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Response from R.T.D. Oliver

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I WAS VERY pleased to be alerted to the recent work from the St Mary's Group on the role of IL-6's action as an autocrine and paracrine factor stimulating aromatase to accelerate breast cancer growth, and to hear that they agreed with the ideas of Alexander reviewed in my Viewpoint [1] in respect of trauma-released cytokines as factors in tumour recurrence after surgery. However, I am less certain that I would be as keen as they are to advocate immunosuppression as treatment for breast cancer, given the reports of Stewart and associates [2] of unblocking of tumour dormancy in breast cancer patients receiving immunosuppression after renal transplantation.

It has been known since the pioneering work of Prehn [3] that sometimes the immune response can accelerate cancer growth. Experimentally it has been shown that, by altering antigen presentation, it is possible to induce an enhancing rather than rejecting type of immune response [4–6]. As there are at least six different mechanisms whereby cancer cells are known to alter antigen presentation (i.e. B2 microglobulin, class 1 molecule, class 2 molecule or transporter gene loss, class 2 gene mutation and adhesion molecule losses, for review see [7]) and some of these changes have been demonstrated in breast cancers [8], I see no reason why such changes should not cause induction of an enhancing immune response rather than total anergy. While using immune suppression to reduce that response might be of transient value, only the induction of unblocking of enhancement and induction of specific rejection response would be likely to lead to long-term durable immune resistance as has been done by Hui and associates [9] in their experiments using histocompatibility gene transfection.

To my mind, the most critical issue in respect of immune surveillance and breast cancer relates to the behaviour of breast cancer during pregnancy. There is no *prima facie* reason for immunosuppression to increase risk of mutagenic transformation, but it might be expected to increase the speed of progression of cancer growth. This view is supported by reports on breast cancer arising in pregnancy [10, 11]. Guinee and associates found only 71 cancers per 1000 women per year of observation in their population rather than 110 expected. However, 87% of pregnant women had tumours larger than 2 cm compared with 48% of those who developed tumours more than 49 months after a pregnancy or had never been pregnant [10]. Clark and Chua's observations also demonstrated that breast tumours arising during pregnancy were more advanced [11].

There is some evidence that tumours arising in immunosuppressed individuals demonstrate less evidence of need to escape immune surveillance as evidenced by less loss of HLA class I or II antigens than tumours arising spontaneously in individuals with normal immune function [12].

Investigating whether pregnancy-associated breast cancer has less loss of HLA than spontaneous breast tumours is a critical as yet unavailable fact that, were it true, would add to the data on the effect of renal transplant immunosuppression [2] in emphasising a central role of immune response in resisting breast cancer. The observation by Stewart and associates [13] that the incidence of breast cancer is lower in women after chronic immunosuppression, although at first sight evidence against immune surveillance may not be due to a direct effect of immunosuppression. As was pointed out earlier, there is no *prima facie* reason why immunosuppression should increase risk of mutagenic transformation. There are other possible reasons why renal transplant patients may have lower breast cancer. Firstly, if immunosuppression decreased sex hormone production, as has been shown for chemotherapy in Hodgkin's disease patients, endocrine dependent tumours might occur less frequently. Secondly, as renal transplant patients have variable periods of animal protein and fat restriction on dialysis, they could have less exposure to the fat-soluble immunosuppressive organochlorine pesticides whose 90% elimination from milk in Israel was associated with a more than 20% reduction in breast cancer in under 65 year old Israeli women between 1976 and 1986 [14].

If the speculations in respect of HLA loss in pregnancy-associated breast cancer were to be confirmed, such tumours could be more responsive to immunotherapy and benefit less from chemotherapy than spontaneous tumours. It is increasingly recognised that pregnancy causes major involution of the thymus [15], favouring development of the TH-2 subset of helper cells that have been demonstrated to increase the chance of allograft and tumour survival. Furthermore, there is increasing evidence that hormone therapy, by inducing castration, is associated with thymic regeneration [16, 17], and lymphocytosis [18] and could boost immune response, thus exerting its anticancer effect, in part due to mechanisms other than hormone withdrawal. This would make hormone therapy preferable to chemotherapy for tumours arising during pregnancy. The fact that less than 25% of patients in Guinee and associates' paper [10] on the effect of pregnancy received hormone therapy could be a factor in their poor prognosis. Given the report from the Scottish/ICRF breast cancer study showing that oestrogen receptor positive tumours do less well with chemotherapy than hormone therapy [19], there is an urgent need for more information on hormone sensitivity of pregnancy-associated breast cancer, not least as a means to resolve the continued and ongoing debate, as manifested by Mokbel's letter, as to whether immune surveillance is of any relevance in breast cancer.

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A Phase I/II Trial of Epirubicin and High Dose Tamoxifen as a Potential Modulator of Multidrug Resistance in Advanced Hepatocellular Carcinoma

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HEPATOCELLULAR CARCINOMA (HCC) is one of the most common malignancies, causing more than 1 million deaths every year, worldwide [1]. Because most patients present with advanced disease and HCC is almost always associated with chronic underlying liver disease, potential curative surgery can be achieved in only a small percentage of cases. There are numerous palliative treatment options in patients with inoperable disease, although none have yet been shown to offer any reproducible therapeutic benefit [2]. The possible explanations for the refractoriness of HCC to chemotherapy include tumour heterogeneity, inherent resistance and the overexpression of the multidrug resistance (*MDR1*) gene [3]. Based on histological studies, indicating that HCC expresses high levels of P-glycoprotein (Pgp) [3, 4], and the resistance-reversing potential and tolerance of high dose tamoxifen [5, 6], which has also been reported to exert therapeutic activity as a hormonal agent in this disease [7], the present disease-oriented phase I study was initiated.

For inclusion in the trial, patients were required to be aged 70 years or younger, have a WHO performance status of < 3, and adequate renal (serum creatinine level < 1.5 mg/dl), liver (total bilirubin level < 2 mg/dl, transaminase levels less than twice the upper limits of normal) and bone marrow functions (leucocyte count > 4000/μl, platelet count > 100 000/μl). All patients had normal pretreatment electro- and echocardiograms (with a left ventricular ejection fraction of more than 50%), and provided informed consent according to institutional guidelines.

Treatment consisted of tamoxifen 80 mg given twice a day for a total of 9 days, and the cytotoxic agent epirubicin, which was administered as a continuous infusion over 24 h

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