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Current concepts of immune based treatments for patients with HCC: from basic science to novel treatment approaches

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Abstract

The recent approval of two immune checkpoint inhibitors for the treatment of malignant melanoma has sparked great interest by physicians and basic scientists searching for novel therapeutics for GI cancer. Chronic inflammation is recognised as a major risk factor for the development of hepatocellular carcinoma (HCC) and makes this type of cancer a potentially ideal target for an immune based treatment approach. Further evidence for a critical role of immune responses in patients with HCC is derived from the fact that immune signatures and profiles predict patients' outcome as well as the fact that tumour-induced spontaneous antitumour immunity can be detected. In addition ablative therapies can lead to changes in the number, phenotype and function of different immune cell subsets, which correlate with patients' survival. Various HCC-specific mouse models have been developed, which improve our understanding of hepatocarcinogenesis and tumour-immune cell interactions, and lead to the development of novel immune based treatment approaches, which are currently being evaluated in preclinical and in early clinical settings. Immune checkpoint blockade along with adoptive immune cell therapy and vaccine approaches are currently being evaluated either alone or in combination with other treatments. Here, we provide an overview for the rationale of immunotherapy in HCC, summarise ongoing studies and provide a perspective for immune based approaches in patients with HCC.

INTRODUCTION

According to the 2014 World Cancer Report liver cancer represents the fifth most common cancer in men with 554 000 new cases per year (ninth most common cancer in women with 228 000 cases per year). Given the high fatality of liver cancer (overall mortality-to-incidence ratio of 0.95) and an estimated number of 746 000 liver cancer related deaths in

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2012 this type of cancer represents a major health burden.[1] Curative treatment options only apply to patients with limited tumour burden and include surgical options and radiofrequency ablation.[2]

It is well accepted that a deregulated microenvironment affects tumorigenesis. This is based on the observation that chronic inflammation is associated with high incidence of cancer.[3] Studies using different murine tumour models indicate that members of the interleukin (IL)-6 family are important mediators linking inflammation and cancer by activating the JAK-signal transducer and activator of transcription 3 (STAT3) SHP-2-Ras- ERK and PI3K-Akt pathways, through which they induce cell proliferation, survival, extracellular matrix (EMT)/invasion, metastasis, angiogenesis and inflammation.[4]

Hepatocellular carcinoma (HCC) represents the best tumour type to study the relationship between tumour cells and inflammatory cells since a majority of HCC arises most frequently in inflammatory livers. Major risk factors for HCC include HBV, HCV, diabetes, obesity, excess alcohol consumption and metabolic diseases, all of which contribute to fibrosis and cirrhosis, a preneoplastic condition for the development of HCC. One plausible hypothesis is that an altered liver microenvironment, through reprogramming of the inflammatory milieu, may contribute to HCC. Thus, studying liver immunology in HCC may improve our understanding of immunological mechanism during hepatocarcinogenesis, and will ultimately lead to novel and better treatment strategies for this deadly disease.

Prophylactic HBV vaccination programmes are in place and have already been shown to prevent the development of hepatomas in children and young adults in Taiwan.[5] Therefore, HBV vaccines might be considered as the first prophylactic cancer vaccine.[6] Immune studies on the pathogenesis of HCC have been a major focus of research by many scientists in the past. The approval of ipilimumab by the US Food and Drug Administration in 2011 and the very recent approval of pembrolizumab, a second immune checkpoint inhibitor, has sparked great interest in immunological treatment modalities in melanoma and many other types of cancer.[7] With so many negative phase II and III studies in HCC in the past 5 years the next obvious step for clinical investigators is to look at alternate therapy options for patients with HCC based on its immunopathogenesis and the availability of novel Food and Drug Administration (FDA) approved drugs. Here, we summarise recent immunological findings in HCC and provide novel concepts for future directions in the medical management of patients with HCC (figure 1).

Our current knowledge on the immunopathogenesis of HCC is based on epidemiological data and the observation that most patients with HCC also suffer from underlying chronic viral hepatitis infection, animal studies in which HCC arise under different experimental settings and gene expression analysis studies from patients with HCC. It is clearly beyond the scope of this review to summarise the available epidemiological data on HCC and viral hepatitis, which has been elegantly discussed previously.[8] Multiple murine hepatocarcinogenesis models have been developed, but only few can be used to study immunological effects on hepatocarcinogenesis as well as the reverse, the effect of tumours on immune cells and antitumour immunity.

SPONTANEOUS IMMUNITY IN PATIENTS WITH HCC

Although overall rare, a significant number of HCC cases associated with spontaneous regression have been reported in the literature. Interestingly, HCC is among the most common types of cancers with spontaneous regression according to two independent reports.[910] Immune-mediated mechanisms as well as vascular events are discussed as the most common cause. Recently, two cases from patients with HCC have been reported, where discontinuation of an immunosuppressive therapy (given for unrelated autoimmune diseases) led to spontaneous regression of histologically proven disease.[11] A different study describes an increased HCC risk for patients with autoimmune disorders including such without digestive tract involvement.[12] Furthermore, abscopal effects (ie, spontaneous regression of a remote non-irradiated tumour resulting from the effect of irradiation) have been described in patients with HCC after radiation treatment,[13–17] but have also been observed in patients after cryotherapy.[11819] Different biological and immunological mechanisms have been suggested as for how thermal ablation may induce antitumour immunity.[220–22] While no systematic and prospective studies on the induction of tumour-specific immune responses upon local ablative therapies (including cryotherapy and radiofrequency ablation), transarterial chemoembolisation and other ablative therapies have been published so far, various reports demonstrate the existence of tumour-specific T cells, activation of natural killer (NK) cells as well as induction and release of cytokines into peripheral blood in patients with HCC.[323]

IMMUNOSUPPRESSOR MECHANISMS

While a lot of evidence exist suggesting that HCC may be a good candidate for immunotherapy one should not oversee that the liver has unique immune regulatory functions that promote the induction of tolerance to antigens encountered locally.[524] Different types of non-parenchymal cells can be found in the liver, which promote tolerance through a variety of mechanisms: The largest macrophage population in the human body can be found in the liver, where they are called Kupffer cells. Other cells include hepatic dendritic cell subsets, liver sinusoidal endothelial cells and hepatic stellate cells. Under physiological conditions these cells protect hepatocytes from bacterial degradation products and pathogen-associated microbial patterns entering the liver through the portal vein.[625] Local immunosuppression by these cells is induced by production of anti-inflammatory cytokines such as IL-10 and TGF-β as well as by expression of PD-L1.[726]

Different immunosuppressor mechanisms can be found in the liver of tumour-bearing individuals and can be potentially subjected to therapy. Different immune cell subsets have been described to suppress antitumour immunity in HCC. Regulatory T cells accumulate in patients with HCC and correlate with their outcome.[827–29] We have shown that these cells can be targeted by low dose cyclophoshamide treatment[91030] and this approach is now widely used in combination with other types of immunotherapy. $CD14^{+}HLA\text{-}DR^{lo}$ myeloid derived suppressor cells (MDSCs) represent a second immune cell subset with potent immunosuppressor function, which accumulates in patients with HCC.[113132] Interestingly, these cells accumulate in the periphery, and in the liver of tumour-bearing mice.[13−1733] Different chemotherapies have been described to target these cells[34] and more specific

approaches using peptide-Fc fusion proteins to eliminate these cells have recently been identified.[35] Another approach to target MDSCs is by blocking STAT3. STAT3 blockade does promote apoptosis in HCC,[36] and there is accumulating evidence that this approach may target MDSCs and other immunosuppressor cells.[37–40] A recent murine study showed that blocking the STAT3 pathway augmented NK cell cytotoxicity against HCC and increased expression of molecules associated with NK cell activation and cytotoxicity.[41] Finally, among other cytokines such as TGF-β and IL-10, IL-17 has also been shown to be an important cytokine with suppressor function, which can be found in serum and tumours from patients with HCC.[4243] We have previously shown that human CCR4+CCR6+Th17 cells suppress autologous $CD8^+$ T cell responses[42] and a recent mouse study demonstrated that IL-17A produced by γδ T cells promotes HCC growth.[44] The fact that IL-6 and STAT3 have recently emerged as main regulators of the differentiation and function of Th17 cells, makes STAT3 an even more interesting target in HCC. A clinical trial evaluating an antisense oligonucleotide inhibitor of STAT3 in patients with HCC is ongoing (NCT01839604).

IMMUNE PATTERNS DERIVED FROM MOLECULAR PROFILING STUDIES

Several studies have employed global molecular profiling of non-tumour liver tissues to dissect molecular changes associated with HCC metastasis and tumour recurrence since they are major factors affecting the outcome of patients with HCC. For example, a comparison between liver tissues from metastasis-inclined microenvironment and those without detectable metastases has revealed that an anti-inflammatory microenvironment condition with a predominant TH2-like cytokine profile that favours a humoral response is linked to HCC metastasis.[45] Colony stimulating factor-1 may be one of the cytokines overexpressed in the liver milieu that is responsible for this shift. The unique Th2-signature is predictive of HCC recurrence following curative resection, revealing the utility of non-tumour derived signatures to predict patient prognosis. Similarly, gene expression profiles of the surrounding non-tumoral liver tissue have also been recognised to be associated with poor prognosis reflecting a risk for de novo HCC development.[46] Again, the poor-prognosis signature contains gene sets associated with inflammation, including those related to interferon (IFN) signalling, activation of nuclear factor-κB, and signalling by tumour necrosis factor α. In contrast, microRNA expression profiling of HCC tissues to determine gender and tumour-related microRNAs has allowed the discovery of the gender-related and tumour-related miR-26, a member of tumour suppressors, to be linked to a poor prognostic HCC subtype.[47] This HCC subtype has a distinct transcriptomic pattern associated with activation of signalling pathways between nuclear factor-κB and IL-6, and is sensitive to adjuvant IFN-α therapy. This study has led to the development of a miR-26 companion diagnostic test for IFN-α therapy in HCC,[48] which is currently being evaluated in a multicentre randomised clinical trial (NCT01681446). A 14 immune-gene signature, which predicts survival of patients with early disease (stages I and II) irrespective of patient ethnicity and disease aetiology includes chemokine genes CXCL10, CCL5 and CCL2, whose expression correlate with $CD8^+$ T cells, NK cells and Th1 cells.[49] Recently, retinoic acid-induced gene-I (RIG-1), an IFN-stimulated gene, has been found to be significantly downregulated in a subset of HCC tissues.[50] Patients with low RIG-1 expression have

shorter survival and poorer response to IFN-α therapy Mechanistically, RIG-I has been shown to enhance IFN-α response by amplifying IFN-α effector signalling via strengthening STAT1 activation.[50] Taken together, these studies indicate that exploring immunopathogenesis of HCC may be effective in developing diagnostic tools to identify a subset of patients with poor prognosis and responding to immunotherapy.

IMMUNOLOGICAL OFF-TARGET EFFECTS OF STANDARD OF CARE IN HCC

Ablative therapies have been shown to induce tumour-specific immune responses and therefore represent potential interesting combination partners for immune-based approaches in HCC as previously described.[23] An alternate option may be to combine immunotherapy with sorafenib. It has been shown that many cytotoxic reagents as well as targeted drugs can have effects on different immune cells.[3451] Sorafenib has been shown to impair the function of dendritic cells thereby impairing induction of tumour-specific T cell responses.[52] A number of investigators have observed a cytotoxic effect of sorafenib on $CD4^{+}CD25^{hi}$ Tregs in peripheral blood[53–55] and tumours,[5657] while an increase of immunosuppressive MDSCs has also been reported in mice.[58] An impairment of NK cell function has also been attributed to sorafenib treatment. In this case it was shown that sorafenib inhibits PI3K and ERK phosphorylation in natural killer cells and thereby their cytotoxicity and IFN-γproduction.[59] The clinical relevance of any of these findings remains a matter of debate. Interestingly, a study by Mulder and colleagues has shown that patients with cancer treated with sorafenib are capable of developing sufficient antibody and cellular immune responses upon influenza vaccination.[60]

ANIMAL MODELS TO STUDY IMMUNOLOGY OF HCC

Different murine HCC models have been used in the past to study immune responses in mice with HCC. From an experimental point of view subcutaneous models represent the most clear-cut model because tumours grow rapidly subcutaneously. These models are widely used to study the effect of different vaccines and other immune-mediated treatments in the preventive and therapeutic setting. However, these models dismiss the role of the local environment and in the case of HCC the effect of cirrhosis and or chronic infection. Orthotopic growth of liver tumours can be achieved by intrahepatic,[33] intraportal[61] and intrasplenic injections.[62] Diethylnitrosamine (DEN) injected mice are widely used and immune responses have been studied in these mice.[3363] Genetically defined liver carcinomas can be generated using transgenic mice,[64] and can also arise in mice injected with genetically engineered bipotential liver progenitor cells[65] or after hydrodynamic injection of plasmids expressing different oncogenes.[66] The analysis of tumour-specific immune responses can be studied in murine HCC models expressing model antigens such as ovalbumin[6768] or SV40 T antigen.[69] However, it should be noted that these tumours are much more immunogenic than tumour antigens arising in naturally arising cancers. Different approaches have been taken in the past to make HCC tumour models better reflect the situation in patients. These include the induction of liver fibrosis,[70] virally induced tumors[69] and non-alcoholic fatty liver disease.[71] Recently, two different HCC models have been

described, in which long-term feeding of a choline-deficient high-fat diet or a conventional high-fat diet induced non-alcoholic steatohepatitis (NASH) in mice and eventually HCC without the need of expressing oncogenes or carcinogen treatments. Mup-uPA mice, in which hepatocyte ER stress is induced by plasminogen activator expression developed typical steatohepatitic HCC, which was dependent on the production of TNF-α by liver macrophages..[72] In an independent study, Heikenwälder's group demonstrated that long-term feeding of a choline-deficient high-fat diet increased and activated intrahepatic $CD8^+$ T cells NKT cells, and inflammatory cytokines, similar to what can be seen in patients with NASH. $CD8^+$ T cells and NKT cells promoted NASH and hepatocarcinogenesis in approximately 25% of the mice within 1 year.[73] In summary, multiple animal models are available which mimic the situation in the patient to different degrees, which can be used to improve our understanding of the immunopathogenesis of HCC, and to develop novel immune-based approaches to treat HCC.

RECENT ADVANCES IN MOUSE MODELS OF HCC

While the number of controlled immunotherapy studies in patients remains unsatisfactorily low and are mainly focused on the use of adoptive cell therapy using non-specifically activated cells, a number of preclinical studies have been published in the past 4 years providing novel and potentially interesting preclinical approaches to treat HCC. Alpha fetoprotein (AFP) vaccines have been successful in priming AFP-specific immune responses and in impairing growth of DEN induced tumours.[7475] While the use of antigen-based vaccines remains debateable as a single agent in the therapeutic setting, this approach may be very valuable in a preventive setting such as patients with advanced cirrhosis and risk for HCC. Antibody treatments using anti-CD137 as single agent demonstrated tumour regression in up to 60% of mice with orthotopic HCCs[76] and the combination of three immunostimulatory antibodies currently in clinical development, anti PD-L1, anti-CD137 and anti-Ox40 demonstrated therapeutic effects against autochthonous liver cancer arising in c-myc transgenic mice.[68] In a different autochthonous setting poly-lactic-co-glycolic acid microspheres followed by booster vaccination with Listeria monocytogene vectors were tested and shown induction of potent antitumour immunity, and complete remission of established tumours and prolonged survival of mice.[77] Closer to potential clinical evaluation are two different approaches, which have recently shown interesting results in preclinical settings. IL-15 treatment resulted in 80–100-fold smaller tumours in mice with DEN-induced tumors[78] and the preclinical development and testing of a chimeric antigen receptor transduced T cell, which recognises a tumour-specific antigen in HCC, has also recently been reported.[79] It should be noted that this adoptive transfer of T cells expressing tumour antigen-targeted chimeric antigen receptors has recently shown some astonishing results in B cell malignancies.[8081] Since this approach is in very early clinical development for the treatment of patients with solid tumours, a number of hurdles still need to be overcome such as finding the right antigen, the correct signalling domain and the best patient population. Finally, so-called 'humanised mouse models', in which human tumour cells are injected into immunocompromised mice ($Rag2^{-/-}\gamma c^{-/-}$) together with human immune cell subsets have been found to enter the tumour immunology area in HCC. In this model human allogeneic

suicide gene-modified killer cells have been shown to behave like NK and NKT cells and demonstrate antitumour activity in an orthotopic model.[82]

ENHANCING ANTITUMOUR IMMUNITY

So far immune checkpoint inhibitors are the most developed molecules used to enhance antitumour immunity. Three different checkpoint inhibitors have been approved by the US Food and Drug Administration for the treatment of patients with melanoma, anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) (ipilimumab), pembrolizumab (anti-programmed cell death protein 1 (PD1)) and nivolumab (anti-PD1), and multiple others are in clinical development.[7] Dramatic clinical responses have been seen in patients with melanoma and non-small cell lung cancer. Some reports have suggested that cancers with a high rate of somatic mutation respond best to immune checkpoint blockade. Vogelstein and colleagues reported approximately 50 non-synonymous mutations per tumour for HCC in comparison to 75 for melanoma and 130 for non-small cell lung cancer (NSCLC).[83] However, it should be noted that patients with renal cell carcinoma have also responded to anti-PDL1 treatment[84] despite the fact that renal cell carcinoma is a tumour with a relatively low somatic mutation frequency rate in comparison to melanoma and NSCLC.[85] One possible explanation may be that the number of immunogenic mutations leading to antigens presented on major histocompatibility complex (MHC) class molecules rather than total mutations will determine whether a tumour responds to immune checkpoint blockade.[86]

Safety, immunological responses and early signs for clinical activity have been reported in a clinical trial using tremelimumab (anti-CTLA4) in 20 patients with HCC.[87] We are currently evaluating this approach in combination with tumour ablation and a study testing nivolumab is ongoing (NCT01658878). More details about these drugs in HCC have recently been reviewed elsewhere and are beyond the scope of this review.[88] The tumor necrosis factor (TNF) receptor family member CD40 is a stimulatory molecule constitutively expressed on a large variety of cells, including dendritic cells, B cells, macrophages and endothelial cells.[89] Targeting CD40 is another approach currently being developed to enhance antitumour immunity either alone or in combination with different cancer vaccines.[90] In a rodent HCC model, adenovirus-mediated CD40 L gene therapy induced humoral and cellular immunity against HCC[91] and CD40 L expressing dendritic cells have been shown to induce regression of HCC in mice in vivo.[92] Combination of three immunostimulatory monoclonal antibodies (anti-programmed death-ligand-1 (PD-L1), anti-CD137 and anti-OX40) was tested in a transgenic mouse model of HCC, in which c-myc drives transformation and cytosolic expression of the model antigen ovalbumin. The investigators demonstrated extended survival of mice in a CD8-dependent fashion and when given in combination with ovalbumin specific CD8+ T cells this antibody combination prevented induction of tolerance of ovalbumin-specific T cells.[68]

LIVER-DIRECTED VACCINATION STRATEGIES

Hepatocytes can be infected by multiple viruses making HCC a potentially ideal target for cancer-directed therapies using viruses as carriers to deliver molecules into liver tumours. Different constructs have been used in preclinical HCC models including adenoviruses,[93]

vaccinia viruses[94] and 1listeria monocytogenes.[95] Oncolytic virotherapy has shown impressive results in preclinical studies. They do have cytoreductive activity and activate innate immune responses and induce long-lasting adaptive responses.[96] HCC-specific targeting can be achieved using an α-fetoprotein promoter in combination with an hypoxia response element limiting expression in the hypoxic tumour microenvironment.[97] JX-594 is an oncolytic and immunotherapeutic vaccinia virus expressing granulocyte-macrophage colony-stimulating factor. Intratumoral injection of this virus in patients with HCC has demonstrated feasibility, safety and an early signal of efficacy.[94] However, a randomised phase 2b study failed to demonstrate improved overall survival in advanced HCC patients who had failed prior firstline chemotherapy, as reported by the company, and did not reach its primary endpoint improvement of overall survival.[98] A phase 3 study in the first-line setting is expected to open in 2015 and is planned to combine JX-594 with sorafenib, the only approved chemotherapy.[99] This study addresses the question if and how immunotherapy can be best combined with systemic sorafenib treatment.

CLINICAL TRIALS COMBINING STANDARD OF CARE IN HCC WITH IMMUNOTHERAPY

Numerous immune-based approaches have been tested in the past in patients with HCC and have been reviewed by others and us.[100–102] Combining immunotherapy with established standard of care treatment represents an interesting option for patients with HCC and a number of investigators have tested such an approach. Transcatheter hepatic arterial embolisation (TACE) has been combined with an intratumoral dendritic cell infusion and preliminary results from 10 treated patients demonstrated safety of this approach.[103] Two rather large randomised studies from Asia with 146 and 174 patients report about the use of cytokine-induced killer cells in combination with TACE. Unfortunately both studies are of limited significance since one of them is not randomised and the other one is a retrospective study.[104105] Safety and signs of immunological activity were shown in a study by Nakamoto and colleagues who treated patients with dendritic cells stimulated with a lyophilised preparation of *Streptococcus pyrogenes* in combination with TACE.[106] Three studies reported on combination treatments in patients undergoing some type of ablation such as cryotherapy, microwave or radiofrequency ablation in combination with adoptive cell therapy using NK cells, γδT and cytokine induced killer cells.[107] Adoptive cell therapy has also been tested in the adjuvant setting,[108] however again no data from randomised controlled trials is currently available. In summary, most studies have been conducted in a rather uncontrolled fashion and therefore provide only very limited information about their efficacy. Furthermore limited data on immunomonitoring is described, which would help better understand the significance of the described findings.

TRANSLATING CURRENT KNOWLEDGE INTO FUTURE IMMUNOTHERAPY STUDIES FOR HCC

How can we use recent advances in cancer biology, our knowledge on liver immunology and the rapid development of novel immunotherapeutics to design future immune-based trials in HCC? (figure 2).

(1) It is important to recognise that not all types of tumours show the same susceptibility to immunotherapy. While anti CTLA-4 and anti-PD1/PDL1 have undoubtedly revolutionised the field in melanoma and a few other indications such as lung, renal cancer and others, we should not forget that most patients with tumours of the GI tract have failed to show any benefit from immune checkpoint inhibitors. Studies are on the way, which may help us better understand this discrepancy.[109] (2) Many research laboratories around the world have successfully identified subclasses of HCC with distinct and unique tumour biology. Furthermore these findings clearly indicate the relevance of immunological mechanisms responsible for the patients' outcome, and may be used in the future to better identify patient subsets amenable to immunotherapeutic approaches. (3) From a clinical point of view it will be critical to find the best patient population in which novel immunotherapies can be tested. HCC represents a somewhat unique situation since ablative therapies are so widely used and may be an ideal combination partner for immunotherapy.[23] In addition, many investigators may probably argue that patients with cancer who have progressed on one line of chemotherapy may no longer be good candidates for immunotherapy. However recent data in lung and pancreatic cancers has shown the opposite.[110111] (4) Finally, drawing conclusions from early clinical trials will prevent us from designing more studies in HCC, that will fail at the phase III levels as has recently been seen. Thorough immunomonitoring including analysis of tumour samples and peripheral blood from patients enrolled on clinical trials, use of the adequate tools to measure tumour responses (modified Response Evaluation Criteria In Solid Tumours (mRECIST), immune modified RECIST,[112] etc) and selection of the correct clinical end points along with optimal mouse models mimicking the situation in patients will ultimately lead to a successful clinical development of this novel treatment approach and an improved outcome for patients diagnosed with HCC.

Rationale for immunotherapy in HCC

- Hepatocellular carcinomas (HCCs) arise frequently in chronically infected livers indicating a link between inflammation and HCC.
- Presence or absence of different immune cell subsets or immune signatures correlate with patient survival.
- Patients with HCC present spontaneous antitumour immunity despite the fact that they arise in a 'tolerogenic' environment.
- Antibodies and other biologics do not require metabolism in the liver and their use is therefore not impacted by the presence of liver cirrhosis.
- Immune signatures may facilitate identification of the optimal patient population.
- Tumour ablation induces antitumour immune responses, which can be enhanced using novel immunomodulatory treatments.
- Immune-based approaches in preclinical and clinical development for HCC
- antigen-based vaccination strategies (peptides, dendritic cells, virotherapy);
- immune checkpoint blockade;
- cytokine-based treatments including cytokine-targeting agents;

- elimination of immunosuppressor cells such as myeloid derived suppressor cells (MDSCs) and Tregs;
- adoptive cell therapy including (chimeric antigen receptor transduced T cells);
- antibodies targeting tumour-specific antigens;
- STAT3 targeting;
- Toll like receptor (TLR) agonists.

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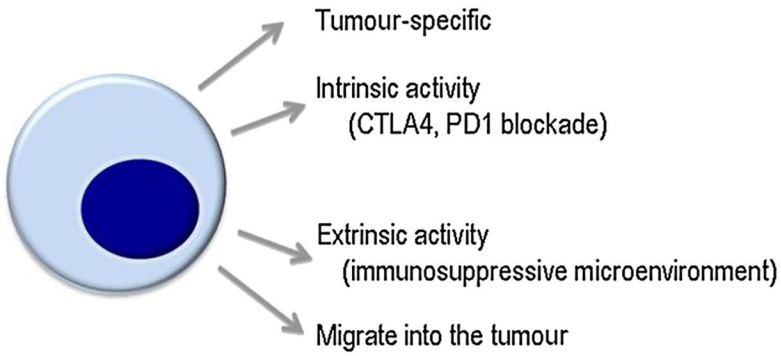

Figure 1.

Activation and enhancing tumour-specific T cells against hepatocellular carcinoma. In order for T cells to be active anticancer agents they have to recognise an antigen presented by the tumour (tumour specificity). The T cell should be active and not inhibited by intrinsic (CTLA4, Pd1) or extrinsic (regulatory T cells, myeloid-derived suppressor cells and cytokines in the tumour microenvironment) mechanisms. Finally T cells need to be present in the tumour.

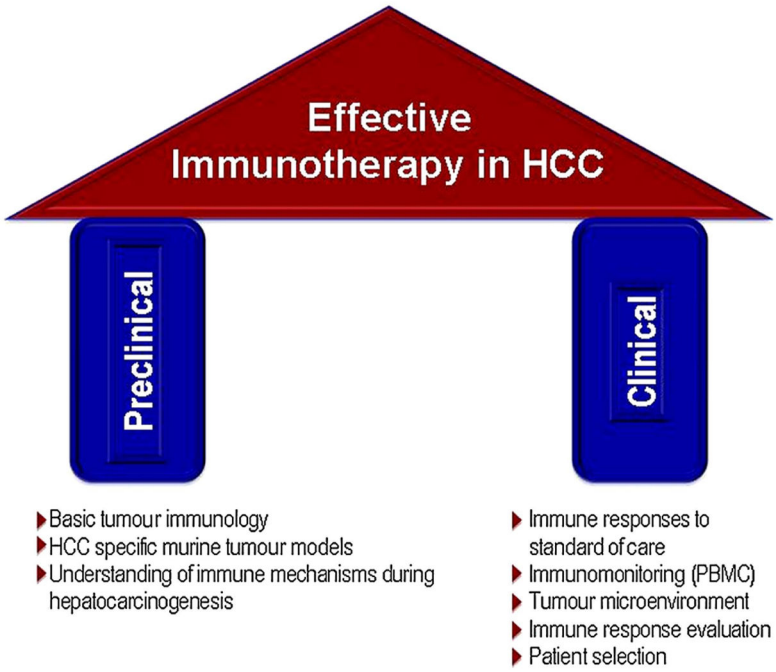

Figure 2.
Requirements for an effective immunotherapy in hepatocellular carcinoma (HCC).