example, aspirin and the nonsteroidal anti-inflammatory drugs. Cyclooxygenase and its downstream (prostanoids) metabolic products have no references later than 1998. The quality of the sections also varies greatly. As the editor-in-chief is Head of Experimental Oncology, it is not surprising that the strength of the text lies in the sections on molecular biology, causes of cancer and pre-clinical models. A number of these chapters are particularly good, in particular those on signals and on cardiosuppression. For a clinician, these sections are well worth reading.

The clinical sections, however, compare poorly with the basic science sections. They are inadequate and too basic for a clinician, whilst not comprehensive enough for a basic scientist. The chapters appear to have been written later than others, with references to papers written in 2000/2001, whilst others have no references later than 1998. The quality of the sections also varies greatly. As the editor-in-chief is Head of Experimental Oncology, it is not surprising that the strength of the text lies in the sections on molecular biology, causes of cancer and pre-clinical models. A number of these chapters are particularly good, in particular those on signals and on cardiosuppression. For a clinician, these sections are well worth reading.

The chapters are oddly structured, with significant sections on science sections. They are inadequate and too basic for a basic scientist. The chapters appear to have been written later than others, with references to papers written in 2000/2001, whilst others have no references later than 1998. The quality of the sections also varies greatly. As the editor-in-chief is Head of Experimental Oncology, it is not surprising that the strength of the text lies in the sections on molecular biology, causes of cancer and pre-clinical models. A number of these chapters are particularly good, in particular those on signals and on cardiosuppression. For a clinician, these sections are well worth reading.
There is, however, very little on current therapeutic modalities. The one chapter focussing on this area is the excellent chapter on bone metastases for breast cancer, but its inclusion beggars the question of what happened to the other chapters on the current treatment of important cancer types.

Overall, this book would be useful for a cancer clinician wishing to have a ready reference of molecular biology, carcinogenesis and pre-clinical models and how they relate to cancer. However, as a book on the clinical aspects of cancer, this text does not fulfil its aim of bridging the gap between researchers and clinicians.

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CANCER OF THE HEAD AND NECK

Author: J Shah
Published by B C Decker (2001)
RRP: AS451.58

To cover, in a meaningful and comprehensive manner, as vast and diverse a topic as cancer of the head and neck in 477 pages would clearly require an expert in the field. It would thus come as little surprise that this goal has been so successfully achieved in this text under the editorial leadership of Jatin Shah, Chief of Head and Neck Services, Memorial Sloan-Kettering Cancer Centre. All the authors are present or past members of the Head and Neck Disease Management Team from the Memorial, some of whom have clearly spread the gospel throughout North and South America. The author freely acknowledges the impossibility for a text of this nature to be either complete or permanently up-to-date, but shortcomings in achieving either of these goals are not obviously manifest.

The book commences with introductory chapters on epidemiology of head and neck cancers, common basic pathology and imaging modalities. This is followed, using a systematic format, by a more detailed description of the key principles and then goes through the important biological and clinical issues in lung cancer including chemotherapy, surgery, radiation and novel approaches, whereas part IV includes a section on the novel uses of radiation therapy. Part V is a short section on the availability and potential benefits of using lung cancer guidelines.

The chapter on techniques for the diagnosis of lung cancer is also well-written, and included a section on endobronchial ultrasound needle aspiration. The newer technique for endobronchial ultrasound appears to be absent although autofluorescence bronchoscopy is mentioned. To its credit, the potential role of Helical CT scanning is briefly discussed. Much has been published in this promising area since the book’s publication.

The overall, book is well-written, and provides brief but quite comprehensive summaries of the relevant areas. In particular, the section on pathology is well-written for non-pathologists and includes a mention of atypical adenomatous hyperplasia as a precursor for bronchioalveolar cell carcinoma. As a book, the reviews unavoidably suffer the disadvantage of not having the latest information, for example DIPNECH as the precursor for carcinoids. Nevertheless, this part is quite concise and well-written.

The parts on treatment are similarly easy to read and are as up-to-date as possible. For instance, there is good discussion on the follow-up studies from the often-quoted Roth and Rossel studies of neoadjuvant chemotherapy for non-small cell lung cancer. There is also a brief discussion on the potential future of small molecules and biological therapy, though it would have been nice to have more information on this rapidly advancing field.

However, this book is to be generally well-written, and certainly well worth reading for all those with an interest in the important biological and clinical issues in lung cancer management.

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Cancer Screening: A Practical Guide To

PHYSICIANS

K Aziz and G Wu (eds)
Published by Humana Press (2002)
RRP: US$59.00

This is a very interesting and useful book. It covers a wide variety of cancers and gives a thorough overview of the issues.

The way the book is set out is interesting. Each chapter starts with key principles and then goes through epidemiology of the particular cancer under consideration, biology of the cancer, rationales of screening and methods of screening. Finally there is a summary, which includes cost effectiveness and controversial issues.

The final two chapters of this book: ‘Future prospects in cancer screening’ and ‘Medico-legal aspects of cancer screening’ are a challenging part of this book. The future looks to be an exciting place to be in the area of cancer screening and a worrying place to be for medico-legal issues!

For a cancer specialist there is, I feel, insufficient detail. This is more a text for the interested generalist. Some general practitioners who have a particular interest in cancer disease may well purchase in. This book would be a useful addition to an institutional library where it could be used by medical students coming to terms with cancer care and screening.

This is an up-to-date and comprehensive coverage of the area and, as such, I would recommend it.

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J M Metz
Published by Lippincott Williams & Wilkins (2002)
RRP: AS50.60

In the preface, the author describes the purpose of the book as ‘to provide clear, concise information that can always remain at a cancer patient’s fingertips’. By its concise nature, the information does not include much detail but rather, focuses on the most important points. The book arose from the author’s work on the Oncolink website, a site that provides information on cancer care.

The book meets its stated purpose and, in my view, is a good initial resource book for people diagnosed with cancer. There is also a section on prevention and screening for individuals interested in this area.

Other areas covered in the text are: dealing with the side effects of cancer treatments; sexuality issues; physician and patient interaction; treatment for breast cancer, and alternative medicine. New, current topics are described in the section on ‘miscellaneous topics’. In section eight, a guide to how to use the Internet is described. In this section, the author offers criteria or parameters to be used in the evaluation of a ‘medical’ website. The final section is a workbook that encourages the reader to keep a record of medications, vitamins, herbal remedies, alternative treatments, medical history, surgical history, past hospitalisations, etc. Such a personal record would be very helpful for the individual who seeks more involvement in their medical care.

As an American text, there are inevitably some differences in terminology. Most of the language that would not be used in Australia, such as drug names, can be quickly clarified with a doctor or nurse. Other terms will be familiar to Australians who watch American television programs or regularly read American books. As the book is written from a medical perspective, the reader is referred to as the ‘patient’ – this may make some readers uncomfortable.

The author presents a section on unconventional medical treatments. There is a constant theme through this section that it is important to share with the physician any unconventional treatments. This is repeated in the workbook section. The tone of this section is clinically focussed, with recommendations by the author against most of the treatments described. Although inclusion of this section is a positive step toward resolving the issues around patients not sharing their non-prescribed treatments with their doctor, patients may continue to be reserved about sharing such information for fear that they will be judged harshly by the doctor.

Overall, this book is highly recommended for people who are undertaking treatment for cancer: it provides information that people consistently state that they need and a framework for discussing issues with their doctor.

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Cancer treatment

C Haskell (ed)
Published by: Saunders (2001)
RRP: AS474.10

As stated by the editor, Charles M Haskell, “The goal of cancer treatment is to provide an authoritative, comprehensive, and up-to-date appraisal of contemporary therapy. Because of advances in molecular medicine and therapeutics, this appraisal requires a more extensive understanding of the basic science of oncology than in the past. An introduction to essential basic concepts is now included to meet this need.”

This weighty tome is divided into 22 parts.

Part I: covers the principles of cancer treatment (including the biology of cancer, principles of cancer genetics, and principles of biologic therapy). Part II: provides detailed information on drug therapy, including a series of monographs for chemotherapy and biological agents. Part III: provides an overview of haematologic considerations in cancer treatment.
no mammography or ultrasound illustrations are given), early disease, through to locally advanced disease, localised (single site) metastasis, and widespread metastatic disease including palliative cases. The book has been supported (albeit it is unclear to what extent) by the drug company AstraZeneca. Each case occupies approximately two pages, and nearly all have clinical and radiological illustrations (some occupying the entire page). The clinical details are brief and to the point and are followed by the question: “What management/treatment/advice would you recommend?” The author then details what actually happened to the patient. In many cases, not all the prognostic information is available. Some of the cases have a very brief conclusion at the end. The illustrations are of high quality. The use of arrows to demonstrate the clinical radiological abnormalities would have been useful. Some of the illustrations are repeated and there are even some personal photos of one of his patients playing golf and sking! The use of the style of the title and sometimes a little disjointed and lacking in scientific depth. There is variability in the details of treatments (from “steroids were given” to where to buy “goat skin gloves”) in patients with lymphoedema. There is no standardisation of drug nomenclature (trade versus generic names). Editorial advice and proof reading is missing. There are inappropriately labelled pages, eg 137. The appendices at the end of the book are not useful – the trials mentioned are not explained; the list of chemotherapy, hormonal and supportive drugs is not complete and is inaccurate, the recommended reading includes five articles and three textbooks. One cannot be critical of the way a particular case was treated, and certainly some management decisions are controversial and some go against current clinical evidence. The author does not make any attempt to calculate the risk benefit assessment of treatments given, particularly in the adjuvant setting.

I believe the usefulness of this book as presented is limited. Breast cancer management is a multidisciplinary effort and a book even of this type can no longer be written by one individual. Perhaps co-authorship with other individual breast cancer specialists would have avoided some of the variations and lack of detail in the modalities of therapy discussed. The usefulness of these cases in terms of teaching students and junior staff is also limited unless it is supplemented by additional information either by the author (not done) or by a tutor using the cases as a starter for discussion. For example, what would the differential diagnosis be; were the investigations appropriate; what is the prognosis in this setting; what are the risks and benefits of treatment, what are the treatment options; and if the patient was treated differently, why. The supply of a model answer supported by referenced evidence would make this a far more useful text. In the absence of these additional features, then I suggest that most clinicians would have similar cases found in other textbooks. It is crucial to read the clinical material and use as resource material such as an atlas of diagnostic oncology from which to obtain appropriate, historical, radiologic and clinical illustrations. As it stands, at the recommended price of $140.00 who should buy this book? Probably no one.

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ENCYCLOPEDIC REFERENCE OF CANCER


In the words of the editor, this reference text is designed to close the language gap between clinical and basic scientists and provide basic information to students and the informed layperson. The aim is to provide readers with an entry point to a plethora of articles, and entries are written in a very accessible style. The encyclopedia covers a broad range of cancer-related topics and represents a huge effort of cooperation with over 250 contributing authors, all internationally recognised experts in their field. The format is reader-friendly, consistent and well-presented. The terms are arranged alphabetically, with each entry consisting of a concise definition and, where appropriate, a list of synonyms. The overview of entries on syndromes, genes and molecular processes also provide further information written in an essay format with reference to key publications. The terms are cross-referenced and, in some cases, are accompanied by helpful illustrations. The entries range from definitions of common acronyms, to concise description of cancer processes including tumour initiation, progression and the cell cycle (particularly useful topics for students and to those new to the field of cancer research), to descriptions of molecular techniques, such as microarray analysis.

Although the encyclopedia includes a number of excellent entries on current and emerging treatments, it should be read by laboratory researchers wishing to understand terms used by clinical cancer research colleagues, it was clear that the encyclopedia is heavily weighted towards explaining basic science terms. Nevertheless, the non-expert should find the useful reference text not only for clinical investigators but also for basic science researchers reading outside of their field of expertise and, as designed, an excellent reference for students. The book is accompanied by a useful CD-ROM, which contains the full text in PDF format.

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FARNESYL TRANSFERASE INHIBITORS IN CANCER THERAPY


The Ras GTPases operate as molecular switches that link extracellular stimuli with a range of biological outcomes including cell proliferation and differentiation. Some 30% of human tumours carry mutations in one of their Ras genes that renders the mutant Ras protein insensitive to normal regulation. The Ras on and delivers a potent proliferative signal that contributes to tumour growth. Ras therefore constitutes an excellent target for drug discovery. Starting with this premise, the book by Sebiti and Hamilton catalogs the efforts of many research groups and pharmaceutical companies that has led to the first generation of therapeutically active Ras inhibitors, which are now undergoing phase I and II clinical trials. This is very much a sequential “basic science to bedside story” that clearly illustrates how in vitro biochemical and cell biological data led to clinical trials and the groundwork for pharmacological exploitation. Here it is a relatively simple set of three observations. Ras must be localised to the inner surface of the plasma membrane to function. A C-terminal membrane anchor to the protease post-translationally mediates plasma membrane localization, and the first enzyme involved in the Ras anchor is farnesyltransferase (FasTase). The success is based on the rationale for developing farnesyltransferase inhibitors (FIs).

The first chapters cover some of this background, but the non-expert would probably be advised to read the last chapter as well to fully appreciate the basic science. Thereafter the book tackles the detailed biochemistry of FTase, plus the two complementary approaches that have been used to identify FIs – rational drug design based on the minimal FTase substrates, and random screening of compound libraries. Each class of FTI that has been developed is then dealt with separately, together with detailed descriptions of the relevant biological chemistry. Subsequent chapters cover the cell biological and animal model testing of the various FTIs followed by a collation of the various I trial results with some of the featured compounds. A summary chapter then pulls together what can be gleaned from these studies and sets out future directions for clinical trials. The final chapter also covers similar ground, but gives an overview of the whole story and sets out some of the biological questions surrounding the future use and development of the FTIs. In particular, how to deal with accumulating data that the Ras-related protein Rhodi, or some other prenylated protein and not Ras, may actually be the molecular target of FTIs. The implications from such work are far-reaching and certainly impact on the design of future clinical trials. On the other hand the relative lack of toxicity of FTIs opens up possible uses outside of oncology. This is touched on earlier in the book, with an examination of the possible use of FTIs and the related GGTase inhibitors as anti-trypansomal drugs.

Inevitably in a multi-author book, there is replication of introductory material between chapters. This is not an exception. The structure of the book could also have been given a little more thought and the chapters presented in a more logical sequence, but these are very minor gripes. There is no doubt that this book contains the whole FTI story and is to be commended for the exhaustive bibliographies that are a feature of every chapter. So who should read it? For the non-Ras expert, it presents a nicely illustrated story of biotechnology at work, from basic biology through rational drug design to actual clinical therapies, highlighting the development steps that are required along the way. To the Ras expert it is a very useful and comprehensive review of a rapidly moving and increasingly intriguing field.

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GROWTH FACTORS AND THEIR RECEPTORS IN CANCER METASTASES

W Jiang, K Matsumoto and T Nakamura (eds) Published by Kluwer Academic (2001)
The growth and spread of cancer cells to other organs is a complex, multistage process that requires cell proliferation, dissociation of tumour cells and formation of new capillary vessels for continued growth as well as for detached tumour cells to enter the circulatory system to settle and grow in distant sites. Tumour growth and metastases are influenced by growth factors and cytokines, and a thorough understanding of their normal physiological roles as well as their actions in cancer cell behaviour underpins attempts to develop new treatments for cancer.

This book is a compilation of reviews by experts providing comprehensive coverage of the growth factors, cytokines and their receptors that are relevant to cancer. The range of topics is broad, and includes chapters on growth factors such as leukemia inhibitory factor, insulin-like growth factor I, TGFα, fibroblast growth factor, hepatic growth, platelet-derived growth factor and other growth factors. The cytokine molecular biology 2 and 11 and as well angiogenic factors interleukin 8 and VEGF are also included. Gene therapy of prostate cancer with interleukin 12 is discussed as well as treatment of tumour invasion with the hepatic growth factor antagonist, NKA.

Each review focuses on the normal physiological roles of a particular factor, its receptor and their relevance to cancer growth, tumour invasion and metastases. The chapters are well-written, easy-to-read, current and extremely well-referenced. They enable the reader to access original articles and pursue in depth any particular topic or aspect of a molecule’s function. The basic concepts are well covered, providing a rapid, yet comprehensive introduction to each subject.

I found the chapters on leukemia inhibitory factor, interleukin 2, interleukin 12, IGF-1 and TGFα particularly useful, and this collection of reviews is rounded up nicely by the excellent last chapter on growth factors and cell adhesion complexes in cytoskeletal assembly.

This book should be compulsory reading for any investigator, undergraduate or postgraduate seeking knowledge about, or pursuing research into, cancer. The breadth and depth of each topic is outstanding.

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Hepatobiliary cancer
L H Blumgart, Y Fong and W R Jarnagin (eds)
Published by American Cancer Society (2001)
RPP: A $5 253.55

The first two chapters cover benign liver lesions and incidentally-found hepatitis lesions. This may seem strange in a book on hepatobiliary malignancy, but it is entirely appropriate. Modern radiology has increased the identification of previously unsuspected liver lesions, but as advances in imaging have occurred, so has the delineation of the nature of the lesion. This has allowed a rational approach to treatment in asymptomatic patients as in patients at risk of primary or metastatic malignancy. The clinical and radiological evaluation of different tumours is covered.

The next three chapters deal with primary and metastatic malignancies. There is a good review of the epidemiology of hepatocellular cancer and cholangiocarcinoma. Diagnosis and treatment strategies are clear and well presented, and the chapter covers some aspects of rarer tumours. Metastatic liver cancer is well covered in two chapters, the first concentrating on colorectal metastases with a short discussion on non-colorectal metastases while the second chapter presents an overview of hepatic surgery for metastatic gastrointestinal neuroendocrine tumours. The determination of resectability and the results of resection are outlined in these two chapters.

The two succeeding chapters cover surgical and non-surgical ablative therapy for liver tumours. The pathophysiology of cryo-ablation is well described along with the advantages and disadvantages of this technique. The chapter on transarterial chemoembolisation gives a good review of the surgical and non-surgical management of hilar cholangiocarcinoma and gall bladder cancer.

The last chapter is in two parts, incorporating chemotherapy for liver tumours and isolated hepatic perfusion. The concentration is on chemotherapy by hepatic artery infusion with a good summary of trials, complications and outcome. A review of the data to date shows the limited place of the complicated procedure of isolated hepatic perfusion. The potential for gene transfer in the treatment of hepatobiliary malignancy is discussed, but as the final chapter. It is in the preliminary phases of investigation and is yet to enter into clinical testing. The final chapter is a comprehensive overview of the principles of liver transplantation for hepatobiliary malignancy – indicating it has a limited, but very definite, place for highly selected candidates.

The growth and spread of cancer cells to other organs is a complex, multistage process that requires cell proliferation, dissociation of tumour cells and formation of new capillary vessels for continued growth as well as for detached tumour cells to enter the circulatory system to settle and grow in distant sites. Tumour growth and metastases are influenced by growth factors and cytokines, and a thorough understanding of their normal physiological roles as well as their actions in cancer cell behaviour underpins attempts to develop new treatments for cancer.

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This book should be compulsory reading for any investigator, undergraduate or postgraduate seeking knowledge about, or pursuing research into, cancer. The breadth and depth of each topic is outstanding.
OF HUMAN CANCER
W Coleman and G Tsongalis (eds)
Published by Humana Press 2002
RPP: US$145.00
This book is intended to provide a source of current information on the molecular mechanisms underlying tumorigenesis in the practical context of medical oncology practice. The authors state that it is primarily directed at advanced graduate students, medical students, postdoctoral trainees and established investigators with basic research interests.

The book is divided into seven sections including: cancer epidemiology, basic molecular biology concepts, molecular themes in oncogenesis; mechanisms of mutation, etiology of human cancers, human tumor systems and future directions. The section on human tumor systems focuses on major organ system cancers including colorectal, hepatocellular, breast, prostrate, lung and skin, as well as haemopoietic malignancies. Future directions include chapters on genetic diagnosis and counselling, novel molecular targets and gene therapy.

Since the majority of the 24 chapters were written by different authors, there is at times a predictable overlap in content. However, this does not detract from the value of the book, as it is most likely to serve its purpose as a reference manual for those interested in gaining insights into a specific area. Each chapter is generally clearly written, providing succinct and up-to-date information. Although general concepts and major signalling pathways are overall well covered, some chapters are imbalanced in their emphasis. For example, the role of the hormone receptors and transcriptional cofactors – as well as information on the ErbB emphasis. For example, the role of the hormone receptors and transcriptional cofactors – as well as information on the ErbB pathway – is poorly addressed in the breast chapter. Both areas require more detailed coverage, given that these are currently topics of intense laboratory and clinical investigation.

The primary aims of this book are well met. It would be a suitable initial reference for clinicians with some basic research interests, and well as a departmental reference for clinicians requiring selective insights into molecular oncology.

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PALLIATIVE NURSING: BRINGING COMFORT AND HOPE
S Kinghorn and R Gamlin (eds)
RPP: A$162.50
This book represents an eclectic collection, principally arising from a conference of the same title. The book is aimed at a nursing audience and aims to offer a foundation for nurses involved in the delivery of palliative care as part or all of their work. The book is an exploration of issues, rather than a clinical text, dealing with contemporary literature in the field although not always making a clear distinction between research-based and opinion-based work. There is excellent use of case studies throughout, helping with the clinical application of the largely literature-based material.

The book is divided into three sections dealing with clinical issues, psychosocial care and broader issues such as research and ethics respectively. The clinical section focuses on pain, other symptoms, cancer treatments, spirituality and complementary therapies. The section on using cancer treatments in palliative care offers an excellent site-specific overview of this often-controversial topic.

The psychosocial section focus on hope and communication. There is a fairly comprehensive review overview of the broad hope literature, which will interest most nurses. The grief and bereavement chapter offers a useful conceptual overview that departs from traditional approaches and will assist with planning interventions. Overall, this section offers a sensitive, human approach to the difficult issues of working with people who are dying.

The final section offers fairly standard ethics and research chapters, a good overview of the issues of providing palliative care in non-malignant disease, and a non-clinical approach to enhancing quality of life, and ends with the important topic of health professional self-care.

Overall, this is a worthwhile addition to the nurse’s cancer library, offering opportunities for reflection and thought rather than a clinical guide for practice.

S Aranda
Director, Cancer Nursing Research, Peter MacCallum Cancer Institute East Melbourne, Vic

THERAPEUTIC GUIDELINES PALLIATIVE CARE
M Mashford et al
RPP: A$53.00
As a palliative care physician I thought reading this type of “review book” would constitute a pleasant interlude and some light reading. I was very pleasantly surprised as it is a book full of little gems, for example “Medications that are not essential – although not always making a clear distinction between research-based and opinion-based work. There is excellent use of case studies throughout, helping with the clinical application of the largely literature-based material.

The book covers all the basic facets of palliative care. Palliative care is about total care – that is, physical and psychological – of the patient and family/carers. This book covers the “circle of care” from diagnosis, treatment, and palliation to death. The chapters covering the self-care of palliative care providers are very pertinent, as we often forget to look after ourselves and burn out. The book touches on communication, ethics and bereavement issues in a holistic approach.

A comprehensive list of common symptoms (fatigue, neurological, musculoskeletal, dermatological and urogenital) and their management in a palliative care setting is useful for the full-time palliative care physician and the general practitioner.

Where symptoms have multiple possible causes, often with more than one solution, alternative management strategies are presented so if one drug doesn’t work then second or third line drugs are suggested.

The book has a very useful section on analgesia, dealing both with the pharmacology of analgesics and adjuvants and with pain management. The different types of drugs used for different types of pain are clearly set out. Very useful are the tables setting out the conversion between different types of opioids.

My only regret is that the book does not stress enough that all symptoms are an “SOS” for help and there should be a sense of urgency by the treating medical team to respond quickly – as there may be no tomorrow.

For completeness the book has excellent chapters on HIV/AIDS palliative care and paediatric palliative care, including appropriate pain charts and drug doses. There is an excellent list of resources in the appendix.

In summary, I found this book easily readable with good information on diverse aspects of palliative care and well worth having in my library. I would like to finish with a quote from the book: “Patients should be left in no doubt that distracting symptoms like pain and nausea can almost always be controlled provided continuous and competent care can be assured.”

P Redelme
Sacred Heart Hospice Darlinghurst, NSW

TREATMENT OPTIONS IN UROLOGICAL CANCER
J Waxman (ed)
Published by Blackwell Science 2002 ISBN: 0632 05589 8. 382 page plus index
RPP: A$264.00
If you have the urge to write a summary about urological cancer, don’t bother, since this excellent book has done so for you. Edited by John Waxman and boasting an international line-up of experts this book is a well-balanced account of the current thinking in management of urological cancers without getting bogged down in unnecessary detail.

The section on renal cell cancer has a heavy leaning towards research-based and opinion-based work. There is excellent use of tables setting out the conversion between different types of opioids – although not always making a clear distinction between research-based and opinion-based work. There is excellent use of case studies throughout, helping with the clinical application of the largely literature-based material.

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The final section offers fairly standard ethics and research chapters, a good overview of the issues of providing palliative care in non-malignant disease, and a non-clinical approach to enhancing quality of life, and ends with the important topic of health professional self-care.

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The final section offers fairly standard ethics and research chapters, a good overview of the issues of providing palliative care in non-malignant disease, and a non-clinical approach to enhancing quality of life, and ends with the important topic of health professional self-care.
TUMOR-SUPPRESSING VIRUSES, GENES, AND DRUGS

H Maruta (ed)

Published by Academic Press (2002)
RRP: A$249.70

The target audience for this compact book includes research scientists, academics, undergraduate and graduate students. There are twenty chapters comprising topics ranging from cell surface receptors, integrins, to signal transducers and nuclear proteins including cell cycle regulators, as well as useful chapters on oncolytic viruses, key tumour suppressors and angiogenesis.

Each area is comprehensively addressed—the text places each molecule of interest in the context of its signalling pathway(s), and describes the mechanisms by which these gene products are deregulated in cancer. Experimental models aimed at restoring growth control using target-specific molecular biology are summarised. Where available, in vivo models are also described, including information on agents entering phase I and II clinical studies. In the latter case, the basic science, rather than clinical outcome data is the main focus. Detailed attention to referencing is notable.

There is a good deal of local content; several chapters were written by Australians with recognised expertise in their respective fields. Authors include Tony Burgess, Marc Achen, Steven Stacker and Hiroshi Maruta (also the editor).

This book would be a suitable reference source in a research institution or clinical trials group library. It should appeal to basic scientists curious to understand diverse areas of tumour biology and where each field is heading in terms of translational research.

G Lindeman
Department of Medical Oncology, Royal Melbourne Hospital and The Walter and Eliza Hall Institute of Medical Research, Melbourne, Vic

CALENDAR OF MEETINGS – AUSTRALIA AND NEW ZEALAND

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<tr>
<th>Date</th>
<th>Name of Meeting</th>
<th>Place</th>
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<tr>
<td>September</td>
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<tr>
<td>9-12</td>
<td>7th Australian Palliative Care Conference</td>
<td>Adelaide</td>
<td>SAPMEA Conventions</td>
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<td>SA</td>
<td>68 Greenhill Road Wayville SA 5034</td>
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<td>Ph: +61 8 8274 6060 Fax: +61 8 8274 6000 Email: <a href="mailto:pallcare2003@sapmea.asn.au">pallcare2003@sapmea.asn.au</a></td>
</tr>
<tr>
<td>19-22</td>
<td>AGITG Annual Scientific Meeting</td>
<td>Hobart</td>
<td>AGITG Coordinating Centre</td>
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<td>TAS</td>
<td>Locked Bag 77 Cambridge NSW 1450</td>
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<td>Ph: +61 2 9562 5000 Fax: +61 2 9562 5094</td>
</tr>
<tr>
<td>29 Sep – 2 Oct</td>
<td>Mobilising Public Health 34th Public Health Association of Australia Annual Conference</td>
<td>Adelaide</td>
<td>PHAA Secretariat</td>
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<td></td>
<td>SA</td>
<td>Ph: +61 2 6285 2373 Email: <a href="mailto:conference@phaa.net.au">conference@phaa.net.au</a></td>
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<tr>
<td>October</td>
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<tr>
<td>21-23</td>
<td>International Clinical Trials Symposium 2002</td>
<td>Sydney</td>
<td>ICMS Pty Ltd</td>
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<td>NSW</td>
<td>Ph: +61 2 9290 3366 Fax: +61 2 9290 2444 Email: <a href="mailto:trials@icms.com.au">trials@icms.com.au</a> Website: <a href="http://www.cts.saylada.edu.au">www.cts.saylada.edu.au</a></td>
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<tr>
<td>November</td>
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<tr>
<td>25-29</td>
<td>The Australian Health &amp; Medical Research Congress</td>
<td>Melbourne</td>
<td>Initiative of Australian Society for Medical Research Website: <a href="http://www.ahmrcongress2002.conf.au">www.ahmrcongress2002.conf.au</a></td>
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<tr>
<td>27</td>
<td>“Improving communications: improving outcomes for patients and health professionals” 2nd National Better Communication, Better Care Conference</td>
<td>Sydney</td>
<td>Fax: +61 9036 3077 Email: <a href="mailto:directorate@nbc.org.au">directorate@nbc.org.au</a></td>
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<tr>
<td>28-30</td>
<td>29th COSA Annual Scientific Meeting</td>
<td>Sydney</td>
<td>Lawrie Wright</td>
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<td>Clinical Oncological Society of Australia</td>
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<td>Ph: +61 2 9380 9022 Fax: +61 2 9380 9033 Email: <a href="mailto:cosa@cancer.org.au">cosa@cancer.org.au</a></td>
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<td>2003</td>
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<td>15-19</td>
<td>6th International Symposium on Paediatric Pain: “Pain in Childhood: The Big Questions”</td>
<td>Sydney</td>
<td>Dianna Crebbin</td>
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<td>Ph: +61 2 9439 6744 Fax: +61 2 9439 2504 Email: <a href="mailto:mail@dcconferences.com.au">mail@dcconferences.com.au</a></td>
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<tr>
<td>16-20</td>
<td>9th International Conference on Oral Cancer</td>
<td>Melbourne</td>
<td>ICMS</td>
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<td>Ph: +61 3 9682 0244 Fax: +61 3 9682 0288</td>
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<tr>
<td>26-28</td>
<td>30th COSA Annual Scientific Meeting</td>
<td>Perth</td>
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<td>Clinical Oncological Society of Australia</td>
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<td>Ph: +61 2 9380 9022 Fax: +61 2 9380 9033 Email: <a href="mailto:cosa@cancer.org.au">cosa@cancer.org.au</a></td>
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### CALENDAR OF MEETINGS – INTERNATIONAL

<table>
<thead>
<tr>
<th>Date</th>
<th>Name of Meeting</th>
<th>Place</th>
<th>Secretariat</th>
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<tbody>
<tr>
<td>August</td>
<td>8-11 1st Asia Reach to Recovery International Breast Cancer Support Conference</td>
<td>Kuala Lumpur, Malaysia</td>
<td>The Treasurer Breast Cancer Welfare Association of Federal Territory and Selangor Ph: +603 7 946 0133 Fax: +603 7 946 0122 Email: bccwfatm.net.my For details, see: <a href="http://www.cancer.org.au/c_c_news.asp">www.cancer.org.au/c_c_news.asp</a></td>
</tr>
<tr>
<td>28 Aug – 1 Sept</td>
<td>12th International Conference on Cancer Nursing 2002</td>
<td>London, UK</td>
<td>Liz Plein/Claire Manning The Conference Office Ph: +44 0 20 7874 0249 Fax: +44 0 20 7874 0298 Email: <a href="mailto:healthcare.conference@emap.com">healthcare.conference@emap.com</a> Website: <a href="http://www.icc.org">www.icc.org</a></td>
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<tr>
<td>September</td>
<td>1-4 9th Central European Lung Cancer Conference</td>
<td>Vienna, Austria</td>
<td>Mondial Congress Vienna, Austria Fax: +43 1 586 91 85 Email: <a href="mailto:congress@mondial.at">congress@mondial.at</a></td>
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<tr>
<td></td>
<td>17-21 21st Annual Meeting of the European Society for Therapeutic Radiology and Oncology (ESTRO)</td>
<td>Prague, Czech Republic</td>
<td>ESTRO Office, Brussels, Belgium Fax: +32 2 779 54 94 Email: <a href="mailto:info@estro.be">info@estro.be</a> Website: <a href="http://www.estro.be">www.estro.be</a></td>
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<tr>
<td></td>
<td>18-21 SIOPT 2002: The 34th Meeting of the International Society of Paediatric Oncology: Brain Tumours</td>
<td>Porto, Portugal</td>
<td>Congress Secretariat Congress Holland BV Amsterdam, The Netherlands Fax: +31 20 50 40 225 Email: <a href="mailto:siopt2002@congresx.nl">siopt2002@congresx.nl</a></td>
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<tr>
<td></td>
<td>23-25 1st International Symposium on Signal Transduction Modulators in Cancer Therapy</td>
<td>Amsterdam, The Netherlands</td>
<td>NDDO Research Foundation Email: <a href="mailto:congress@nodoxy.nl">congress@nodoxy.nl</a> Website: <a href="http://www.nodoxy.nl">www.nodoxy.nl</a></td>
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<tr>
<td></td>
<td>29 Sep – 4 Oct World Assembly on Tobacco Counters Health 2002 (WATCH 2002)</td>
<td>New Delhi, India</td>
<td>Fax: +91 11 694 4472 Email: <a href="mailto:cancer@rnodl.com">cancer@rnodl.com</a>/nt.net.in Website: <a href="http://www.watch2002.org/">www.watch2002.org/</a></td>
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<tr>
<td>October</td>
<td>6-9 44th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO)</td>
<td>New Orleans, Louisiana, USA</td>
<td>G Smith, ASTRO Farifax, Virginia, USA Fax: +1 703 502 7852 Email: <a href="mailto:gsmith@astro.org">gsmith@astro.org</a> Website: <a href="http://www.astro.org">www.astro.org</a></td>
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<tr>
<td></td>
<td>14-17 Frontiers of Cancer Prevention Research: Genetics, Risk Modeling, and Molecular Targets</td>
<td>Boston, MA, USA</td>
<td>American Association for Cancer Research Ph: +215 440 9300 Fax: +215 351 9165 Email: <a href="mailto:meetings@aacr.org">meetings@aacr.org</a> Website: <a href="http://www.aacr.org">www.aacr.org</a></td>
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<tr>
<td></td>
<td>18-22 27th European Society for Medical Oncology (ESMO) Congress</td>
<td>Nice, France</td>
<td>ESMO Congress Secretariat Lugano, Switzerland Fax: +41 91 950 27 01 Email: <a href="mailto:16apcc@paci.com.ph">16apcc@paci.com.ph</a></td>
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<tr>
<td></td>
<td>24-25 2nd Colorectal Cancer Conference</td>
<td>Rome, Italy</td>
<td>Gabriella Vaccara/Daniela Mengato European School of Oncology Viale Beatrice D’Este, 37 20122 Milan, Italy Ph: +39 02 4335 9611 Fax: +39 02 4335 9640 Email: ecosmt@it</td>
</tr>
<tr>
<td>November</td>
<td>1-3 Oncology Nursing Society 3rd Annual Institute of Learning</td>
<td>Seattle, Washington, USA</td>
<td>Oncology Nursing Society Pittsburgh, Pennsylvania, USA Fax: +1 412 921 6565 Email: <a href="mailto:meetings@ons.org">meetings@ons.org</a> Website: <a href="http://www.ons.org">www.ons.org</a></td>
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<tr>
<td></td>
<td>5-8 19th International Conference of the International Society for Quality in Health Care</td>
<td>Paris, France</td>
<td>Biqua Level 9, Akrohead Centre, St Vincent’s Hospital 41 Victoria Parade Fitzroy VIC 3065 Ph: +61 3 9417 6971 Fax: +61 3 9417 6851 Email: <a href="mailto:isqic@biqua.org">isqic@biqua.org</a> Website: <a href="http://www.biqua.org.au">www.biqua.org.au</a></td>
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<tr>
<td></td>
<td>19-22 2002 Meeting of the European Organisation for Research and Treatment of Cancer (EORTC), the American Association for Cancer Research (AACR) and the National Cancer Institute (NCI): Molecular Targets and Cancer Therapeutics</td>
<td>Frankfurt, Germany</td>
<td>L Hendrick, FICS Conference Unit Brussels, Belgium Fax: +32 2 775 02 00 Email: <a href="mailto:info@fecs.be">info@fecs.be</a> Website: <a href="http://www.fecs.be">www.fecs.be</a></td>
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<tr>
<td></td>
<td>16-18 3rd International Sentinel Node Congress &quot;Sentinel Node 2002 – Universal Applications of Sentinel Node Technology&quot;</td>
<td>Yokohama, Japan</td>
<td>Professor John Thompson Ph: +32 955 5075 Email: <a href="mailto:john@tm.epa.cs.nsw.gov.au">john@tm.epa.cs.nsw.gov.au</a></td>
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<tr>
<td>December</td>
<td>6-10 44th Annual Meeting of the American Society of Haematology</td>
<td>Philadelphia, Pennsylvania, USA</td>
<td>American Society of Haematology Washington, DC, USA Fax: +1 202 857 1164 Email: <a href="mailto:ash@haematology.org">ash@haematology.org</a> Website: <a href="http://www.haematology.org/meeting/">www.haematology.org/meeting/</a></td>
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<td>8-11 18th World Congress of Digestive Surgery</td>
<td>Hong Kong, China</td>
<td>Congress Secretariat Ph: +852 2818 0232/852 2855 4235 Fax: +852 2818 1186 Email: <a href="mailto:sldhkh@hksc.hku.hk">sldhkh@hksc.hku.hk</a></td>
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<td></td>
<td>8-11 9th Hong Kong International Cancer Conference</td>
<td>Hong Kong, China</td>
<td>9th HKICC Secretariat Fax: +852 2818 1186 Email: <a href="mailto:mededcon@hku.hk">mededcon@hku.hk</a> Website: <a href="http://www.hku.hk/">www.hku.hk/</a></td>
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<tr>
<td></td>
<td>11-14 25th San Antonio Breast Cancer Symposium</td>
<td>San Antonio, Texas, USA</td>
<td>L Dumooting San Antonio Cancer Therapy and Research Center San Antonio, Texas, USA Fax: +1 210 940 5009 Email: <a href="mailto:lddumoting@sacri.org">lddumoting@sacri.org</a> Website: <a href="http://www.sabcs.saci.org">www.sabcs.saci.org</a></td>
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<td>2003</td>
<td>March 6-9 56th Annual Cancer Symposium of the Society of Surgical Oncology</td>
<td>Los Angeles, California, USA</td>
<td>D K Rudin, Society of Surgical Oncology 85 W Algonquin Rd, Suite 55 Arlington Heights, IL – 60005, USA Ph: +1 847 427 1400 Fax: +1 847 427 9656 Email: <a href="mailto:dianekel@surgeon.org">dianekel@surgeon.org</a> Website: <a href="http://www.surgeron.org/">www.surgeron.org/</a></td>
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<tr>
<td></td>
<td>12-15 Adjutant Therapy of Primary Breast Cancer</td>
<td>St Gallen, Switzerland</td>
<td>St Gallen Oncology Conferences c/o Prof H J Senn Post Office Box St Gallen – CH-9006, Switzerland Ph: +41 71 243 0032 Fax: +41 71 245 6805 Email: <a href="mailto:abc@2002ts.gznet.ch">abc@2002ts.gznet.ch</a> Website: <a href="http://www.oncoconferences.ch">www.oncoconferences.ch</a></td>
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<tr>
<td>16-19</td>
<td>ICR 2003: 2nd International Conference on Translational Research and Pre-Clinical Strategies in Radiation Oncology</td>
<td>Lugano, Switzerland</td>
<td>Jacques Bernier, Oncology Institute of Southern Switzerland, San Giovanni Hospital Bellinzona, CH-6094, Switzerland. Tel: +41 91 820 9944. Email: <a href="mailto:bernier@usi.ch">bernier@usi.ch</a>. Website: <a href="http://www.usi.ch/icr2003.html">www.usi.ch/icr2003.html</a></td>
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<tr>
<td>April</td>
<td>8th Congress of the European Association for Palliative Care</td>
<td>The Hague, The Netherlands</td>
<td>KENES International, PO Box 5006, Tel Aviv, Israel. Ph: +972 9 908 0488. Fax: +972 2 127 5944. Email: <a href="mailto:sales@kenes.com">sales@kenes.com</a>. Website: <a href="http://www.kenes.com/">www.kenes.com/</a></td>
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<td>2-5</td>
<td>94th American Association for Cancer Research Annual Meeting</td>
<td>Toronto, Canada</td>
<td>AACR, Public Ledger Building, Suite 816, 150 South Independence Mall West, Philadelphia, PA 19106-3, USA. Ph: +1 215 440 9300. Email: <a href="mailto:meetings@aacr.org">meetings@aacr.org</a>. Website: <a href="http://www.aacr.org">www.aacr.org</a>.</td>
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<tr>
<td>May</td>
<td>Oncology Nursing Society 28th Annual Congress</td>
<td>Denver, USA</td>
<td>Oncology Nursing Society Meetings Services Team, Suite 375, 501 Holiday Drive, Pittsburgh, PA 15220-2, USA. Ph: +1 412 921 7373. Email: <a href="mailto:member@ons.org">member@ons.org</a>. Website: <a href="http://www.ons.org">www.ons.org</a>.</td>
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<td>September</td>
<td>ECCO 12 – the European Cancer Conference</td>
<td>Copenhagen, Denmark</td>
<td>FECS Conference Unit, Ms. Kris Virtomäki, Federation of European Cancer Societies, Av E Mounier, 83, Brussels, B-1200, Belgium. Ph: +32 2 775 0205. Email: <a href="mailto:ecco12@fecs.be">ecco12@fecs.be</a>. Website: <a href="http://www.fecs.be">www.fecs.be</a>.</td>
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THE CANCER COUNCIL AUSTRALIA
The Cancer Council Australia is the peak national cancer control organisation. Its members are the leading state and territory cancer councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

MEMBERS
The Cancer Council ACT
The Cancer Council New South Wales
The Cancer Council Northern Territory
The Cancer Council South Australia
The Cancer Council Tasmania
The Cancer Council Victoria
Cancer Foundation of Western Australia
Queensland Cancer Fund

AFFILIATED ORGANISATIONS
Australasian Association of Cancer Registries
Clinical Oncological Society of Australia Inc
Palliative Care Australia
Prostate Cancer Foundation of Australia
Cancer Foundation of Western Australia
Queensland Cancer Fund

CEO
Professor A Coates MD, FRACP, AStat

THE CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA INC
The Clinical Oncological Society of Australia (COSA) is a multi-disciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.

It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with The Cancer Council Australia.

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Prof P Yates BA, DipAppSc, MSocSc

MEMBERSHIP
Further information about COSA and membership applications are available from
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Membership fees for 2002
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Associate Members: $60
(includes GST)

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Surgical Oncology