HSPPC-96 is a protein peptide complex consisting of a 96 kDa heat shock protein (Hsp), gp96, and an array of gp96-associated cellular peptides. Immunisation with HSPPC-96 induces T-cell specific immunity against these peptides; gp96 is not immunogenic per se. The non-covalent binding of gp96 to peptides is neither selective nor restricted to cell types. Thus, the collection of gp96-associated peptides represents the antigenic peptide pool of a cell; this is the basis of the peptide-specific immunogenicity elicited by HSPPC-96. Since the repertoire of antigenic peptides in the cell is different between normal and tumour cells and is also distinct among tumours of the same histology due to the randomness of tumour-specific mutations, a purified sample of HSPPC-96 can only effectively immunise against the tumour from which it originates. The immunisation effect is, therefore, specific to both the individual patient and the tumour type. This true custom-based vaccine has been shown to induce protective T-cell immunity against a variety of tumours in animal models. The major mechanism of action is thought to be the ability of HSPPC-96 to prime peptide-specific MHC class I-restricted CD8+ T-cells by interacting with antigen-presenting cells in a receptor-dependent manner. HSPPC-96 is now being widely tested against human malignancies for which effective therapies do not exist. The major challenges of the human studies are immunological monitoring and the determination of optimal dosing, scheduling and route of administration. HSPPC-96 has been well tolerated at all dose levels. Clinical applications are being addressed by numerous studies including an international, multi-centre, double-blind Phase III trial for the treatment of stage III renal cell carcinoma in the adjuvant setting.

Keywords: cancer vaccine, gp96, heat shock protein, HSPPC-96

1. Introduction

Despite the tremendous advancements in cancer biology research, the main weapons against this devastating disease remain surgery, radiation therapy and the rather non-selective cytotoxic drug therapy known customarily as chemotherapy. With a few exceptions, such as testicular cancer, childhood leukaemia and Hodgkin’s disease, the outcomes of most human malignancies are currently no better than they were three decades ago [1].

The renewed interest in the concept of immunotherapy against cancer is due to the following three principles [2]:

- critics have not yet been able to disprove the concept that tumours are the consequence of failed immunosurveillance by the immune system
tumours are indeed recognisable by the immune system because they express either tumour-specific antigens (such as viral antigens and oncogene products), or antigens that are preferentially expressed by the tumours (such as early embryonic antigens)

- the adaptive immune system can be manipulated or optimised by vaccination, passive immunisation or modulation of the immunological climate by systemic therapy with cytokines or other immunomodulating agents

HSPPC-96 was first isolated in a murine fibrosarcoma cell line called Meth A. In the process of identifying tumour specific antigens capable of immunising Balb/c mice to mediate rejection of Meth A [3], it was shown that Meth A-derived gp96 but not gp96 from another tumour or from normal tissues, can immunise mice against challenge with live Meth A tumour cells. Since gp96 is expressed abundantly in both tumour cells and normal tissues, it was thought that tumour specific mutations of gp96 were the basis of the observed tumour-specific immunogenicity [4]. It took nearly 10 years to realise that gp96 exists as a protein-peptide complex and the immunogenicity of gp96, like that elicited by other Hsps, is in fact due to associated peptides [5,6]. No structural mutation of gp96 itself has ever been identified. In addition, it is now known that gp96 is a bona fide protein chaperone and is a member of the Hsp family, which is involved in the folding and unfolding of cellular proteins [5].

This paper aims to examine the principle of immunotherapeutic strategy with HSPPC-96. It will highlight the immunological properties of this molecule and update the experience so far in the clinical development against human malignancies.

2. Mechanism

2.1 HSPPC-96 carries antigenic peptides

gp96 is the most abundant protein in the lumen of the endoplasmic reticulum (ER) [7]. The role of gp96 in facilitating protein folding was suggested initially by the finding that the introduction of misfolded protein in the ER increases the expression of gp96. Like other Hsps, gp96 can interact directly with numerous substrates such as collagen, heparin, immunoglobulin heavy chain and glycoprotein of herpes simplex virus. The broad spectrum of substrates is consistent with the notion that Hsps interact with their substrates loosely through hydrophobic associations [8]. The binding of peptides to gp96 was confirmed by the following studies. The first showed that disruption of HSPPC-96 with a mild acid led to the liberation of peptides, which could be identified by structural analysis as well as immunological assays using peptide-specific cytoytic T-lymphocytes (CTL) activity as a read-out [5,9,10]. Additionally, gp96 isolated from cells containing known antigens (viral antigens, bacterial antigens or other model antigens) were able to immunise mice against these antigens; this was strong evidence that antigen-specific peptides were present in gp96 preparations [9-12]. Finally, it was found serendipitously that heat treatment of gp96 allowed the protein to bind with exogenous peptides, which could be measured by gel electrophoresis or other biophysical means [13]. By this method, along with cross-linking, protease mapping and microsequencing, a minimal peptide-binding site of gp96 was recently defined [14].

Despite these advances, several important questions remain to be answered. The stoichiometry of gp96 to peptide binding is still unclear. Also, although gp96 does bind to ATP and has intrinsic ATPase activity, ATP has not been shown to affect peptide binding to gp96 in vitro (Z Li, unpublished). All efforts so far to unload gp96 in another physiological way have not met with much success. Therefore, it is still unclear what prompts peptide dissociation in vivo. Related to this, it is also unknown how the peptides associated with gp96 are eventually transferred to MHC class I molecule in the cell [15].

2.2 HSPPC-96 interacts with antigen-presenting cells

HSPPC-96 immunisation has several unique features. It operates independently of adjuvant in mouse models [3]. Moreover, the amount of peptide in the complex required to elicit T-cell immunity is several orders of magnitude less than what would be required if free peptides were used alone [16]. The immunisation effect of HSPPC-96 is also exquisitely dependent on phagocytic cells [17]. These features together suggest that HSPPC-96 might bind to a receptor-like molecule on the surface of professional antigen-presenting cells (APC) which then present gp96-bound peptides to induce optimal T-cell priming [18]. Indeed, it was found that soluble gp96 can stimulate dendritic cells, which are one of the most powerful APC types, to secrete pro-inflammatory cytokines and to upregulate the...
expression of co-stimulatory molecules such as CD86 and MHC class II [19,20]. gp96 was shown to bind some receptor-like molecules on the surface of APCs in a saturable and competitive manner [21]. By using affinity purification with a gp96-conjugated column, Binder et al. were able to isolate a cell surface ligand (receptor) for gp96 from a macrophage cell line, RAW 264.7, to homogeneity [22]. A polyclonal antibody raised against this protein can block the representation of gp96 chaperoned peptide to MHC class I, providing strong evidence that this could well be the main method of gp96-mediated peptide delivery to APCs. Microsequencing of this molecule by mass spectrometry confirmed it to be CD91, a protein known as α2-macroglobulin receptor or low density lipoprotein-related protein (LRP). Further evidence to support CD91 as a receptor for gp96 is that α2-macroglobulin, a previously known CD91 ligand, inhibits macrophages from re-presenting gp96-chaperoned antigenic peptides [22]. However, CD91 is a complex molecule and its mechanism of action may not be so straightforward. There is evidence that CD91 may not be the only surface molecule that interacts with gp96. It has also been found that gp96 binds less efficiently to APC from mice that have homologous deletion of CD36, an 88 kDa scavenger receptor, suggesting that CD36 may be another receptor for gp96 [23].

2.3 HSPPC-96 primes CD8+ T-cells

HSPPC-96 immunisation can prime CD8+ T-cells against many intracellular antigens, such as tumour, viral, minor histocompatibility and bacterial antigens. The depletion of various subsets of T-cells before and during the immunisation period with Meth A-derived HSPPC-96, led to the conclusion that the priming of Meth A tumour-specific CD8+ T-cells by HSPPC-96 is independent of help from CD4+ T-cells [17]. Interestingly, HSPPC-96 fused with a model peptide can also prime CD8+ T-lymphocytes in a CD4+ T-cell independent manner [24,25]. It is important to make a distinction between direct and cross priming of CD8+ T-cells. Direct priming strictly means direct activation of naïve T-cells by antigen expressing target cells, which mandates the presence of antigen in the context of the same MHC molecules in both the T-cells and the target cells, in addition to the appropriate co-stimulatory molecules. Cross priming was originally described as the priming of CD8+ T-cells by target cells that do not share the same MHC alleles as the antigen specific T-cells [26]. In this case, the antigens from the target cells have to be released exogenously and then cross-presented to the T-cells by APCs which possess the proper MHC molecules. Recent data have confirmed that cross priming is the predominant, if not exclusive, mode of T-cell activation. Antigens from non-haematopoietic cells can be released and then taken up and presented by the professional APCs to T-cells [27]. The mechanism of cross priming in the case of gp96 is not entirely clear: One possibility is the release of HSPPC-96, either from cell death or stress [28]. The extracellular HSPPC-96 may then interact with APCs through a specific gp96 receptor such as CD91 or CD36. Two events then ensue. First, the peptides of HSPPC-96 are unloaded within the cell and eventually presented on MHC class I molecules. Second, APCs are activated to the ‘priming mode’ due to increased cell surface expression of co-stimulatory molecules and the secretion of pro-inflammatory cytokines.

2.4 HSPPC-96 primes CD4+ T-cells

Can HSPPC96 present the peptides to MHC class II pathway and thereby activate CD4+ T-cells? Sequencing by Edman degradation of the pooled peptides from gp96 showed that the average length of gp96-associated peptides is around 12 amino acids (Z Li, unpublished), although longer peptides of over 20 amino acids can be successfully charged to gp96 in vitro. Therefore, it is conceivable that MHC class II, which has the capacity to bind to longer peptides, may present some of the peptides associated with gp96. Thus far, however, researchers have not identified any MHC class II-associated peptide epitopes from HSPPC-96. The only evidence that HSPPC-96 may be able to prime CD4+ T-cells comes from functional studies. Meth A-derived HSPPC-96 generates CD4+ T-cells in immunised mice. In addition, APCs pulsed with Meth A HSPPC-96 can stimulate a Meth A-specific CD4+ T-cell clone to produce cytokines (Matsutake T and Srivastava PK, personal communications). At high doses, HSPPC-96 immunisation activates a subset of CD4+ T-cells that have a suppressive phenotype [29]. It is unclear; however, whether or not these T-cells are antigen-specific.

2.5 Non-immunological function of HSPPC-96

Surprisingly, it has been shown that gp96 also binds to platelets [30]. Although the binding does not seem to lead to any functional consequences in platelets, such as adhesion or activation, it is prudent to keep in mind
that many possible functions of HSPPC-96 have not been completely characterised.

3. General strategy for clinical applications

Unlike traditional cancer drugs, HSPPC-96 vaccine is individually based and truly tailored towards an individual tumour from an individual patient [31]. As early as the 1940s, it was appreciated that effective tumour immunity is exquisitely specific, i.e., using two histologically identical tumours in mice, A and B, tumour A could only immunise against itself, not against tumour B and vice versa [28]. This demonstrated clearly that tumours are antigenically distinct from one another. We can now speculate that this observed phenomenon is most likely due to the difference in peptide pools as a result of random mutations in the transformed cell. Depending on the different types of tumour, the grade, differentiation stage or genetic background, HSPPC-96 should also be expected to be individually unique, due to the different composition of peptides associated with gp96. Therefore, in order to generate effective immunity against tumour A, HSPPC-96 has to be delivering the peptides specific to tumour A, not tumour B.

The general strategy is thus given the acronym ‘OTHER’, meaning, stepwise, (a) Obtain tumour (by surgery or other means) from the patient; (b) HSPPC-96 extraction in the laboratory; (c) Return (or reinjection) of HSPPC-96 to the patient. Since HSPPC-96 purification is now standardised and tumours are often routinely excised for diagnostic or therapeutic purposes, this truly custom based and unprecedented approach has become feasible. More than 200 patients have now been tested by this OTHER approach worldwide.

4. Dosage and schedule

Drug development for use in human cancer treatment must progress through different phases. The primary goals of each phase are:

- Phase I: to define maximum tolerated dose (MTD)
- Phase II: to monitor efficacy
- Phase III: to define long-term risks and benefits

HSPPC-96 is an autologous protein-peptide complex. It is not directly cytotoxic, so MTD may not be definable in this case. In addition, high dose is clearly not optimal for HSPPC-96, as shown in animal studies [29]. Using HSPPC-96 purified from a Meth A fibrosarcoma, it was found that the optimal dose to immunise mice against Meth A challenge varied depending on the route of administration. The optimal doses for intradermal, sc. and ip. route were 1 µg, 10 µg and 50 µg respectively [29]. As mentioned previously, doses higher than the optimal dose can even cause antigen-specific immunosuppression in a manner that is still unclear, although CD4+ T-cells seem responsible for the suppression [29].

To determine the optimal human dose of HSPPC-96, a Phase I study was performed using patients with stage IV renal cell carcinoma. A total of 42 patients were initially enrolled in this study, of whom 38 had enough HSPPC-96 purified from resected primary tumours to be included in the study. The study looked at three different doses, 2.5, 25 and 100 µg of autologous tumour-derived HSPPC-96 given id. weekly for a total of four injections. There were no significant toxicities observed, even at the 100 µg dose level. From this preliminary trial, the dosage of 25 µg per injection seemed to be optimal. There were significantly more treatment failures in both the 2.5 µg and 100 µg groups, underscoring the fact that HSPPC-96 does have a narrow therapeutic window [32]. A similar study is being done for gastric cancer patients who have had gastric surgery with curative intent. As of May 2000, 5/6 patients progressed after immunisation with 2.5 µg id. weekly, whereas 3/4 patients remained tumour free at dose level of 25 and 100 µg per injection [33].

The schedule of HSPPC-96 administration is also not yet optimally defined. In the preclinical animal models, two weekly injections of tumour-derived HSPPC-96 led to protection against subsequent tumour challenge. In contrast, tumour-bearing animals have to be vaccinated with HSPPC-96 more often in order to slow down the tumour growth. There are at least two reasons to explain this difference [34]. First, T-cells from tumour-bearing animals may be tolerant to the tumour antigens since tumour cells do not express co-stimulatory molecules. Second, too great a tumour burden may out-weigh the antitumour responses. Therefore, it is conceivable that multiple injections of HSPPC-96 will have to be given, even in the adjuvant setting, since microscopic metastases are common in cancer patients even when the primary disease is no longer detectable.
5. Safety and tolerability

Theoretical risks of HSPPC-96 injections are:

- endotoxin-like reaction due to the secretion of pro-inflammatory cytokines such as TNF-α as a result of the activation of APCs [19,20]
- autoimmune phenomena as a consequence of T-cell activation against the self-peptides in HSPPC-96

Studies have shown so far that these potential side effects do not occur: HSPPC-96 has been shown to be very safe and well-tolerated. In the first pilot trial [35], 16 patients with various advanced malignancies (seven gastrointestinal tract, one pancreatic, two hepatocellular, three thyroid, one breast, one mesothelioma and one unknown primary), which had become refractory to established therapies, were treated with autologous tumour-derived HSPPC-96. Patients were injected sc. with 25 μg autologous HSPPC-96 once a week for four weeks. After each vaccination, patients were carefully monitored clinically and serologically. No unacceptable toxicities or autoimmune phenomena were observed. Three patients reported mild hot flushes between 30 - 48 minutes after immunisation, without the need for medical intervention. Of these, two experienced hot flushes after each immunisation, while one experienced them again only after the second immunisation. In four patients, pain or fever occurred during the immunisation period, however their onset was unrelated to the timing of immunisation and the events were attributed to tumour progression. None of these patients mounted significant titre of the following auto-antibodies: antinucleoprotein antibody, antibody to dsDNA or ssDNA, antibodies to mitochondria, thyroglobulin, microsomes, perinuclear or cytoplasmic antigens after HSPPC-96 immunisation. One patient died 4 days after the second immunisation, which was determined to be due to the progression of his disease. Thus, at this point there is no evidence of acute HSPPC-96 induced side effects due to self-destructive immune reactions.

Similarly, no significant adverse effects have been observed in subsequent trials on renal cell carcinoma, gastric cancer, colorectal cancer, melanoma, pancreatic cancer or non-Hodgkin’s lymphoma.

6. Clinical trials

There are a total of 11 clinical trials on HSPPC-96 to date. These trials are classified into three categories. First is a pilot trial that has been completed and reported, which involved 16 patients with various cancers treated with 25 μg HSPPC-96 [35]. The second category includes five trials that are either closed (pancreatic cancer), or enrolment completed (dose-defining trial on stage IV renal cancer; HSPPC-96 plus IL-2 for renal cancer; dose-defining studies for colorectal cancer and melanoma). The final category includes five active trials that are still enrolling patients. They are:

- one Phase III adjuvant therapy study for renal cell carcinoma
- several Phase II studies for low-grade non-Hodgkin’s lymphoma, gastric cancer, sarcoma
- a recently re-launched pancreatic cancer trial

It is important to point out that the primary objectives of all of the trials except the Phase III renal carcinoma trials are feasibility and toxicity. Efficacy is not the end point for these studies. In addition, the follow-up for all studies is still not long enough to be conclusive. Therefore, it is premature and even prohibitive to comment on the efficacy of HSPPC-96 at this early stage of clinical development.

To comply with the ethical and scientific standard, only published results will be summarised.

6.1 The HSPPC-96 pilot study

In the pilot study, all patients had refractory metastatic disease and had exhausted other therapeutic options [35]. Immunisation was performed weekly using 25 μg HSPPC-96 per dose. Of interest, six out of twelve patients had increased MHC class I-restricted IFN-γ-producing CD8+ T-cells specific against autologous tumours or tumour membranes as measured by an IFN-γ ELISPOT assay. Moreover, eight out of thirteen patients had expanded NK cell population by flow cytometric analysis of CD16+ and CD57+ cells. Clinically, four patients experienced stabilisation of their disease for 3 - 7 months although the details and site of extent of diseases are not available. One patient with advanced hepatocellular carcinoma was found to have extensive tumour necrosis of over 50% of the primary tumour after the third injection with HSPPC-96, accompanied by a strong and specific
anti-HCC CD8+ cell response. With exception to this patient, no significant tumour lysis was observed in other patients. These data suggest that HSPPC-96 is able to stimulate T-cell immunity even in patients with advanced stage malignancies.

6.2 Renal cell carcinoma

Renal cell cancer is a good model for immunological interventions involving the use of tumours because the primary tumour burden is often large and the initial diagnosis and treatment are radical nephrectomy, allowing for easy purification of HSPPC-96. Moreover, although there is no satisfactory treatment for this disease, spontaneous remission has been observed and a subset of patients can be cured with IL-2 and/or interferon.

The first Phase I renal cancer trial involved a total of 42 stage IV patients treated in three dosage groups (2.5, 25 and 100 µg per injection) [32]. A total of 38 patients were evaluable. Clinical activity has been demonstrated in 24% of patients for over 14 months, which compares favourably to the other available therapies for this population of patients. Full details in the Phase I trial have not yet been published. A total of 70 patients have been enrolled in a Phase II trial [36]. All patients received four weekly 25 µg id. injections of HSPPC-96, followed by two additional 25 µg doses at two week intervals. Responding or stable patients were continued with four additional doses of 25 µg at two week intervals; those patients who exhibited disease progression continued with vaccine every two weeks, plus a 5 day per week course of 11 million units of IL-2 delivered subcutaneously for four consecutive weeks. As reported in October 2000 [37], 25 patients have completed the therapy, of whom 8 patients (32%) have continued on HSPPC-96 therapy alone. Of these eight, one patient is in complete remission, one has had a partial response and six have stable disease. Other patients have progressive disease requiring addition of IL-2. Since this study is not yet complete, it remains unclear whether combination of IL-2 with HSPPC-96 is effective for this population.

A multi-institute worldwide randomised Phase III study was launched in the summer of 2000 to study the effect of autologous tumour-derived HSPPC-96 vaccination in stage III renal cell cancer patients who have undergone curative surgery. Relapse-free survival and overall survival will be the sole objectives of this study.

6.3 Pancreatic cancer

HSPPC-96 was tested in a Phase I clinical trial for patients with pancreatic cancer [36]. Patients who had primary, resectable pancreatic cancer were enrolled in the trial. After surgery to remove their primary tumour, patients were treated with 5 µg of vaccine intradermally. It was not possible to test higher dose levels due to the small size of tumours in these patients. The vaccine was prepared successfully from 5/15 pancreatic cancer samples. It was not possible to prepare HSPPC-96 from the remaining specimens due to the presence of proteolytic enzymes in the pancreatic tissue that break down proteins, including Hsps. Tumour-specific T-cell mediated immune responses were demonstrated in two of the five patients. These two patients were treated in 1997 and are still alive and disease free in November 2000 (Lewis J, personal communication). A third patient was known to be free of disease at 12 months and was subsequently lost to follow-up. The fourth patient is alive with recurrent disease at 10 months and the fifth patient died seven months after starting HSPPC-96 treatment. Due to these encouraging clinical results, the pancreatic trial has now been expanded to treat more patients.

6.4 Gastric cancer

Patients with a diagnosis of gastric carcinoma underwent gastric surgery with curative intent [33]. At least 1.5 grams of resected tumour was procured from each patient and HSPPC-96 was purified. Beginning four to eight weeks after surgery, patients were vaccinated intradermally four to nine times in either weekly or two-week intervals with either 2.5, 25 or 100 µg of HSPPC-96. Vaccine preparation was successful in 12 out of 15 patients, showing the greater feasibility of vaccine preparation from resected gastric carcinoma than pancreatic cancer. As of May 2000, six patients received 4 x 2.5 µg, two patients 4 x 25 µg, one patient 8 x 25 µg and one patient 9 x 100 µg HSPPC-96. All five stage IIIb and IV patients and one stage IIIa patient developed tumour progression after a median of 6.5 months after surgery. Four patients with tumour stages II and IIIa remain free of disease. Five out of six patients with tumour progression were in the lowest vaccine dose level of 2.5 µg, while the three of four patients remaining disease free were vaccinated with 25 µg and 100 µg vaccine doses.

The vaccination did not induce increased frequencies of CD8+ T-cells reacting with autologous monocytes. HSPPC-96 vaccination also did not lead to increased frequencies of patient CD8+ T-cells reactive with
certain defined tumour peptide antigens from CEA, p53 or Her2/neu. However, an increase of NK-like cytotoxicity could be observed in two of the four patients with no evidence of disease. Clonal expansions of CD8+ T-cells taken from patients during vaccination are currently being analysed by T-cell receptor (TCR)-Vβ-spectrotyping.

6.5 Melanoma
In a Phase I study, 36 patients were enrolled after resection of a > 3cm melanoma metastasis [41]. Of these patients, 26 were graded stage IV and 10 were graded stage III, 30 patients had had prior systemic therapy and 10 had indicator lesions. HSPPC-96 was purified in sufficient quantities for vaccination from samples weighing as little as 2 mg. Patients were given id. vaccination at doses of 2.5, 25 or 100 µg weekly for four weeks. Patients showed no serious toxicities to therapy. As of April 2000, one patient at each dose level had stabilisation or mixed response after initial progression in nodal or lung metastases, all lasting over seven months. Eleven of the stage IV adjuvant patients (eight of whom were stage IV M1B) remained disease free a median of 11+ months. With 9 month median follow-up, 19 patients remain on study with 29 (80%) alive. In vitro studies to assess antitumour immunity elicited by HSPPC-96 vaccination in these patients are ongoing. Previous in vitro data have shown that HSP70 purified from human melanoma cells was able to induce MHC class I-restricted antitumour CTL activity when presented to MHC-restricted APCs, offering supportive evidence for a potential in vivo CTL response [42].

7. Expert opinion
HSPPC-96 is truly a personalised tumour vaccine. Being distinct from the traditional chemotherapeutic agents, HSPPC-96 is made from a patient’s own cancer and is generally not in itself cytotoxic. The underlying mechanism is to stimulate antitumour immune responses against the tumour-specific peptides chaperoned by the ubiquitous Hsp, gp96. Preclinical studies have shown that HSPPC-96 is broadly effective against a variety of tumours. The clinical development of this unprecedented vaccine has met with several unique challenges. First, can personalised vaccine be reliably produced and delivered? The answer to this question is certainly yes. The manufacturing of HSPPC-96 is highly reproducible, predictable and can eventually be automated. Second, what are the best surrogate immunological markers to determine successful HSPPC-96 immunisation [34]? There are no answers to this question. Clearly, measuring antitumour T-cell response is not enough, as the functions of APCs and NK cell components are also important for the therapeutic effect of HSPPC-96. What are the contributions of antibody, or B-cell responses? What are the roles of other components, such as complement, phagocytic cells and systemic or local cytokines? To summarise, without a proper surrogate marker, the efficacy of HSPPC-96 can only be judged by clinical response. This also needs to be better defined, since HSPPC-96 itself is not directly cytotoxic.

Fourth, how should the clinical response with HSPPC-96 vaccination be evaluated? It is clear from animal studies and many of the ongoing clinical trials that the immune responses stimulated by HSPPC-96 are blunting tumour growth but tumours do not generally melt away. The hope, therefore, is to convert cancer into a manageable chronic disease, which requires new rules and regulations and new ways of thinking in order to measure the success of a biological therapy such as immunotherapy with HSPPC-96. Finally, how can immunotherapy with HSPPC-96 be incorporated into existing cancer strategies, such as chemotherapy and radiation therapy? Both chemotherapeutic agents and radiation are known to cause bone marrow suppression. How, then, can immunological competence of the patient be ensured? How much immunosuppression is ‘safe’ and at what level does it become prohibitive for active immunisation with HSPPC-96? These questions await further research.

Nevertheless, the principles learned in rodents about the immunological features of gp96 are so far holding firmly in other animals ranging from xenopus to humans [38]. The gp96 molecule itself is among the most conserved molecules in these animals. It is therefore certain that HSPPC-96 will find a way into the list of emerging arsenals in the fight against human malignancy [40].

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HSPPC-96: a personalised cancer vaccine


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