

Cancer Forum

July 2002

Volume 26 Number 2

ISBN 0 9588 143 8 4

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Current and future directions for cancer immunotherapy

OVERVIEW



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Theory and potential of immunotherapy

Cancer immunotherapy aims to exploit and maximise the body's own immune system in order to target and destroy cancer cells. The immune system is a complex and effective integrated network of specialised cells, organs and factors (cytokines and antibodies) that can quickly and efficiently identify and 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 harm¹. 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 molecules². Finally, cells can secrete immunosuppressive soluble cytokines such as IL-10³ and TGF- β ⁴ 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 genes⁵. 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 tumours⁶. 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 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)⁷. 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)⁸. 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 expression⁹. 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

for cervical cancer. Finally, antibodies can be used to carry cytotoxic drugs to specific cells that express the ligand¹⁰. This method aims to target only the cancer cells to receive cytotoxic agents by conjugating the toxic agent to the antibody that has been shown to be specific for only the cancer cell using TAAs. In each method, antibodies can be used to specifically target cancer cells and can be exploited by choosing the appropriate antibody to achieve altered cellular outcomes.

Cytokines are soluble factors that direct and modulate the nature of an immune response. Granulocyte-Colony Stimulating Factor (G-CSF) is regularly administered to chemotherapy patients to boost neutrophil counts following treatment. Furthermore, cytokines (ie FLT-3 Ligand) can also be used to differentiate cells in vivo for later harvesting for more invasive immunotherapy applications¹¹. Finally, it has been shown that cytokines can have local toxic effects in high doses and some direct applications of cytokines to tumours can cause tumour regression (IL-2)^{12,13}. Therefore, cytokines can have both supportive and therapeutic roles in treating cancer patients.

Cellular immunotherapy involves the alteration of autologous 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 cells^{14,15}) and the lack of methods to generate DC in vitro. There are two major ways of isolating human DC:

- n separation of CD34+ cells from mobilised peripheral blood mononuclear cell (PBMC) harvests; or
- n isolation of monocytes from PBMC by adherence to plastic. Both cell subsets are then stimulated to develop into DC via culture in the presence of several human cytokines, such as GM-CSF, TNF- α , SCF or IL-4^{16,17}.

The fundamental role of DC in orchestrating the different arms of the immune system defines them as important mediators of the immune response. Cell-mediated responses include adaptive responses facilitated by CD4+ and CD8+ T cells and the innate response facilitated by natural killer (NK) and natural killer T cells (NKT) cells. DCs engage and activate these lymphocyte subsets via separate mechanisms in order to control and define the nature of the immune response generated. Each lymphocyte subset has a unique mechanism for killing target cells, but they all produce the anti-tumour cytokine IFN- γ in response to activation. DCs present peptide antigens within the context of MHC class I and II to CD8+ and CD4+ T cells respectively. CD8+ cytolytic T cells kill quickly via granzymes when activated after ligation with MHC I and co-stimulation molecules such as a B7 family member. CD4+ T helper cells, when activated – also through co-stimulation molecules and ligation with peptide-MHC II – can kill target cells through Fas-FasL interactions. NKT cells recognise lipid and glycolipid antigens within the context of CD1a expressed on DC while NK cells recognise and kill cells that do not express MHC I molecules. This dynamic arrangement allows the interplay between initiators and effectors to produce a multi-pronged attack against antigen-bearing cells.

Dendritic cells in cancer immunotherapy

Immunisations using autologous dendritic cells loaded with tumour antigens should overcome two of the major issues in cancer therapies today – donor suitability and engraftment

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 humans. These studies have shown that DC pulsed with specific antigens induces both protective and therapeutic tumour immunity in immunocompetent mice [A Porgador 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 peptides^{18,19,20}, cell sonicates²¹ and RNA^{22,23} 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 monocyte-derived DC (MoDC), which demonstrated that sufficient numbers of MoDC could be generated in vitro to fulfil dose requirements. Cryopreserved MoDC were then administered to patients without any adverse effects²⁴. 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 by tumour-specific T cell activation and IgM/IgG antibody production^{25,26}. 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.

Immunocompetency of cancer patients

The status of immune system function in cancer patients has recently been of interest with respect to new approaches of anti-cancer therapies. However, these studies have focused on immunocompetency following chemotherapy, and baseline data prior to chemotherapy is lacking. Patients with acute lymphoblastic leukaemia (ALL), Hodgkin's disease, or solid tumours were examined for immune function after successful chemotherapy (with or without radiotherapy)²⁷. Immune responses to specific antigens were lower than normal for both the humoral and cellular arms of the immune system in most patients, with only 19% demonstrating normal responses 12 months post-chemotherapy²⁷. Further studies involving the cytokine profiles of cancer patients have shown that IL-2 is deficient in PBSC after traditional chemotherapy and bone marrow transplantation²⁸, and mononuclear cells in patients with advanced cancer show deficiency in T helper 1 responses (decreased IFN- γ , IL-10, IL-12 and increased IL-4)²⁹. While it is important to assess immune function following chemotherapy, baseline immunologic data is necessary to draw meaningful conclusions as to the status of immune function in cancer patients prior to therapy.

Conclusion

There have been many advances recently in the field of cancer immunotherapy, and with the forthcoming publication of clinical trials underway we are certain to refine and improve our methods and efficacy for future therapies.

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Monoclonal antibodies for cancer therapy



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Abstract

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 had been conducted which has furthered our understanding of the potential clinical applications of mAbs. At present, five monoclonal antibodies have been approved by the US 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 therapeutic agents 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 disorders¹. 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 injections. Advances in molecular biology and protein engineering technologies for creating and producing better-tolerated antibodies have led to a renewed

interest in the development of mAbs as therapeutic products. Numerous clinical trials have shown that antibodies can deliver therapeutic activity without long-term toxicity. There are now five monoclonal antibodies approved by the FDA for the treatment of cancer, and a growing number of mAbs are being developed (Table 1). This turnaround has resulted from two major developments:

- n recognition of the critical importance of the choice of appropriate tumour-associated antigens as targets, and the development of genetic engineering techniques that have allowed production of human/rodent chimeric and humanised antibodies. Antibodies have several potential advantages over traditional therapies, including fewer unwanted side effects as a result of high specificity for the disease target; and
- n an ability to deliver various payloads, including drugs, radiation and toxins, to specific disease sites, as well as an ability to elicit an immune response, principally through Fc function.

Tumour antigens recognised by monoclonal antibodies

Significant progress has been made in the last few decades in the detection and classification of defined tumour-associated antigens (TAA) recognised by monoclonal antibodies. Most of these antigens are expressed not only by malignant cells, but also by at least one subset of normal adult cells. However, tumours often express these antigens at higher levels than normal tissues (often up to 100-fold). In addition, accessibility of antigen on tumour to circulating mAbs may be greater than on normal tissue. Therefore, these antigens are not tumour-specific, but often referred to as tumour-associated.

Identification and characterisation of TAA reactive to mAbs involves comparative serological, immunohistochemical and proteomic-based approaches to analysis of normal tissues and tumours². It is often the case that molecular nature and function of the tumour-associated antigens (especially cell surface antigens in solid tumours) are poorly defined. They represent a diverse group of molecules, including proteins, glycoproteins and glycolipids. The expression of TAA is often heterogeneous, and loss of expression may be observed in anaplastic transformation and as a result of immune escape.

Importantly, tumour-associated antigens recognised by antibodies are potential targets for antigen-specific cancer immunotherapy, they can be used for diagnostic purposes, and often serve as prognostic markers in cancer. Different categories of tumour antigens have been identified in a variety of malignancies, and include:

- n hematopoietic differentiation antigens – glycoproteins usually associated with cluster differentiation (CD) groupings (eg CD5, CD19, CD20, CD33, CD45, CD52);
- n cell surface differentiation antigens, including glycoproteins [such as carcinoembryonic antigen (CEA), sialyl Tn antigen (TAG-72), polymorphic epithelial mucin (PEM), epithelial cell adhesion molecule (Ep-CAM), A33, G250, prostate-specific membrane antigen (PSMA) and prostate-specific antigen (PSA)], glycolipids (such as gangliosides, eg GD2, GD3, GM2) and carbohydrates (such as blood group-related antigens, eg Le^a and Le^b);
- n growth factor receptors, including epidermal growth factor receptor (EGFR) and its mutant form EGFRvIII, HER-2/neu and IL-2 receptor; and
- n angiogenesis and stromal antigens, including fibroblast activation protein (FAP), vascular endothelial growth factor receptor (VEGFR), tenascin and integrin $\alpha_3\beta_3$.

Chimerisation and humanisation of antibodies

The development of genetic engineering has been central to the clinical use of antibodies. This technology allowed construction 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, or CDRs, derived 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* macaques and constant regions derived 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 1985³. 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 gene's 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 antibodies (bsAbs) carry dual specificity because of their two binding regions – one specific for tumour-associated antigen, and the other to immunological anti-tumour effector cells. The chimerisation and humanisation technologies have had a key impact upon the reduction of immunogenicity of the mAbs, their capacity to recruit cytotoxic cells and complement, and stability in circulation. Despite these advances, chimeric and humanised mAb have the potential to stimulate HACA (human anti-chimeric antibody) or HABA (human anti-human antibody) immune responses directed to the variable regions of the mAb, although the incidence of such responses is generally low⁴.

Mechanisms of action of unconjugated antibodies

Unconjugated mAbs may induce therapeutic effect by a variety of different mechanisms, including blocking receptor–ligand interactions; initiating cellular ablation via recruitment of effector cells and/or complement; and cross-linking target molecules and delivering transmembrane signals that control cell cycle progression and/or induce apoptosis/cell death.

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. Alternatively, receptor binding by mAb may prevent receptor homodimerisation or heterodimerisation, and result in inhibition of downstream signalling events. Important examples of this mechanism of action of mAbs include ErbB2 (eg Herceptin), EGFR (eg C225), and VEGFR (eg IMC-IC11). The binding of mAb against these receptors induces measurable changes in the phosphorylation status of the receptor and key signalling molecules, and inhibition of cellular functions that can be linked to signalling events including apoptosis, therapy resistance, and angiogenesis⁵. Herceptin has been approved for the treatment of patients with advanced

breast cancer, and a number of antibodies against the EGFR⁶ are being developed (Table 1). Anti-angiogenesis has been proposed as a potential strategy for the treatment of cancer⁶⁻⁸, and mAbs are also being studied in clinical trials to prevent the interaction between VEGF and its receptors⁹⁻¹². The cross linking of tumour cell surface receptors and induction of signalling inhibition by mAb has also been reported with other antigen systems, including CD20.

Tumour cell killing via Fc function

A key component of mAb-based therapy of cancer is dependent upon Fc function. This mechanism of cell killing may be through activation of the classical pathway of complement; the recruitment of cellular effectors against target tumour cells; and the induction of apoptosis and phagocytosis. The relative contribution of such mAb-effector mechanisms to cancer cell killing in vivo is difficult to assess, however in experimental settings the Fc regions of antibodies have been shown to make major contributions to mAb biologic activity¹³. In mice lacking activation Fc receptors FcγRI and FcγRII, the anti-tumour effects of trastuzumab (Herceptin) and rituximab (Rituxan) were reduced, while mice deficient in inhibitory FcγRIII receptors showed inhibition of tumour growth and enhanced antibody-dependent cellular cytotoxicity (ADCC). There are a number of examples of mAb with highly potent Fc function that have demonstrated biologic efficacy in the clinic, including mAb against GD2, GD3 and Lewis^x antigens^{14,15}. Campath1H, a humanised version of rat anti-CD52 mAb, which is licensed for treatment of refractory chronic lymphatic leukaemia 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 patients^{16,17}.

Anti-idiotypic network cascade

Monoclonal antibodies can also serve as immunogens for cancer vaccines through the anti-idiotypic-network cascade. Anti-idiotypic antibodies bind to the antigen-binding sites of antibodies, thus effectively mimicking the three-dimensional structures of antigens. Hence, anti-idiotypic antibodies can serve as surrogate antigens for active specific immunotherapy. Numerous studies in animal models have demonstrated the efficacy of the anti-idiotypic antibodies as vaccines for triggering specific anti-tumour responses, and clinical trials are underway in a number of tumours (eg ovarian, melanoma) with this approach.

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, chemotherapy drugs or cytokines that require cell entry or close proximity to tumour cells to be effective¹⁸⁻²⁰. Conjugated mAbs and antibody fragments have been developed for solid tumours and hematological malignancies, and intensively characterised for their biological activity in vitro, as well as in in vivo animal models.

Radioisotopes can be chemically linked to anti-tumour mAbs and administered to patients to deliver radiation selectively to tumour sites. Radioimmunoconjugates are constructed either by covalently binding the radioisotope directly to the antibody, or by crosslinking through a chelating agent or chemical linker. The cytotoxic efficacy of a given radioimmunoconjugate depends on the kinetics of antibody localisation and retention of the radionuclide. Lymphoma cells are particularly sensitive to radiation. The anti-CD20 mAb radiolabelled with yttrium ⁹⁰Y (Zevalin) has been shown to increase delivery of radiation

to neoplastic versus normal tissue by nearly 1000-fold^{21,22}, and is now approved for treatment of B-cell lymphomas. Another anti-CD20 mAb conjugated to ¹³¹I (Bexxar) has completed phase III trials and is awaiting FDA approval²³. There are no clinically approved immunoconjugates for the treatment of solid tumours as yet, although numerous trials are underway using this approach. The selection of appropriate isotopes, eg alpha versus beta emitters, is a key component of the optimisation of this approach.

Biological toxins, such as ricin or diphtheria toxins, and cytotoxic drugs, such as doxorubicin and calicheamicin, can also be attached directly to anti-tumour mAbs. Discovery of the in vitro and in vivo potential of recombinant immunotoxins has led to their preclinical development, and to the initiation of clinical trial protocols in patients with cancer refractory to traditional ways of treatment. The linking of calicheamicin to an anti-CD33 mAb has achieved success in the treatment of elderly patients with AML, and Mylotarg has been approved for this indication. Another strategy for mAb-mediated drug delivery involves a two-step approach known as ADEPT, or antibody directed enzyme-prodrug therapy²⁴, where mAbs are used to localise enzymes to tumour cell surface antigens. Once the mAb-enzyme conjugate binds neoplastic cells and excess conjugate is cleared from circulation, anti-tumour prodrugs are administered and are converted to active drugs by the targeted enzyme. This 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 such as Fv (non-covalently associated heavy and light chain variable domains), single chain Fv (scFv; heavy and light chain variable domains covalently linked by short peptide linkers), Fab (non-covalently associated heavy and light chain antigen-binding domains) and diabodies/triabodies (linked recombinant scFv fragments) maintain the parental antibodies' specificity and penetrate tumours more easily²⁵. They are often used as vehicles to deliver toxins and drug conjugates. One drawback, however, is that these smaller molecules tend to have short half-lives, and are rapidly eliminated from circulation. Some of the small therapeutic Ab fragments have been modified by linking to various agents, such as polyethylene glycol and albumin, to block reabsorption in kidneys²⁶⁻²⁸.

Bispecific antibodies

Bispecific antibodies (bsAbs), F(ab)₂ fragments and diabodies can override the natural specificity of an effector cell for its target, and re-direct the lysis towards a cell population it would otherwise ignore. Immunological effector cells that can potentially be recruited by bispecific agents include granulocytes, macrophages, natural killer and T cells. For example, cytotoxic T lymphocytes can be re-directed against a tumour by bsAbs that have specificities for a constant component of the T cell antigen receptor complex (TCR) such as CD3, and a molecule expressed on the neoplastic cells surface. This technique was pioneered in the 1980s and confirmed in many recent animal studies and in clinical trials²⁹⁻³⁵. The combining of tumour cell specificity with cytokine effector mechanisms (eg IL-2, TNF) is another potential approach that has shown encouraging preclinical results. Recent clinical trials of bsAbs using both TCR and FcRs as triggering molecules have also been reported.

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 signalling inhibition on tumour cell proliferation and repair mechanisms. The majority of data exists from combining mAb-based therapy with chemotherapy^{5,36-41}. The combining of radiotherapy with EGFR-targeted mAbs, and chemotherapy with radioimmunotherapy, 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 targeted immunotherapies. Optimisation of monoclonal antibody therapies will be directed towards design of better antibodies and immunoconjugates, enhancement of tumour-specific cytotoxicity, and the development of more effective combination therapy approaches. Clearly, the full potential of mAb-based immunotherapy is yet to be reached.

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

Antigen Target	Cancer	Antibody	Antibody Type	Company / Institute	Trial Status
CD33	AML	Zamyl Mylotarg (Gemtuzumab ozogamicin)	Humanised Humanised	Protein Design Labs Wyeth-Ayerst	Phase III FDA approval 2000
CD20	NHL	Rituxan (Rituximab) Zevalin (Ibritumomab Tiuxetan) Bexxar (Tositumomab)	Chimeric Murine, radiolabelled (⁹⁰ Y) Murine, radiolabelled (¹³¹ I)	IDEC Pharm/Genetech IDEC-Pharm/Schering AG Corixa Corporation	FDA approval 1997 FDA approval Feb 2002 Phase III
CD22	NHL	LymphoCide (Epratuzumab) LymphoCide Y-90	Humanised Humanised, radiolabelled (⁹⁰ Y)	Immunomedics, Inc Immunomedics, Inc	Phase III Phase I
HLA-DR	NHL	Smart1D10 (Remitogen)	Humanised	Protein Design Labs	Phase II
CD52	B-CLL	Campath1H (Alemtuzumab)	Humanised	Millenium Pharm/ ILEX Oncology Inc	FDA approval 2001
HER2/neu (ErbB-2)	Breast, Colon, NSCLC	Herceptin (Trastuzumab)	Humanised	Genentech	FDA approval 1998 (breast cancer)
CEA	Solid Tumours	CEA-cide Y-90	Humanised, radiolabelled (⁹⁰ Y)	Immunomedics, Inc	Phase I/II
EpCam	Colorectal	Panorex	Murine	Glaxo-Smith Kline	Approved in Germany in 1995
EGFR	Head and Neck, NSCLC, Colon	IMC-C225 (Erbixub) ABX-EGF h-R3	Chimeric Human Humanised	Imclone Sys Abgenix CMI	Phase I/II/III Phase I/II Phase I/II
VEGF	Solid Tumours	Bevacizumab	Humanised	Genentech	Phase II/III
VEGFR-2	Solid Tumours	IMC-1C11	Chimeric	Imclone Sys	Phase II and III
A33	Colorectal	huA33	Humanised	LICR	Phase I/II
Lewis ^x	Solid Tumours	SGN-15 hu3S193	Chimeric Humanised	Seattle Genetics LICR	Phase I/II Phase I
GD3	Melanoma	KW-2871	Chimeric	Kyowa Hakko Kogyo / LICR	Phase I
G250/MN	Renal, Biliary	cG250	Chimeric	LICR / Willex	Phase I/II
PSMA	Prostate	MLN591	Humanised	Millenium Pharm	Phase I/II
CTLA-4	Prostate, Melanoma	MDX-010	Human	Medarex	Phase I/II

Abbreviations: AML – acute myeloid leukaemia; B-CLL – B-cell chronic lymphocytic leukaemia; CEA – carcinoembryonic antigen; CMI – Centre for Molecular Immunology, Cuba; CTLA-4 – cytotoxic T lymphocyte-associated antigen 4; EGFR – epidermal growth factor receptor; FDA – US Food and Drug Administration; HLA – human leukocyte antigen; LICR – Ludwig Institute for Cancer Research; NHL – Non-Hodgkin's lymphoma; NSCLC – non-small cell lung carcinoma; PSMA – prostate-specific membrane antigen; VEGFR-2 – vascular endothelial cell growth factor receptor-2.

Dendritic cell biology and application for tumour immunotherapy



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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 naïve and tumour antigens^{1,2}. These cells have generated intense interest in the scientific community because of their potential use as "autologous adjuvants" in cancer vaccination³.

DC biology

DC differentiate from early myeloid and lymphoid progenitors. In man at least two blood subsets are described – the CD11c⁺/CD123^{dim} "myeloid" DC and the CD11c/CD123⁺ "lymphoid" DC. They have different properties². Current suggestions are that the CD11c⁺/CD123^{dim} DC provide epithelial and non-epithelial surveillance and migrate 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 populations⁴.

DC integrate signals from the environment to link the innate and cognate (T cell and antibody) immune responses. In their role of immunosurveillance, CD11c⁺ DC encounter and take up antigen from the tissues. Exogenous and endogenous protein antigen (the handling of the latter is better characterised than other forms of antigen) is processed by the proteasome into short peptide sequences. Peptide epitopes are then complexed to MHC class I and II molecules and transported to the cell surface. Peptide epitope antigen (the sequence of which is specific for a particular MHC allele) can only be recognised by corresponding CD4 or CD8 T cell receptors when it is presented in conjunction with the respective MHC class II or I molecule. Danger signals upregulate DC antigen uptake and processing, migration (controlled by chemokines), costimulatory membrane molecule receptors and cytokine release. Their complex control of gene products and functions allows for great DC diversity, specialisation and their fine control of immune responses, including self-tolerance^{1,2}.

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 (CTL). 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 naïve 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 establishment 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 patients⁵ and abnormal DC function has been noted in breast adenocarcinoma⁶⁻¹⁰, renal cell carcinoma¹¹, prostatic adenocarcinoma¹², colonic adenocarcinoma¹³, basal cell carcinoma¹⁴, multiple myeloma¹⁵, melanoma¹⁶⁻¹⁸ and transitional cell carcinoma of the kidney and bladder¹⁹.

DC function can be suppressed by the release of tumour-derived inhibitory factors. Interleukin (IL)-10 release from melanoma²⁰, multiple myeloma²¹ and bronchogenic carcinoma²² may impair DC function. IL-6 and macrophage colony stimulating factor (M-CSF) released by renal cell carcinoma inhibited the differentiation of CD34-derived DC from CD34⁺ progenitors²³. Vascular endothelial growth factor (VEGF) release from human tumours can alter dendritic cell maturation⁷, and high serum levels of VEGF have also been associated with the presence of immature myeloid cells in the blood, which in turn were closely correlated with the stage and duration of clinical neoplastic disease²⁴.

In multiple myeloma, DC numbers are relatively normal but CD80 induction is reduced¹⁵. In colorectal carcinoma, there was low or absent expression of the costimulatory molecules CD80 and CD86 on DC obtained from the tumour site. In addition, data from analyses of breast carcinoma⁸⁻¹⁰, renal cell carcinoma¹¹, transitional cell carcinoma¹⁹ and prostatic adenocarcinoma¹² 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 immunity, as evidenced by the presence of anergic melanoma-specific T cells²⁵. The notion that DC abnormalities in cancer may have clinical consequences is supported by the fact that low DC numbers in tumour biopsy specimens were associated with a poor prognosis in bowel adenocarcinoma²⁶, cutaneous T cell lymphoma²⁷ and prostatic adenocarcinoma²⁸.

In addition to immune evasion, as a result of abnormalities in DC priming of CTL, impaired immune responses to tumours may occur due to intrinsic defects in neoplastic cells themselves. Down-regulation of MHC molecules and antigen processing into tumour cell surface complexes prevents effective recognition by effector CTL, and has been described in many tumours²⁹⁻³¹. Abnormal tumour antigen expression can allow "immune escape" in an analogous fashion to the acquisition of metabolic alterations by malignant cells, which confers chemotherapy resistance.

DC in immunotherapy

Rationale

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 conjunction with self-MHC molecules, providing the immune system with a recognisable therapeutic target. The second premise 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 preparation of DC vaccines 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 loading³².

DC preparations

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

The most commonly used preparation is the monocyte-derived DC (MoDC)³³. Large numbers of these DC-like cells can be generated from peripheral blood samples or apheresis products and for this reason, they have become the most common form of DC to be used in laboratory and clinical research. After approximately five days of culture with GM-CSF and IL-4, monocytes differentiate into a cell with an immature DC-like phenotype, with loss of CD14, low CD40, CD80 and CD86 expression but no CD83. MoDC can be activated to a mature phenotype with various cytokine cocktails³⁴ prior to antigen loading and vaccination.

CD34 cells can be differentiated into DC^{35,36} and have been used in vaccination studies³⁷, but are extremely cumbersome to produce and are seen as a less popular alternative.

Blood DC precursors (BDC), obtained by immunomagnetic selection from leucapheresis products, are the focus of increasing attention³⁸. Production does not require a long period of culture or exogenous cytokines and can be undertaken following good manufacturing practice (GMP) guidelines^{39,40}. It is also tempting to speculate that BDC can be harvested at an appropriate stage of differentiation for antigen loading and CTL priming.

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 down-regulated with disease progression. 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 preparation 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 encompass a range of epitopes specific for multiple different MHC alleles. As the range of antigen and epitope coverage increases, so too does the likelihood of autoimmune injury after vaccination. Despite the theoretical risks, there is relatively little evidence to suggest that autoimmunity will pose a major impediment to anti-tumour vaccination⁴¹.

Clinical trials

Since the first clinical trial of DC immunotherapy⁴² was published in 1996, a large number of trials in many different diseases have been undertaken. Virtually all of these trials have been phase I/II trials and only recently have phase III studies 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^{43,44} and CD34DC³⁷ 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 trial³⁷, in which subjects were vaccinated with CD34DC pulsed with four melanoma-derived peptides, clinical responses (albeit at an early stage of 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 immunologic therapies such as IL-2⁴⁵ and lymphokine activated killer cells⁴⁶ (LAK). Excellent results were achieved (4/17 attained complete remission) in renal cell carcinoma patients through vaccination with allogeneic DC:tumour hybrids⁴⁷. Characterisation of the cell preparation used in this trial is under further study.

Multiple myeloma⁴⁸ and non-Hodgkin's lymphoma⁴⁹ are promising candidates for immunotherapy, particularly in the setting of minimal residual disease post-autologous transplant. A recently reported study of follicular non-Hodgkin's lymphoma patients showed impressive results after vaccination with idiotype protein pulsed DC⁵⁰. 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 inconsistent⁵¹⁻⁵⁴, mainly being restricted to stabilisation of tumour marker levels. CTL responses after vaccination with MoDC have been noted in vivo in breast, ovarian⁵⁵ and colonic adenocarcinoma⁵⁶ amongst others, demonstrating the feasibility of this approach.

Vaccination protocols

One of the problems with assessment of the accrued data is that all 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, state of activation, dose, route and frequency of vaccination 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 immunological responses have not been forthcoming, although the vast majority of clinical responses occur in patients who have an immunological response³. This may be due to the fact that the immune response in the peripheral blood 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 data⁵⁷ to support one preparation over another. Available evidence suggests that immature MoDC may not be the optimal preparation for tumour immunotherapy. Human vaccination studies have suggested that the use of immature MoDC may lead to antigen-specific tolerance⁵⁸, clearly an undesirable outcome for tumour immunotherapy. Certainly,

accumulating data suggest they may be less efficacious.

Data on DC dose has not been established, however some information regarding route of administration is coming to light. In one study it appeared that intradermal (id) or intralymphatic (il) administration was preferred over intravenous (iv), as the id and il routes produced interferon- γ (IFN- γ) responses while iv vaccination was only able to elicit an antibody response⁵⁹. Trials examining direct intranodal injection of DC under ultrasound guidance have also shown clinical and immunological responses⁴³.

Vaccination frequency is another contentious issue. Most current schedules involve weekly vaccination, however this has been based largely on data obtained from experience with infectious disease. Whether this data will translate to the field of tumour immunotherapy remains to be seen. In tumour immunotherapy, particularly in phase I/II trials, the subject is vaccinated in a state in which there is a large antigenic load of tumour, in contrast to preventive vaccinations in infectious disease. It is suggested that tumour immunotherapy will be more effective if administered at a stage of minimal residual disease. Vaccination on a high frequency schedule may be detrimental⁶⁰.

Complications

To date, relatively few complications have been seen with DC immunotherapy. By far the most common events are low-grade fever or the occurrence of a local injection site reaction. Biopsy-proven delayed type hypersensitivity is usually regarded as a good sign and indicates an immunologic response. There is one report of an allergic reaction to bovine serum albumin in a DC vaccine⁶¹. As most tumour antigens are self-antigens, there is always the potential for devastating autoimmune consequences after vaccination. This appears to be less commonly seen than intuitively expected (reviewed in reference 41). To date, the only commonly seen autoimmune condition after DC vaccination is vitiligo – the expected outcome. This has been noted in up to 43% of vaccinated patients with metastatic melanoma (F O Nestle – unpublished observation). Despite the safety data noted in reported trials thus far, it would be prudent at this early stage to avoid vaccination of patients with a tendency to autoimmune disease.

Monitoring

Monitoring the response of a DC vaccination subject should involve two aspects. Obviously, clinical parameters are of prime importance and the success of DC immunotherapy will ultimately be judged in this regard in large phase III studies. Efforts are also underway to define immunologic “surrogate” parameters that may be useful in predicting clinical responses. Immune responses in the peripheral blood, at the vaccination site, DLN and within the tumour tissue are being assessed. The most accessible tissue for monitoring is obviously the peripheral blood, however immunohistochemical and histologic analysis is also being used to define the nature of a response at the vaccination site, DLN and within tumour tissue.

Techniques such as the ⁵¹chromium release cytotoxicity assay using CTL isolated from peripheral blood are specific indicators of tumour killing but are very insensitive as the in vivo frequency of tumour-specific CTL is usually very low (<1% PBMC). Fluorochrome-conjugated MHC:peptide tetramers are highly sensitive and bind TCR-specific for a given peptide antigen. Unfortunately, not all tetramer-positive CTL have the capacity to produce IFN- γ and induce cell lysis. IFN- γ ELISPOT, intracellular staining for IFN- γ and IFN- γ secretion assays are also very sensitive markers. The latter assay has the advantage that it can be used alone or in combination with tetramer analysis and fluorescence-activated cell sorting to produce populations of antigen specific

CTL for use in cytotoxicity assays. Expansion of IFN- γ secreting CTL populations is being explored for adoptive immunotherapy. Other cytokine staining techniques can elucidate the nature of a Th1 or Th2 immunologic response. With all of these methods, considerable expertise is needed for accurate detection of low frequency tumour-specific CTL. Now that the technology and tumour peptides are more refined, serious analysis of CTL correlations can begin. These staining techniques are also applicable to tumour fine needle biopsies.

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 inappropriate DC preparations may be quite detrimental. Clearer characterisation of the in vitro conditions required to break tolerance to self-antigen is critical. This is obviously not a minor undertaking. Future directions include targeting antigen to various cellular compartments, including helper epitopes or constructs, improving activation markers and adding migratory signals to improve in vivo induction of immune responses. The promising beginning indicates that the effort expended in optimising the many aspects involved may yield great dividends.

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Many epidemiologic studies now support a hypothesis, formulated 20 years ago by Gissmann and Zur Hausen, that papillomaviruses (PV) are a major cause of cervical cancer and other anogenital malignancies. PVs come in many varieties or genotypes. Persistent infection with one of a few high risk types of human papillomaviruses (HPV), of which HPV16, 18 and 33 are the most common examples, conveys significant risk of anogenital malignancy. There exists approximately a one in 20 lifetime risk of development of cervical cancer following persistent infection with a high risk type of HPV. The World Health Organization has determined that high risk HPV infection is therefore a "necessary" factor for development of cervical cancer¹, 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 for development of 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 PV infection point the way to a vaccine

Generally, effective viral vaccines 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 genotypes². These demonstrated that papillomavirus infection naturally induces relatively low titres of neutralising antibody, and that some infected individuals seemingly acquire 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 to PV are largely directed against conformational epitopes displayed 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 epidemiologic 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 specific³. Papillomaviruses 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 DNA technology, assembled into virus-like particles (VLP)⁴, and these VLPs have become the basis of the current efforts in PV 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 reported at a recent international meeting included a post-hoc analysis of the results of a number of phase I and II studies of HPV16 specific PV vaccines based on recombinant L1 virus-like particles. While post-hoc analysis can be deceptive, the results, taken at face value, demonstrated absolute protection against new incident HPV infections of type 16 amongst individuals vaccinated with a range of doses and formulations of HPV16 VLPs (0 cases in 66 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 differences were unlikely to be due to chance variation in risk, and also confirmed the type specificity of vaccine-induced host protection. Several reported studies in human volunteers of VLP-based HPV vaccines of types 11 and 16 show good 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 PV genotypes⁵. Modelling the decline of 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, though the limits to this 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 incorporated into a multivalent vaccine, an issue not easily resolvable in animal trials. 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, however, would need to be demonstrated to be of comparable duration and protection as systemic delivery before it could be considered a preferred delivery route for vaccine in developing countries. Confidence that VLP-based vaccines have the potential to prevent PV infection has focused attention 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 trialled in animals. Polynucleotide vaccines 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 accesses women immediately prior to the onset of sexual activity. Polynucleotide vaccines incorporating the L1 gene of PV induce neutralising antibody in beagle dogs, and we have recently demonstrated that codon modification to allow better expression in eukaryotic systems improves immunogenicity of such polynucleotide vaccines⁶. The L2 protein of the PV capsid, while not as effective at inducing immune responses during natural infection as the L1 protein, has been shown to induce immune responses as a part of a vaccine which virus neutralising in vitro, and may therefore prove useful if a significant number of subjects are proven unable to respond to

an L1 vaccine delivered either as VLPs or as a polynucleotide. Therefore, there has been considerable progress in vaccine development for the prevention of PV infection. However, developing vaccines for the treatment of existing infections and particularly treatment of malignancies due to infection present a different set of problems to researchers.

Vaccines to treat PV infection and cervical cancer

It can be estimated that, globally, about 100 million women have already been infected with high risk genital PVs, and that about five million of these will have persistent infections that will in due course give rise to anogenital cancer if untreated. For this large group, there is no evidence that capsid protein-based vaccines, designed to produce virus-neutralising antibody, have much to offer for eradication of existing infection. Rather, therapy will be targeted at eliminating epithelial cells in the anogenital tract that are already infected with PV⁶. Specific antiviral immunotherapy, either given alone or in conjunction with specific antiviral drugs, might achieve this goal. Papillomaviruses generally encode six non-structural proteins (termed E1, E2, E4, E5, E6, E7) and two structural proteins (L1 and L2) which are expressed differentially across the maturing epithelium, though all are expressed at low abundance in the infected self-renewing stem cell populations at which immunotherapy would have to be targeted to eliminate clones of infected epithelial cells. Natural immune responses to PV-encoded antigens are generally weak and unpredictable, although a humoral immune response is observed to E7 in most cases of invasive cervical carcinoma⁷. Some evidence suggests that cell mediated immune response to the E2 and E6 proteins may be predictors of regression of PV-associated disease. Further, immunocompromised individuals due to HIV infection or following transplantation is a well-characterised risk factor for progression of PV infection to premalignancy and malignancy. Thus, targeting immunotherapy to some or all of these PV-encoded proteins is held to have potential for treatment of PV infection. However, in general, effective active immunotherapy is still a goal that has not been realised for any human disorder, despite some early successes of tumour antigen-specific immunotherapy in subsets of patients with cancer. Further, there are extra problems in targeting immunotherapy to PV-associated skin lesions, which lack the inflammation necessary to recruit innate immune responses.

Against this background, what has been achieved so far by ourselves and others – recently reviewed by Breitbart⁸ – is to demonstrate firstly that the PV non-structural proteins are adequately immunogenic, inducing responses 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 cottontail rabbit papillomavirus, partial therapeutic efficacy against natural infection has also been demonstrated. The optimal choice of antigen, means of production, dose, route of delivery, and frequency of immunisation has yet to be established, though many such delivery systems have been proposed and have been shown to be of benefit in at least one animal model⁹. 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 and pre-cancer. One recent study undertaken by the centre demonstrated immunogenicity of HPV6 VLPs without adjuvant in patients with existing warts, and hinted at possible

therapeutic efficacy¹⁰.

A major effort will be needed to develop laboratory assays that predict vaccine efficacy that might be used to allow cost-effective dose-ranging studies of potential therapeutic vaccines in man. Therefore there is great interest in the epidemiologic studies currently being undertaken, to evaluate whether viral load is predictive of clinical outcome for PV, which has been the case for other viruses. Similarly, studies of cellular immune responses to vaccine proteins in man are being undertaken, though the constraint of only being able to access blood, and in limited quantity, 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.

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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 year¹. 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 the sub-groups of patients with high-risk primary disease or metastatic disease, the outlook is very poor. The one-year survival of metastatic melanoma is 41-59%¹ and the median survival is approximately 7.5 months, although this varies according to the site of metastasis². No intervention has been shown to improve the outcome of patients with metastatic disease. Clearly, better treatment approaches are required.

There is 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 it is possible that these patients simply have indolent 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 6%) of patients who achieve a complete response to IL-2 have a high probability of long-term complete remission and presumed cure³. This is very rare with conventional chemotherapy and indicates an important qualitative difference in the mechanism of action of this agent – induction of immune memory. Many of these patients develop vitiligo due to T cell-mediated killing of normal melanocytes, indicating that the immune response is specific for antigens in cells of the melanocyte lineage. The development of vitiligo in these patients indicates a higher probability of response to immunotherapy⁴. High 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 fact 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 BCG⁵ or sources of undefined antigens such as tumour cell extracts or lysates⁶. Since the first human cancer antigens that could be recognised by T cells were defined⁷, the field has

advanced rapidly. Numerous potential vaccine targets are now available, and there are also many new adjuvants that can predispose towards the T cell responses that 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 expressed by normal cells (“cancer-testis” 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 spermatogonia⁸, 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 protein⁹. NY-ESO-1 is expressed in a wide variety of cancers¹⁰ and is very immunogenic: spontaneous immune responses to NY-ESO-1 occur in 50% of patients whose tumours express this antigen¹¹. Both antibody and T cell responses are seen *de novo*, and patients treated with NY-ESO-1 peptides commonly develop T cell responses¹². 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 an early cytoreductive effect while awaiting 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 immunosuppressants such as corticosteroids are used. Responses to cancer antigens are similar to those against viral antigens in that most cancer antigens are intracellular and hence only able to be recognised by T cells. Various regimens combining chemotherapy and immunotherapy (“biochemotherapy”) have been tried and these have been reviewed recently¹³. Single arm studies indicated good response rates although, interestingly, this was schedule dependent – ie responses when the two modalities were given concurrently were superior to those in which the immunotherapy preceded the chemotherapy. 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 biochemotherapy 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 survival¹⁴, overall survival was not significantly prolonged. The highly selected study population had substantial toxicity in the experimental arm. However, long term responders have been described¹⁵ 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 extrapolated 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 rejecting large volumes of tissue – this is the bane of the transplanters. 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 rejection response. It is this deficiency 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 inflammatory response in 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 cytokines such as GM-CSF or interferon- α . In 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 delivered *in vivo* using appropriate adjuvants. Alternatively, 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.

Who and when?

So far, most work in cancer immunotherapy has involved patients with advanced disease. Although these patients offer the opportunity to observe tumour responses 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 (assuming that 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 can be elicited. The short median survival of 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 also relatively uncommon. 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 much 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

now turning to patients with earlier stages of disease. We are

performing a series of small studies involving patients who have had cancers that express the antigen of interest but which have been removed. These patients are eligible if they arbitrarily have a risk of relapse of at least 25% over five years. For melanoma, this means patients with a primary melanoma of ≥ 1.5 mm, or ≥ 1.0 mm if ulcerated. Patients with resected 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 is 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 mediate an anti-tumour 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 effective antigen presentation can take place 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 or “dangerous” microenvironment in the region 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 tissues and are capable of recognising 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 treatment modalities, such as chemotherapy, radiotherapy, or in combination with newer biological agents such as inhibitors of tumour angiogenesis, receptor tyrosine kinase inhibitors, cell cycle inhibitors and monoclonal antibodies. 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 ebb. Trials in this clinical setting can only be justified once the optimal method of vaccination has been determined.

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



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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 pregnancies¹. Historically breast cancer concurrent with pregnancy, also known as gestational breast cancer (GBC), was thought to carry a poor prognosis². This adverse outlook, and the fact that most clinicians' experience and knowledge of GBC is limited, has continued to impact upon the medical psyche³. 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 cancers⁴⁻⁸. Overall, the incidence appears low, but in premenopausal women, incidence of GBC is reported to be between 7-14%⁹⁻¹¹.

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 cancers¹²⁻¹⁵. 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

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



Ultrasound of a baby



Ultrasound of breast cancer

for GBC of 57% (95% CI, 33-81) and non-GBC of 61% (95% CI, 47-75)^{9,16,17}. The main reason for worse outcomes in GBC has been reported to be due to delay in diagnosis. Most delays appear to be due to the woman or her clinician assuming that the breast symptom is because of the physiological changes of pregnancy and not anything more sinister. Delays of two to 15 months longer from first symptoms to confirmed diagnosis in pregnancy-associated breast cancer than in their non-pregnant counterparts have been reported^{4,6,7,9,14,17,18}. Sadly such delays, even in such an uncommon condition, may have medico-legal implications for the clinician^{19,20}.

Approximately 70% of GBCs are found to be node positive at surgery, again an indication of late presentation^{21,22}. Very little research has been carried out on the histological appearance of GBC, but there appears to be no difference from those in non-GBC^{1,23,24}. Similarly, little evidence is available regarding the genetic aspects of GBC, although BRCA1 and BRCA2 mutations have been identified in some cases^{1,25,26}.

Most young women with operable breast cancer can be offered breast-conserving surgery and postoperative radiotherapy. Radiotherapy is contraindicated during pregnancy due to the high radiation dose to the foetus, thus for many pregnant women mastectomy is the surgical treatment of choice. When breast cancer is diagnosed in the third trimester, it may be possible to perform breast-conserving surgery with radiotherapy delayed until after delivery of the child^{1,3}.

Chemotherapy results in unacceptably high levels of fetal abnormality when administered during the first trimester^{3,27}. Administration of chemotherapy during the second and third trimester is generally safe (a malformation rate of 4% is reported – similar to the 3% risk during a normal pregnancy), although it may be associated with low birth weight and early delivery^{28,29}. Specific agents that should be avoided as treatment during pregnancy include antimetabolites such as methotrexate³⁰.

Termination of pregnancy is sometimes considered as a management option in GBC. There is however, no evidence that termination of pregnancy is associated with a survival benefit – it may actually have a deleterious effect^{9,13,22}. This reporting may be biased, as many women who undergo termination of pregnancy for GBC have more advanced disease and would have a poor prognosis irrespective of whether their pregnancy was terminated or not¹.

Subsequent pregnancy

Contraception and fertility are two important issues for premenopausal survivors of breast cancer, particularly when their lifespan may be limited³. Most clinicians advise against pregnancy in the first two years following treatment^{31,32}. This is mainly to ensure the woman does not develop early recurrence and that all adjuvant treatments have been completed prior to conception. Contraception is therefore likely to be necessary, but hormonal contraception is not recommended. Breast cancer survivors who subsequently conceive have equivalent survival or in some studies better survival matched for stage^{9,21,22,33-36}. This improved survival may be due to bias, with only a select group of healthy women going on to become pregnant – a “healthy mother” effect³⁷.

At the other end of the spectrum chemotherapy can induce infertility. Women under 35 years of age are less likely to experience permanent amenorrhoea than women aged over 40. Reports of between 37% and 97% of premenopausal women becoming amenorrhoeic following chemotherapy

have been recorded, and this is very much related to age and type of chemotherapy treatment^{27,38,39}. Various strategies have been proposed to protect the fertility of a woman undergoing chemotherapy, but with little success thus far. It has been estimated that only 7% of fertile women go on to conceive following breast cancer treatment. Whether this is by choice or not is as yet unknown^{3,39,40}.

Population-based research in Australia

The rarity of GBC means that a randomised controlled trial is not an appropriate method to study 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^{4,6,12,21}. 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 has 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 around 13 million records and consists of population-based hospital morbidity data, birth and death records, mental health services data, cancer registrations and midwives' notifications, linked back to 1980. This linkage system is one of only five such projects 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 trials⁴¹. We expect to identify about 300 cases (approximately 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 hospitals. The data file will be de-identified for research purposes.

This work will enable further research to be conducted in the pathological, biological and imaging characteristics of the malignancies in the pregnant and lactating breast. Future prospective studies are envisaged that will look at changes in the management of breast cancer related to pregnancy, and the psychosocial issues (including fertility) which surround such a diagnosis. We anticipate that this study will lead to a greater understanding of breast cancer and pregnancy, providing new, population based evidence to contribute to the body of knowledge about managing breast cancer and pregnancy. And, most importantly, it should enable young women to make informed choices about their health.

Acknowledgements

We would like to thank the Raine Medical Research Foundation

for the priming grant, which allows us to carry out this important project.

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Living with cancer in Australia

Report of a conference held in Canberra on 4 February 2002

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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

- n Deeply troubled by the professional and universal impact of cancer on human life, human suffering, and on the productivity of nations,
- n Committed to the humanitarian treatment and equal partnership of people with cancer in the ongoing effort against this disease,
- n Anticipating the rapidly rising tide of cancer incidence throughout the globe, in developed and developing nations alike,
- n Recognising the need for intensified innovation in all avenues of cancer research, prevention and healthcare delivery,
- n Believing that quality healthcare is a basic human right,
- n 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,
- n Certain that lives can and will be saved by increasing access to existing technologies,
- n 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:

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

* A copy of the proceedings of the Living with Cancer conference is available on request from The Cancer Council Australia.

Table 1 – Action points

<p>1. Coordinators of cancer care</p> <ul style="list-style-type: none"> n Specially trained, defined role, funded, qualification n Based in treatment centres and regional areas n Members of multidisciplinary team/liaison n Networked, inserviced, relieved, supported <p>2. Education</p> <p>(i) Healthcare professionals</p> <ul style="list-style-type: none"> n "The ideal oncology curriculum" n Early involvement of palliative and supportive experts n Better communicators n Understand survivorship <p>(ii) Community</p> <ul style="list-style-type: none"> n Cancer as chronic, controllable disease n Reduce stigma and discrimination n Peculiar needs of people living with cancer <p>3. Information (and helpful advice)</p> <ul style="list-style-type: none"> n National Cancer Information Service (13 11 20) n Quality assurance, accessibility, availability n Public and professional awareness of the CIS n Business cards with 13 11 20 and "tips" n GP referral point <p>4. Infrastructure (and practical matters)</p> <ul style="list-style-type: none"> n Review of patient, accommodation and transport scheme (PATS) and isolated patient, transport and accommodation scheme (IPTAAS) n Accommodation near treatment centres n Parking near treatment centres n Schedule appointments conveniently n Financial relief and respite care <p>5. Empowerment (patients and carers)</p> <ul style="list-style-type: none"> n Information about options n Explanation about possible implications n Help with formulating questions 	<ul style="list-style-type: none"> n Guidelines and "tip sheets" <p>6. Support (for support groups)</p> <ul style="list-style-type: none"> n Evidence-based guidelines eg narrative therapy n Support for informal carers n Practical help at community level <p>7. Standards for care</p> <ul style="list-style-type: none"> n Minimum national standards defined n Routine best practice n Take luck out of process <p>8. Research</p> <ul style="list-style-type: none"> n Option to participate in clinical trials n Encourage translational, psychosocial, behavioural and epidemiological research to inform Cancer Councils n Evaluate existing programs n What works and what does not n Monitoring quality of life indicators <p>9. Prevention and early detection</p> <ul style="list-style-type: none"> n Participation rates in screening programs n Advocacy for application of current knowledge <p>Actions/targeted outcomes</p> <p>Some examples are:</p> <ul style="list-style-type: none"> n National review of PATS/IPTAAS by end of 2002 n Increase number of medical schools using the Ideal Oncology Curriculum (all by 2005). n Training program for cancer care coordinators by 2004 n Increase GP referrals to the CIS by 10% per annum
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14th Lorne Cancer Conference

W Phillips

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In February, Australia's cancer researchers meet at Erskine House in Lorne, Victoria for the 14th Lorne Cancer Conference. Over 350 delegates listened to a selection of top 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 Cyclacel Ltd, Dundee, Scotland, who discussed the p53 pathway as a target for anti-cancer therapy. p53 is a tumour suppressor protein with potent 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 multiple sites for potential therapeutic intervention. The p53 pathway is thus a major focus for anti-cancer drug development.

Lane discussed potential therapeutic strategies based around the p53 pathway. A key regulator of p53 is 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 up stream signalling pathways, small peptides designed to block the interaction between p53 and Mdm2 can be used to activate p53 and trigger a full p53 response. In the case of human cervical cancer, the human papilloma virus (HPV) uses a protein known as E6 to inactivate p53. Lanes group has overcome this mechanism by using Actinomycin D and Leptomycin B to selectively inhibit E6 mRNA levels. Together, these two drugs can reduce E6 expression and reactivate the p53 response in HPV-expressing tumour cells.

In tumours that lack a functional p53, a number of approaches can be used, including gene therapy to reintroduce the wild type p53 and drugs designed to mimic the downstream effectors of p53. Lane's group has taken the later approach. In cells, p53-mediated cell death can be induced via the apoptotic pathway by blocking the function of cyclin A/Cdk2. Using rational drug design and "in silico" screening, the group has identified promising lead small molecule inhibitors of cyclin A/Cdk2 function. Lane said they show clear anti-tumour activity in pre-clinical models, and the first therapeutic Cdk inhibitors are now in clinical trial.

Mdm2 inhibitors were also discussed by Karen Vousden from the National Cancer Institute at Fredrick, USA. Her lab has developed a high throughput screen to identify small molecules that will inhibit Mdm2 and allow stabilisation and activation of p53.

ARF-dependent regulation of p53 by β -catenin

Moshe Oren from the Weizmann Institute of Science in Rehovot, Israel, also discussed the regulation of the p53

pathway. In his presentation, Oren reported a link between p53 and the β -catenin pathway.

In colon cancer, one of the earliest detectable events is the stabilisation of β -catenin and its conversion into an active transcription factor. Oren showed that deregulation of β -catenin can lead to stabilisation of p53. He also demonstrated that β -catenin's effects on p53 are mediated by another tumour suppressor protein, ARF. ARF binds to Mdm2 and inactivates it, thereby relieving p53 from the inhibitory influence of Mdm2 and allowing it to accumulate and exert its biological effects. Oren's group found that β -catenin was unable to stabilise p53 in ARF-deficient cells and that β -catenin induces expression of ARF by activating the ARF promoter.

Oren also discussed new data demonstrating a link between p53 and the phosphoinositide 3-kinase/Akt pathway. Inactivation of Mdm2 is a major mechanism leading to the disruption of p53 regulation and induction of cellular p53 activity. Such 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 its 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 general lack of specificity. 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 cancer cells. Adenoviruses 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 a deregulated cell cycle, adenoviruses that have been engineered to remove the E1 proteins should be able to replicate in cancer cells but will be unable to replicate in normal cells. Such E1-deficient adenoviruses should thus, in theory, eventually cause the lysis of tumour cells while leaving normal cells intact.

However, Antony Braithwaite from the University of Otago in Dunedin, New Zealand, is not convinced that such viruses are 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-55k protein deleted, which should mean it can only replicate in cells with a mutant p53 protein. Braithwaite 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 the virus killed p53 wild type cells with similar efficiency 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 to 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 membrane and extra cellular matrix has been widely accepted for many years. However, Matrisian argued that the role of MMPs is much more complex, and discussed data which challenged 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. Recent data has indicated that MMPs are involved in the growth of primary tumours, including benign tumours such as colonic 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, indicating the potential for MMPs to have a much broader influence on the tumourigenic 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 phase III clinical trials with synthetic 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 appropriate model systems, whereas 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.

Australian Behavioural Research in Cancer

This is a regular feature in Cancer Forum describing behavioural applications in cancer prevention.

Australia has five behavioural research centres: the Centre for Health Promotion and Cancer Prevention Research (CHPCPR) of the University of Queensland; the Cancer Education Research Program (CERP) of The Cancer Council New South Wales; the Centre for Behavioural Research in Cancer (CBRC) of The Cancer Council Victoria; the Centre for Behavioural Research in Cancer Control (CBRCC) at the Curtin University of Technology Perth; and the Centre for Cancer Control Research (CCCR) of The Cancer Council South Australia.

This report has been edited by Anne Gibbs (CBRC) from the reports received. No report was provided from the CBRCC.

New Results

n Centre for Behavioural Research in Cancer
(CBRC), VIC

Socially cued smoking in bars, nightclubs and gaming venues: A case for introducing smoke-free policies

Knowing that restrictions on smoking in the workplace and at home reduce levels of smoking in adults, Lisa Trotter, Melanie Wakefield and Ron Borland sought to determine if this may also be the case for recreational venues such as pubs and clubs. A cross sectional survey found that 69% of smokers report patronising bars, nightclubs or gaming venues at least monthly, and 70% of those who patronise social venues at least monthly report smoking more in these settings (socially

cued smokers). These people are aged under 30 years, have made previous quit attempts, and believe there is a safe number of cigarettes that can be smoked before their health can be affected. Further, 25% of smokers who frequently patronise social venues report that they would be more likely to quit altogether if there were bans in these venues. These people are likely to be aged under 30 years, contemplating or preparing to quit, and approve of bans in social venues. These findings suggest that smoking restrictions in social venues may reduce smoking prevalence among this group of smokers.

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 in 1995. Surgeons identified by population-based cancer registries as having treated a new diagnosis of DCIS between 1 April and 30 September 1995 completed a questionnaire on the presentation and management of each case. The study was conducted by a national consortium of researchers and funded by the National Breast Cancer Centre. The report was prepared by Victoria White and Myee Pruden from the 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



detected at other mammography centres. Twenty-six percent of tumours were palpable at presentation, 33% were multifocal and 55% were high grade (including comedocarcinoma). Breast-conserving therapy (BCT) rather than mastectomy was used in 260 (62%) of cases. Tumours that were of low grade, small in size and not multifocal were more likely to be treated by BCT. Surgeons seeing six or more DCIS cases in the six-month period were more likely to use BCT. Of the conservatively treated cases, 22% were referred for a radiation oncology consultation. The most common reasons for treating DCIS with mastectomy were that the tumour was too extensive or multifocal (63%), it extended to margins of the specimen (42%), or patient concerns about recurrence (34%).

The results from this representative national data set provide an historical comparator for future studies examining DCIS management.

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 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 (up to \$395), while the 34 women in the control group received their hospitals' 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 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.

n 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 smoking in enclosed spaces, 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 public knowledge of ETS-related health issues, as well as attitudes and practices in relation to ETS in homes, motor vehicles and licensed premises. Results are encouraging, with self-imposed bans on smoking in a high proportion of NSW homes and motor vehicles and with relatively high acceptance of ETS risks (despite some knowledge gaps). Support has also been indicated for further intervention at a

government level.

Success of new year quit-smoking resolutions

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 least 12 months prior to 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 birthday resolutions had no 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 says 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.

n Centre for Health Promotion and Cancer Prevention Research (CHPCPR), QLD

Interim results from a longitudinal study of the levels of intensity of palliative care received by cancer patients in Brisbane

This ongoing, prospective, National Health and Medical Research Council (NHMRC) funded study examines the intensity of palliative care received by cancer patients in Brisbane, and examines their adequacy in terms of pain relief, symptom control and quality of life. By sampling a representative group of patients receiving care for metastatic, incurable cancer, it aims to begin to provide an evidence base for the debate surrounding palliative care treatment options. The study commenced in January 1999, with patient recruitment commencing in September 1999. Potentially eligible patients being identified through the Queensland Cancer Registry, and a total of 159 patients and 148 carers participated. Patients and their family carers were followed up every four to eight weeks with a comprehensive questionnaire covering symptoms and symptom control, quality of life, psychological well-being and service use. To date, 105 patients (67%) have died and 19 patients (13%) have withdrawn from the study. Additional funding has been obtained to allow interviews to continue with surviving patients. This will also provide a common baseline (death) for the majority of patients.

Preliminary analysis of the longitudinal data from the first 91 patients with evaluable data indicates that there are strong time effects for commonly experienced symptoms such as pain and fatigue, with both increasing towards death. Both these symptoms have a significant effect on quality of life. Although less commonly experienced, symptoms such as diarrhoea and vomiting also have a considerable impact on quality of life. There are similar effects for well-being and depression, with well-being decreasing and depression increasing as death approaches. While some of these findings may appear predictable, it is the identification of the point in the disease trajectory and the factors associated with this that distinguish this study. Data collection and analysis are ongoing.

n Centre for Cancer Control Research and the Tobacco Control Research and Evaluation Program (CCCR & TCER), SA

Participation in the Breast Cancer Support Service (BCSS)

Data from the SA Cancer Registry and the BCSS (1993-1998) were used to determine the distinctive profiles of women diagnosed with breast cancer in SA, who used the BCSS. Older women and women born in countries other than Australia, the United Kingdom and Ireland were less likely to use the BCSS. There was also considerable variation according to the treating hospital, which was independent of patient characteristics or type of surgery. Having had a mastectomy was the strongest predictive factor for using the BCSS. No association was found between using the BCSS and socio-economic status or place of residence. The decline in use of the BCSS was not explained by changes in the type of surgery or other factors examined in this study. These results suggest that access to the BCSS may not be simply a matter of personal choice, but is likely to be affected by information and the referral practices of healthcare providers.

Sun protection policies and practices of childcare centres and kindergartens in SA

In November 2001, 125 kindergartens and 125 childcare centres were surveyed in regard to their sun protection policies and practices. Response rates of 71% and 67% were achieved for kindergartens and childcare centres respectively. Sun protection was regarded as a high priority issue in almost all centres, with 93% having formal written policies. While a large proportion of these policies mentioned hat-wearing by children (100%) and staff (82%) and the provision of sunscreen (93%), fewer mentioned educational strategies (65%), minimising UV exposure (57%), shade provision (55%) or information provision for parents. Hat-wearing by parents when attending centre activities or excursions was rarely mentioned (19%). Forty two percent of centres did not have adequate levels of shade. The pattern of practice across centres generally reflected the activities most often mentioned in policies. While there are certainly areas that need improvement, a large proportion of early childhood centres are in a good position to become SunSmart-accredited centres. A repeat of this survey in 2004 will indicate whether the SunSmart Centre's Program has had a follow-on effect more generally throughout SA's early childhood centres.

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 cancers. About 90 people die from these cancers each year – 22 of them in their fifties or younger. The monograph shows time trends in incidence, prognostic indicators 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 respiratory organs, throat and mouth, is due for release around the end of May. From the scientific literature, it is estimated that elimination of use of (and exposure to) tobacco smoking, plus a reduction in excess alcohol consumption, would reduce the numbers of these cancers by about 75%. 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 more generally, and for other regions 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 1977-91. 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 directed at tobacco control, avoiding 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 and improvement in outcomes. 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 (melanoma), 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 which are considering implementing smoking bans, and also to counter hospitality industry arguments of reduced patronage in the event of bans. 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 community support for such bans. Results showed a significant increase in community support for smoking bans in both bar and gaming venues over this period. Support for bans in bars increased significantly to 68% among the community 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.

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 study investigating the impact of specialists referring their 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 comprise:

- n specialist referral with CISS outcalls within one week of diagnosis and again at six weeks, three months and six months post-diagnosis;
- n specialist referral with one CISS outcall; and
- n 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.

n 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 oncologists/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-hr 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.

n CHPCPR

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, counselling and 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.

n CCCR & TCRE

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

n CERP

In April, CERP hosted the 6th Behavioural Research in Cancer Control Conference that was attended by approximately 70 delegates from across Australia. The conference began with a thought-provoking keynote presentation delivered by Professor Rob Sanson-Fisher from the University of Newcastle, giving an overview of behavioural science's contribution to cancer research and directions for the future. This was followed by a lively and entertaining conference dinner which, among many things, explored delegates' joke repertoire and miming abilities. Plenary sessions included: a presentation by Professor Mark Elwood, Director of the National Cancer Control Initiative, on the National Cancer Control Initiative's program; 'Tobacco Control and the Future', presented by Dr Ron Borland, Director of the VicHealth Centre for Tobacco Control at The Cancer Council Victoria, and; 'Understanding and influencing physical activity within a cancer prevention research agenda', presented by Professor Neville Owen, Director of the Health Promotion and Cancer Prevention Research Centre, University of Queensland. A wide range of papers were presented show-casing the quality of work being undertaken by researchers across Australia. Sessions included cancer prevention; smoking uptake and cessation; tobacco policy research; cervical and breast cancer; and psychosocial care. Overall, the three-day conference proved to be an excellent forum for discussion and exchange of

ideas and provided many opportunities for the establishment of collaborative links. Copies of the conference proceedings are available from CERP.

n Copies of CERP's annual report for 2000-2001 are now available from CERP.

n Afaf Girgis gave an invited keynote presentation on preparing patients for medical imaging at the 53rd Annual National Conference of the Australian Institute of Radiography and the 20th Radiation Therapy Symposium at Coffs Harbour. Janice Perkins and Jill Cockburn ran an interactive session on 'patient care and medical imaging' and Janice delivered an invited keynote presentation on the 'definition and measurement of quality of life'.

n CCCR & TCRE

The Tobacco Control Research and Evaluation Program has recently published its triennial Tobacco Control Research and Evaluation Report Volume 1, 1998-2001, which summarises research and evaluation projects undertaken over the three year period. Hard copies of the report will be distributed soon, and an online version is available at the new TCRE website (www.cancersa.org.au) by clicking on the TCRE link under 'Research'.

With thanks to Narelle Mills (CERP), Cathy Swart (CHPCPR) and David Roder (CCCR & TCRE) for contributions to this report.



The Editor
Cancer Forum
GPO Box 4708
Sydney NSW 2001



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 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, they brought to the study views that were considered and informed.

The results, analysed and reported by Julie Billett, 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:-

- n Patient communication and information – need for more accessible, timely and authoritative information tailored to women's needs, and communication skills training for health professionals.
- n Integrated, multidisciplinary, 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.
- n Supportive care – need improved services and support mechanisms to address women's psycho-social, practical and information needs.
- n 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 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 insights 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.

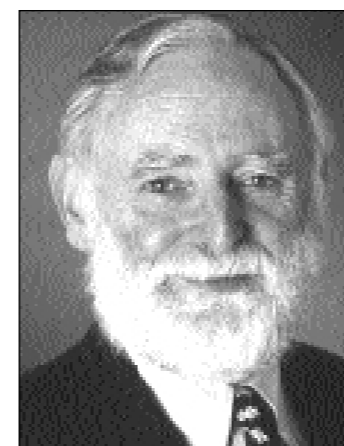
We intend to present the results to cancer conferences such as COSA. A copy of the report is available from either The Cancer Council NSW or from BCAG NSW.

Yours faithfully

PATRON: Her Excellency Professor Marie Bashir AC Governor of NSW
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Awards



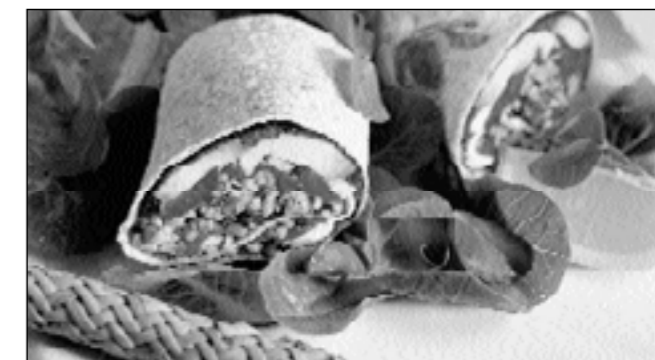
Prof Alan Coates AM

Professor Alan Coates, Chief Executive Officer of The Cancer Council Australia, has been made a Member of the Order of Australia (AM) in this year's Queen's Birthday Honours. He received the award for service to medicine in the field of oncology, particularly through breast cancer research.

Professor Bernard Stewart, long-time member of Cancer Forum's editorial board, was highly commended at The 2002 Cancer Council NSW Awards. He received this award for his contribution to the Marlene Sharp vs Port Kembla RSL Case. Victory in this case signalled an admission by the legal system that passive smoking is a significant danger to health, and forced employers to take responsibility for health-related risks in the workplace.

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.



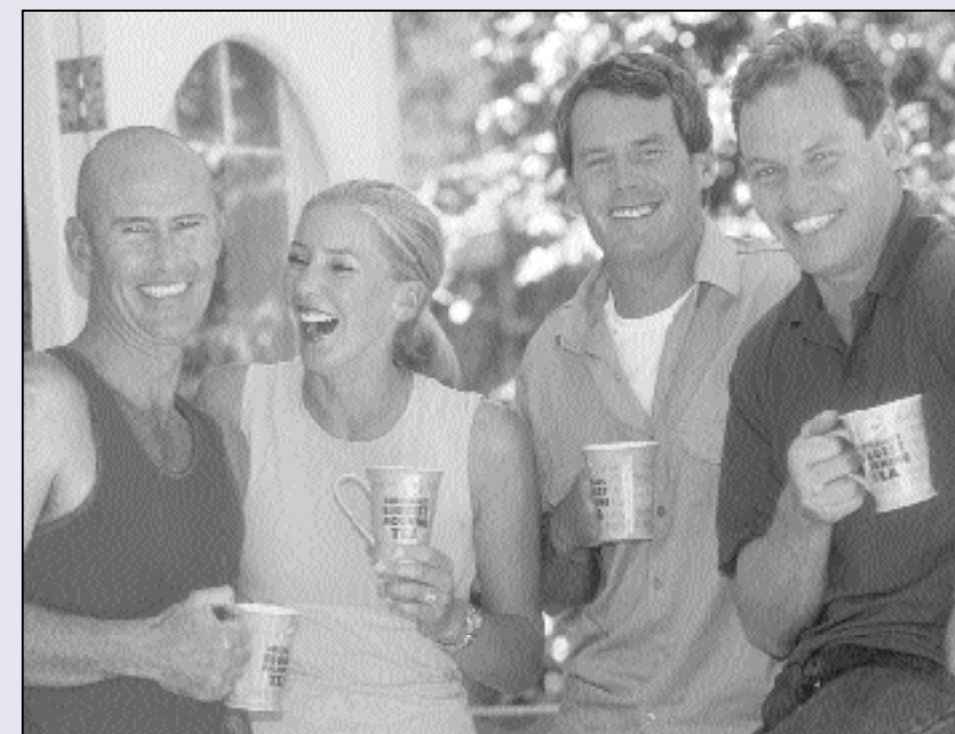
Australia's Biggest Morning Tea

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.



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."



Prof Alan Coates, Prof Ray Lowenthal, Senator Marise Payne and the Hon John Fahey

ADVANCES IN CANCER RESEARCH, VOLUME 79

G F Vande Woude and G Klein (eds)

Published by Academic Press (2000)
ISBN: 0-12-006679-3. 276 pages plus index.
RRP: A\$257.40

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, Strawn and Shawver, 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, focussing 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 p16^{INK4} 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 (Ghia and Caligaris-Cappio, Turin); EBV latency (Longnecker, Chicago); Mucin-associated antigens in GI tract cancer (Baldus and Hanisch, Cologne); and Polyoma virus persistence (Berke and Dalianis, Karolinska Institutet, Sweden).

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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: A\$243.10

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 toxicology 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

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 pharm-aceutical benefits branch of the Commonwealth Department of Health and Aged Care.



Jennifer Denholm

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).

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APPLIED RADIOBIOLOGY AND BIO-EFFECT PLANNING

D Wigg

Published by Medical Physics (USA) (2001)
ISBN: 1-930524-05-6. 482 pages plus index.
RRP: 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 (time, dose fractionation 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 α/β ratio of 10 Gy or more for obliteration of arterio-venous malformations (AVM), single 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 tumors for application in predictive models and bio-effect planning. Chapter nine describes the use of such models to predict tumor control probability and late effects risk for a variety of well-established treatment protocols. The final chapter describes the clinical utility of a real time interactive bio-effect planning system developed by Dr Wigg and his physicists in Adelaide, and points out some of the pit-falls that may beset those who plan on the basis of physical dose distributions alone. The treatise concludes with a light-hearted poem entitled *Shades of Gray*, to re-enforce the point that physical dose is only the first layer of complexity in optimising radiotherapy treatment planning.

This book is published by Medical Physics Publishing in Madison, Wisconsin and is available from them at a cost of US\$180.00. As a treasure trove of information, it would seem to me a bargain at this price for all radiation oncology and radiation physics department libraries. It is a shame that the computer program to support the Adelaide Bio-Effect Planning System is not also offered.

L Peters AM
Dept of Radiation Oncology
Peter MacCallum Cancer Institute
East Melbourne, Vic

ATLAS OF BREAST CANCER, 2ND EDITION

D F Hayes (ed)

Published by Hardcourt (2000)
ISBN: 07234 31760. 1,322 pages plus index.
RRP: A\$166.71

Rather than an Atlas of Breast Cancer, this beautifully presented book is more a well-illustrated textbook of predominantly early breast cancer. Whilst the last chapter deals briefly with locally recurrent and metastatic breast cancer, the book focuses on early breast cancer.

The editor's stated aim was to produce "a single source from which the non-expert can rapidly come 'up to speed' in the entire field of breast oncology". I believe he achieves this in all but the advanced or recurrent disease area.

This is not a detailed textbook, but each carefully chosen chapter covers the basic biology of the area, including the history of its development and the current state of treatment in that area. The areas covered include genetics, risk and prevention, imaging, surgery, pathology of benign and malignant disease, radiotherapy and the principles of systemic therapy and adjuvant systemic therapy.

The line drawings, tables, graphs and 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 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 their limitations.

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 this size, and I found it 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 care nurses. It is well-referenced, 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.

J Collins

Breast Unit, Royal Melbourne Hospital
Melbourne, Vic

BREAST CANCER: A PRACTICAL GUIDE

O E Silva and S Zurrirao (eds)

Published by Elsevier (2000)
ISBN: 0-444-50565-2. 489 pages.
RRP: US\$49.95

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 epidemiology, risk factors and screening, treatments, breast reconstruction, psychosocial sequelae, palliative care, breast cancer liability 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 published, 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.

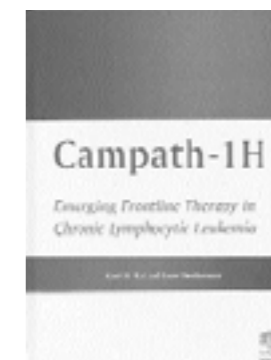
Although this handbook is written for an American audience and contains information which is specific to the American health care system such as the directory of local and national support systems in the United States and local guidelines about screening which are not in line with those in Australia, the enormous wealth of content does not detract from this book's value and relevance to Australian clinicians. The breadth and depth of information make this a suitable text for experienced and not-so-experienced clinicians alike, as well as for students of breast oncology or nursing. The authors intended that this book be used as a 'bedside' resource and have designed the content and the handy size of the book with this in mind. Although probably too comprehensive a text for practitioners who do not have an express interest in breast cancer, the authors have been successful in providing a useful and user-friendly text for the briefcase, the bedside or on the desk and one which is unlikely to gather dust on the bookshelf.

H Zorbas
National Breast Cancer Centre
Camperdown, NSW

CAMPATH-1H: EMERGING FRONT LINE THERAPY IN CHRONIC LYMPHOCYTIC LEUKAEMIA

K Rai and J Stephenson (eds)

Published by Parthenon (2001)
ISBN: 1-84214-060-4. 115 pages plus index.
RRP: US\$65.00



This book provides a detailed overview of the current status of Campath-1H, a monoclonal antibody directed against the CD52 molecule, specifically in the treatment of B-cell Chronic Lymphocytic Leukaemia (B-CLL)

and its further potential in clinical practice. The use of Campath-1H in the treatment of T-cell malignancy is not discussed, but its role as a preparative regimen for stem cell transplantation is reviewed in the context of marrow transplantation for B-CLL. The book is 128 pages in length and divided into five chapters, the first giving an excellent overview of the pathophysiology of B-CLL, important prognostic markers in the disease and the regulation of apoptosis. The second chapter outlines the various therapies available in B-CLL, commencing with the history and development of the use of chlorambucil as a single agent through to combination chemotherapy and the use of purine analogues.

Chapter three outlines the use of monoclonal antibodies for therapeutic use in cancer in general with the mechanisms of action, and then focuses on development of Campath-1H, including sections on the 'humanisation' of the antibody and in vivo effects following infusion. Campath-1 antibodies were first developed at Cambridge Pathology by Professor Herman Waldmann and colleagues in the early 1980s, and the antibody was clustered as CD52 in the 4th International Workshop on Human Leukocyte Differentiation Antigens in 1989. The antibody clearly has a high degree of clinical activity but has had a slow and protracted route to general clinical availability, and a minor criticism is that this prolonged development and reasons for it are not discussed. Chapters four and five discuss the role of Campath-1H in B-CLL specifically. The first of these chapters, details the dosage regimens and previous studies in refractory disease. These studies were performed over a number of years and often with relatively small numbers of patients. However, they certainly confirmed the drug is both highly active and relatively safe, with the main side effect being immunosuppression and infection. The final chapter – chapter five – discusses the role of Campath-1H as a preparative regimen and T-cell depletion method prior to bone marrow transplantation in refractory B-CLL, and includes both myeloablative and non myeloablative marrow transplant strategies.

The book gives an excellent, up-to-date, concise, comprehensive, and authoritative review of the role of Campath-1H in chronic lymphocytic leukaemia by leading authorities in the area. It would be a very useful book for anyone planning to use the drug for patient treatment in the clinical setting, and also those with a wider interest in B-CLL or monoclonal antibody therapy.

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CANCER CHEMOPREVENTION

R Bergen (ed)

Published by Kluwer Academic (2001)
 ISBN: 079237259X. 306 pages plus index.
 RRP: US\$205.00

This book, coming as it does in a series of oncology publications, marks again the entry of cancer chemoprevention into mainstream academic thinking in oncology. The National Cancer Institute's definition of a comprehensive cancer centre pays equal credence to the pre-diagnostic management of cancer as it does to the more conventional post-diagnostic phase. It is perhaps no surprise therefore that the editor and many of the chapter authors come from the Robert H Lurie Comprehensive Cancer Center at Northwestern University School of Medicine in Chicago. As Australia heads also to build its cancer services to the US model, the book is a timely entry into the field.

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 admirably, medical folklore from cultures around 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 with a placebo. So there develops an understanding of the mechanisms of action and pharmacodynamics of agents like curcumin (from tuberose plants in India), polyphenols (from green teas in the Far East) and others. Of course, the NCI also supports more traditional approaches to agents identified through observational epidemiology on humans. For example, after Professor Gabriel Kune's groundbreaking observation about the possible protective role of aspirin in the Melbourne Colorectal Cancer Case-Control study in the early 1980s, the singularly consistent reproduction of the 50% risk reduction from well over 50 case control and cohort studies world-wide has made aspirin an obvious target for the NCI's attention. This is well-described in the chapter and, indeed, the role of cyclooxygenase and its downstream (prostanoids) metabolic products in cancer promotion is a theme throughout the book – as well as possible non-cox inhibitor mechanism of action of aspirin and the nonsteroidal anti-inflammatory drugs.

The agency is also engaged in carrying ideas forward that may emerge from "high tech" discoveries such as DNA microchip technology, or functional proteomics. The steps that follow are impressively comprehensive, including mechanistic pre-screening through a variety of standard assays (eg signal transduction modulation, including those targeting growth factors, oncogenes and tumor suppressors; anti-hormones, anti-inflammatories, antimutagens, antioxidants, apoptosis and angiogenesis). In vitro efficacy models, in vivo short-term screening using intermediate endpoints and animal model efficacy testing are all described in the systematic process of candidate product development before clinical trials. Safety and dosage information is collected in the later phases of toxicology and pharmacology studies in an equally systematic

fashion.

The intermediate biomarker chapter highlights the gap between the need for biomarkers to hasten the drug evaluation process in humans, and the difficulty in validating such markers as truly surrogate for the cancer endpoint. Despite millions being spent in this area by the NCI, there is lingering uncertainty with most markers about their validity. Molecular biological (LOH, mutations in oncogenes, methylation) and cell biological (proliferation apoptosis), growth, factor or receptor status consistency is comforting, but the ultimate validation must come from years of prospective observation to the cancer endpoint in question – in humans. Thus there are doubts about even historically the earliest putative intermediate endpoints described such as proliferation (titrated thymidine, PCNA, etc studies).

Tissue microdissection and processing has truly been a breakthrough as the ability to isolate even single cells from frozen and paraffin-embedded sections has bolstered substantially both the sensitivity and specificity of molecular biological observations and enabled much more finely tuned, stage-specific information to emerge. This is well-described.

To the pharmacologically-lay reader, the chapter on kinetics and dynamic principles points out the essential need for expert pharmacology to be engaged in the process of development of preventive agents. It is no surprise, therefore, that the best centres in chemoprevention in the USA have pharmacology expertise at their helm (eg Dave Alberts in Tucson).

The balance of the book is organ-specific chapters on chemoprevention. These become repetitive to the comprehensive reader, although necessarily may be so to cater for organ specialists delving exclusively into their own niche. The repetitious themes do, to this reviewer, highlight the tremendous contribution made by investigators such as Knudson (two hit hypothesis) and Vogelstein (the Vogelgram of cumulative genetic events leading to cancer) to our understanding of cancer. The variety of these latter events in different cancers appears sprinkled throughout the chapter texts, without any attempt to draw them together as a "cancer theme". Of course the state of knowledge is emerging, especially with respect to our understanding of the downstream consequences of perturbations to these oncogene and tumour suppressor phenomena, but the book would have contributed more with such an overview. It is clear that knowledge is advancing much more rapidly in organs more accessible to premalignant observation and diagnosis (eg skin, bladder, colon, upper GI tract) as the molecular events that characterise these early developments are pinned down mechanistically and statistically with the help of clinical investigators. So too are clinical trials of the new agents, as the more advanced intermediate endpoints (actinic keratoses, early transitional cell carcinoma, adenomatous polyps, Barretts dysplasia) can be effectively monitored. The understanding of skin cancer proved particularly impressive to this non-dermatologist.

Throughout the organ-specific chapters, there was a surprising consistency of themes of cancer chemoprevention candidates. NSAIDs, including particularly the COXibs, isoflavones (from the epidemiological dietary literature on vegetables), genistein (a soy derivative) difluoromethyl ornithine (from studies of the role of polyamines in cancer proliferation), oltipraz, n-acetyl cysteine and retinol and its derivatives (over 4000!). Of the latter, fenretinide received a promising brief (efficacy and safety) from a number of chapter authors. In contrast, the late 20th century fixation on antioxidants in pharmacological and suprapharmacological doses provides an historical rendition

of the gap between high-flying expectation and reality, as the trials in high risk subjects for lung cancer using betacarotene unfolded with their quite unanticipated adverse outcomes in scrupulous randomised controlled trials.

The final chapter on cancer immunology and vaccine development is a gem. It would be difficult to find a clearer explanation of the fundamentals of immunology anywhere, let alone its relevance as cancer immunology. The chapter leads one to the excitement and real prospects of cancer control through immunological strategies, particularly with respect to the slowly expanding role of oncogenic viruses (hepatitis B – obviously a win for cancer immunology through vaccination, hepatitis C, EB virus, HPV virus in skin and cervical cancer, helicobacter pylori). But non-infectious agent vaccination also holds promise and reality as we see that BCG vaccination in bladder cancer is one of the few strategies surviving the rigorous development process through to randomised controlled trials and FDA registration.

In fact, despite all the effort, very few other approaches have reached this far to be exposed as "mainstream medicine". Celecoxib, in the field of colorectal carcinogenesis, is another, with its efficacy established in an RCT in familial adenomatous polyposis. With a meritable force of large trials of agents already "through" extensive preclinical testing, currently in progress, we can look forward to an exciting decade ahead. Implementation to populations at risk or at large will be the next challenges, with the implementation hurdle perhaps even higher than the simpler negative (but so important) truths already well entrenched in the public health message (don't smoke, for example).

From a technical standpoint of publication, this book left something to be desired. Firstly, it was completely devoid of illustrations (cartoons, as our Pacific neighbours would have it) that are so tremendously informative to the reader in the complex field of molecular pathogenesis. That is a lost opportunity to spread contemporary understanding to a whole cohort of young investigators with concept-fusing intellectual capacity (many advances come this way). Secondly, simple proofreading seemed overlooked with glitches that threatened the reader's comfort and confidence in the book. Even the printing left out sentences and lines in a few places rendering a few sections as non-sequiturs.

Overall, this is an excellent reference book painting a good picture of the state of the art of the science of chemoprevention for the first years of the century, and will provide all readers with exciting glimpses of understanding and opportunities for investigation within one's own realm of resources – intellectual, laboratory or clinical.

F Macrae

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THE CANCER HANDBOOK

M Alison (ed)

Published by Nature Publishing Group (2001)
 Distributed in Australia by Macmillan Academic (Special discount offer closes 15 December 2002)
 ISBN: 0-333-968220. Two volumes.
 RRP: A\$1,078.00

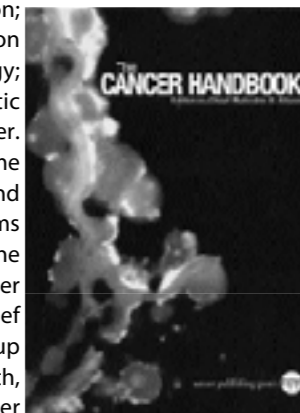
The Cancer Handbook is a new reference work designed to bridge a perceived gap in cancer medicine, which lies between laboratory scientists and clinicians. It is thus aiming to be a

comprehensive text, covering laboratory science, translational research, and the diagnosis and treatment of cancer.

The book is split into six major sections: the molecular basis of cell and tissue organisation; the causation and prevention of cancer; systemic oncology; pre-clinical models; diagnostic imaging and treatment of cancer. This is a handsome two-volume work, attractively packaged and a manageable size, both in terms of the actual physical size of the books as well as in the number of pages. The editor-in-chief has had an impressive group of section editors to work with, and a number of the chapter authors are definitely leaders in their respective fields – eg John Reed and Apoptosis, Adrian Harris and Angiogenesis, and V Craig Jordan and Endocrine therapies for breast cancer, to name a few. The introduction is excellent, the chapters are well set-out, easy to read and relatively short and to-the-point, and there is excellent use of figures and tables. A useful feature is the addition of a 'suggested reading' section at the end of each chapter, as well as suggested Internet sites.

There are, however, a number of significant deficiencies. As is inevitable with all collaborative efforts, the book is already dated. Some 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 Pathology, it is no surprise 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 signalling and on carcinogenesis. 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 are oddly structured, with significant sections on basic anatomy and histology (which most readers of this text will be familiar with), – and yet with very little on current treatments – in particular chemotherapy which presumably would be of significant interest to most readers and of importance in The Cancer Handbook. The chapters are patchy in quality with some good chapters (eg 'Pancreas' and 'Neuromuscular') mixed with some poor ones (eg 'Respiratory' and 'Breast'). This inconsistency appears to be the result of poor selection of some chapter authors, and poor editing. There are a number of obvious errors – for example, the chapter on the respiratory system states that naso-pharyngeal carcinoma accounts for 2% of all tumours in the USA, using a paper published in 1941 to support this! It also states that only 20% of patients with small cell lung cancers present with advanced disease, when the number is generally accepted to be 60-70%. The chapter on breast cancer, one of the major cancers in our society, is also poor, being very brief (only six pages, in comparison the chapter on the ear which has 10 pages), and poorly referenced. It was disappointing to see authors referencing their own papers in publications such as the Journal of the Florida Medical Association, and ignoring seminal papers in journals such as The Lancet and The Journal of Clinical Oncology. The final section on 'The treatment of human cancer' does an excellent job of covering individual cancer drugs and also in describing the exciting new areas of targeted therapy.



There is, however, very little on current therapeutic modalities. The one chapter focussing on this area is the excellent chapter on hormonal therapy for breast cancer, but its inclusion begs 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)
ISBN: 1-55009-084-4. 477 pages plus index.
RRP: A\$481.58

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 anatomical regions of the upper aerodigestive tract. With each region the important anatomical considerations, disease processes, clinical presentations, diagnostic tests and treatment options are discussed. Further chapters cover skull base, salivary tumours, thyroid and parathyroid glands, vascular tumours of the head and neck and soft tissues and bony tumours. The concluding chapters cover more comprehensively bone and soft tissue reconstruction, radiation oncology, chemotherapy, rehabilitation and quality of life assessment.

Each chapter is masterfully crafted and covers a specific topic or region comprehensively. Treatment recommendations are based on an analysis of a vast literature base and address all available modalities, particularly emphasising the role of multi-modality therapy in advanced or biologically unfavourable disease and the importance of an appreciation of the functional disability associated with the various treatment options. Whilst not purporting to be a textbook of operative surgery, broad principals relating to surgical technique and goals are included in an insightful manner.

This is a beautiful text that was a joy to read, being clearly written in a concise style and glittering with photographs, illustrations, radiographs, charts and tables of the very highest standard. Good things do not come cheaply, but it is hard to put a price on quality. This is a text that those interested or

practising in any region of head and neck cancer treatment would enjoy. For those involved in teaching the accompanying CD-ROM, containing the complete texts and illustrations, offers many exciting possibilities.

R Judson
Parkville, Vic

CANCER OF THE LUNG: FROM MOLECULAR BIOLOGY TO TREATMENT GUIDELINES

A Weitberg (ed)

Published by Humana Press (2002)
ISBN: 0-89603-830-0. 332 pages plus index.
RRP: US\$125.00

This book is edited by Alan Weitberg with a foreword by Jean Klustersky, and was published this year. It contains five parts. Part I includes some background epidemiology, basic science including pathology, molecular biology and diagnostic techniques as well as lung cancer staging. Part II details surgical, multimodality treatment of regionally advanced non-small cell lung cancer, stage IV non-small cell lung cancer and new treatments. Part III looks at the treatment of small cell 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 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.

Overall, the 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 bronchioloalveolar 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 Rosell 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.

Nonetheless, I found this book 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.

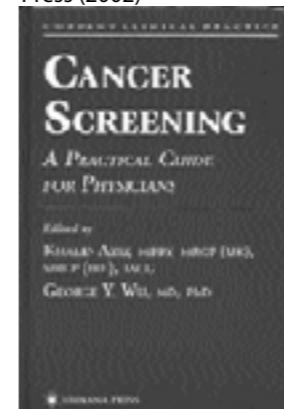
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CANCER SCREENING: A PRACTICAL GUIDE TO

PHYSICIANS

K Aziz and G Wu (eds)

Published by Humana Press (2002)



ISBN: 0-896-03865-3. 313 pages plus index.
RRP: US\$89.00

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

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 choose to purchase it.

This text 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.

H Fardy
Shellharbour, NSW

CANCER TIPS: A HANDBOOK FOR CANCER PREVENTION AND MANAGEMENT

J M Metz



Published by Lippincott Williams & Wilkins (2002)
ISBN: 0-7817-2564-X. 163 pages plus index.
RRP: A\$50.60

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; oncologic emergencies; and alternative medicine. New, current topics are described in the section on 'miscellaneous topics'. In section eight, a guide on 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, herbs, unconventional 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)
ISBN: 0-7216-7833-5. 1,639 pages plus index.
RRP: A\$474.10

As stated by the editor, Charles M Haskell, "The goal of cancer treatment is to provide an authoritative, compressive, scholarly 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.

Part IV: provides information on supportive care and selected management issues, and an overview of management issues including supportive care, oncological emergencies, pain, psychosocial care and nutrition.

Part V: 'Cancer in special populations'. Includes a review on cancer in pregnancy and cancer in the elderly.

Part VI: 'Investigational therapy'. Discusses clinical trial design, gene therapy and investigational drugs.

Part VII: Clinical practice issues has a North American bias regarding economic and regulatory issues affecting oncology, but also discusses ethical issues in cancer treatment.

Part VIII – XX: deals with primary cancer arising in various organ systems (including breast, lung and bowel).

As a practising medical oncologist, I decided to test out *Cancer Treatment* by using it as a reference for some rare or unusual cases seen within the practice. Unfortunately, the book was not as easy to use as more portable references such as *Manual of Medical Oncology*, and it lacked the detail of some other comprehensive standard texts such as *Principles and Practice of Oncology – 6th Edition (De Vita et al)*. Many of the chapters served as reasonably comprehensive reviews on each topic. However, I did find that I was drawn inevitably to the references for each chapter to seek more detail than that discussed within the chapter, or went to another sub-specialty text or to Medline for a literature search.

The editor in his preface also states that he tried to provide useful and explicit recommendations on management, but that these recommendations are subject to change. On his first point, I think unfortunately this may have been better achieved with the use of different layouts or highlighting recommendations made within the detailed text. His second point highlights the problems of publishing comprehensive textbooks, with an inevitable inability to include very recent information. Nevertheless the chapters provide a fairly recent review of the current state of play.

Cancer Treatment may be found useful by general physicians, general trainees and other health professionals, but I think ultimately medical oncologists, radiation oncologists and their trainees would probably find the detail lacking.

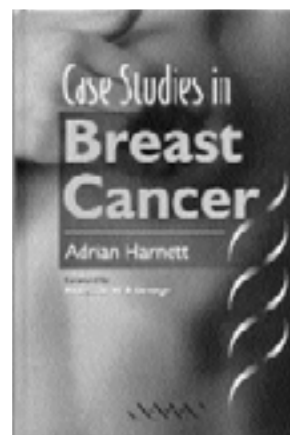
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CASE STUDIES IN BREAST CANCER

A Harnett

Published by Blackwell (2002)

ISBN: 1 84110 000 5.
145 pages plus index.
RRP: A\$104.50



Dr Harnett is a consultant in clinical oncology (radiotherapy). He presents 37 case histories of patients treated by himself at the breast unit and Beatson Oncology Centre at the Western Infirmary, Glasgow. Although this unit is a multidisciplinary unit, the book has single authorship. The cases have been sequenced starting with diagnosis (although

no mammography or ultrasound illustrations are given), early disease, through to locally advanced disease, localised (single site) metastatic disease and widespread metastatic disease including palliative cases. The book has been supported (although 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 comment 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 skiing! The style of the presentation is conversational 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 lymphedema. 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 the other 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 they are 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 from their clinical practice to draw the clinical material and use as resource material such as an atlas of diagnostic oncology from which to obtain appropriate histological, radiologic and clinical illustrations.

As it stands, at the recommended price of \$104.00 who should buy this book? Probably no one.

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ENCYCLOPEDIA OF CANCER

M Schwab (ed)

Published by Springer (2001)

ISBN: 3-540-66527-7. 992 pages plus index and CD-ROM
RRP: US\$195.00

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 particular topic, 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 contributory 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. A number 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 clinical topics, when put to the test 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 encyclopedia is a useful reference text not only for clinical investigators but also for basic research scientists reading out 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

S Sebti and A Hamilton (eds)

Published by Humane Press (2001)
ISBN: 0-89603-619-4. 273 pages plus index.
RRP: US\$125.00

The Ras GTPases operate as molecular switches that link extracellular stimuli with a diverse 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 switch is permanently 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 Sebti and Hamilton catalogues the work 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 experiments establish 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 that is added to the Ras protein post-translationally mediates plasma membrane localization, and the first enzyme involved in constructing the Ras anchor is farnesyltransferase (FTase) – therein lies the rationale for developing farnesyltransferase inhibitors (FTI).

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 FTIs – 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 phase 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 RhoB, 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 clearly 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-trypanosomal drugs.

Inevitably in a multi-author book, there is replication of introductory material between chapters. This one is no 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 the book comprehensively covers 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 therapeutics, 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)

ISBN: 0-7923-7141-0. 290 pages plus index.
RRP: US\$115.00

The growth and spread of cancer cells to other organs is a complex, multistage process that requires cell proliferation, disaggregation 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 should therefore underpin 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, TGF β , fibroblast growth factor, hepatic growth, platelet-derived growth factor and their respective cognate receptors. The cytokines interleukins 2 and 11 as well as 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, NK4.

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 clearly explained, providing a rapid, yet comprehensive introduction to each subject.

I found the chapters on leukemia inhibitory factor, interleukin 2, interleukin 12, IGF-1 and TGF β particularly useful, and this collection of reviews is rounded up nicely by the excellent last chapter on growth factors, receptors 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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HEPATOBIILIARY CANCER

L H Blumgart, Y Fong and W R Jarnagin (eds)

Published by American Cancer Society (2001)
ISBN: 1-55009-132-8. 296 pages plus index.
RRP: A \$ 253.55

The first two chapters cover benign liver lesions and incidentally-found hepatic 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 scenarios is comprehensively 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 cryoablation and radiofrequency ablation are well described. It is pointed out that the follow-up data, especially for radiofrequency ablation, is inadequate at this time and that these techniques complement resection and are not a replacement as first line treatment.

The chapter on techniques of hepatic resection in a book of this size is of necessity somewhat limited in detail, but with line drawings and operative photographs, the principles are well outlined. The following two chapters are an up-to-date review of the surgical and non-surgical management of hilar cholangiocarcinoma and gall bladder cancer.

The next 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 outlined in a chapter. It is in the preliminary phases of investigation and is yet to enter the clinical arena. The final chapter is a comprehensive overview of the place of liver transplantation for hepatobiliary malignancy – indicating it has a limited, but very definite, place for highly selected candidates.

Overall, the book is well presented and beautifully illustrated, with extensive and comprehensive references. By necessity, the magnitude of the topic limits how much can be accomplished, but it is easy to read, the surgical subjects are well covered, and it includes a CD-ROM disc.

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METASTASIS RESEARCH PROTOCOLS, VOLS I AND II

S A Brooks and U Schumacher (eds)

Published by Humana Press (2001)
ISBN: 0-89603-615-4. 298 pages plus index.
RRP: US\$99.50

Cancer metastasis – that is, the spread of tumours to secondary sites in the body – is the major cause of cancer mortality. Metastasis is a complex, multi-stage process which remains poorly understood. Better definition of this process at the molecular level is an important goal of current cancer research and should lead to new approaches to therapy. This pair of volumes provides a valuable resource for experimentalists in the field. It is a laboratory manual providing detailed descriptions of a wide range of procedures, ranging from basic biochemical methods through to in vivo models for evaluating metastatic potential. In general, the chapters have the format of an introduction followed by materials, detailed step-by-step methods, notes commenting on the choice of reagents, troubleshooting etc, and references. The extent of

the introduction varies considerably between the chapters – in some cases it consists of brief comments on the history and applications of the method, in others (eg Vol I, chapter six: 'Understanding metastasis through integrin expression') an excellent, concise review is provided.



Volume I, 'Analysis of cells and tissues', describes methods such as histology, and analysis of protein expression, tumour proliferation and vascularisation. It also provides protocols for a range of methods for evaluating nucleic acids in tumour specimens including in situ hybridisation, basic techniques for studying nucleic acids, analysis of methylation, and the use of the polymerase chain reaction for the detection of circulating tumour cells. Finally, there is a chapter on mathematical modelling of metastasis (which is in its infancy). In general, the protocols are clearly presented and easy to follow. In some instances I would have liked to have seen some

recommendations as to suitable reagents. For example, there are many antibodies to integrins on the market, which give very variable results. As these are enormously expensive, trial and error to find the best reagents is generally not possible. A major disappointment was the lack of discussion of molecular markers known to be associated with progression (eg Erb-B2 in breast cancer, and CD9 and CD82 down-regulation in various epithelial cancers). In addition, the advent of microarray technology is set to have a profound effect on the field of tumour classification and prognosis. Hopefully this will be addressed in any new edition. Another disappointment was the limitation of methods for the study of cell proliferation to cell cycle analysis and DNA synthesis. Flow cytometric methods that use fluorescent dye retention (CFSE or PKH26) are widely used by cancer cell biologists to quantitate cell proliferation and survival, as are methods for detection of apoptotic cells – which also fail to get a mention.

Volume II, 'Analysis of cell behaviour' in vitro and in vivo, describes further methods of cell biology – in particular, cell purification methods and genetic manipulation. The bulk of the volume deals with in vitro and in vivo assays of metastasis. Several in vitro motility and invasion assays, mostly using extracellular matrix protein-coated porous membranes, are described. To my mind the most valuable part of these volumes is that dealing with animal models of metastasis. Given the complexity and the multi-step nature of the process, it is ultimately necessary to study it in vivo. Starting with a chapter on basic principles for the study of metastasis using animal models, different systems are described, including the chick embryo and various types of murine model – xenogeneic, syngeneic, transgenic and orthotopic. Finally, the application of green fluorescent protein-labelled cells for the study of metastasis is described.

Overall, these volumes are a valuable addition to any laboratory interested in studying metastasis in defined cell systems through to evaluation in physiologically relevant animal models.

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METHODS IN MAMMARY GLAND BIOLOGY AND BREAST CANCER RESEARCH

M Ip and B Asch (eds)

Published by Kluwer Academic (2000)
ISBN: 0-306-46397-0. 316 pages plus index.
RRP: US\$125.00

This volume came together under the auspices of the Committee on Mammary Gland Biology, a group first formed over two decades ago and whose membership includes many of the originators of our current knowledge of mammary gland biology and the methods used for its study. The impetus for publication of this book came from the realisation that progress in understanding mammary gland biology relied on appropriate deployment of well-characterised animal models, but that existing and emerging methods were difficult to source. Moreover, the emergence of gene knockout techniques and animals with selective ablation of particular genes has opened out a new potential for mammary gland research to unravel basic mechanisms in mammary development and carcinogenesis. The editors have assembled an outstanding collection of contributors, many of who are legends in the mammary gland biology field.

This book presents a compilation into one practical guide of methods that are well established in mammary gland biology as well as methods whose potential has yet to be fully realised. The book is in four sections: in vivo model systems; special techniques for in vivo studies; in vitro model systems; molecular analysis; and gene transfer techniques. The in vivo sections cover all established models of mammary cancer and include a very helpful comparison of the features of mouse, rat and human mammary carcinogenesis – essential in evaluating which aspects of rodent carcinogenesis are sufficiently similar to the human for these models to be used. They also include very helpful descriptions of fundamentally important methods in mammary gland biology such as mammary fat pad clearance, transplantation, whole mount preparation, and hormonal treatment. The in vitro section covers methods for culture of mammary cells, both normal and malignant, including methods to grow mammary cells under conditions which recapitulate growth in structures similar to those found in the mammary gland in vivo. The final section covers molecular techniques such as in situ hybridisation and PCR in the mammary gland, gene transfer by viral and non-viral methods, conditional gene deletion, and more recent and challenging in vivo techniques such as tissue recombination and intraductal injection.

The volume is extremely well presented. The chapters are clear, detailed and very well referenced. They are primarily practical guides, and the material is clearly presented and beautifully illustrated with diagrams and pictures. The volume is designed to be a laboratory manual, and is bound in spiral for easy opening. This volume would be an outstanding practical addition and an indispensable aid to any laboratory engaged in research on mammary gland biology. Very highly recommended!

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THE MOLECULAR BASIS

OF HUMAN CANCER

W Coleman and G Tsongalis (eds)

Published by Humana Press 2002
ISBN: 0-89603-634-0. 565 pages plus index.
RRP: 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, prostate, lung and skin, as well as haemopoietic malignancies. 'Future directions' includes 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 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)

Published by: Baillière Tindall (2001)
ISBN: 0 7020 2422 8. 270 pages plus index.
RRP: A\$62.50

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 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.

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THERAPEUTIC GUIDELINES PALLIATIVE CARE

M Mashford et al

Published by McPherson's Printing Group (2001)
ISBN: 0-9586198-1-6. 294 pages plus index.
RRP: A\$33.00

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 for symptom control should be ceased" (often overlooked, especially when started by a different specialist). It was well worth the time to read. Of particular value is the Australian relevance of the material, with regard to medications and services available in this country.

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 distressing symptoms like pain and nausea can almost always be controlled provided continuous and competent care can be assured."

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TREATMENT OPTIONS IN UROLOGICAL CANCER

J Waxman (ed)

Published by Blackwell Science 2002
ISBN: 0632 05589 8. 382 page plus index
RRP: 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 expert authors this book is a well-balanced account of the current thinking in the management of urological cancers without getting bogged down in unnecessary detail.

The section on renal cell cancer has a heavy leaning towards the molecular biology of the disease. The immunotherapy is a good review without being ponderous. However, the surgical treatment for renal cell cancer was lacking, not discussing new techniques such as laparoscopic nephrectomy or the possible survival benefit of nephrectomy in the face of metastatic disease.

The section on bladder cancer also has a heavy emphasis on molecular biology. The chapter on treatment options were generally up-to-date, especially the section on adjuvant chemotherapy by Connie Steinberg. Surprisingly there was no discussion about combined



radiotherapy/chemotherapy as an alternative to cystectomy despite this predominantly being a UK textbook.

The section on prostate cancer was probably the climax of the book with Waxman giving us a glimpse of the complex interaction between cells, stroma, steroids and genes within normal and malignant prostate. A chapter on surgical pathology was a mixture of the academic and practical perhaps too long in parts but containing some gems of information. Radical radiotherapy, although brief, covered all the contentious issues and was obviously written by oncologists with a firm practical knowledge. The chapter discussing immediate versus deferred hormone therapy was particularly interesting with Kirk having a chance to answer some of the criticisms of the MRC study giving additional detail not available in the original publication. Hormone therapy was fairly well covered except for the annoying unreferenced and recurring comment throughout the book that only 80% of patients respond to hormone therapy. Second line hormone therapy and hormone withdrawal response were only mentioned in passing. The chapter on prostatectomy made the statement that this modality gives the highest cure rate, with the basis for this statement being no good reason other than their say so! Chemotherapy for hormone-refractory prostate cancer was comprehensively summarised by Malcolm Moore and colleague bringing home the message that this is now acceptable treatment for such patients.

Chapters on testicular cancer and penile cancer were also relatively up-to-date and comprehensive. A description of the genetics of testicular cancer was especially informative.

In conclusion, this book is a good summary of the current status (circa 2001) for urological cancers. The chapters are detailed enough to be informative but not too long for the uninitiated to loose interest. I suggest it is an excellent starting point for those wanting a quick update, such as advanced trainees and oncologists who are branching into this area as a sub-speciality. It will need to be updated next year.

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TUMOR-SUPPRESSING VIRUSES, GENES, AND DRUGS

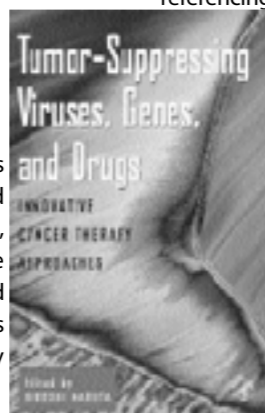
H Maruta (ed)

Published by Academic Press (2002)
ISBN: 0-12-476249-2. 415 pages plus index.
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

CALENDAR OF MEETINGS – AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
2002			
September			
9-12	7th Australian Palliative Care Conference	Adelaide SA	SAPMEA Conventions 68 Greenhill Road Wayville SA 5034 Ph: +61 8 8274 6060 Fax: +61 8 8274 6000 Email: pallcare2003@sapmea.asn.au
19-22	AGITG Annual Scientific Meeting	Hobart TAS	AGITG Coordinating Centre Locked Bag 77 Camperdown NSW 1450 Ph: +61 2 9562 5000 Fax: +61 2 9562 5094
29 Sep – 2 Oct	Mobilising Public Health 34th Public Health Association of Australia Annual Conference	Adelaide SA	PHAA Secretariat Ph: +61 2 6285 2373 Email: conference@phaa.net.au
October			
21-23	International Clinical Trials Symposium 2002	Sydney NSW	ICMS Pty Ltd Ph: +61 2 9290 3366 Fax: +61 2 9290 2444 Email: trials@icms.com.au Website: www.ctc.usyd.edu.au
November			
25-29	The Australian Health & Medical Research Congress	Melbourne VIC	Initiative of Australian Society for Medical Research Website: www.ahmrcongress2002.conf.au
27	"Improving communications: improving outcomes for patients and health professionals" 2nd National Better Communication, Better Care Conference	Sydney NSW	Fax: +61 2 9036 3077 Email: directorate@nbcc.org.au
28-30	29th COSA Annual Scientific Meeting	Sydney NSW	Lawrie Wright Clinical Oncological Society of Australia GPO Box 4708 Sydney NSW 2001 Ph: +61 2 9380 9022 Fax: +61 2 9380 9033 Email: cosa@cancer.org.au
2003			
November			
15-19	6th International Symposium on Paediatric Pain: "Pain in Childhood: The Big Questions"	Sydney NSW	Dianna Crebbin DC Conferences Pty Ltd PO Box 571 St Leonards NSW 2065 Ph: +61 2 9439 6744 Fax: +61 2 9439 2504 Email: mail@dcconferences.com.au
16-20	9th International Conference on Oral Cancer	Melbourne VIC	ICMS 84 Queensbridge Street Southbank VIC 3006 Ph: +61 3 9682 0244 Fax: +61 3 9682 0288
26-28	30th COSA Annual Scientific Meeting	Perth WA	Lawrie Wright Clinical Oncological Society of Australia GPO Box 4708 Sydney NSW 2001 Ph: +61 2 9380 9022 Fax: +61 2 9380 9033 Email: cosa@cancer.org.au



CALENDAR OF MEETINGS – INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
2002			
August			
8-11	1st Asia Reach to Recovery International Breast Cancer Support Conference	Kuala Lumpur Malaysia	The Treasurer Breast Cancer Welfare Association of Federal Territory and Selangor Ph: +603 7 954 0133 Fax: +603 7 594 0122 Email: bcwa@tm.net.my For details, see: www.cancer.org.au/c_c_news.asp
28 Aug – 1 Sept	12th International Conference on Cancer Nursing 2002	London UK	Liz Piem/Claire Manning The Conference Office Ph: +44 0 20 7874 0294 Fax: +44 0 20 7874 0298 Email: healthcare.conference@emap.com Website: www.isncc.org
September			
1-4	9th Central European Lung Cancer Conference	Vienna Austria	Mondial Congress Vienna, Austria Fax: +43 1 586 91 85 Email: congress@mondial.at
17-21	21st Annual Meeting of the European Society for Therapeutic Radiology and Oncology (ESTRO)	Prague Czech Republic	ESTRO Office, Brussels, Belgium Fax: +32 2 779 54 94 Email: info@estro.be Website: www.estro.be
18-21	SIOP 2002: The 34th Meeting of the International Society of Paediatric Oncology: Brain Tumours	Porto Portugal	Congress Secretariat Congrex Holland BV Amsterdam, The Netherlands Fax: +31 20 50 40 225 Email: siop2002@congrex.nl
23-25	1st International Symposium on Signal Transduction Modulators in Cancer Therapy	Amsterdam The Netherlands	NDDO Research Foundation Email: congress@nddo.nl Website: www.nddo.nl
29 Sep – 4 Oct	World Assembly on Tobacco Counters Health 2002 (WATCH 2002)	New Delhi India	Fax: +91 11 694 4472 Email: cancerak@ndf.vsnl.net.in Website: www.watch-2000.org/
October			
6-9	44th Annual Meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO)	New Orleans Louisiana USA	G Smith, ASTRO Fairfax, Virginia, USA Fax: +1 703 502 7852 Email: gsmith@astro.org Website: www.astro.org
14-17	Frontiers of Cancer Prevention Research: Genetics, Risk Modeling, and Molecular Targets	Boston MA USA	American Association for Cancer Research Ph: +215 440 9300 Fax: +215 351 9165 Email: meetings@aacr.org Website: www.aacr.org
18-22	27th European Society for Medical Oncology (ESMO) Congress	Nice France	ESMO Congress Secretariat Lugano, Switzerland Fax: +41 91 950 27 07 Email: 16apcc@pcsi.com.ph
24-25	2nd Colorectal Cancer Conference	Rome Italy	Gabriella Vocaturo/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: esomi@tin.it

Date	Name of Meeting	Place	Secretariat
November			
1-3	Oncology Nursing Society 3rd Annual Institute of Learning	Seattle Washington USA	Oncology Nursing Society Pittsburgh, Pennsylvania, USA Fax: +1 412 921 6565 Email: member@ons.org Website: www.ons.org
5-8	19th International Conference of the International Society for Quality in Health Care	Paris France	ISQua Level 9, Aikenhead Centre, St Vincent's Hospital 41 Victoria Parade Fitzroy VIC 3065 Ph: +61 3 9417 6971 Fax: +61 3 9417 6851 Email: isqua@isqua.org.au Website: www.isqua.org.au
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	Frankfurt Germany	L Hendrickx, FECS Conference Unit Brussels, Belgium Fax: +32 2 775 02 00 Email: info@fecsb.be Website: www.fecsb.be
16-18	3rd International Sentinel Node Congress "Sentinel Node 2002 – Universal Applications of Sentinel Node Technology"	Yokohama Japan	Professor John Thompson Ph: +61 2 9515 5075 Email: john@mel.rpa.cs.nsw.gov.au
December			
6-10	44th Annual Meeting of the American Society of Haematology (ASH)	Pennsylvania USA	American Society of Haematology Washington, DC, USA Fax: +1 202 857 1164 Email: ASH@haematology.org Website: www.haematology.org/meeting/
8-11	18th World Congress of Digestive Surgery	Hong Kong China	Congress Secretariat Ph: 852 2818 0232/852 2855 4235 Fax: 852 2818 1186 Email: isdshk@hkucc.hku.hk
8-11	9th Hong Kong International Cancer Conference	Hong Kong China	9th HKICC Secretariat Fax: +852 2818 1186 Email: mededcon@hku.hk Website: www.hku.hk/
11-14	25th San Antonio Breast Cancer Symposium	San Antonio Texas USA	L Dunnington San Antonio Cancer Therapy and Research Center San Antonio, Texas, USA Fax: +1 210 949 5009 Email: ldunning@saci.org Website: www.sabcs.saci.org
2003			
March			
6-9	56th Annual Cancer Symposium of the Society of Surgical Oncology	Los Angeles USA	D K Kubis, 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: diannekubis@acaai.org Website: www.surgonc.org/
12-15	Adjuvant Therapy of Primary Breast Cancer	St Gallen Switzerland	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: abc-2003@sg.zetup.ch Website: www.oncoconferences.ch

Date	Name of Meeting	Place	Secretariat
16-19	ICTR 2003: 2nd International Conference on Translational Research and Pre-Clinical Strategies in Radiation Oncology	Lugano Switzerland	Jacques Bernier Oncology Institute of Southern Switzerland San Giovanni Hospital Bellinzona – CH-6504, Switzerland Fax: +41 91 820 9044 Email: jbernier@iosl.ch Website: www.osg.ch/ictr2003.html

April

2-5	8th Congress of the European Association for Palliative Care	The Hague The Netherlands	KENES International PO Box 50006 Tel Aviv – 61500, Israel Ph: +44 22 908 0488 Fax: +44 845 127 5944 Email: eapc8@kenes.com
5-9	94th American Association for Cancer Research Annual Meeting	Toronto Canada	AACR, Public Ledger Building, Suite 816 150 South Independence Mall West Philadelphia – PA 19106-3, USA Ph: +1 215 440 9300 Fax: +1 215 351 9165 Email: meetings@aacr.org Website: www.aacr.org/

May

1-4	Oncology Nursing Society 28th Annual Congress	Denver USA	Oncology Nursing Society Meetings Services Team, 501 Holiday Drive Pittsburgh – PA 15220-2, USA Ph: +1 412 921 7373 Fax: +1 412 921 6565 Email: member@ons.org Website: www.ons.org
21-24	12th Reach to Recovery International Conference “Bridging the Gap: the Needs and their Assessment”	Lisbon Portugal	Vencer e Viver: Dr Henriette Nesbitt de Almeida Lima Nucleo Regional Do Sul Da Liga Portuguesa Contra O Cancro Rua Professor Lima Basto Lisboa – P-1099-023, Portugal Ph: +351 21 726 5786 Fax: +351 21 726 3363 Email: cmatos@dpp.pt

August

3-8	12th World Conference on Tobacco or Health: Global Action for a Tobacco Free Future	Helsinki Finland	CongCreator CC Ltd Ms Aira Raudasoja/Ms Hanne Heikkinen PO Box 762 FIN-00101 Helsinki Finland Ph: +358 9 454 2190 Fax: +358 9 454 2193 Email: wctoh2003@congcreator.com Website: www.wctoh2003.org
10-14	10th World Conference on Lung Cancer	Copenhagen Denmark	International Conference Services Suite 604, 850 West Hastings Street Vancouver – V6C 1E1, Canada Ph: +1 604 681 2153 Fax: +1 604 681 1049 Email: conference@2003worldlungcancer.org Website: www.2003worldlungcancer.org

September

21-25	ECCO 12 – the European Cancer Conference	Copenhagen Denmark	FECS Conference Unit Ms Kris Vantongelen Federation of European Cancer Societies Av E Mounier, 83 Brussels – B-1200, Belgium Ph: +32 2 775 0205 Fax: +32 2 775 0200 Email: ecco12@fecsc.be Website: www.fecsc.be
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Date	Name of Meeting	Place	Secretariat
21-25	European Society for Therapeutic Radiology and Oncology 22nd Annual Meeting	Copenhagen Denmark	ESTRO Office, Av E Mounier 83/4 Brussels – B-1200, Belgium Ph: +32 2 775 9340 Fax: +32 2 779 5494 Email: info@estro.be Website: www.estro.be

October

19-23	American Society for Therapeutic Radiology and Oncology 45th Annual Meeting	Salt Lake City USA	ASTRO 12500 Fair Lakes Circle, Suite 375 Fairfax – VA 22033-3, USA Ph: +1 703 502 1550 Fax: +1 703 502 7852 Email: meetings@astro.org Website: www.astro.org
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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.



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

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Australasian Association of Cancer Registries
Clinical Oncological Society of Australia Inc
Palliative Care Australia
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Dr K White PHD

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
GPO Box 4708, Sydney, NSW 2001.

Membership fees for 2002

Ordinary Members: \$110

Associate Members: \$60

(includes GST)

INTEREST GROUPS

Breast Oncology

Cancer Research

Data Managers

Epidemiological

Gastrointestinal Oncology

Gynaecological Oncology

Lung Oncology

Medical Oncology

Melanoma and Skin

Oncology Nursing

(Cancer Nurses Society of Australia)

Paediatric Oncology

(ANZ Childhood Cancer Study Group)

Palliative Care

Pharmacy

Psycho-Oncology

Radiation Oncology

Regional & Rural Oncology

Social Workers

Surgical Oncology