Histol Histopathol (2007) 22: 687-696

**http://www.hh.um.es**

**Histology and Histopathology**

*Cellular and Molecular Biology*

## *Review*

# Immune based therapies in cancer

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**Summary.** Immunotherapy of cancer has become a more promising approach in the past decade. Developments in both basic immunology and tumor biology have increased our knowledge of the interactions between the tumor cells and the immune system. The molecular identification of tumor-associated antigens and understanding of immunological pathways have cleared the way for development of different strategies for anti-tumor vaccines. The success of any cancer vaccine relies on the induction of an effective tumor-specific immune response to break tolerance and to elicit a long lasting anti-tumor immunity. It is also increasingly clear that the interactions of host-tumor are quite complicated leading to tumor escape mechanisms, which add another level of difficulty to this interaction. This review will summarize the recent developments in tumor immunotherapy as well as the clinical trials addressing novel immunotherapeutic approaches to cancer.

**Key words:** T cell, Dendritic cell, Vaccine

### Introduction

Cancer remains one of the leading causes of death worldwide. Over the last decade, molecular discovery of tumor antigens as well as new findings in basic immunology has led to novel options to develop active immunotherapeutic approaches for prevention and treatment of cancer (Fig. 1).

Evidence from a number of different investigations suggests a possible role of the immune system to treat cancer. A positive correlation between tumor infiltrating T lymphocytes and patients survival has been observed (Wada et al., 1998; Zhang et al., 2003). Spontaneous tumor-specific T cell responses occur in individuals with premalignant lesions (Dhodapkar et al., 2003; Suzuki et al., 2005; Garbe et al., 2006) and have been found in patients with a variety of different tumors (Nagorsen et al., 2003; Korangy et al., 2004). However, tumors have also developed a number of different strategies to escape immune surveillance such as loss of tumor antigen expression, MHC down regulation, expression of Fas-L, which can induce apoptosis in activated T cells, secretion of VEGF and other cytokines such as IL-10 or TGF-ß (Gabrilovich et al., 1996; Ferrara et al., 2003; Dunn et al., 2004). Other mechanisms include the generation of regulatory T cells and myeloid suppressor cells (Ormandy et al., 2005; Zou, 2006; Kusmartsev and Gabrilovich, 2006).

The requirements for an immune-based strategy against cancer are the induction of an effective tumor-specific immunity in a way that will break tolerance to the tumor and generate anti-tumor immunity. To achieve this goal, a variety of strategies both in preclinical models and in clinical trials are currently being investigated.

The identification of defined tumor antigens in humans has encouraged the development of cancer vaccines using recombinant or synthetic tumor vaccines as well as adoptive T-cell therapy. The most appealing strategy is vaccination, which is anticipated to induce both therapeutic T cell immunity (tumor-specific effector T cells) and protective T-cell immunity (tumor-specific memory T cells). We will discuss the different approaches currently used for immune-based therapies in this review.

### Whole tumor cell vaccines

Whole tumor cell vaccination is an attractive approach to tumor immunity. Theoretically, autologous tumor cells are the ideal vaccine against cancer, since they carry all the relevant tumor antigens. In this setting, the antigens do not necessarily have to be known to design a "personal" vaccine for the patient. The tumor cells are inactivated i.e. by irradiation and then injected into the patient. It is proposed that the antigens from the tumor are then picked up by professional antigen-presenting cells such as dendritic cells and either

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directly- or cross-presented (see below) to T lymphocytes. It has been shown that genetic modification of tumor cells to express different cytokines such as IL-2, IFN-γ and GM-CSF, can boost the immune response against the tumor (Fig. 2) (Pardoll, 1995; Glick et al., 1997; Coughlin et al., 1998).

GM-CSF has been shown to be the most potent cytokine for recruiting immune cells to the site of vaccination (Dranoff et al., 1993; Salgia et al., 2003). Local expression of GM-CSF recruits dendritic cells; the most potent and powerful antigen-presenting cells to the tumor site. Dendritic cells then take up tumor antigen and present it to $CD4^+$ as well as $CD8^+$ T cells, a process that is known as "cross-presentation". This type of vaccine has been used in several trials including prostate, melanoma and pancreatic cancer patients (Simons et al., 1997; Soiffer et al., 1998; Jaffee et al., 2001).

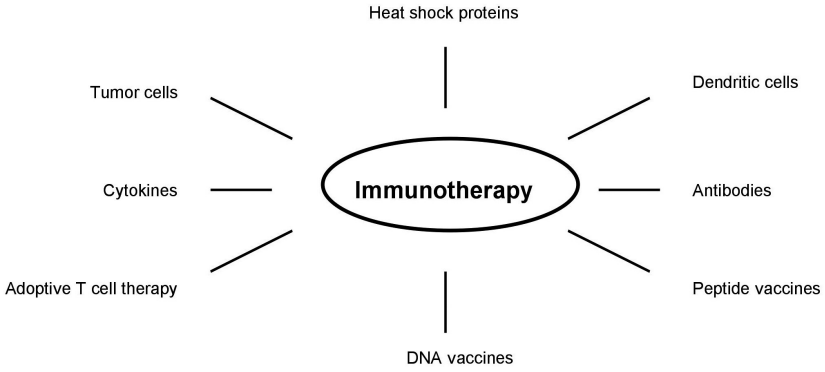


**Fig. 1.** Different immunotherapeutic approaches

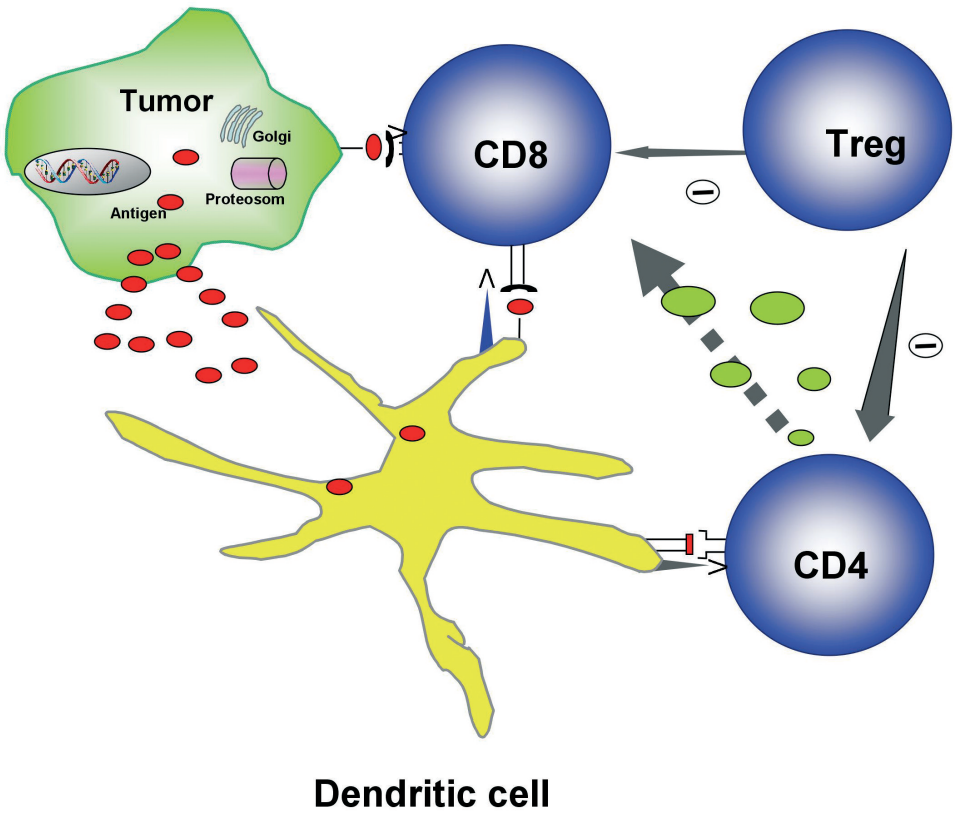


**Fig. 2.** Tumor antigens can either be directly presented to $CD8^+$ T cells or taken up by professional antigen presenting cells such as dendritic cells. These cells process the antigen and present it $CD8^+$ T cells by a mechanism called cross priming as well as $CD4^+$ T cells. The expression of co-stimulatory molecules on dendritic cells facilitates the stimulation of T cells. In addition, $CD4^+$ T cells provide cytokine help for $CD8^+$ T cells. A number of different mechanisms exist, which prevent or suppress anti-tumor T cell responses. One of these mechanisms is the suppression of antigen-specific T cell responses by $CD4^+CD25^+$ regulatory T cells.

The generation of individual cell vaccines for every patient can be time- and labor intensive. Moreover, enough tumor material is not always available, which is needed to prepare a new vaccine for every patient. To circumvent these issues, allogeneic vaccines have been designed. In this setting, the vaccine is not generated from the patient's own tumor but from different cell lines, which are injected together with an adjuvant to enhance the immunogenicity of the vaccine. An example for this technique is the allogeneic vaccine for pancreatic cancer developed by Jaffee and colleagues (Jaffee et al., 1998). Pancreatic cancer cell lines were generated from different patients and retrovirally transfected to produce GM-CSF (Jaffee et al., 1998). The vaccine contains several antigens, which are shared by the majority of pancreatic adenocarcinoma tumors (e.g. CEA, MUC-1 and the oncogenic product of K-ras). Phase I clinical trials have shown that this vaccine is safe and does not lead to major toxicities. Although survival rates were not primarily addressed in this study, three patients showed long-term survival of now more that 7 years (Laheru and Jaffee, 2005), while the mean life expectancy in patients with local disease is 12-18 months and with metastatic disease 3-6 months after resection (Laheru and Jaffee, 2005).

A different approach has been described by Mitchell and colleagues (Elliott et al., 1993). Their study about the melanoma vaccine, Melacine® was initiated in 1985. This vaccine is derived from two different and well-defined tumor cell lines, which were cultured from subcutaneous nodules of two patients. For generating the actual vaccine, the cell lines were disrupted both mechanically and by performing several freeze-thaw cycles. The final preparation, a cell lysate, contained, among others, the common melanoma antigens tyrosinase, gp100, and MART-1/Melan A. Before injection, the lyophilized vaccine was mixed with the adjuvant Detox-PC. The investigators were able to show a significant tumor regression, especially in patients with certain HLA haplotypes (e.g. HLA-A2 and C3) (Sondak et al., 2002; Sosman et al., 2002).

### Identification of tumor antigens

Over the past decade, numerous MHC class I and class II restricted tumor antigens have been identified through both genetic and biochemical approaches (Renkvist et al., 2001; Boon et al., 1994). The first antigens were identified using tumor-specific cytotoxic T lymphocytes obtained from cancer patients (Boon et al., 1994). CTL lines and clones were generated from blood of cancer patients and used to screen a cDNA library derived from autologous tumor. This approach has identified many antigens from cancer patients such as MAGE-1, BAGE-1 and Gage-1 (van der Bruggen et al., 1991; Coulie et al., 1994).

Most of the antigens recognized in both murine and human tumors fall into 3 categories: a) Tumor-specific antigens which are unique to an individual patient's tumor, b) tumor-associated antigens expressed in tumor but silent in normal tissue, also known as cancer testis antigens, c) differentiation antigens which are expressed in both normal tissue and tumor (Stevanovic, 2002).

So far, antigens recognized by $CD8^+$ T cells have been selected for the majority of clinical trials performed. There are now several biochemical and genetic approaches that have led to successful identification of tumor antigens recognized by both $CD4^+$ and $CD8^+$ T cells (Simpson et al., 2005; Sahin et al., 1997).

### Peptide vaccination

Identification of the antigenic peptides from the tumor antigens has paved the way for design of peptide vaccines. The first antigen-specific vaccines used have taken advantage of antigenic peptides presented by common HLA alleles. Algorithms have been developed that allow for predicting epitopes derived from protein antigens. These peptides can be synthesized and tested for HLA-binding capacity and to generate epitope specific CTLs. The peptide-specific T cells will prove whether these peptides are actually present on the tumor cells (Stevanovic, 2002) and can be recognized. Induction of immune responses targeted to one of these peptide epitopes can lead to selective tumor rejection and a number of trials have been performed using peptide-based vaccination in patients with different types of cancer. Most studies have been performed in patients with melanoma using tumor specific peptides such as Melan-A, gp100, tyrosinase and others.

Delivery of the peptides with adjuvants such as cytokines or chemokines is another approach to amplify the generated immune response. Recently, a HER2/neu peptide was given in combination with GM-CSF to patients after resection of breast cancer. Only minor toxicities have been observed in this study and all patients demonstrated clonal expansion of antigen-specific T cells that lysed HER2/neu expressing tumor cells. Although this study was clearly too small to draw definite conclusions from, it was interesting to note that the tumor recurrence rate was clearly higher in the non-vaccinated group (Peoples et al., 2005). Similar results have been observed in a different trial using mutant K-ras and p53 derived peptides. In this trial of 29 patients with evident disease, five experienced a period of stable disease indicating a possible clinical benefit after peptide vaccination. Numerous other trials have been performed or are under investigation using different peptides. NY-ESO-1 peptides, derived from the cancer testis antigen NY-ESO-1 have also been tested in several trials. NY-ESO-1 antigen was originally identified in esophageal cancer, but is also expressed in other tumors such as melanoma and HCC (Korangy et al., 2004; Vaughan et al., 2004; Barrow et al., 2006), and has been shown to be quite immunogenic and capable of inducing antigen-specific $CD4^+$ and $CD8^+$ T cell responses. A number of groups have searched for universal peptides derived

from tumor antigens, specific for many tumors. Telomerase peptides are one possible candidate and immune responses can be observed after vaccination of patients with different types of tumors (Vonderheide et al., 2004; Brunsvig et al., 2006). In general, no serious toxicities were observed in any of these trials. Moreover, these trials have shown that it is possible to mount peptide-specific immune responses in vaccinated cancer patients. It is still too early to analyze the potency of these vaccines, but preliminary data suggest a possible benefit from these vaccinations. A potential drawback with using one single or a few peptides for vaccination is the outgrowth of tumor cell clones that down regulate the antigen and therefore escape from the immune system.

### Adoptive T cell therapy

A quite attractive albeit relatively cumbersome method for treating patients in an antigen-specific manner is the generation of antigen-specific T cells for further adoptive transfer. Generally, for adoptive T cell therapy, several criteria have to be met for it to be successful. Primarily, sufficient numbers of antigen-specific T cells have to be generated in vivo. These T cells have to home to the tumor and finally have effector functions such as lysis or cytokine secretion to destroy the tumor.

Generally, for adoptive transfer of T cells it is necessary to obtain PBMC or tumor infiltrating lymphocytes (further referred to as TIL) from the patient, isolate the $CD8^+$ T cells and expand them *in vitro* in an antigen-specific manner. There are a number of different ways to culture antigen-specific T cells *in vitro*. Briefly, one can use peptide-pulsed dendritic cells as natural antigen-presenting cells on one hand or so-called artificial antigen presenting cells on the other hand. The latter are based on either cells or on magnetic beads or liposomes as cellular systems (Kim et al., 2004). Following the *in vitro* culture, the T cells are infused back into the patient, where they traffic to the tumor sites (Yee et al., 2002; Meidenbauer et al., 2003) or kill the infected cells.

People have studied the effect of transferred lymphocytes on a growing tumor or virally infected cells since the 1970s, and so far, this treatment has been used for patients with viral infections, such as HIV (Brodie et al., 2000) (Riddell and Greenberg, 2000), CMV (Riddell et al., 1994; Walter et al., 1995) or EBV (Heslop et al., 1994, 1996; Haque et al., 1998; Savoldo et al., 2001, 2002), as well as cancer patients such as malignant melanoma patients (Rosenberg et al., 1988; Dudley et al., 2002a,b; Rosenberg and Dudley, 2004; Yee et al., 2002).

Greenberg's group was one of the first, to study the role of $CD8^+$ T cells in adoptive transfer more in detail. Their studies have shown that it is not only necessary to have cytolytic T cells available *in vivo*, but also cytokines like IL-2 (either injected as adjuvant or secreted by "helping" $CD4^+$ cells) which lead to proliferation and thus expansion of the transferred T cells *in vivo* (Greenberg, 1986). The specificity of the T cells in the initial studies declined during several rounds of non-specific in vitro stimulation with IL-2 and anti-CD3 antibody (Crossland et al., 1991), a frequently seen problem in an unspecific setting. However, this problem was addressed in subsequent studies on CMV positive bone marrow transplant recipients, where the T cells were stimulated with anti-CD3 antibody, IL-2 and peptide transfected fibroblasts. For injection, T cell clones were selected based on their specific lytic capability (Walter et al., 1995).

A method to isolate TIL from patients, expand them *in vitro* and reinfuse them back into patients was first described by Rosenberg (Rosenberg et al., 1986; Topalian et al., 1987). Consistent with the findings from Greenberg et al., this group has also injected IL-2 together with tumor-specific T cells. They have been able to show remarkable success in the treatment of single patients with late stage melanoma. One patient showed a partial remission for more than 24 months and five more for shorter periods, although autoimmune reactions against normal melanocytes were detected in some of the patients (Dudley et al., 2002). In a different approach, the same group showed the regression of large melanomas in a single patient, although after an initial period of tumor regression, the tumor grew out due to a loss of HLA-A2 expression.

A disadvantage of this method, as opposed to vaccination with whole tumor cells as mentioned above, is that the target has to be known exactly to be able to generate T cells directed only against the transformed cells. On the other hand, this feature renders the reinfused T cells extremely specific, which minimizes side effects, although a selection process occurs that sometimes makes long-term therapy impossible (Rosenberg et al., 2003).

Another potential problem encountered in adoptive T cell therapy is the tolerance generated against tumor antigens (which are expressed as normal self antigens), which limits the number and function of tumor reactive T cells. In a recent study, it was shown in a mouse model of $CD8^+$ T cell tolerance that IL-15 instead of IL-2 could be used to rescue tolerized T cells and functionally restore them (Teague et al., 2006).

### DNA vaccination

DNA vaccination includes naked DNA plasmids encoding tumor antigens under the control of a constitutively active promoter. The immune response to DNA vaccines is a multi-step event: When the plasmids are delivered into the host (e.g. via a helium driven "gene gun", with a conventional needle or by topical application), most of them are directed into host cells at the site of injection such as dendritic cells. There, the protein is processed by the cells and presented on the cell's MHC class I complexes and is also released and

taken up by antigen presenting cells, which can initiate the immune response via direct and cross presentation on their MHC class I and II molecules (Prud'homme, 2005; Yu and Finn, 2006). There are also immunostimulatory molecules such as IL-2 that are co delivered together with the vaccine (either as protein or also as DNA) to enhance the immune response. Natural enhancers such as CpG motifs can also be included in the vaccine. The CpG motifs help to activate the innate immune system by binding to TLR, which leads to the secretion of a variety of cytokines and chemokines (Schneeberger et al., 2004; Sawamura et al., 2005).

First promising results from phase I clinical trials using DNA vaccines are reported for the treatment of HPV associated cervical cancer and anal dysplasia (Klencke et al., 2002; Sheets et al., 2003). Palefsky and colleagues used a vaccine called ZYC101, a plasmid DNA, which encodes for multiple HLA-A2-restricted epitopes derived from the HPV-16 E7 protein to treat patients with high-grade anal dysplasia. Three out of 12 subjects showed partial histological responses, which means a switch from high-grade dysplasia at the beginning of the trial to low-grade dysplasia after the treatment. Furthermore, 10/12 patients had lasting immune reactions against the peptides, as assessed by ELISPOT assay (Klencke et al., 2002). The same vaccine was used for a group of patients with high-grade intraepithelial cervical neoplasia. In this phase I trial, the investigators found a complete reversion of the initial histological findings in 5/15 women and a T cell response in 11/15 women, while there were no serious adverse reactions (Sheets et al., 2003).

### Dendritic cell-based vaccination

Dendritic cells (DCs) are the most potent professional antigen-presenting cells at the interface between innate and adaptive immunity, with the ability to initiate and maintain primary immune responses and activate many effector cells such as NK cells, T cells, B cells and NKT cells (Conrad and Nestle, 2003). DCs normally reside in tissues in an immature form where they capture antigens and in response to inflammatory stimuli, mature and migrate to lymph nodes to induce protective immunity (Banchereau and Steinman, 1998). The potent ability of DCs to activate as well as inhibit immune responses makes them one of the best candidates for vaccines for many types of immune mediated diseases but also in anti-tumor immunity. Furthermore, studies in mice have shown that *ex-vivo* generated DCs can induce antigen-specific T cell immunity and are superior to other types of vaccines (Inaba et al., 1990; Sornasse et al., 1992; Celluzzi et al., 1996). These studies have formed a foundation for the design of DC-based vaccination trials in humans. To date, more than 60 different clinical trials involving DC vaccines against cancer have been performed. In recent years, many techniques have been developed to generate large number of active dendritic cells from precursor cells such as peripheral blood monocytes as well $CD34^+$ stem cells. There are many parameters to consider in designing dendritic cells for immunotherapy; source of dendritic cells as well as their *ex-vivo* manipulation; source of antigen, antigen preparation, loading and route of administration (Morse et al., 1997; Cerundolo et al., 2004; Figdor et al., 2004; Banchereau and Palucka, 2005; Nestle et al., 2005).

Most of the dendritic cells used so far in human trials have been generated in vitro from either $CD34^+$ bone marrow derived or peripheral blood progenitor cells after culture with different cytokine combinations including tumor necrosis factor (TNF)-, granulocyte-macrophage colony-stimulating factor (GM-CSF), Flt3 ligand, CD40 ligand (CD40L), stem cell factor (SCF), or transforming growth factor (TGF) (Romani et al., 1994; Sallusto and Lanzavecchia, 1994; Bernhard et al., 1995; Mackensen et al., 2000; Maraskovsky et al., 2000; Pulendran et al., 2000; Banchereau et al., 2001; Figdor et al., 2004). Immature DCs derived from monocytes cultured in IL-4 and GM-CSF can be matured further in vitro by a combination of IL-1ß, IL-6, TNF and PGE-2. Other protocols have looked at alternative ways to generate DC and to skew the differentiation of monocytes into dendritic cells with different function and haplotype. As an example, monocytes grown in IL-4 and GM-CSF, are known as IL-4 DCs (Sallusto and Lanzavecchia, 1994; Schuler-Thurner et al., 2002). Similarly, monocytes that encounter IL-15 or TNF are also called TNF-DCs or IL-15 DCs. However, the *in vivo* efficiency of these DCs as compared to "gold standard" method (grown in GM-CSF and IL-4 and maturation with IL-1ß, TNF, IL-6 and PGE-2) needs to be addressed in detail in clinical studies. Enhancing DC migration by chemokines or toll like receptors are also being studied (Cella et al., 1997).

Dendritic cells have to be loaded with the right tumor antigen in order to effectively stimulate antigen–specific $CD4^+$ and $CD8^+$ T cells. The most widely used vaccines are DCs pulsed with MHC class I and class II restricted peptides derived from a known tumor-associated antigen (TAA) (Gilboa, 1999; Figdor et al., 2004). This application is limited to use in patients who express a defined HLA haplotype and requires the determination of the T-cell epitopes from the tumor antigen.

Other techniques that do not require the definition of the tumor associated epitopes or HLA haplotype of the patients include use of full-length proteins or tumor lysate (Berard et al., 2000; Chang et al,., 2000; Figdor et al., 2004; Neidhardt-Berard et al., 2004), which allow the induction of immune responses against different epitopes (Goldszmid et al., 2003). In addition, transfection of DCs with RNA, another antigen delivery method, has the advantage that it encodes for a broad spectrum of tumor antigens, but it can also encode for auto-antigens. (Boczkowski et al., 1996, 2000). It has been shown that DCs transfected with RNA from the tumor (mRNA) are able to induce potent antigen and

tumor-specific T-cell responses directed against multiple epitopes (Su et al., 2003).

It is important to note that DC vaccines used so far have been safe with minimal side effects (Mackensen et al., 2000; Banchereau et al., 2001; Jonuleit et al., 2001; Schuler-Thurner et al., 2002). Although the results have been variable, there is evidence that vaccination with DCs can induce antigen-specific T cell responses even in patients with advanced cancer (Schuler-Thurner et al., 2002). Recently, a survival benefit for a subgroup of patients with prostate cancer has been demonstrated after a dendritic cell vaccination demonstrating the potential of this therapeutic approach (Small et al., 2006).

### Heat shock proteins

Heat shock proteins are a group of proteins which are expressed in cells constitutively at low levels (see (Srivastava, 2005) for a review on the role of HSP in cancer immunotherapy). Under environmental stress such as increasing temperature or hypoxia, their expression is up-regulated. They serve as chaperons, which means that they help proteins to fold correctly. When the cell is exposed to stress, proteins as well as tumor antigens bind to the chaperons, and form complexes, which can be isolated from cell lysates. Dendritic cells have a receptor for HSP (CD91), and HSP-peptide complexes (HSPPCs; HSP or peptide alone are not effective) are internalized by receptor-mediated endocytosis, after which they induce maturation of the dendritic cell. In specialized compartments inside the cell the peptides are released and subsequently bind to new MHC molecules. They can either enter the classical pathway towards MHC class II mediated presentation to $CD4^+$ T cells as well as be cross presented on MHC class I molecules to $CD8^+$ T cells (Srivastava, 2002, 2005; Parmiani et al., 2004).

HSPPC are unique for the specific tumor they are isolated from because they display the particular antigen repertoire, which can only be found in that tumor, a mechanism which is based on the varying degree of mutations in tumors. This phenomenon has been called "antigenic fingerprint", which has already been applied to developing a vaccine strategy (Oncophage®), and is being tested in large multi-center studies. A portion of each patient's tumor is excised, sent to the manufacturer, the HSPPCs are isolated and the vaccine is then used to vaccinate the patient. However, results from a phase III trial testing this approach for patients with advanced melanoma have shown limited success (Richards et al., 2006).

### Future perspectives

During the last decade, many different approaches to cancer immunotherapy have been evaluated. The clinical studies done so far have shown that the majority of approaches to cancer immunotherapy are safe and have no major side effects. The objectives are to see whether the vaccination strategy is able to stimulate systemic anti-tumor immune responses and whether the induction of such responses correlates with T cell infiltration and/or clinical outcome. The T cell responses specific for defined tumor antigens can be monitored by different approaches, such as ELISPOT assay, Intracellular cytokine staining, tetramers, proliferation assay, ELISA (enzyme linked immunosorbent assay), cytotoxicity assay and real time PCR for cytokines (Asai et al., 2000; Banchereau et al., 2001; Schuler-Thurner et al., 2002; Schuler et al., 2003). Delayed type hypersensitivity reaction (DTH) has also been done for some vaccine studies (Fong and Engleman, 2000). However, many problems remain to be resolved. Obviously, all of the parameters mentioned above require further standardization and carefully controlled clinical trials are required to determine the best and most optimal conditions for inducing portent anti-tumor immunity; optimal source of antigens for clinical application, the optimal way of loading and route and frequency of vaccination. Standardization of all these procedures will not only determine the efficacy of any cancer vaccination, but will allow for a comprehensive comparison of the clinical studies and their results in the future.

Finally, future challenges lie in combining immune-based therapies with chemotherapy, radiation or anti-angiogenic therapy, which might prove to be more beneficial for treatment of cancer. A number of different groups including ours are currently investigating this field in preclinical models.

*Acknowledgements.* This work has been supported by grants from the Deutsche Forschungsgemeinschaft, Paul Blümel Foundation, Roggenbruck Foundation and the Association for International Cancer Research UK (AICR).

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Accepted December 11, 2006