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Frontiers in Anti-Cancer Drug Discovery

Volume 8

Editors:
Atta-ur-Rahman, *FRS*
M. Iqbal Choudhary

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Frontiers in Anti-Cancer Drug Discovery

(Volume 8)

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Preface

Cancer is a grand health challenge of modern times, being the second leading cause of death. Despite tremendous investments in this field, the prognosis of cancer has not improved substantially. There have been some advances in cancer chemotherapy and radiation therapy, but other treatment options, such as surgery, burn, immunotherapy, *etc* remain primitive and far from being perfect. Chemotherapy, the "holy grail" of cancer treatment, is based on targeting certain biomolecular pathways in the complex cascade of cancer progression. However, the limited understanding of cancer biology often makes this a *fishing expedition*. As a result, many of the currently available anti-cancer drugs are non-specific and less effective. Heterogenicities in cancer pheno- and geno-types, often make the identification of genuine targets difficult. However recent advancements in genomics, metabolomics, transcriptomics, and molecular biology have fuelled major research projects in the fields of oncology and anti-cancer drug discovery and development. The scientific literature is now full of exciting discoveries against this disease of modern society, cancer. It is often difficult, even for a prolific reader, to keep pace with these developments. Thus, the need of a comprehensive book review series is greatly felt.

The last seven volumes of the *e*book series "*Frontiers in Anti-Cancer Drug Discovery"* have attracted major interest, making this series a welcome addition to the global literature on this dynamic topic. The present 8th volume of this internationally recognized books series comprises six carefully selected topics focused on various aspects of cancer chemotherapy and cancer biology, contributed by leading experts in this field. Each chapter deals with anti-cancer drug discovery and development based on various innovative approaches, including identification of new molecular targets, manipulation of cancer microenvironment, and outcomes of pre-clinical and clinical studies on new drugs, and combination therapies.

Amedei *et al.* have reviewed the recent progress in the use various immunotherapies in cancer treatment in chapter 1. Their emphasis is on the treatment of gastrointestinal cancers by T-cell based immunotherapies. T-Cells, also called T-lymphocytes, are a subtype of white blood cells that play a central role in cell-mediated immunity. T-Cell based immunotherapies have attracted considerable scientific attention. However, T-cell based immunotherapy of cancers is not free of adverse side effects.

In chapter 2, Cheng *et al.* have contributed a comprehensive review on the anticancer activity of the newly discovered compound adjudin, a well-known male reversible contraceptive used in animals. Adjudin is a structural analogue of the anticancer drug lonidamine. Apart from its known potent anti-spermatogenic activities, adjudin is found to have many other biological properties. Notable among them is its activity against neuroinflammation, protection against gentamicin-induced ototoxicity, and prevention of cancer growth and development. The authors have critically reviewed the recent literature on new indications of this old contraceptive drug. The focus of the article is on recently discovered anticancer activities of adjudin, either alone or in combination with other anticancer drugs as well as with nanocarriers. Adjudin, similar to lonidamine, inhibit cancer growth by targeting mitochondria and blocking energy metabolism in certain kinds of tumor cells in mice, indicating that it is potential anticancer agent.

Tumor microenvironment (TME) plays an important role in the progression of tumor growth, and treatment outcome. This cellular environment includes surrounding blood vessels, immune cells, fibroblasts, bone marrow-derived inflammatory cells, lymphocytes, signalling molecules and the extracellular matrix (ECM). Recently TME has been identified as potential

target for novel cancer chemotherapies. Mabtel and Pepper have contributed a comprehensive review in chapter 3 on the role of tumor microenvironment in tumor progression, angiogenesis, cellular invasion, metastatic dissemination, resistance against chemotherapy and its potential as drug target. Recently developed treatments which can modulate TME against tumor growth, along with their mechanisms of action, have also been discussed.

In chapter 4, Fatima *et al.* have focussed on the current and emerging therapies for the treatment of hepatocellular carcinoma (HCC) or malignant hepatoma. Hepatocellular carcinoma accounts for most liver cancers, and is a leading cause of cancer related deaths. HCC occurs more frequently in men than women and is usually diagnosed in people of age 50 or older. HCC's prognosis is among the poorest of all cancer types. This review provides a detailed description of various treatment options for HCC, and their advantages and disadvantages. Future directions of development in this field are also reviewed.

Gold complexes are known for a variety of biological activities. In chapter 5 Sun *et al.* discuss the anti-cancer properties of gold-based compounds and their potential. After the serendipitous discovery of cisplatin, a platinum (II) based compound, as a potent anti-cancer agent, interest in metal complexes has increased exponentially. Sun *et al.* have critically reviewed the recent literature on the therapeutic potential of novel gold complexes (I and III), particularly against various cancers.

In the last chapter, Anreddy *et al.* have reviewed the application of nanostructures as oral drug delivery vehicles for the treatment of various cancers. One of the key issues in cancer chemotherapy is that the most potent anticancer therapies can only be administered through injection, as their oral drug delivery is associated with many limitations. This makes cancer chemotherapy quite challenging. Recently many new classes of nanoparticles (NPs), such as liposomes, polymeric NPs, polymeric conjugates, micelles, dendrimers, polymersomes, and metallic and inorganic NPs, have been developed as new drug delivery vehicles for oral administration in cancer chemotherapy. These nanoparticle-based anti-cancer drugs are often devoid of problems such as poor solubility, low intrinsic permeability, and metabolic changes. The potential of NPs in on-target and sustained administration of drugs is also discussed.

We wish to express our sincere gratitude to all the authors for their excellent scholarly contributions to this 8th volume of this book series. We also appreciate the efforts of the impressive production team of Bentham Science Publishers for the efficient processing the treatise. The efforts of Ms. Fariya Zulfiqar (Assistant Manager Publications) & Mr. Shehzad Naqvi (Senior Manager Publications) and excellent management of Mr. Mahmood Alam (Director Publications) are greatly appreciated. We also hope that like the previous volumes of this internationally recognized book series, the current volume will also receive wide readership and recognition.

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CHAPTER 1

T Cells in Gastrointestinal Cancers: Role and Therapeutic Strategies

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Abstract: Conventional treatments of gastrointestinal cancers based on surgical resection and chemotherapy are not enough to eradicate potentially relapsing tumor cells and can also impair the immune system functions. Immunotherapies aim to help the body to eradicate cancer and other diseases, by modulating the immune system. They can be performed by active approaches, usually orchestrated by dendritic cell vaccines that present a specific tumor associated antigen to T cells, or passive approaches, which have the T cells as protagonist, and are based on antitumor antibodies, or adoptive cell transfer. T lymphocyte subsets can exhibit different role face to a tumor scenario, varying from an effective cellular antitumor response to a regulatory participation. Although a lot of protocols to combat cancer progression have been proposed, T cell-based immunotherapies in gastrointestinal cancers are still not approved for clinical applications mainly because of their side effects. Nowadays, promising protocols combining two or more approaches, aiming to create an efficient therapy without or with fewer side effects. In this chapter, we made a review about the role of T cells on cancer, especially focusing on gastrointestinal cancer immunotherapeutic methods.

Keywords: Adoptive immunotherapy, Gastrointestinal cancer, Immunotherapy, Infiltrating lymphocyte, Tumor lymphocyte engineering, T lymphocytes.

INTRODUCTION

Gastrointestinal (GI) cancers, including colorectal (CRC), gastric, pancreatic, liver and bile duct cancers, are complex diseases that figure among the ten most frequent types of cancers annually diagnosed worldwide [1], which incidences have a variable geographic distribution [2]. Most of these tumors occur in a sporadic way, and the distribution variability is closely associated with diet

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culture and lifestyle [3 - 6]. The development of GI cancers could also be associated with microbial infections, which seems to play an important role on both, initiation and progression. For instance, *Streptococcus bovis* is an important inducer of CRC development [7], while *Helicobacter pylori* is highly associated with gastric cancer [8], and the Hepatitis C virus induces liver cancer [9]. The association of these pathogens with previously stabilized chronic inflammatory microenvironment can induce DNA damage in proliferating cells through the action of reactive oxygen species (ROS) and inflammatory cytokines that can culminate in gene mutations and/or epigenetic changes [10].

Conventional treatment of patients with localized GI cancers consists in surgical resection of tumor tissue. However, post-surgery relapsing disease frequently develops within 2 years in approximately 40% of patients. Therefore, adjuvant therapy is required to improve anti-cancer responsiveness in high-risk patients, and then, surgery is usually followed by adjuvant chemotherapy or adjuvant chemo-radiotherapy. Frequently, patients are submitted to perioperative chemotherapy [11, 12] (also called neoadjuvant therapy administrated before surgery), in order to reduce the tumor mass and facilitate surgical intervention. Despite these combinations, metastasis and relapsing diseases are until the main causes of death in GI patients. Moreover, *in vitro* and *in vivo* studies have shown that cytotoxic chemotherapy, as well as the surgery stress itself, can impair the immu-nological steady state and also the ability to develop an antitumor immune res-ponse [13].

The immune system plays an important role in the battle against cancer development. The capacity to promote an effective immunological reaction against tumor antigens was firstly described by Macfarlane Burnet and Lewis Thomas and called immunosurveillance [14]. Immunosurveillance occurs when some antigens, encoded by mutated genes and expressed by tumor cells, became a functional target and are quickly recognized and destroyed by innate effector cells such as natural killer cells. This concept of surveillance can be extended to recognition, processing, and presentation of tumor antigens by professional antigen-presenting cells (APCs) to *naïve* lymphocytes (Ly) [15, 16]. In this scenario, autologous $CD4^+$ and $CD8^+$ T lymphocytes recognize these antigens, and attack transformed cells inducing their lysis [17]. In fact, the presence of strong lymphocyte infiltration in tumor site such as in melanoma, CRC and ovarian cancers is associated with a good clinical outcome, since they have the function to inhibit the tumor growth [18].

Lymphocytes originate from a common lymphoid precursor cell in bone marrow. During fetal development, some of these lymphoid precursors move to thymic epithelium to develop this organ where all T lymphocytes will evolve (Fig. **1**). T cells have surface receptors (TCRs) that recognize antigen peptide linked to

molecules of the Major Histocompatibility Complex (MHC), especially expressed on the surface of the APCs such as macrophage and dendritic cells (DC), or also on the target cells, such as allogeneic cells and virus or intracellular bacterial - infected cells.

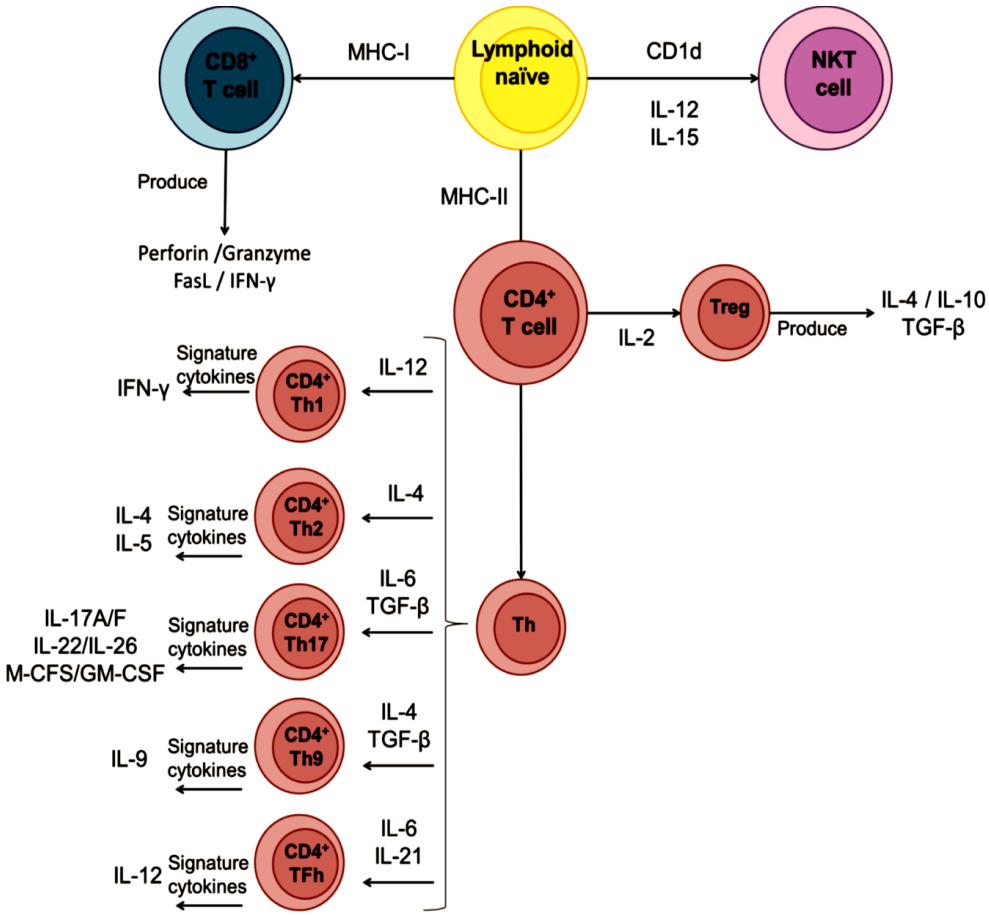

Fig. (1). T lymphocytes' differentiation: from the common progenitor to the different subpopulations CD8, CD4 and Natural killer T lymphocytes (NKT). When a naïve lymphocyte recognizes an antigen, which was presented by a major histocompatibility complex class I (MHC-I) is induced to differentiate to a $CD8^+$ profile. However, the recognition of antigen presented by MHC-II in turn, guides the lymphocytes' differentiation for a $CD4^+$ subpopulation, which after activation may enter several different pathways depending on antigen-presenting cell (APC) co-stimulatory factors and cytokine setting. The presence of Interleukin (IL)-12, for example, directs the $CD4^+$ to Th (T helper) -1 profile, while IL-4 to Th2, IL-6 and TGF-β to Th17, IL-4 and TGF-β to Th9, IL-6 and IL-21 to T follicular helper (TFh) cells and finally, the presence of IL-2 conducts the $CD4^+$ T lymphocytes to differentiate in T regulatory (Treg) cells. The differentiation of NKT cells in the other hand occurs when naïve T lymphocytes recognize CD1d in the presence of IL-12 and IL-15.

CHAPTER 2

Adjudin - A Male Contraceptive with Anti-Cancer, Anti-Neuroinflammation and Anti-Ototoxicity Activities

Yan-ho Cheng[1,2], Weiliang Xia[3], Xiang Xiao[1,4], Elizabeth Tang[1], Haiqi Chen[1], Qing Wen[1], Ying Gao[1], Dolores Mruk[1], Bruno Silvestrini[5] and **C. Yan Cheng[1,*]**

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Abstract: Adjudin, 1-(2,4-dichlorobenzyl)-*1H*-indazole-3-carbohydrazide, is an indazole-based compound and a testis-specific adherens junction disruption inducer. Adjudin is also an analog of the anticancer drug lonidamine. Studies have shown that adjudin is an effective male contraceptive in rats, rabbits, and beagle dogs. Adjudin is known to exert its effects primarily at the testis-specific actin-rich adherens junction known as ectoplasmic specialization (ES), most notably in the adluminal compartment called apical ES at the Sertoli-spermatid (step 8-19) interface in adult rat testes. Similar ultrastructures of apical ES are also found in the mouse, dog and human testes.

Specifically, adjudin has been shown to perturb the organization of actin microfilament bundles at the ES, which in turn, perturbs adhesion protein complexes that utilize F-actin for attachment.

The net result thus perturbs spermatid adhesion to the Sertoli cell in the testis, leading to massive exfoliation of elongated/elongating spermatids, to be followed by round spermatids, spermatocytes and differentiated spermatogonia, but not undifferentiated spermatogonia. This thus induces reversible infertility in rats, rabbits and beagle dogs due to the loss of germ cells in the seminiferous epithelium; and undifferentiated

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spermatogonia gradually replace all classes of germ cells *via* spermatogenesis, making the adjudin treated animals fertile again. Recent studies, however, have shown that adjudin also possesses biological activities to disrupt cancer growth and tumorigenesis. It also interferes with neuroinflammation by reducing ischemia-induced microglial activation in mice. Furthermore, adjudin protects rodent cochlear hair cells against gentamicin-induced ototoxicity *via* the SIRT3-ROS (SIRT3 also known as Sirtuin 3, silent mating type information regulation 3 homolog (a mitochondria NAD-dependent protein deacetylase)-reactive oxygen species) pathway. In this review, we summarize some of the recent findings, in particular the likely mechanism(s) of action, regarding the multiple biological activities of adjudin, illustrating this potential male contraceptive has other added health benefits, such as preventing cancer growth and development. Furthermore, its use as novel anti-cancer drug is an area of research that can be further explored. Using a multidrug nanocarrier to deliver adjudin, in combination with other anti-cancer drug(s) (*e.g.* doxorubicin), this approach has been used successfully to eradicate drug resistant cancer cells.

Keywords: Adjudin, Anti-cancer drug, Anti-inflammatory drug, Anti-ototoxicity drug, Male contraceptive, Spermatogenesis, Testis.

INTRODUCTION

Design of optimal chemotherapy to treat different human cancers is a rapidly changing field [1 - 3]. Interestingly, the use of “old” drugs, either alone or in combination with other drug(s), intended for treating other illnesses has shown to be promising for cancer therapy. Also, this approach saves time by reducing hurdles for clinical trials. For instance, the use of metformin (an anti-diabetic drug) or insulin in cancer therapy [4, 5], chloroquine (an anti-malarial and anti-rheumatoid drug) in treating glioma [6, 7], and silibinin (a liver detoxifying drug) in cancer therapy [8] have illustrated that the use of some “old” drugs save time, efforts and resources for development. This is because their safety has already been proven in earlier clinical trials for intended applications. Adjudin, a second generation indazole-based compound, closely related to the anti-cancer drug lonidamine, has been investigated as a potential male contraceptive [9 - 11]. Studies in the 1970s and 1980s have shown that indazole-based compounds also possess potent anti-spermatogenic activities by targeting mitochondria found in germ cells [12 - 14], perturbing germ cell energy metabolism [15, 16]. Subsequent studies have shown that lonidamine also possesses potent activity to perturb cancer cell metabolism by acting as a mitochondrial hexokinase inhibitor [15, 17, 18]. In fact, lonidamine by itself is a new class of anti-cancer drug by blocking tumor cell energy metabolism instead of an anti-mitotic drug [19, 20]. Earlier studies have shown that adjudin, 1-(2,4-dichlorobenzyl)-1H-indazole-3-carbo-hydrazide, formerly called AF-2364, is less toxic based on both acute toxicity and subchronic toxicity tests [9] when compared to lonidamine. This thus raises the expectation that adjudin may have similar anti-cancer activity as of lonidamine,

but considerably reduced cytotoxicity. Indeed, adjudin is known to possess anti-proliferation activity on cancer cells *in vitro*, and also on lung and prostate tumors inoculated in athymic nude mice in *in vivo* by shrinking the solid tumors considerably [21]. A recent report has also demonstrated the use of a multi-drug nanocarrier approach using adjudin and doxorubicin to treat drug-resistant cancer cells [22], illustrating the potential of using adjudin as an anti-cancer drug. In this Chapter, we review data regarding the mechanism of action of adjudin in perturbing spermatogenesis in the testis. We also briefly summarize findings that investigate its mechanism of action in cancer cells. Furthermore, adjudin is known to possess anti-inflammatory and anti-ototoxicity activities. Collectively, this information will provide a solid basis to better understand the different mechanisms of action of adjudin in mammalian cells and tissues (Fig. **1**). This information should appeal to cancer biologists, and investigators interested in illnesses in the brain such as Alzheimer's disease, as well as reproductive biologists.

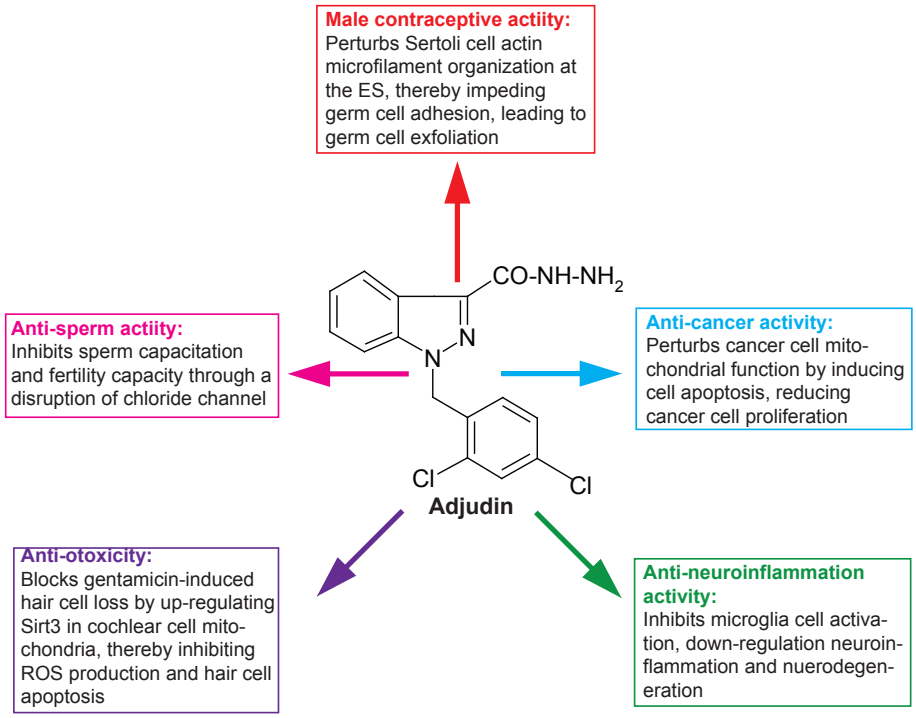

Fig. (1). Adjudin and its various activities in rodents based on studies *in vitro* and/or *in vivo*. Structural formula of adjudin, 1-(2,4-dichlorobenzyl)-*1H*-indazole-3-carbohydrazide, illustrating adjudin, similar to lonidamine, is an indazole-based drug but without the toxicity of lonidamine. Based on recent studies using various *in vitro* and *in vivo* models as discussed in text, adjudin is now known to be a reversible male contraceptive in rats and rabbits. Interestingly, adjudin also possesses anti-cancer, anti-neuroinflammation/anti-neurodegeneration, and anti-hearing loss activity. These other potential health benefits provide additional incentives to explore this drug as a male contraceptive in humans.

CHAPTER 3

Manipulating the Tumor Microenvironment: Opportunities for Therapeutic Targeting

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Abstract: Over the years, there has been a marked change in the modalities of cancer treatment from the use of surgery and radiation therapy as gold standards to the employment of chemotherapy and combination approaches using a variety of modalities. Despite the advances, prognosis generally remains poor due to patients who develop toxicity or become refractory to therapy. The focus of treatment approaches has largely been on eliminating tumor cells. However, recent studies have shown that there is cross talk between tumor cells and their immediate environment, collectively known as the tumor microenvironment (TME).

The TME contributes to certain characteristics of cancer such as hyperproliferation and angiogenesis. As such, the TME has been recognized as an important contributor to cancer progression, cellular invasion and metastatic dissemination. In addition, the TME has been reported to promote adaptive resistance to therapy in a number of cancers.

Herein, we provide a brief overview of the pathophysiology of aspects of the tumor microenvironment. We further review emerging treatment modalities that target this niche and the mechanisms underpinning the efficacy of these therapies.

Keywords: Angiogenesis, Cancer, Chemotherapy, Drug delivery, Endothelial cells, Extracellular matrix, Targeted therapy, Tumor associated fibroblasts, Tumor associated macrophages, Tumor microenvironment.

INTRODUCTION

The key objective of conventional anti-cancer therapies is to eliminate cancer cells [1 - 3]. Despite recent advances in cancer chemotherapy, the efficacy of

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these treatments has been limited by toxicity and the development of resistance [4, 5].

There is increasing recognition that tumor growth relies on an interplay between tumor cells and their adjacent stroma [6 - 9]. Physiology dictates that the structure and composition of the stroma should support cell function. The stroma also changes dynamically to maintain homeostasis [10]. The tumor stroma has a composition that is different to what would be considered to be physiologically appropriate [11].

The tumor stroma is made up of mesenchymal cells, mainly fibroblasts, immune cells, vascular cells, as well as the extracellular matrix (ECM). Stromal components, together with tumor cells, constitute the tumor microenvironment (TME) [12].

In response to stimulation by various factors including low oxygen levels, tumor cells release molecules which can alter both the structure and the composition of the TME [11, 13]. These changes support tumor perfusion and ultimately enable neoplastic growth and progression; in some instances, they also support metastatic dissemination [13]. The importance of the TME to tumor progression is further reinforced by observations from studies on the influence of the TME on human metastatic cancer cells implanted in different organ environments [14, 15].

These studies have shown that ectopically implanted colon cancer cells do not metastasize, neither regionally nor to distant sites, despite the aggressiveness of the cancer from which the cells were isolated [14]. Yet when the same cells were implanted orthotopically (*i.e.* tumor cells implanted in the tissue of origin), metastatic dissemination occurred. The incidence of metastasis was associated with an increase in the activity of tumor-derived ECM enzymes such as collagenase [14 - 16]. The TME components such as cancer associated fibroblasts (CAF) appear to play a role in ECM remodelling as well as neoplastic expansion [4, 11, 17 - 20].

Cellular components of the TME are influenced by growth factors and enzymes secreted by tumor cells [11]. These cells in turn stimulate angiogenesis and lymphangiogenesis in order to support tumor progression [6, 21]. Also, interaction between various cell populations in the TME have implications for treatment efficacy [22].

THE RATIONALE FOR TARGETING THE TUMOR MICRO-ENVIRONMENT

Conventional chemotherapy remains the mainstay for the treatment of neoplastic

disease [1]. This form of therapy has been limited by a number of factors which include poor selectivity and toxicity [13, 23].

Several studies have shown that components of the tumor stroma can interfere with drug extravasation at the tumor site and also promote drug resistance [10, 24]. Therefore, targeted treatment strategies that overcome these barriers within the TME may be of clinical importance.

The objectives of targeted approaches would be i). to realize optimal dosing, ii) to enhance drug accumulation at the tumor site, iii) to reduce non-specific targeting and iv) to reduce adverse effects [20, 25].

MODES OF DRUG TARGETING

Drugs are transported through convection, which is the 'movement of molecules within fluids' as well as through diffusion, which involves the movement of low molecular weight particles along a concentration gradient [26]. Several factors influence the penetration of tumors by drugs [27 - 30]. These factors include hydrostatic pressure, oncotic pressure, electrostatic and concentration gradients between blood vessels and the interstitium, vessel permeability, the surface area over which the exchange will occur and the structure of the ECM [28].

In the context of tumors, due to alterations in both the ECM and the vasculature, drug movement through convection is especially restricted, necessitating the employment of targeted drug delivery approaches. Generally, drug targeting approaches are classified into two categories, passive and active [31].

Passive Targeting

Passive targeting utilizes carriers to achieve drug accumulation at a specific site (Fig. **1**) [31]. This form of targeting seeks to exploit the unique properties of the TME such as the leakiness of the tumor vasculature and dysfunctional fluid drainage due to the abnormal tumor lymphatic vasculature [23, 32].

The carriers commonly used in passive anti-cancer drug targeting include lipid based nanoparticles such as liposomes and micromicelles, polymers and metal (inorganic) carriers such as nanogels and gold nanoparticles respectively [26].

Designed drug carriers with selective extravasation into tumor tissue promote the enhanced permeability and retention (EPR) effect [23]. The selectivity of the carriers for the tumor site relies on the leakiness of the tumor vasculature. Poor lymphatic drainage within the TME further enhances the retention of the therapeutic molecules. For example, nanoparticle-albumin-bound (NAB) technology has been employed as a carrier for taxol in the formulation Abraxane,

CHAPTER 4

Current and Emerging Cancer Therapies for Treatment of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer related deaths worldwide, especially in Asia. Late diagnosis and/or underlying cirrhosis, and limited treatment options with marginal clinical benefit are the reasons for its dismal prognosis. Surgical resection and liver transplantation are curative treatment options but are suitable for patients with small tumours or well-compensated liver diseases. For patients with non-resectable HCC, treatment options include ablative and systemic therapies. However, the results are unsatisfactory with limited long-term survival. In the last few years there has been active research in the area of molecularly targeted agents for HCC including anti-angiogenic therapy, immunotherapy, antiviral therapy, and other agents targeting mammalian target of rapamycin (mTOR), and c-met among others. This chapter will look into current treatment options, discuss their advantages and disadvantages, as well as introduce new therapies that are under clinical investigation but not yet recommended by acceptable guidelines. Although there is tremendous research in progress, the treatment modalities offer limited survival benefit and thus the battle against HCC is far from over.

Keywords: Anti-angiogenic therapy, Antiviral therapy, Chemotherapy, c-Met inhibitors, Hepatocellular carcinoma, Immune based therapy, Local ablative therapy, mTOR inhibitors, Sorafenib, TACE.

INTRODUCTION

Liver cancer is the second leading cause of cancer-related deaths worldwide. In 2012, there were 782,000 new cases and an estimated 746,000 deaths [1]. Among

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primary liver cancers, HCC is the most common subtype. The highest rates of HCC are reported in south-east Asia with more than 50% of HCC cases occurring in China. The incidence of HCC is also on the rise in the western world due to an increase in hepatitis C virus (HCV) infection [2].

The main aetiology of HCC is underlying cirrhosis with about 80%-90% of patients with cirrhosis go on to develop HCC and the remaining 10%-20% develop HCC without cirrhosis. Cirrhosis is caused by chronic hepatitis B virus (HBV) or HCV infection, fatty liver diseases, exposure to aflatoxins, chronic alcohol intake, non-alcoholic steatohepatitis (NASH) or less commonly due to other factors such as autoimmune or genetic metabolic liver diseases (hereditary hemochromatosis, α1-antitrypsin deficiency) [3, 4].

HCC suffers from a high rate of mortality due to lack of diagnostic methods and limited treatment options for patients with advanced HCC. Despite efforts to screen for early HCC by ultrasound screening and serum alpha fetoprotein (AFP) levels, patients are commonly asymptomatic until decompensation of their cirrhosis resulting from replacement of functional liver tissue by tumour tissue. Ultrasound surveillance is operator-dependant with low reproducibility and AFP levels are also dysregulated in benign liver diseases [5]. Furthermore, about 15% of patients show metastasis at the time of diagnosis. The most common sites for metastasis are the lungs, abdominal lymph nodes, bone, and adrenal glands [6]. The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) both endorse the Barcelona clinic liver cancer (BCLC) staging classification as criteria for the management of patients with HCC. Table **1** lists the BCLC classification. Treatment options for HCC are stage dependent and can be categorised into three groups: curative, palliative and symptomatic (Fig. **1**). For early stage tumours, curative treatment options include resection and percutaneous ablation which may achieve a five year survival rate of 70%. Patients who are not suitable for first-line therapy are treated with the next BCLC stage. This includes HCC patients with no macrovascular invasion or extrahepatic spread. These patients are suitable for transarterial chemoembolization (TACE). However, patients with advanced-stage HCC, with evidence of portal invasion, lymph node involvement and distant metastasis have 1 year survival rate of only 50% and before the introduction of sorafenib there was no treatment option shown to improve survival [7]. This book chapter aims to review the current and emerging treatment modalities for HCC patients.

Table 1. BCLC staging classification of HCC [8, 9].

		Tumour Characteristics		
Stage	**PST**	**Tumour Stage**	**Okuda Stage**	**Liver Function**
Stage A (early HCC)				
A1	0	Single tumour, <5cm	I	No portal hypertension and normal bilirubin
A2	0	Single tumour, <5cm	I	Portal hypertension and normal bilirubin
A3	0	Single tumour, <5cm	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumours < 3cm each	I-II	Child-pugh A-B
Stage B (intermediate HCC)	0	Large multinodular	I-II	Child-pugh A-B
Stage C (advanced HCC)	1-2[a]	Portal invasion, nodal metastases, distant metastases	I-II	Child-pugh A-B
Stage D (end stage-HCC)	3-4[b]	Any	III[b]	Child-pugh C[b]

PST: Performance status test; Stage A and B, all criteria should to be fulfilled; [a]: Stage C, at least one criteria to be fulfilled, PST 1-2 or portal invasion/extrahepatic spread; [b]: Stage D, at least one criteria to be fulfilled, PST 3-4 or Okuda stage III/ Child-pugh C.

Surgical and Local Ablative Therapies

Surgery is the preferred treatment option for HCC patients because it is associated with a 5-year survival rate of 70% [7]. However, at the time of diagnosis, only about 10%-30% of HCC patients are amenable to liver resection. According to the BCLC guideline, surgery is limited to only early stage cancers (a single HCC < 5cm in diameter or up to 3 HCCs < 3cm in diameter) with good hepatic function and performance status. This criteria is sometimes considered restrictive as tumour size and number are not considered contraindication for surgery as long as there is sufficient hepatic reserve and that the tumour is resectable [10]. Studies have shown that resection may be the only hope for cure in large multinodular HCC with 5-year overall survival (OS) and disease-free survival of 39% and 26% respectively being achievable [11, 12]. For patients without cirrhosis, the least remnant liver volume for surgical resection is about 25% and 50% for HCC patients with cirrhosis [12].

CHAPTER 5

Recent Development (from 2013 to 2015) of Gold-Based Compounds as Potential Anti-Cancer Drug Candidates

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Abstract: Cisplatin (Fig. **1**) is a platinum(II) compound which contains two chlorido and two ammino ligands. In 1965 the biological activity of this compound was serendipitously discovered by Rosenberg *et al.* At present, this platinum(II) compound remains one of the effective chemotherapeutic agents for the treatment of various cancers in clinic [1]. The clinical success of this platinum compound has subsequently prompted the studies to identify other new metal-based therapeutic agents. As compared to organic molecules, metal-based compounds have unique physical, chemical and/ or biophysical properties. In this book chapter, we summarized the very recent progress (2013-2015) from the worldwide effort in the development of novel metal-based compounds. Some recent works on the anti-cancer studies of gold compounds including that of gold(I) and gold(III) will be discussed.

Keywords: Cancer, Cytotoxicity, Drugs, Encapsulation, Gold(I), Gold(III), *In vitro*, Medicine, Metal Complexes, MTT Assays.

INTRODUCTION

According to the recent released facts (February, 2015) from the World Health Organization (WHO), cancer is the leading cause of worldwide mortality, with approximately 8.2 million cancer-related deaths and 14 million new cases in year of 2012 [2]. It is also expected that the annual new cancer cases will rise to 22 the million within the next two decades. Although technological advancements

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in surgery, cancer chemotherapeutics and radiotherapies have been achieved, cancer patients are not infrequently encountering problems associated with resistant cancer strains, cancer metastases and toxic/ harmful side effect from different types of anti-cancer treatments [3]. Moreover, the cancer facts tell us that there still remains a great urge in the discovery of new anti-cancer agents/ options for the treatment of cancers, especially for patients who are suffering from relapsed cancers. Inorganic compounds indeed open an avenue for new classes of anti-cancer agents since different metal compounds and their corresponding metal ions may have different sizes, charges, coordination geometries, ligand to metal binding kinetics, reactivity patterns in related to redox/ charge transfer, *etc.* [4]. Thus all these properties render metal compounds very often to have unique chemical, physical, biophysical and hence special (or favorable) biological and medical properties compared to conventional organic moieties [5].

In recent decades, a number of review articles have substantially covered the medicinal development of various metal-based drugs [5, 6]. This book chapter mainly focuses on the development of new metal-based drugs of gold in the recent three years (from 2013 to 2015).

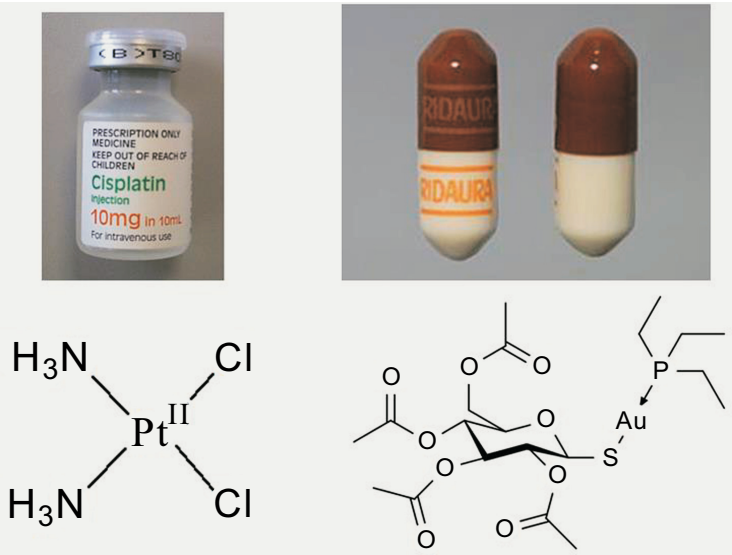

Fig. (1). Cisplatin (Left) and Auranofin (Right).

Gold Compounds

The oxidation states of gold exist from -1 to +5. In biological systems, the relative stable oxidation states include 0 [Au^0 or gold(0)], +1 [Au^I or gold(I)] and +3 [Au^{III} or gold(III)]. Gold compounds have a long history in medicinal chemistry for the treatment of tuberculosis and notably, rheumatoid arthritis. Since the discovery of

the cytotoxic activities of a gold(I) compound (Auranofin, Fig. **1**) by Lorber and co-workers in 1979 [7], the anti-cancer properties of various gold(I) and gold(III) compounds have been uncovered afterwards [8]. Nevertheless, there are various factors hindering the medical development of gold compound to be used clinically. These factors include stability, solubility, toxicity, cancer-cell specificity and cellular uptake efficacy, *etc.* [9]. With the efforts contributed by researchers worldwide, various highly anti-cancer active gold(I) and gold(III) compounds have been identified [10]. Some of them even possess promising anti-tumor activities in animal studies.

Gold(I) Compounds

Since 1979, a number of gold(I) compounds have been identified to display anti-cancer activities [7]. Berners-Price and co-workers in the recent decade have developed a series of gold(I) carbene and phosphine compounds [11]. In 2013, she worked with Barnard *et al.* to discover a binuclear luminescent gold(I) N-heterocyclic carbene (NHC) compound which displays promising *in vitro* cytotoxicity [12]. By using fluorescence and X-ray absorption spectroscopy the anion binding capability of this compound were investigated (Fig. **2**).

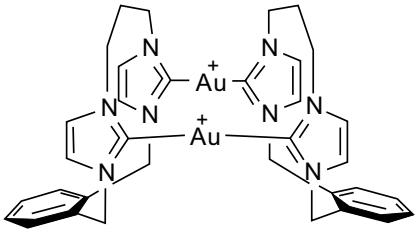

Fig. (2). Chemical structure of a gold(I) compound reported by Berners-Price, Barnard and co-workers [11].

Casini and co-workers in 2013 has re-investigated the anti-cancer property of Auranofin [13]. They found that this compound exerts inhibition effects of glutathione S-transferase P1-1 (GST P1-1) with a calculated IC_{50} value of 32.9 ± 0.5 I1/μM. According to the results from the inhibition assays of GST P1-1 and its cysteine mutants, the authors suggested that the cysteine residues are crucial for the enzyme inactivation in contrast to the reported inhibitors. Casini, Rigobello and co-workers have also developed various anti-cancer active gold(I) and silver(I) compounds containing ligands with a fluorescent anthracenyl ligand [14]. The gold compounds were found to induce oxidation of the thioredoxin system. With the fluorescent properties of the gold compounds, fluorescence microscopic study revealed that tumor cells have a much higher uptake rate of these compounds with respect to normal cells. Several caffeine-based gold(I) N-hetero-cyclic carbenes were identified as possible anticancer agents in 2014 (Fig. **3**) [15].

CHAPTER 6

Oral Delivery by Nanostructures for the Treatment of Cancer

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Abstract: Oral administration of a drug is the most convenient route of treatment for the majority of diseases/disorders. However, there are limitations such as poor solubility, low intrinsic permeability, efflux transport, and extensive metabolism by the gastrointestinal (GI) tract/liver. To overcome these problems, nanoparticles (NPs) have been extensively studied as drug carriers. Previous results suggest that NP therapy can enhance the efficacy, while reducing side effects simultaneously. The development of nanotechnology for the management of cancer, a PEGgylated liposome NP formulation filled with anticancer drug (doxorubicin) had been developed as a first NP based therapy and received FDA approval in 1995. Approximately 20 varieties nanomedicine preparations are in for cancer chemotherapy clinical investigation. Various nano carriers used for cancer therapy need stabilization without effecting the physiological action of drug, its deposition at site of intended tumour and also decrease toxicity. The chapter emphases on NP technology with main focus on the formulation of nanomedicine for cancer therapy. This technique involves liposomes, polymeric NPs, polymeric conjugates, micelles, dendrimers, polymersomes and inorganic/metallic NPs.

Keywords: Cancer therapy, Intravenous, Nanoparticles, Nanomedicine, Oral drug administration, Treatment.

INTRODUCTION OF ORAL DRUG ADMINISTRATION

Oral administration is a route of drug administration where the drug is taken by mouth. It is a widely used route of administration in clinically. Also it is the most frequently used route of drug administration since it is most convenient, economic and painless. The mammalian intestinal inner layers are very absorptive also

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consists of microvilli which can even expand the 1 absorptive area in the gastrointestinal(GI) lumen to 300-400 m2 [1]. Intestinal cells (absorptive) and cup cells (bodily fluid emitting) spread the microvilli, having sprinkled with follicle associated epithelium (FAE). Tissues like lymphoid areas, Peyer's patches, secured with folded cells specifically detecting an antigen. M cells specialized for epithelium of mucosa-associated lymphoid tissues are critical in medication conveyance, because these are less ensured when taken up by body fluids [2, 3] and need more transcytotic limit [4]. Transcytosis is the vesicular transport of macromolecules from one side of a cell to the other. In spite of these potential favorable circumstances, oral delivery presents a few basic issues, especially for proteins: (i) poor steadiness in the stomach pH (ii) low bioavailability and (iii) fluid boundaries can also obstruct drug uptake affecting resulting ingestion. To overcome these restrictions, nanoparticle (NP) solutions are prepared in such a way that entire body and ensure a timely release in a controlled way. The NP surface area is adjusted to improve or decrease biological adhesion to target tumour cells. The barriers for the NPs to penetrate into the epithelial surfaces are mucus form layers protecting the epithelial layer surfaces [5 - 11].

Mucus is formed in our body professionally to protect surface layers of epithelial tissues by trapping pathogens, external particles and removing them rapidly. It is secreted to clear pathogens and also helpful in lubrication of the epithelium as and when materials passes through them, due to which NPs that fail to penetrate the upper layers of GIT decreasing their time of residence.

Role of Mucus in GIT

Mucus is composed of sugars, amino acids, peptides, lipids, salts, antibodies, bacteria and cellular debris. Mucin is a component of mucus made of protein, it is found free or bound to cells [6, 12]. The mucin monomers secreted will bind together by disulfide bonds to give a polymer [13]. It comprises of 2-5% of mucus net weight, mucin polymers bind forming cross-links forming dynamic viscoelastic gel in GIT required for protection and lubrication [14]. In GIT there exists always a constant turnover of adherent and glycocalyx layers constantly working on removal of organic debris and toxic substances entering through diet [15 - 17]. Hence a balanced mechanism exists between secretion of mucus and its removal degradation for maintenance of thickness of mucus layer. Stomach maintains pH of 1.5 to 7 over a mucus thickness of only about 200μm so always there raises a question of how food is able to digest in stomach region without being digesting itself, classical answer for this is only existence of dynamic protective mucosal secretions. Stomach degrades mucus and continuously maintains counterbalance of mucus secretion even at constant presence of low pH and digestive enzymes [13, 18]. The process of lubrication is an important

protective mechanism of mucus in GIT. Mucus entraps biologically active substances which induce inflammation or healing processes after their release, like trefoil factors.

NANOTECHNOLOGY AND NANOMATERIALS

Nanotechnology is widely acknowledged as one of the main techniques of this century and accordingly huge advances have been made in with increased funds in global research on nanomaterials technologies [19]. A wide variety of nanoparticles are formulated and nanotechnology has evolved as main research area in the modern scientific era. The studies on NPs shows novel and varied properties differentiated from large scale unique applications. Nanotechnology is defined by size naturally varied on study of diverse fields including bio chemistry, molecular biology and immunology. Nanomaterials are nowadays widely attracted scientists because of their highly desirable properties [20]. NPs are structures of molecular sizes 1- 100 nm at least in one dimension. The word "nano" is prefixed commonly for particles of hundred nanometers in size. Optimized nanocarriers in terms of physical, chemical and biological properties are thereby absorbed by cells faster than particles of large size, for the effective treatment of many diseases [21] for successful delivery of bioactive substances available in the market. NPs are usually formulated as nanocapsules and nanospheres. The 3 uptake of orally delivered NPs by intestinal cells and its fate is determined by its size. NP surface properties direct the extent of NP uptake into the cells. Based on the nature of the drug to be encapsulated and of the polymers constituting the carrier various techniques are devised for preparation of NP.

NP surface properties are of utmost importance for their absorption by intestinal epithelial cells. Therefore, many approaches have been developed to increase mucosal uptake of NPs, by modifying their surface properties or by coupling a targeting molecule at their surface.

Surface properties can be modified by coating the NP surface with hydrophilic stabilizing, bio-adhesive polymers or surfactants or by incorporating hydrophilic biodegradable copolymers in the formulation. Modification of zeta potential, hydrophobicity, influences formulation of colloidal stability, protein adsorption and NP muco-adhesive properties at the surface, and ultimately oral absorption of the NPs. The main target of preparation these NP by addition of hydrophilic polymers like PEG (polyethylene glycol) or chitosan is to increase their passage across the intestinal mucosa *via* specific interactions between intestinal epithelium and nanocarriers [22]. Thus, modified NP's either by improving non-specific interactions with the cell apical surface or by grafting a specific ligand targeting epithelial intestinal cells ensure drug encapsulation in protective synthetic

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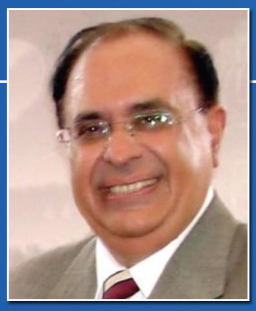

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