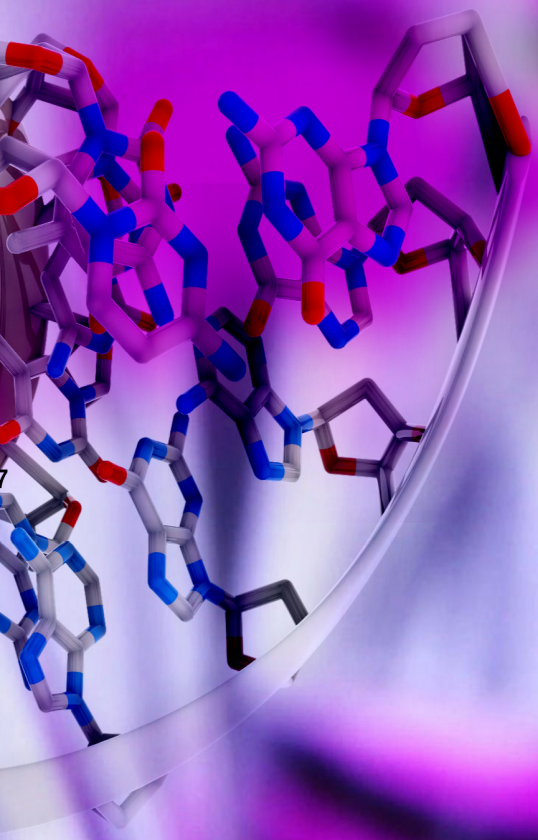
eISSN: 2213-3585
ISSN: 2468-5860
eISBN: 978-1-68108-333-9
ISBN: 978-1-68108-334-6

Volume 5

Topics in Anti-Cancer Research



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Bentham Books

Topics in Anti-Cancer Research

(Volume 5)

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Topics in Anti-Cancer Research

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ISSN (Print): 2468-5860

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ISBN (Print): 978-1-68108-334-6

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CONTENTS

INTRODUCTION

The fifth volume of this series entitled “Topics in Anti-Cancer Research” presents an overview of recent developments in the field of cancer. The topics covered include regulatory policies, cell based anticancer drug delivery systems, anticancer agents targeting heat shock proteins, and tumor homing peptides (THPs) for treatment of cancer.

PREFACE

The fifth volume of the Book series entitled “Topics in Anti-Cancer Research” is based on new contributions from eminent scientists working in the field of cancer research and therapy. The topics presented cover recent advances in cancer drug development targeting carbonic anhydrase IX and XII.

Frost *et al.* discuss the roles of carbonic anhydrase IX and XII in stabilizing pHe in physiological conditions and their use in anti-cancer targets. Studies on the recent patents of CA IX and XII targeted inhibitors are also discussed, especially with reference to sulfonamide-based small molecule inhibitors, derivatives of boron cluster compounds, metal complexes of poly(carboxyl)amine-containing ligands, nitroimidazole-, ureidosulfonamide and coumarin-based compounds and G250 and A610 monoclonal antibodies for cancer therapy.

Zhu *et al.* present an analysis of patents and patent applications associated with cancer drug development in China including existing regulatory policies, data and trend of Chinese domestic anti-cancer drug patents, exploration of Chinese applicants in other countries and recent case study of liver cancer. Bosnakovski has reviewed the promising field of cell based anti-cancer drug delivery systems and studied recent patents and current developments.

Tutar discuss the potential role of heat shock proteins in the metabolic processes of cancer cells and the interaction of heat shock proteins with other proteins and kinases to inhibit cancer cells leading to apoptosis, for better therapy. Patents using this mechanism are also reviewed.

Dhama *et al.* reviewed the data of recent searches and patents on tumor homing peptides (THPs) functioning for targeted drug delivery in cancer cell and the significance of THPs in cancer therapy.

We expect that these topics on new drug targets, drug delivery approaches and techniques in cancer research & therapy will prove to be of great interest to researchers and scientists in the field of cancer and its treatment.

The editors are obliged to the authors for their excellent and timely contributions and to the reviewers for their thorough reviewing, which has enabled us to improve the quality of these chapters. We also extend our thanks to Mr. Mahmood Alam and Mrs. Rafia Rehan, as well as other colleagues of Bentham Science Publishers, for their rigorous participation and support in the accomplishment of the present eBook.

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CHAPTER 1

Advances in Anti-Cancer Drug Development Targeting Carbonic Anhydrase IX and XII

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Abstract: The microenvironment within a solid tumor is heterogeneous with regions being both acidic and hypoxic. As a result of this, cancer cells upregulate genes that allow survival in such environments. Some of these genes are pH regulatory factors, including carbonic anhydrase IX (CA IX) and in some cases XII (CA XII). CA IX helps to maintain normal cytoplasmic pH (pHi) while simultaneously contributing to the extracellular pH (pHe). CA XII is also thought to be responsible for stabilizing pHe at physiological conditions. Extracellular acidification of the tumor microenvironment promotes local invasion and metastasis while decreasing the effectiveness of adjuvant therapies, thus contributing to poor cancer clinical outcomes. In this review, we describe the properties of CA IX and CA XII that substantiate their potential use as anticancer targets. We also discuss the current status of CA isoform-selective inhibitor development and patents of CA IX/XII targeted inhibitors that show potential for treating aggressive tumors. Some of the recently published patents discussed include sulfonamide-based small molecule inhibitors including derivatives of boron cluster compounds; metal complexes of poly(carboxyl)amine-containing ligands; nitroimidazole-, ureidosulfonamide-, and coumarin-based compounds; as well as G250 and A610 monoclonal antibodies for cancer treatment.

Keywords: Bicarbonate transport, cancer therapeutics, carbonic anhydrase, carbonic anhydrase IX, carbonic anhydrase XII, CO_2 transport, coumarins, drug development, ERα, estrogen response element, HIF-1α, hypoxia response element, immunotherapy, pH regulation, prognostic marker, RNAi technology,

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sulfonamides, therapeutic target, tumor microenvironment, zinc metalloenzymes.

1. INTRODUCTION

Carbonic anhydrase (CA, EC 4.2.1.1) is a family of metalloenzymes (mainly zinc) that catalyze the reversible hydration/dehydration of CO_2 to bicarbonate: $CO_2 + H_2O \rightleftharpoons HCO^-_3 + H^+$ via a two-step ping-pong mechanism. Present in both prokaryotes and eukaryotes, these enzymes have evolved into six distinct classes: α, β, γ, δ, ζ, and η [1 - 21]. Of these classes, only α-CAs are present in humans, of which fifteen isoforms are encoded [1, 9, 22]. Among these isoforms, only twelve coordinate a zinc in the active site and are catalytically active (CAs I–IV, CAs VA–VB, CAs VI–VII, CA IX, and CAs XII–XIV). Isoforms VIII, X, XI are termed CA-related proteins (CARPS) as they lack at least one amino acid in the active site to coordinate the zinc and therefore are catalytically inactive. The active human CA isoforms differ in kinetic properties along with cell and tissue distribution. CAs play crucial roles in many physiological processes including CO_2 and bicarbonate transport between metabolizing tissues and lungs, pH and CO_2 homeostasis, bone resorption, and electrolyte secretion [1, 9, 11 - 13, 22]. Of the human isoforms, only the membrane-associated isoforms IX and XII have been implicated in tumorigenicity, cancer metastasis, and as clinical prognosticators [19 - 25]. In this chapter, the characteristics, expression patterns, and functions both in normal and neoplastic tissue of the cancer associated CA IX and CA XII will be discussed. We will also discuss the anti-cancer targeting strategies for both isoforms.

1.1. Active Site Structure and Catalysis of CA IX and CA XII

The amino acids that form the active site of α-CAs are highly conserved, and at the core of the active site is a zinc (Zn^{2+}) ion that is essential for catalysis (Fig. (**1**)) [25 - 27]. The zinc is located at the base of a 15Å deep active site cleft and is tetrahedrally coordinated by three histidines (His94, His96, His119; CA II numbering used throughout this manuscript unless otherwise specified) and a water/hydroxyl [28 - 30]. The first step of catalysis in the hydration direction is the nucleophilic attack by the Zn-bound hydroxyl group on CO_2 to produce

HCO^-_3. The HCO^-_3 is then displaced by an active site water and released. In the second step of catalysis, the Zn-bound water is regenerated to a hydroxyl through the transfer of a proton mediated by a highly ordered solvent network and conserved histidine residue (His64) found in most isoforms, termed the proton shuttle residue [1, 25, 31].

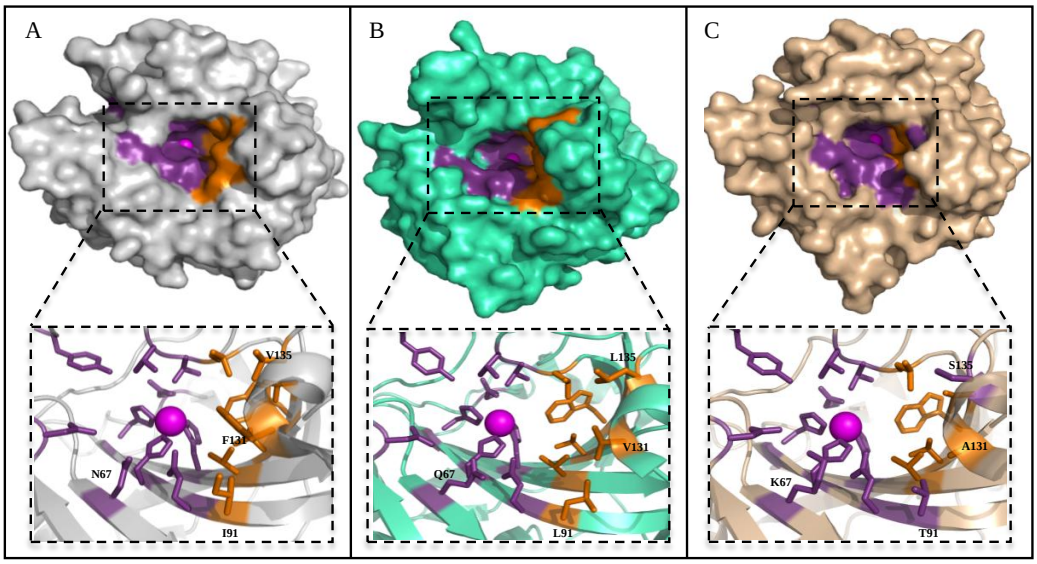

Fig. (1). Structure of human α-CAs. Surface depiction of (A) CA II, PDB ID 3KS3 (grey), (B) CA IX, PDB ID 3IAI (green), C) CA XII, PDB ID IJCZ (wheat). Active site zinc (magenta sphere), hydrophilic (purple) and hydrophobic (orange) residues are shown. Residues within the active site that are different between these CAs are labeled (CA II numbering). CA II (N67, I91, F131, V135), CA IX (Q67, L91, V131, L135) and CA XII (K67, T91, A131, S135).

The proton transfer step is the rate-limiting step in this catalysis reaction. Isoforms CA II, CA IX and CA XII exhibit extremely fast catalytic activity (Table **1**) [1, 22]. It is thought that this catalytic efficiency is in part due to the ability of His64 to shuttle protons with a low energy barrier between an inward (pointing towards the active site) and outward (pointing away from the active site) conformations [1, 25, 31]. The active sites of CAs also exhibit a divided active site cleft with a hydrophobic and a hydrophilic side (Fig. (**1**)). The hydrophobic side supports the pathway for substrate and product entry and exit, while the hydrophilic side provides the amino acids that define an ordered solvent network for proton transfer [32].

CHAPTER 2

Tumor Homing Peptides: Promising Futuristic Hope for Cancer Therapy

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Abstract: Tumor homing peptides (THPs) are cyclic or linear peptides of few amino acids having inherent property to recognize the tumor cells, which specifically bind to the receptors present on the tumor cells, tumor blood vessels or tumor lymphatic vessels. These can be utilized as major tool for targeted drug delivery particularly to cancerous cells, hence these are important for efficient cancer treatment. The present chapter summarizes the recent progression in the researches, databases and patents available in the field of cancer therapies utilizing THPs. It elucidates details about THPs; their modes of functioning, the molecules these may translocate; different methods of entry into the cells as well as diverse uses like gene correction and targeting of various tissues. Screening of THPs from phage library, natural occurrence of THPs in bacteria like *Salmonella*, *Pseudomonas* and engineered baculovirus have also been explicated. The specificity of THPs can be further enhanced by blending these with amphipathic conjugates, whereas the penetrability may be improved by adding cysteine or maleimidohexanoic acid to their N-terminal. Their half-life can also be increased by

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adding unnatural amino acids and modifying backbone or cyclization of THPs. For diagnostic and therapeutic purposes, several THPs have already been entered in different stages of clinical trials. THPs could serve as an ideal futuristic approach for targeting tumors based on their higher specificity, improved penetrability and half-life, acting as efficient delivery cargos for anticancer drugs and large therapeutic molecules.

Keywords: Angiogenesis, anticancer therapy, barrel stave pore, cancer therapies, CendR pathway, cell-penetrating peptides, clinical trials, inverted micelle, nanoparticles, phage display, RGD domain, toroidal pore, THP receptors, tumors, tumor homing peptides, vascular supply.

INTRODUCTION

'Cancer' is amongst the frightening diseases which is inexorably seeking attention for the search of its cure, as its occurrence is dynamically increasing in living beings. This disease has become a challenge to both developed and developing countries of the world. It is no more amongst the rare diseases now, since it has got a greater frequent incidence rate among the masses. One of the challenges in designing drugs for treating cancer is the necessity of focused medication towards cancerous cells pardoning normal body cells from its lethal effects. Many treatment options such as radiation therapy, chemotherapy, surgery, photodynamic therapy etc. have been explored for this deadly disease but none has been effective to provide absolute cure without ill effects [1, 2]. Drugs often have issues like non-specificity, residual toxicity and poor efficacy within the *in vivo* system [3]. Designing cancer therapeutics in such a way that they can smartly differentiate between normal and altered cells will definitely reduce the systemic toxicity of present anti-tumor agents. Tumor cells and tumor vasculature have shown to express significantly different molecules on their surface than the normal ones. Drug resistance is also one of the bottlenecks of cancer treatment that usually arises due to many drug and host related factors. Monoclonal antibodies are one of the options available in case of targeted therapeutics but they suffer from many shortcomings such as low tissue penetration owing to their large size and toxicity due to non-specific trapping in the liver/reticuloendothelial system (RES).

In this direction, one amongst the pioneering innovative initiatives is the

identification of certain peptides termed as "tumor homing peptides", which are specific to certain receptors on cancerous cells or cancer vasculature [4, 5]. It has increased the efficacy of targeted delivery since these functioning in conjunction with therapeutic molecules/ drugs are able to minimize the side effects of the drugs. Tumors have low blood vessel perfusion and high interstitial pressure due to dysfunctional lymph vessels that result in low drug absorption [6]. This problem of low absorption of anti-cancerous agents can be overcome by employing such delivery agents that are smaller in size with no binding to RES and it can further reduce the cost of cancer treatment as well [7].

Cancer is just one dimension, where these peptides find useful applications, but their use is not limited up to here. Even, these can be used to design placenta based therapeutics to treat any condition in foetus [8]. Certainly, these are one amongst the most wonderful findings in the field of medical science for the benefit of the mankind and animal kingdom and definitely in providing the relief from many deadly conditions. These can be used in different ways to treat cancer such as they themselves acting as drugs or carriers of the drug, hormone etc. at the site of action. Seeing the potential of these tumor targeting peptides, it is required to increase the pace of their identification using computer aided approach so that we get a collection of these in our hands readily available for present and futuristic therapeutics.

TUMOR HOMING PEPTIDES (THPS)

Tumor homing peptides (THPs) are short peptide sequences, generally having 3 to 15 amino acids; however Porkka *et al*. derived a 31-aa synthetic peptide [9], and possessing certain common motifs in them can target specific tumor [10 - 12] on its surface or tumor vasculature after their delivery. Homing peptides can be grouped into three classes (i) peptides that home to specific target site recognizing cell surface molecules without internalization, (ii) peptides that recognize the cell surface molecules and are internalized; and (iii) peptides capable of targeting, internalization and destruction [13, 14].

Tumor-specific internalizing peptides' (TSIPs) are capable of translocating on the plasma membrane of the cell. TSIPs have target specificity as well as penetration

CHAPTER 3

Cell-Based Anticancer Drug Delivery Systems

Darinka Gjorgieva Ackova[1], Katarina Smilkov[1] and **Darko Bosnakovski[1,2,3,*]**

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Abstract: Most explored approaches to developing cell-based drug delivery systems (DDSs) are encapsulation of the drug into the cells, cell surface modification, genetic modification of cells to secrete desired therapeutic proteins, and generating new biosynthetic systems. Tumor-tropism of mesenchymal stem cells (MSCs), as demonstrated in many studies, can be coupled with appropriate engineering with anticancer genes to enable their employment in anticancer therapy. Furthermore, MSCs can be loaded with nanoparticles (NPs), providing transport across the blood-brain barrier and accumulation of anticancer agent at the tumor site. Another attractive cell type for DDS are dendritic cells (DC), monocytes and macrophages because of their ability to accumulate in large numbers at hypoxic sites of the tumors. To this moment, exosomes are very attractive and investigated cellular entities that are used to be loaded with RNA, proteins, or other small molecules, including anticancer agents. Some of the above-mentioned cells can also be used as membrane sources in the production of anticancer delivery systems. A number of recent research papers and patents in this field are evidence of the growing interest in cell-based DDSs. In this chapter, we summarize recent developments in the field, present a newly established methodology and approaches, give an overview of the recently published inventions (patent databases FPO and Delphion were searched to locate newly published patents: US20150079631, WO2015058148A1, US20160220613, etc.), and discuss further possible developments. Further expansion in this field is expected, although limitations in design and use of DDSs exist and must be overcome before these innovative formulations can reach clinical trials and marketing authorization.

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Keywords: Anticancer agents, anticancer therapy, cell membrane vesicles, dendritic cells, drug delivery systems, exosomes, genetic engineering, mesenchymal stem cells, nanoparticles, recent patents.

1. INTRODUCTION

The bioavailability of many drugs is often compromised by their poor hydrosolubility, disintegration, metabolic activation/inactivation or excretion. Many of these problems could be resolved through the use of new and modified drug delivery systems (DDSs), which is one of the focuses of current pharmaceutical research [1, 2]. Different DDSs currently in use for pharmaceutical applications (clinical or cosmetic) are artificial and chemically synthesized (liposomes, micelles, nanoparticles, dendrimers…), or based on autologous cells or cell membranes. DDS using similar membrane structures compared to body cells are considered safest with good biocompatibility and low toxicity. In recent years, novel cell membrane-coated particles combining advantages of natural cells and synthetic polymers with various applications, such as drug delivery, have also been developed [3, 4]. Different types of DDSs that are currently in advanced phase of clinical investigation are given in Table **1** [5 - 19]. In addition, as a confirmation of the growing potential of these systems, some cell-based DDS have already been marketed (e.g., sipuleucel-T).

Despite the known advantages, there are also some concerns pointing that these DDSs are not ideal, as possibilities for the development of an antibody-antigen reaction, tumor progression and differentiation or development of toxic response to some of the components exist. Therefore, the selection of suitable cell-type for drug delivery must be accompanied with great attention. As targeting delivery of anticancer agents is still a great challenge, this chapter will focus on three main kinds of DDS for anticancer agents: whole cells - MSCs, immunological cells (DCs) and cell membrane vesicles (particles). This chapter will also present facts about fabrication processes, unique properties and their applications as promising tools to help in the search of effective cancer therapy.

Table 1. Artificial, Whole Cell or Cell Membrane-Based Drug Delivery Systems.

Carrier	Source/Target	Carrier for	Reference
Artificial			
Liposomes	Cationic cardiolipin liposomes/ prostate cancer	Nucleic acid (RAF siRNA)	[5]
Micelles	Styrene-maleic acid-copolymer micelle	Drugs (cisplatin)	[6]
Nanoparticles	Glycoengineered MSCs /ovarian tumor	Drugs (paclitaxel)	[7]
Dendrimers	PAMAM dendritic polymers coupled with folic acid/ human KB cell line	Drugs (methotrexate)	[8]
Whole Cell or Cell Membrane-Based			
Bacteria/Bacterial ghost	Mannheimia haemolytica/human colorectal adenocarcinoma cells (Caco-2) *Vibrio cholerae* ghosts /	Drugs (doxorubicin) Vaccine (outer membrane protein of *Chlamydia trachomatis)*	[9] [10]
Viruses	Adeno-associated virus (AAV)/ liver cancer cells	Nucleic acid (miRNA)	[11]
RBCs/ Erythrocyte ghost	Red blood cell membrane-cloaked nanoparticles Pravastatin chitosan nanogels-loaded erythrocytes/ HepG2 cell lines	Various drugs Various drugs	[3] [12]
Macrophages	Tumor-associated macrophages/ liver metastases	Albumin bound paclitaxel	[13]
Dendritic cells	Regulatory DCs	Nanoparticles encapsulating siRNA	[14]
Mesenchymal stem cells	Gene-manipulated adipose-tissue derived MSCs/colon cancer Gene-manipulated adipose-tissue derived MSCs/colon cancer	Prodrug (5-fluorocytosine) Prodrug (gancyclovir)	[15] [16]
Exosomes	Exosomes Exosomes from MSCs/ human pancreatic cell line CFPAC-1	Drugs (curcumin) Drugs (paclitaxel)	[17] [18]
MSC NGs	Nano ghosts derived from MSCs/ PC3 cell line	Protein (sTRAIL)	[19]

CHAPTER 4

Studies on Patents and the Associated Anti-cancer Drug Development in China

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Abstract: This chapter consists of five sections. The first part analyzes the macro policies of Chinese anti-cancer drugs, sorts the existing policies and regulations in China and clarifies the main departments of Chinese domestic drug regulation.

The second part is the analysis of Chinese domestic anti-cancer drug patents. Based on the domestic Chinese invention patents as the data source, this section analyzes Chinese domestic anti-cancer drug patents, major competitive countries and regions, developmental characteristics of patented technology, and the main applicants. It can be found that Chinese local patent applications have increased yearly since China began to protect drug patents in 1992. Up to the retrieval date, there is a total of 57,280 pieces of invention patents in China. Patent applications of China, the United States,

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Japan, Germany and Britain occupy the top 5 positions. Among them China has the most patent applications. However, high-level patents are few The patent applications of the United States rank second, but the patent quality is considerably ahead, with rapid development in the Chinese patent markets. In addition to the focus and hotspots of patent applications of China, the United States, Japan, Germany and Britain also are analyzed in this part. Bode Gene Dev. Co., Ltd. Shanghai, Roche Holding Ltd., Merck & Co., Ltd., Pfizer Inc., Novartis AG are the top 5 patentees in terms of patent applications, with differences in development in the Chinese market, technical focus and hotspots.

The third part is the analysis of patent applications in foreign countries by Chinese applicants. Up to the retrieval date, Chinese applicants have a total of 4,036 invention patents in foreign countries. Since China's accession to the WTO, the amount of patent applications through the WIPO and EPO has increased rapidly. The United States is the most popular country for Chinese inventors. From the view of technical fields, patent applications in the field of A61K 31/00 (pharmaceutical preparations containing organic components) are the highest, up to 645 pieces. The top 10 of the International Patent Classification (IPC) accounts for 45% of the total applications. From the view of applicants, Roche Holding Ltd. is the most powerful company, occupying the leading position through their technical strength and number of patents. The patent applications of Medipharma SA are far ahead, but are relatively weak in strength. There is a large gap between these two companies and the other companies both in strength and the number of patents.

The fourth part is a case study. According to the statistics of GLOBOCAN, new liver cancer cases in China accounted for about 50% of cases (up to 782,000) in 2012. Based on the analysis of Chinese local anti-cancer drugs, the attention of Chinese inventors concerning liver cancer has increased in recent years. From the perspective of Chinese domestic patents, China's patent applications account for 74.6% of total applications, however important patents and core patents account for only 2%. The number of top 10 IPC patent applications is 2,430, accounting for 43% of the total. From the perspective of applicants, the applications of Fudan University and the Chinese Academy of Sciences are the highest, at 80 pieces each. The technical strength of the Chinese Academy of Sciences is the highest, while GlaxoSmithKline plc. is relatively weak. From the perspective of Chinese applicants in foreign countries, Chinese inventors contributed 738 pieces of patents for liver cancer drugs from 1985 to 2015. The United States, Japan, South Korea, Canada and Australia are the main countries where Chinese inventors apply for patents. The five countries account for 67.8% of the total patent applications. The patent applications of the top 10 IPCs is up to 371, accounting for 50.3% of the total. Among them, A61K 31/00 (pharmaceutical preparations containing effective organic components) is the key IPC. Hangzhou Bensheng Pharmaceutical

Co., Ltd. has applied for 34 pieces of patents, located at the right end of the horizontal axis, indicating the patentee's powerful technology.

Keywords: Anti-cancer drugs, bubble analysis, Chinese applicants, competitor analysis, competitive countries, China market, design, IPC distribution, liver cancer, patent analysis, policies analysis, patent application analysis, patent application, patent for invention, patent strength, technical fields, text clustering, utility model.

INTRODUCTION

The incidence of cancers in China is not optimistic. However, it takes time, higher costs and higher risks for scientists from industry and academia to pursue anti-cancer drug R&D. Mining information from patent data can provide decisive support for inventors, investigators and competitors in the field. The present work aims to study the development of Chinese anti-cancer drugs. On the basis of macro policies of anti-cancer drugs in China, we systematically analyzed the competitive status of anti-cancer drugs in the Chinese domestic markets, explored patent distributions and trends of inventors in the field of anti-cancer drugs, and did a deep analysis using liver-associated cancer drugs as a specific case.

The patent is a kind of scientific and technical document which records the contents of the invention and contains technical, legal and economic information. Many inventions were published in patents which could not be found in other scientific literature. The British Derwent Information Ltd. believes 70%-90% of patents are not published in other publications, however, the European Patent Office (EPO) believes that this ratio is 80%.

China is changing from labor-intensive to knowledge-intensive endeavors, and the importance of intellectual property rights is increasing. In 2008, the State Council of the PRC promulgated the "National Program for Intellectual Property" in which the creation, application, protection and management of intellectual property rights have been promoted to the national strategic level. In 2016, the first year of China's 13th Five-Year Plan, it was put forward to implement the strategy of innovation-driven development, put the developmental basis on innovation with scientific and technological innovation at its core, and develop

CHAPTER 5

Recent Developments in Anticancer Agents Targeting Heat Shock Proteins

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Abstract: Proteins are metabolic factors to perform biochemical functions. For proper protein function, these macromolecules must be in their properly folded-native states. Under stress, cells employ Heat Shock Proteins (Hsps) to overcome this folding problem. For this reason, Hsp proteins play essential roles in the metabolic processes. In cancer cells the situation is different than healthy cells. Since the metabolic rates of cancer cells are faster than that of healthy cells, cancer cells overexpress Hsps to rescue unfolded proteins to perform biochemical functions. Thus, several research groups have been focused on Hsps. This protein family consists of several members and interacts with several cell signaling proteins, kinases, and transcriptional factors. All these interactions provide key controlling points to inhibit cancer cells and drive them to apoptosis for therapeutic purposes. Different approaches on Hsp mechanism were employed for cancer cell inhibition either by interrupting Hsp90-apoptosis inhibitor protein interactions or by blocking Hsp90-proteasome function. In a similar way, topoisomerase-Hsp90 interaction was perturbed. Small molecules as well as peptides

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Atta-ur-Rahman and Khurshid Zaman (Eds.)

were employed to inhibit functions of Hsp70 and Hsp27. Several designs were performed and patented using Hsp cascade and this study summarizes the innovative patents in the area.

Keywords: Antigenic peptide complex, apoptosis, berberine, cancer, chimeric peptide, delivering an anticancer agent, heat shock protein targeted therapy, hepatitis, hepatoma, Hsp27, Hsp70 inhibitors, Hsp90 NTD inhibitors, Hsp90 CTD inhibitors, oncogenic client proteins, peptides, proteasome, protein folding, protein-protein interaction inhibitor, secreting modified heat shock protein, topoisomerase I.

INTRODUCTION

Heat shock proteins (Hsps) are highly conserved chaperone protein family and Hsps are essential biomolecules for the maintenance of cell viability. Hsps are involved in protein hemostasis pathways (folding and stabilization of proteins, prevention of protein aggregation, degradation of aggregated proteins, and protein translocation) in all living organisms. The molecular weights of Hsps are between 10 and 110 kDa, and Hsps can be divided into six groups according to their molecular weights (small Hsps, Hsp40, Hsp60, Hsp70, Hsp90, and Hsp110). Hsps are localized at different compartments of the cell and their expression level is highly increased in response to cellular and external stress factors (metal ions, tumorogenesis, UV light, pH alterations, oxidative stress, fever, and temperature variation). Hsps and their different isoforms are expressed either inductively or constitutively in the cell [1 - 4].

Pathogenesis of diseases is related with expression level of the Hsps and therefore, Hsps are considered as target biomolecules for drug design studies. To protect and repair cellular proteins against stress factors, Hsp inducers have been developed for the treatment of neurodegenerative diseases, cardiovascular diseases, febrile diseases, and gastrointestinal diseases [5]. Expression of Hsps in cancer cells has been extensively investigated in relation to the pathogenesis of tumorogenesis. Especially, Hsp27, Hsp70, and Hsp90 are key chaperone proteins in all phases of tumorogenesis (apoptosis, angiogenesis, metastases, invasion, and cell differentiation), and their expression level is increased significantly in cancer

cells. Hsp27, Hsp70, and Hsp90 provide stabilization and proper folding of the oncogenic proteins in cancer cells. Several methods of inhibition were designed. Small molecule inhibition as well as peptide dependent inhibition gave promising results and an innovative approach interrupted protein-protein interaction through blocking key steps in biochemical pathways by designed compounds. Protein-protein interactions are important in Hsp coordinating-cooperating mechanism. Therefore, inhibition of chaperone activity of Hsp27, Hsp70, and Hsp90 has been a remarkable therapeutic strategy for target specific cancer treatment [5 - 7].

Heat Shock Protein 90

Commonly investigated macromolecule in chaperone inhibition is Hsp90. Hsp90 is a 90 kDa chaperone protein which plays vital roles in stabilization and proper folding of oncogenic client proteins (transcriptional factors, transmembrane tyrosine kinases, metastable/chimeric/mutated signaling proteins, and cell cycle regulators) for the growth and survival of cancer cells.

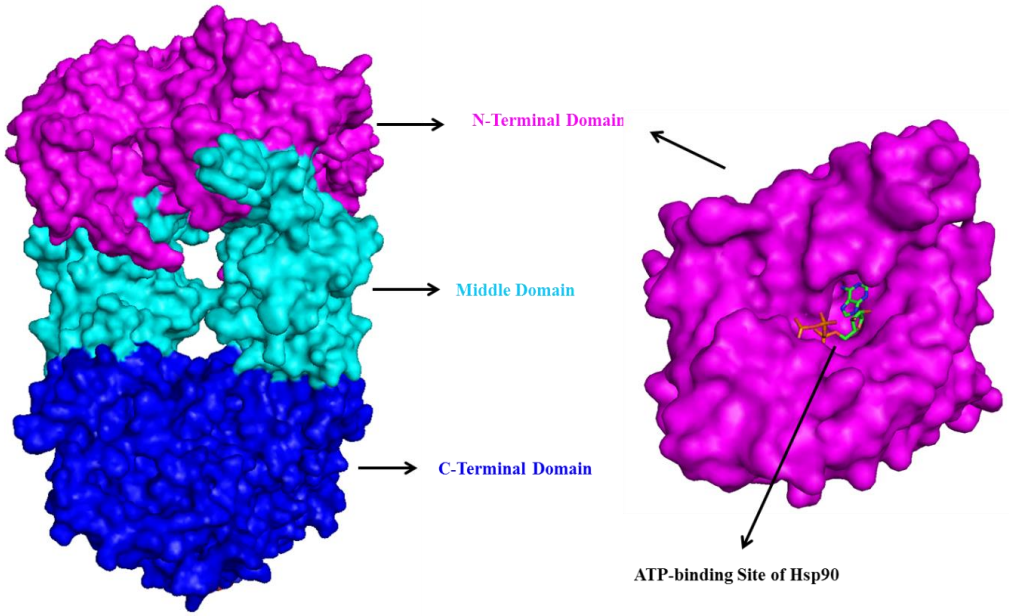

Fig. (1). Structure of Hsp90 (PDB ID 2CG9).

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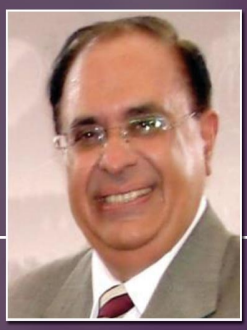

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1020 international publications in several fields of organic chemistry including 727 research publications, 37 international patents, 68 chapters in books and 188 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 50 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.