Old Herborn University Seminar Monograph 13:
Polyspecific immunoglobulins, their possible role in the normal (physiologic) clearance of microorganisms and tissue fragments.
Editors: Peter J. Heidt, Volker Rusch, and Dirk van der Waaij.
Herborn Litterae, Herborn-Dill, Germany: 93-107 (2000).

INTRAVENOUS IMMUNOGLOBULIN (IVIg) AS AN INHIBITOR OF TUMOUR GROWTH: FROM AUTOIMMUNITY TO CANCER

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SUMMARY

The relationship between autoimmunity and cancer is described in this manuscript from the pathogenic and therapeutic point of view. In our view, autoantibodies derived from patients with autoimmune conditions, may be utilised for cancer treatment. In addition to these therapeutic modalities, IVIg is an example of how the autoimmune-cancer relationship generated novel treatment for cancer. The efficacy of IVIg as an inhibitor of tumour spread was shown in experimental murine models of melanoma, sarcoma and carcinoma. The mechanism through which IVIg acts entail its capability to induce IL-12 production (an anti-cancer and anti-angiogenic factor) and a subsequent activation of natural killer cells (NK), the presence of antibodies against tumour associated antigens within the IVIg preparations as well as antibodies against adhesion molecules. It may thus be concluded that IVIg exerts its anti-cancer activity through multifactorial mechanisms involving each step in the process of metastatic spread.

INTRODUCTION

Cancer and autoimmunity share similar aetiological and pathological mechanisms such as uncontrolled cell proliferation, impaired apoptotic pathways, cytokine disregulation, hormonal balance alterations, changes in membrane adhesion molecule expression etc. Autoimmune conditions and malignancy co-exist frequently: Cancer may develop in patients with autoimmune diseases, while autoimmune conditions may follow malignancy (*Sela* and Shoenfeld, 1988; *Swissa* et al., 1990).

Haematological malignancies, including leukaemia, Iymphoma, Hodgkin's disease and multiple myeloma may follow autoimmune diseases (*McCarty*, 1985; *Vainio* et al, 1983; *Shoenfeld* et al., 1983). The strongest association is found between Sjögren's syndrome and lymphoma. The lymphomas are usually of the B cell origin, although T cell lymphomas have also been found (*Mouydopoulodan*, 1992; *Chevalier* et al., 1991). Patients with rheumatoid arthritis (RA) have a 2-3 times greater risk of developing lymphoproliferative malignancy, even in the absence of immunosuppressive therapy. The risk is further increased following treatment with cytotoxic drugs (*Pries*, 1985; *Prior*, 1985). Similarly, systemic lupus erythematosus (SLE) has been associated with lymphoma both in animal models, such as NZB and MRL/lpr, and in humans (*Green* et al., 1978; *Wyburn-*

Table 1: Neoplasms in autoimmune conditions

Malignancy	Autoimmune disease
Lymphoproliferative malignancy	Sjögren's syndrome, SLE, RA
Thymoma	myasthenia gravis
Lung cancer	scleroderma, PM, DM
Breast carcinoma	scleroderma, stiff-man syndrome, DM, PM
Gynaecologic carcinoma	DM, PM

Mason, 1979; *Berliner* et al., 1983).

Other autoimmune conditions may be associated with different malignancies. The most prominent examples are myasthenia gravis and high incidence of thymoma (*Wu* and *Low*, 1996) systemic sclerosis (scleroderma) with lung cancer or with breast carcinoma (*Davis* et al., 1996; *Winkelmann* et al, 1988) and stiff-man syndrome in breast cancer (*Rosin* et al., 1998). Three additional autoimmune diseases - mixed connective tissue disease (MCTD), polymyositis (PM) and dermatomyositis (DM) - may be associated both with haematological neoplasms and with epithelial tumours (*Black* et al., 1982; *Schulman* et al., 1991; *Seda* and *Alarcon*, 1995; *Maoz* et al., 1998). Table 1 summarises the different malignancies and the associated autoimmune conditions.

Several explanations were introduced for the induction of malignancy in autoimmune conditions: susceptibility of the patients to both diseases (*Shoenfeld* and *Shwartz*, 1984; *Schreinemachers* and *Everson*, 1994); immunological predisposition (*Raubinain* and *Talal*, 1978; *Mountz* et al., 1984); oncogene activation and expression (*Kinlen*, 1985); the treatment of autoimmune diseases with immunosuppressive drugs may induce Iymphoproliferation and even trigger other tumour growth (*Fishman*, 1994).

Another association between autoimmunity and cancer is the occurrence of autoantibodies in patients with both haematological and epithelial malignancies. *Swissa* et al. (1990) examined different autoantibodies in the sera of 150 lymphoma patients and 164 cancer patients. Antinuclear antibodies (ANA) were detected in leukaemia. Anti-ss-DNA, anti-RNP and anti-Sm were found in the sera of patients with lymphoma. Among patients with epithelial malignancies, those with breast cancer had ANA and anti-smooth muscle antibodies. Lung cancer patients had anti-smooth muscle antibodies, antineuronal antibodies and autoantibodies to fibrillar collagen (*Lucchinetti* et al., 1998; *Fernandez* et al, 1996). Patients with head and neck carcinoma having higher serum immunoglobulin IgA levels, also exhibit IgA-anti-F(ab')2 autoantibodies (*Lorenz* et al., 1988) and patients with hepatocellular carcinoma have antinuclear antibodies (*Covini* et al., 1977).

Our group have recently defined tyrosinase, an enzyme which participates in the process of melanin production, as an autoantigen in vitiligo (*Baharav* et al., 1996). Autoantibodies to tyrosinase were detected in melanoma with a correlation to disease stage and to the development of white patches on the patient's skin (*Fishman* et al., 1997). Table 2 summarises the various autoantibodies which were defined in cancerous diseases.

It was suggested that the generation of autoantibodies in malignant condi-

Table 2: Autoantibodies in malignancy

Malignancy	Autoantibodies
Lymphoma	anti-ssDNA, anti-RNP, anti-SM
Breast carcinoma	ANA, anti-smooth muscle
Lung cancer	anti-smooth muscle, anti-neuronal, anti-fibrillar, collagen
Head & neck carcinoma	IgA-anti-F(ab')2
Hepatocellular carcinoma	ANA
Melanoma	tyrosinase

tions are an aspect of immune deficiency or an immune response against proteins which are involved in proliferative functions.

The common treatments aiming at similar targets and therapies based on the understanding of immune mechanisms in both diseases, are the subject of the current article.

An improved understanding of immune mediated tumour suppression should therefore greatly benefit immunotherapy of autoimmune diseases, and the two areas of research would benefit from an interdisciplinary endeavour.

COMMON THERAPIES FOR CANCER AND AUTOIMMUNITY

Similar strategies based on disease pathogenesis are employed to combat autoimmunity and cancer. The main pathways to be attacked in autoimmunity are modulation of immunoglobulin production, immunosuppression and interfering with inflammatory reactions. In cancer, tumour cell proliferation inhibition, immune system stimulation and metastasis prevention are targeted.

Shared pathogenic mechanisms lead to the implementation of therapies used in cancer for the treatment of autoimmune diseases and vice versa. The followings are some common treatments for both diseases.

Chemotherapy

Uncontrolled cell proliferation is shown in both cancer and autoimmunity. Chemotherapy, the gold standard for the therapy of malignant conditions, is used in cancer to inhibit tumour cell growth and in autoimmune conditions to modulate proliferating B cells producing pathogenic antibodies. Two cytotoxic agents, cyclophosphamide and methotrexate act via inhibition of nucleotide biosynthesis and are widely used in cancer therapy and in some autoimmune conditions. The clinical use of cyclophosphamide in autoimmunity is for the treatment of renal and cerebral lupus, vasculitis, especially in the context of Wegener's granulomatosis and rheumatoid arthritis. Methotrexate is used for the treatment of rheumatoid arthritis and several malignant conditions. It inhibits the enzyme dihydrofolate reductase. It exerts an anti-inflammatory effect through its capability to induce adenosine release in sites of inflammation (*Cronstein* et al., 1995; *Bouma* et al., 1994). Adenosine has an anti inflammatory effect due to its capability to inhibit the production of inflammatory cytokines such as TNF-α, IL-6, and IL-8 (*Tey* et al., 1992). Extracellular adenosine was shown by us (*Fishman* et al., 1998) and others (*Tey*

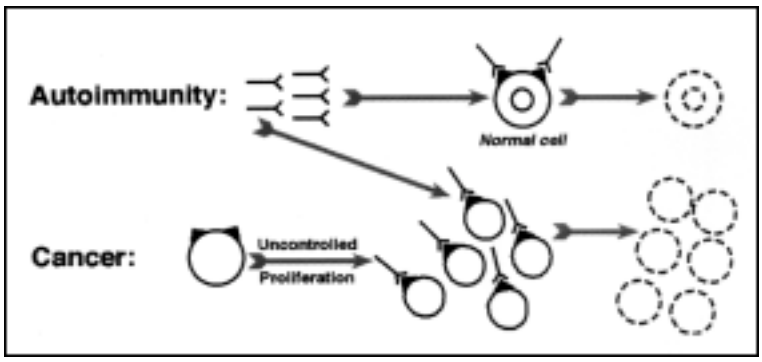

Figure 1: Autoantibodies from patients with autoimmune diseases bind and destroy normal cells presenting certain autoantigens. Such autoantibodies will bind to, and destroy the respective cancer cells which are of the same cellular origin as the normal cells and display the same autoantigens.

et al., 1992) to act as an anti cancer agent by binding to specific cell surface receptors and to inhibit specifically tumour cell proliferation. Thus, adenosine which acts as both an anti-inflammatory agent and an inhibitor of tumour cell growth, may serve as a treatment for cancer as well as autoimmune conditions.

Non-steroid anti-inflammatory drugs (NSAIDs)

Aspirin and other NSAIDs are widely used for the treatment of autoimmune conditions and are considered as potent anti-inflammatory drugs. These agents act by blocking the enzymes cyclo-oxygenase I and II, thus inhibiting the synthesis of prostaglandins and Thromboxane A2 (TXA2). Recently, we reported a novel mechanism by which a low dose aspirin was found to be extremely beneficial for the treatment of anti-phospholipid syndrome (APS). This syndrome is characterised by repeated thrombo-embolic phenomena and recurrent foetal loss. Our studies indicated that only low dose aspirin affected and prevented the pregnancy loss by increasing production of interleukin-3. We demonstrated that this cytokine is deficient in mice with experimental APS and has instrumental role in normal pregnancy (*Fishman* et al., 1992; *Fishman* and *Shoenfeld*, 1993).

Individuals who regularly take aspirin or other NSAIDs have been reported to be at reduced risk for the development of cancers of the colon (*Thun* et al., 1991; *Thun* et al., 1993; *Giovannucci* et al., 1995; *Berkel* et al., 1996) and possibly other sites including the stomach, oesophagus, lung and breast cancer (*Farrow* et al., 1998; *Schreinemachers* and *Everson*, 1994). NSAIDs exert their anti-cancer activity through the inhibition of prostaglandin synthesis, blockade of prostaglandin induced immunosuppression (thereby enhancing immune response) and induction of apoptosis and inhibition of tumour cell proliferation (*Samaha* et al., 1997; *Elder* et al., 1996). Aspirin was also found to stimulate the production of interleukin-12, a potent cytokine with anti-cancer activity, known to activate NK and cytotoxic lymphocytes which subsequently combat tumour cells (unpublished data).

Bone marrow transplantation

Bone marrow stem cell transplantation is currently used to treat patients with haematological and other malignancies such as breast and ovarian neoplasms. Autografts or allografts are

transplanted to cancer patients allowing the administration of high dose chemotherapy or radiotherapy and confer an anti-tumour effect separate of the chemotherapy effects. With the clinical development of haematopoietic growth factors, peripheral blood derived stem cells can be transplanted instead of bone marrow stem cells (*Blank* et al., 1995). Autoimmune conditions seems to be a stem cell disease and therefore can be transferred by bone marrow transplantation (*Blank* et al., 1995; *Sherer* and *Shoenfeld*, 1998). Yet it seems currently that if there is any cure for autoimmune conditions it is following heterologous bone marrow transplantation after total B and T cell ablation or autologous transplantation after proper purging of pathogenic T cells. Indeed the experience with patients seems encouraging although as yet, has not been widely tested.

Idiotypes and anti-idiotypes

Idiotypic immunomodulation is an additional harnessed therapy in both cancer and autoimmunity. The idiotypic network is an important mechanism for controlling the immune system (*Shoenfeld* et al., 1997; *Jerne*, 1974) and autoimmune diseases may be attributed to the disturbances of the network. Thus, one may speculate that manipulation of idiotypes ("pathogenic", "cross-reactive") of autoantibodies (anti-idiotypic immunity), may be effective in the treatment of autoimmune diseases.

Indeed, there are encouraging reports which show the beneficial effect of anti-idiotypic antibodies in the treatment of B cell tumours (*Levy* and *Miller*, 1990). In this approach, the target of the anti-idiotypic antibodies is the tumour specific antigen which is the idiotype of the cell surface immunoglobulin present on B cells. This modality was expanded to the use of anti-idiotypes generated against tumour associated antigens (*Merimsky* et al., 1997; *Blank* et al., 1994). Anti-idiotypes can directly regulate autoantibodies or indirectly, following active immunisation with a dominant idiotype. Needless to say, IVIg (see below), is also considered to affect autoimmune diseases by its content of polyspecific anti-idiotypes.

HARNESSING AUTOREACTIVITY FOR CANCER TREATMENT

In this section two therapeutic approaches making use of the "positive" relationship between autoimmunity and cancer, are discussed.

The first presents the use of autoantibodies derived from patients with autoimmune diseases as a potential therapy for cancer and the second introduces intravenous gamma globulin (IVIg), a common therapy for autoimmune diseases, as a treatment for the prevention of tumour metastases.

Autoantibodies

Autoantibodies in patients with autoimmune diseases are capable of binding and destroying normal cells presenting certain autoantigens. We presented recently a concept (*Fishman* et al., 1997) based on the realisation that such autoantibodies will bind to and destroy the respective cancer cells which are of the same cellular origin as the normal cells and display the same autoantigens (Figure 1).

This concept is wide and applicable for many autoimmune diseases and diverse malignant conditions. To illustrate the therapeutic and practical potential of this novel linkage several examples of autoantibodies and the respective cancer cells are depicted in Table 3 and are detailed below.

Table 3: Pairs of autoimmune diseases and the respective neoplasms

Autoimmune disease	Cancer disease
Vitiligo anti-melanocyte Abs.	Melanoma
Autoimmune haemolytic anaemia anti-red blood cell Abs.	Polycythaemia vera, Erythro-leukaemia
Antiphospholipid syndrome anti-phosphatydilserine Abs.	Cancer cells exhibiting phosphatydilserine on the outer cell membrane
SLE , other auto immune diseases anti-lymphocyte Abs.	Chronic lymphocytic leukaemia
Pemphigus vulgaris anti-keratinocyte Abs.	Squamous cell carcinoma of the skin

Vitiligo and melanoma

Vitiligo is a dermatologic autoimmune disorder presented as depigmented skin areas. The destruction of the pigmented cells (melanocytes) is mediated by autoantibodies. Autoantibodies against membranal and cytoplasmic components of melanocytes were found in the sera of patients with vitiligo and were identified as IgG antibodies (*Moellmann* et al., 1985). Recently, we and others defined tyrosinase, an enzyme which participates in the melanin synthesis, as the autoantigen in vitiligo (*Song* et al., 1994; *Baharav* et al., 1996). Melanoma represents an uncontrolled growth of pigmented cells (melanocytes). The tumour is highly immunogenic and the patients are producing antibodies against the melanoma cells. Since these antibodies react against normal melanocytes, some patients develop vitiligo and are considered to have a better prognosis (*Merimsky* et al., 1994). These relationships between the two diseases have led us to raise the question whether the autoantibodies produced in vitiligo could destroy melanoma cells and serve as a "natural immunotherapy" for melanoma.

Binding of sera from patients with vitiligo to melanoma cells (B-16 murine melanoma cells or M-14 human melanoma) was shown by ELISA studies. Sera derived from patients with diffuse vitiligo yielded the highest titres of anti-melanoma antibodies in comparison to the controls, while patients with localised vitiligo showed lower titre of autoantibodies.

Lysis of tumour melanoma cells in the presence of autoantibodies from patients with vitiligo and complement was demonstrated by proliferation as well as morphological studies and served as the basis for the mice studies.

In vivo studies in which IgG fractions from the sera of patients with diffuse vitiligo were purified on absorption columns and employed for the treatment of melanoma bearing mice. Melanoma metastatic foci were inhibited by 80% (*Fishman* et al., 1993). Additional example for an autoantigen which appears both in melanoma and vitiligo is tyrosinase. Tyrosinase is an enzyme which participates in the process of melanin production in normal melanocytes and melanoma cells. Enzymes are known to be autoantigens in various autoimmune disorders, thus following the detection of anti-tyrosinase antibodies in vitiligo and melanoma, tyrosinase was defined by us as an autoantigen in these condi

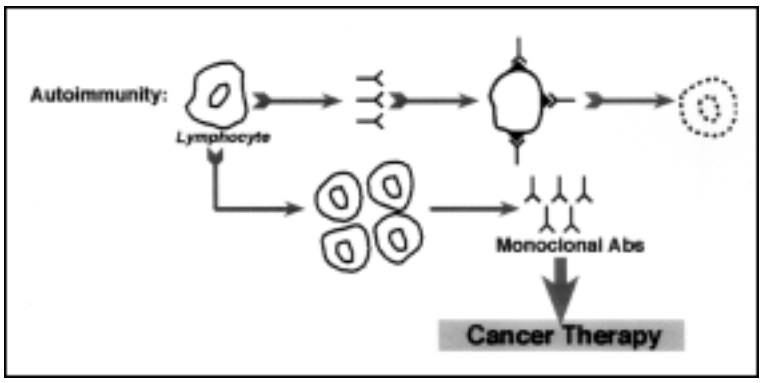

Figure 2: Membranal phospholipids are known to be asymmetrically distributed between the two leaflets of the bi-layer cell membrane. Phosphatydilserine (PS) is localised exclusively in the inner leaflet of the cell membrane of normal cells (Top left). The translocation of PS from the inner to the outer cell membrane is typical to tumour cells which express 7-8 fold more PS on their outer leaflet than normal cells (Top right). Patients with anti-phospholipid syndrome have in their serum anti-phospholipid antibodies including anti-phosphatydilserine antibodies. The hypothesis is that these autoantibodies are capable to bind to tumour cells through the PS.

tions (*Baharav* et al., 1996). In some patients with melanoma the disease is associated with the appearance of "vitiligo-like" white patches on the skin, namely melanoma associated hypo-pigmentation (MAH). In patients with melanoma, those with a metastatic disease showed a higher titre of anti-tyrosinase antibodies in comparison to healthy subjects, while patients with MAH and those with no evidence of disease had similar titres to the control group. The titre of anti-tyrosinase antibodies in patients with metastatic melanoma treated by vaccination with anti-idiotypic antibodies mimicking the high molecular weight melanoma associated antigen, increased following the vaccination and then decreased. High titres of anti-tyrosinase antibodies were detected in patients with diffuse vitiligo in comparison to patients with localised disease and to the healthy control (*Merimsky* et al., 1994).

Mice immunised with tyrosinase, generated a high titre of anti-tyrosinase antibodies and following the inoculation of melanoma cells developed lower number of lung metastases compared to an unvaccinated control group.

These studies confirmed the efficacy of the autoantibodies as cytotoxic against melanoma cells and prompted us to look for additional "pairs" of autoimmune disease and related neoplasm.

Anti-phospholipid syndrome (APLS) and cancer

This pair of conditions consist of various types of cancer cells which express the phospholipid phosphatydilserine on the outer layer of the cell membrane and, the autoimmune condition antiphospholipid syndrome (APS) (Figure 2). Patients with anti-phospholipid syndrome have in their serum anti-phospholipid antibodies including anti-phosphatydilserine antibodies (*Teruhiro* et al., 1991). These pathogenic autoantibodies were shown to induce the clinical manifestations of the disease characterised by thrombocytopenia, thromboembolic recurrent phenomena and repeated foetal loss.

Membrane phospholipids are known to be asymmetrically distributed between the two leaflets of the bi-layer cell membrane. Phosphatydilserine (PS) is

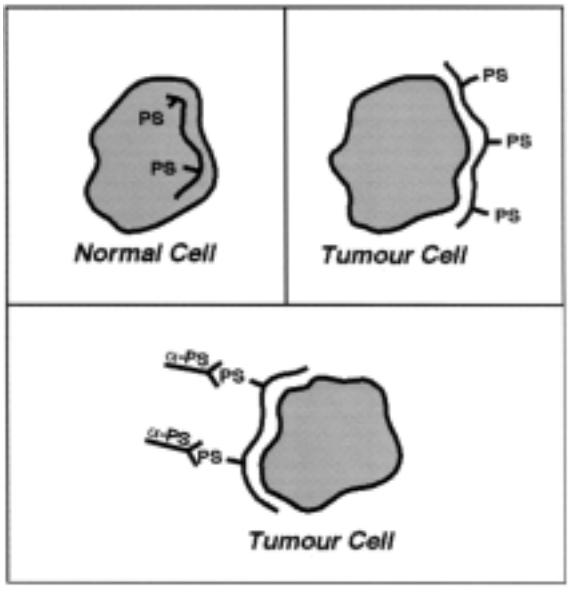

Figure 3: Lymphocytes of patients with autoimmune diseases produce autoantibodies which bind to and destroy normal cells (Top). Lymphocytes from these patients can be expanded and by hybridoma or other techniques, monoclonal antibodies effective against cancer cells can be produced.

localised exclusively in the inner leaflet of the cell membrane. The translocation of PS from the inner to the outer cell membrane is typical to tumour cells which express 7-8 fold more PS on their outer leaflet than normal cells (*Fishman* et al., 1993). We purified the IgG anti-PS antibodies from patients with anti-phospholipid syndrome and examined their *in vivo* efficacy against melanoma tumour cells as was specified above in the studies of vitiligo and melanoma. The anti-PS antibodies exerted inhibitory effect of 76% on the development of lung metastatic foci in the mice inoculated with B-16 melanoma cells. We believe that anti-PS antibodies may be employed in the future for treatment of diverse malignant conditions.

Autoimmune haemolytic anaemia (AIHA) and haematological malignancies

Autoimmune haemolytic anaemia is an autoimmune disease in which the red blood cells (RBC) are destroyed by anti-red blood cell haemolytic autoantibodies. These autoantibodies may be effective against cells in polycythaemia vera (PV), a condition of pseudo-malignant proliferation of RBCs causing clogging of blood vessels and against another proliferative malignant condition - erythro-leukaemia. Binding of serum from a patient with autoimmune haemolytic anaemia to human RBCs or to erythro-leukaemic cells from the murine Friend's cell leukaemia cell line was demonstrated. These kind of autoantibodies eventually can be employed to treat PV and erythro-leukaemia.

Anti-lymphocyte antibodies and lymphoproliferative diseases

In SLE and other systemic autoimmune conditions autoantibodies directed against lymphocytes can be found. These cytotoxic antibodies can be used to treat malignant diseases originated from lymphocytes such as chronic lymphocytic leukaemia, or lymphomas.

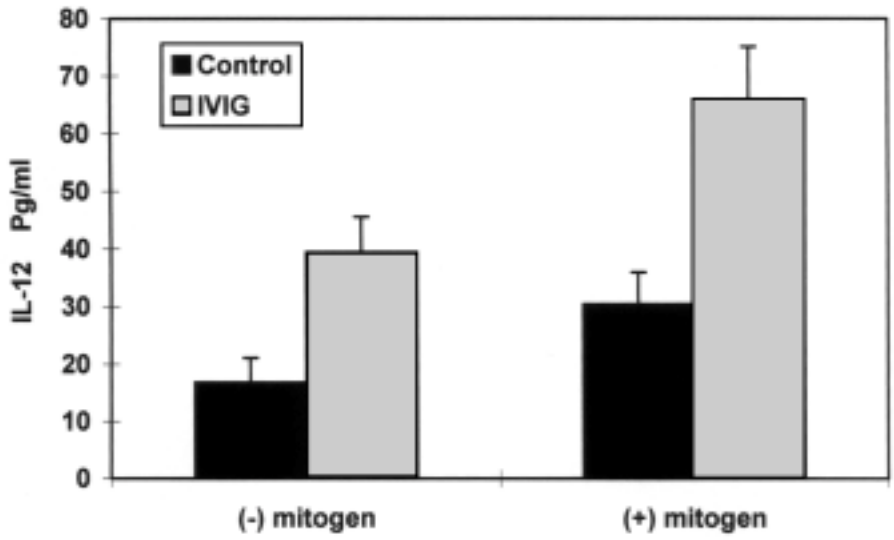

Figure 4: Effect of IVIg (100 μg/ml) on the *in vitro* production of IL-12 by peripheral blood mononuclear cells derived from healthy volunteers. IVIg stimulated the mitogenic induced as well as the spontaneous IL-12 production.

Pemphigus vulgaris and squamous cell carcinoma

The anti-keratinocyte antibodies produced in pemphigus vulgaris are appealing candidates for therapeutic modality to squamous cell carcinoma derived from the skin or other organ origin.

The diversity of autoimmune diseases provides a great source for human performed highly specific autoantibodies which can be used as an effective immunotherapy by themselves. Lymphocytes derived from these patients have the "know- how" to generate *in vitro* monoclonal antibodies which can be implemented for cancer therapy (Figure 3).

UTILISING IVIg, A COMMON TREATMENT IN AUTOIMMUNITY, FOR CANCER THERAPY

IVIg (intravenous immunoglobulin) is the human serum immunoglobulin fraction that is mainly composed of IgG which is prepared from large plasma pools of more than 15,000 healthy blood donors and is suitable for intravenous use. High dose IVIg was first employed to treat patients with immunodeficiencies and later on for patients with diverse autoimmune states. The IVIg was found to affect autoimmune conditions through multifactorial mechanisms (*Kazatchkine*, 1996). These are divided into humoral mechanisms which include Fc blockade by the IVIg, effects on autoantibody binding and production via the idiotypic anti-idiotypic network, prevention of immune complex formation and neutralisation of microbial toxins (*Freitzs* et al., 1991). IVIg also exerts its effects via cellular mechanisms entailing immune modulation of T and B cell number and function, as well as inhibition of anti-inflammatory cytokine production (*Skansen-Saphir* et al., 1994).

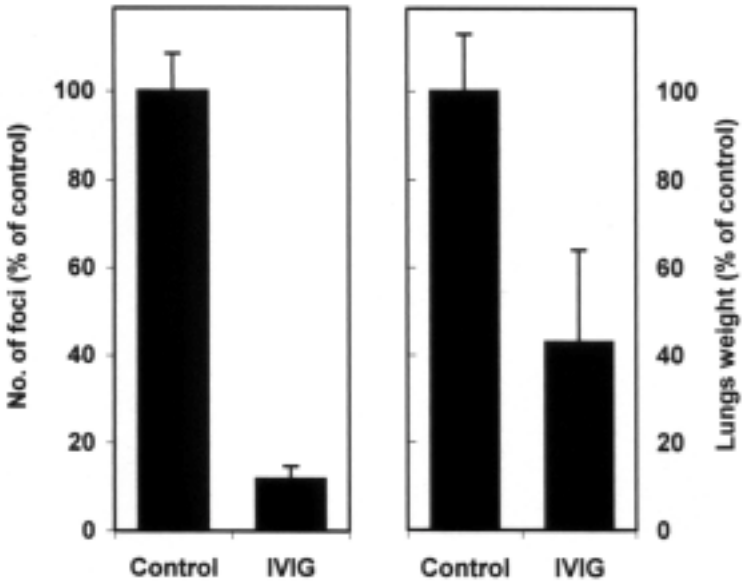

Figure 5: Lung metastatic foci and lung weight of SCID mice, i.v. inoculated with SK-28 human melanoma and treated with IVIg.

Several findings explored recently by our group and others have prompted us to employ IVIg for the treatment of cancer. IVIg was shown to bind to several tumour associated antigens (PSA, CA-125) facilitating its activity as an anti-tumour antibody; it stimulates IL-12 production (Figure 4), a cytokine known to induce anti-cancer activity by activating NK cells and by inducing anti-angiogenic effect (*Hiscox* and *Jiang*, 1997; *Trinchieri*, 1998; *Voest* et al., 1995). Indeed, enhanced NK activity of peripheral blood cells was observed by us and others following incubation with IVIg (*Sgadari* et al., 1996; *Vassilev* et al., 1996) showed that IVIg contains antibodies to a peptide that covers the Arg-Gly-Asp (RGD) sequence which defines the binding site of a variety of adhesive proteins. Thus IVIg may act as an anti-adhesive agent and prevent tumour spread.

This body of evidence led us to carry out a set of *in vivo* experiments which exemplified the efficacy of IVIg as an anti metastatic agent (*Shoenfeld* and *Fishman*, 1999).

The efficacy of treatment with gamma-globulin in murine melanoma was demonstrated by using two models. Its effect (at either high or low doses) was shown by the reduction in the number of lung metastases in mice inoculated with melanoma cells (Figure 5). Furthermore, injecting the gamma-globulin to mice after inoculation of the malignant cells to the foot pad and before amputation of the inoculated limb, was found to prolong survival and to induce 50% cure in the treated mice (Figure 6). The latter model actually mimics the situation in patients in whom the primary tumour is resected and after which treatment is implemented. IVIg was also effective in preventing the development of the lung MCA-105 sarcoma (Figure 6).

As detailed above it seems that the mechanism through which IVIg prevents metastatic spread may be multifactorial and as was detailed above in the

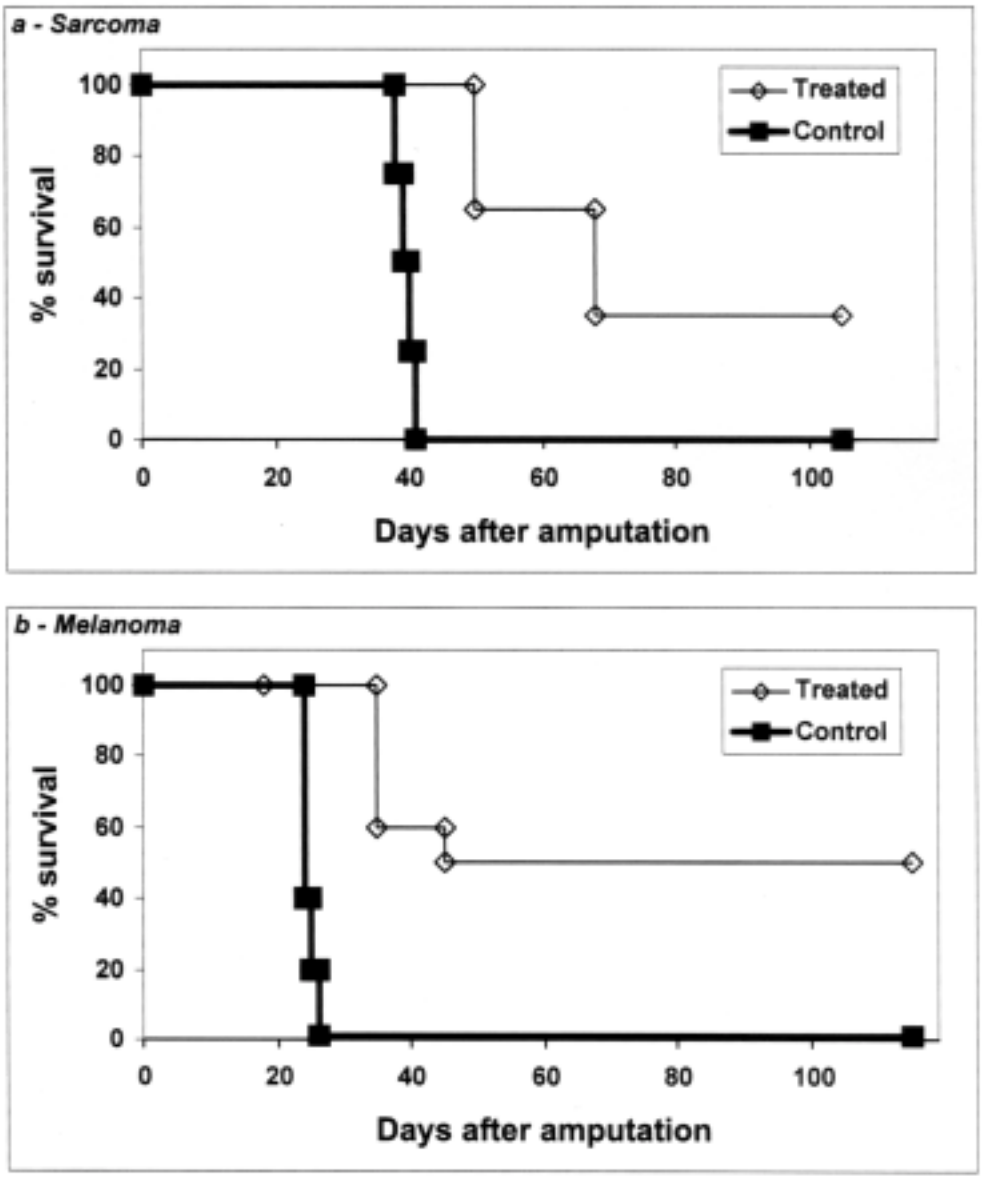

Figure 6: Survival time of mice inoculated with MCA-105 Sarcoma or B-16-F10 melanoma following treatment with IVIg.

paragraph summarising our *in vitro* studies, IVIg practically can affect each step in the process of metastatic spread, from angiogenesis to direct killing (lysis) of the malignant cell.

Thus, IVIg, a classical treatment for autoimmune diseases was found to act as an inhibitor of tumour spread and is currently being tested in clinical trials.

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