

## Review Article

# Mini Review: The Application of Omics in Targeted Anticancer Biopharmaceuticals Development

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## Abstract

Cancer is a complex invasive genetic disease and a significant cause of mortality worldwide. To effectively treat cancer using targeted biopharmaceuticals, it is essential to uncover the biological functions of genes, proteins and metabolites underlying abnormal cancer cell growth. The high-throughput Omics technologies have been proved as efficient approaches to investigate the initiation, development, and progression of cancers. This article reviews the cancer Omics and its applications in targeted anticancer biopharmaceuticals development. We first discuss how the established Omics knowledge and integrated data mining tools have been used to discover cancer biomarkers that reveal the clinically relevant diagnoses, prognoses and therapies. Deciphering cancer drivers has led to the specific design of effective cancer therapeutic approaches such as those target specific regulator, core pathways, glycolysis, and mitochondria. The developments of targeted cancer therapy, biopharmaceutical, and personalized medicine facilitated by Omics technologies are then described. Development of therapeutic proteins to treat various cancers has been greatly benefited from the significant findings in cancer mechanism studies using Omics. For instance, the recent advances in CHOmics have enabled the rational bio processing design to improve clinical efficiency of biopharmaceuticals. The potential applications of CHOmics in Chinese hamster ovary (CHO) cell-based therapeutic proteins production are finally presented.

**Keywords:** Omics; Cancer; Targeted therapy; Anticancer biopharmaceuticals.

## Abbreviations

CHO: Chinese Hamster Ovary; EGFR: Epidermal Growth Factor Receptor; HER: Human Epidermal Growth Factor Receptor; KEGG: Kyoto Encyclopaedia of Genes and Genomes; mAb: Monoclonal Antibody; NSCLC: Non-Small-Cell Lung Cancer; PKM2: Oncofetal M2 Isoform of Pyruvate Kinase; RNAi: RNA Interference; VEGF: Vascular Endothelial Growth Factor.

## Introduction

Cancer is a complex invasive genetic disease that causes a significant mortality worldwide. The American Cancer Society predicts that the total number of cancer patients will continue increasing steady, with approximately 1,660,290 new cancer cases diagnosed and about 580,350 deaths happened in 2013 in the United States. Cancer is characterized by various hallmarks, such as abnormal cell growth, enhanced proliferation, reduced apoptosis, angiogenesis, shifted metabolic activity, etc [1-3]. Although the detailed mechanisms remain to be determined, it is well appreciated that the incidence of cancer is associated with the mutual interactions of genetic mutations (e.g., single nucleotide change and germ line copy number change) and environmental toxins (e.g., infectious agents, chemicals, X-rays, UV, smoking, high calorie, and high salt intake) [4]. To effectively treat cancer, it is essential to uncover the biological functions of genes, proteins and metabolites underlying the autonomous tumor cell growth. The high-throughput and high-resolution Omics technologies have been proved as efficient

approaches to investigate the initiation, development, and progress of cancers.

The completion of human genome project and the access to public cancer genomics databases, e.g., International Cancer Genome Consortium and The Cancer Genome Atlas, have provided us the opportunity to study cancer at genome scale [5,6]. The genome comparison between normal and transformed cells has opened the door to understand the genome background of cancer. Furthermore, the development of new-generation DNA sequencers, such as Illumina HiSeq 2000 and Life Tech SOLiD, enables the comprehensive and complete analysis of whole genome, DNA copy number, methylation, and transcription. Transcriptomics is a functional genomics analysis by qualifying and quantitating mRNA expression at transcription level. The complied human gene expression data can be downloaded from the database of Gene Expression Omnibus [7]. The advances in microarray [8] and next-generation sequencing [9] which has significantly reduced sequencing cost to about \$1,000 each sample, allow for the interpretation of gene expression and transcription regulation in the research labs. Moreover, multiple gene expression signatures in cancer cells have been recognized by the quantitative characterization of genome-wide transcriptional profiles [10,11].

More interests have been directed toward proteomics study because the cell functions relating to post-transcriptional modifications and protein interactions can't be captured by genomics or transcriptomics analysis [10,12]. Proteomics quantify the expression of large number of intracellular proteins, so the biomarkers

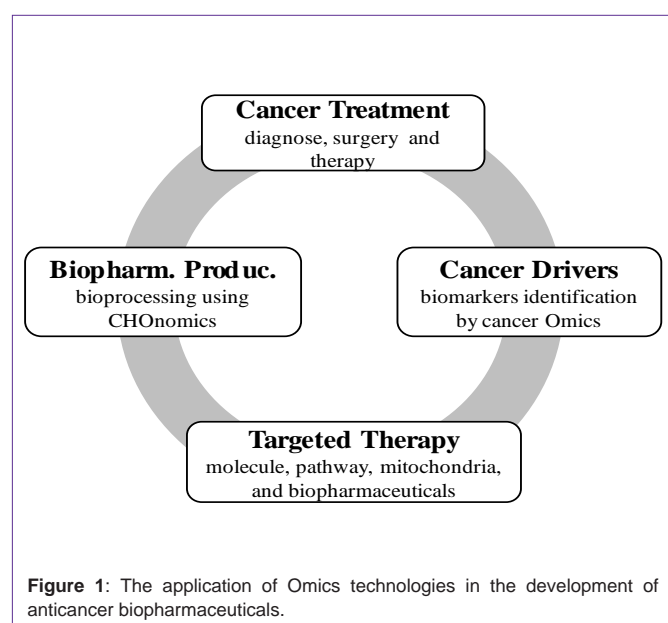
specifically expressed in the transformed cells can be identified from the global proteome profiling [13]. Various analytical tools have been developed for proteomics study including: 1) SELDI-TOF-MS is used to directly analyze protein mass without enzymatic digestion [14,15]; 2) UPLC-MS/MS is applied to analyze the whole protein repertoire of the samples partially digested; and 3) MALDI-TOF-MS enables the sub-femtomole resolution of compound detection [16-18].

Metabolomics is a qualitative and quantitative approach for the analysis of cellular metabolites using HPLC, GC-MS and/or LC-MS/MS. The integration of intracellular and extracellular metabolism analysis offers the dynamic profiling of the overall outcome of cellular metabolism, genome control, and enzyme regulation [14,19]. Therefore, the metabolic biomarkers identified from metabolic profiling can support cancer diagnosis and cancer treatment [20].

Omics have provided powerful analytical tools that generate big data. The applications of Omics data sets in targeted anticancer biopharmaceuticals development include, but not limited to, key information extraction from public databases, cancer biomarker identification for diagnosis and therapy, targeted cancer therapies development by regulating the suitable targets, and expression of drugs with high clinical efficiency. As shown in Figure 1, we will first overview the application of Omics in discovering the single molecular and network cancer biomarkers; then discuss the development of targeted cancer therapy, biopharmaceutical, and personalized medicine facilitated with Omics technologies; and finally present the potential to apply CHONomics in Chinese hamster ovary (CHO) cell-based therapeutic proteins production, thereby improving the clinical utilization.

### Omics in Cancer Biomarker Identification

Intensive research showed that the malignance transformation of cancer is caused by the mutations of oncogene and tumor suppressor genes. Most cancers are signalled by molecular, pathway, and network markers. These biomarkers indicate the diseased cells, tissues, or individuals, so the investigation of biomarkers can



**Figure 1:** The application of Omics technologies in the development of anticancer biopharmaceuticals.

benefit cancer diagnosis, prognosis, patient response prediction, and therapy development. The challenge in discovering biomarker is the lack of a complete understanding of cancer development. The high-throughput Omics technologies have generated a large amount of global molecular profiling, which opens the door to study the driving mechanism of cancer.

### Single molecular biomarker

Single molecular biomarkers include gene, mRNA, miRNA, protein, glycan, and metabolite, which are caused by gene mutations, transcription modifications and translation or post-translational modifications. Several Omics databases are available for single molecular biomarker study [12,21,22], including Entrez gene and Mouse Genome Databases for gene annotation [21,23], Uniprot for protein annotation [24-26], and Gene Oncology annotation [27-29]. In addition, several Omics data analysis tools have been developed to map gene, mRNA or metabolite to biological protein, such as UniProt Knowledgebase [30,31], iProClass [32,33], Protein Information Resource [34], DAVID gene ID conversion tool [35], and Protein Identifier Cross-Reference [5,36,37].

The functional profiling of annotated genes and proteins has been successfully used to identify biomarkers of breast cancer, lung cancer, prostate cancer and other cancers. Previous breast cancer research showed that estrogen receptor  $\alpha$  is an estrogen-inducible transcription factor, and its dysfunction accounts for the majority (70%) of breast tumor [12]. Human epidermal growth factor receptor 2 (HER2), a tyrosine kinase receptor, is over expressed in approximately 15-25% of breast cancer patients. A proteolytic fragment of  $\alpha$ -antitrypsin has also been identified as a diagnostic and prognostic marker of breast cancer [21,38,39]. It is reported that the tumor suppressor proteins play a key role in DNA repair through the homologous recombination mechanism [14,40,41], so the germline mutations of breast cancer repressor genes (i.e. *BRCA1* and *BRCA2*) are the fundamental defects in hereditary breast cancer and ovarian cancer. For lung cancer patients, the gain of chromosome 5p occurs in a high number (60%). Other alteration genes that are frequently involved in lung cancer are *EGFR/HER1* and *KRAS* [42,43]. The proteomics analysis has indicated that pyrophosphatase 2 and Ezrin are the potential markers of metastatic prostate cancer [44]. In addition to functional genomics, epigenetics has been used to evaluate the aberration of DNA methylation in cancer cells. Jones and Baylin have observed the global and locus-specific (e.g., CpG island-rich promoters) hypomethylation in abnormal methylation of cancer cells [45,46]. Another study reported that *PITX2* DNA methylation is an epigenetic marker to predict adjuvant tamoxifen therapy in the treatment of early stage cancer [47].

### Network biomarker

Another classification of biomarker is network-based regulator (i.e. panel biomarker), such as cell signalling, biological pathway, and gene regulating network. The multiple network databases, e.g., Kyoto Encyclopaedia of Genes and Genomes (KEGG) [48], Pathway Interaction Database [49], and Pathway Commons [1,49,50], have been established for metabolic pathway and signalling pathway analysis. Mapping experimental data to network pathways is a key step in the functional interpretation of Omics data, which has been achieved by utilizing the systems of pathway analysis, such as

Ingenuity IPA and Gene GO Meta Core [51]. Additional datasets, such as Intact and Molecular Interaction, have been built for protein-protein interaction annotation to reveal cancer classification and indicate the mutation genes [52,53].

Some network biomarkers in various leading cancers have been discovered using cancer Omics. For instance, genomics studies have shown that: (i) the switcher between proliferation and differentiation occurs in the cellular networks of breast cancers [54]; (ii) twelve core signalling pathways alter in human pancreatic cancers [55]; (iii) the dysregulation of the transforming growth factor  $\beta$  plays a key role in epithelial ovarian cancers [56]; and (iv) Some cancer cells exhibit defective genetic-epigenetic networks in different parts of tumor tissues [57,58]. The proteomics study of breast and lung cancers showed that the co-activation of multiple receptor tyrosine kinases sustains cell proliferation in glioblastoma multiforme, indicating the importance of targeting multiple receptor tyrosine kinases [42,59,60]. In addition, the functional proteins can interfere with various signalling cascades, so the aberrant post-translational modification of regulating proteins in a network plays a critical role in the oncogenesis of various malignancies.

All above progresses in network biomarker studies are attributed to the rapid advancement of systems biology that has accumulated a large amount of Omics data. Although various bioinformatics tools have been developed to facilitate functional analysis and data interpretation, it is still challengeable to extract key information from the big data. To solve this issue, various statistical frameworks, computational and mathematical formulas, and genome-scale models have been applied to infer cellular network [61-64]. For example, Alberghina et al. investigated the enhanced glycolysis and mitochondrial metabolic remodelling of cancer cells and identified multiple pathway biomarkers [65]. They characterized four basic cancer properties using the developed model, including enhanced cell proliferation, evasion from apoptosis, genomics instability, and instability of cancer cells to enter senescence, based on their modelling work.

### MicroRNA

The microRNA (miRNAs), derived from non-coding primary messenger RNAs (mRNAs), are single-stranded RNAs of approximately 22 nucleotides in length [66]. The miRNAs bind to the complementary sequence of targeted gene and repress targeted mRNA through direct cleavage or translational repression. Therefore, the deregulation of miRNAs affects both gene expression and metabolic activity involved in cancer pathogenesis. Eventually, the identified predictive or prognostic miRNA signatures can be clinically translated to diagnose cancer disease. Over the last decade, the advanced next-generation sequencing technology and the accumulated transcriptomics knowledge have been utilized for effective and quantitative analysis of both mRNA and miRNA. For example, studies have found that miR-10b, miR-15, miR-16, and miR-20 are anti-angiogenic miRNAs that target the mRNA of epidermal growth factor receptor (EGFR) [67,68]. In other studies, miR-500 has been identified as a potential diagnostic marker of hepatic cell carcinoma [21,69].

Taken together, Omics technologies have enabled the identification of a number of predictive biomarkers that can be used

for early cancer detection. The discovered biomarkers also spurred the development of targeted cancer therapies, as discussed in the following sections.

## Omics in Targeted Anticancer Biopharmaceuticals Development

### Targeted therapy development

After discovering biomarkers and understanding the mechanism of cancer regulation, targeting the abnormal gene, pathway or metabolic activity plays a critical role in cancer therapy development. The typical targeting strategies are discussed below.

**Target specific regulator:** In cancer therapy development, it is very important but challengeable to target epigenetically and genetically abnormal molecules or pathways. The ideal targets should have the following features: unique to the specific cancer cell, cancer cell survival dependent, representative with high frequency, and feasible to be targeted with medicine. In traditional therapy development, targeting specific regulator requires complicated experimental design and systematic test. With the guidance of Omics, it is more efficient to predict the patient's response to the targeted therapy, and, therefore, to define the rational targeting strategy in cancer treatment. One substantial target for cancer therapy is epidermal growth factor receptor (EGFR), a tyrosine kinase receptor, which is over expressed in solid tumors in lung and colorectum [14]. The non-small-cell lung cancer (NSCLC) harbouring *EML4-ALK* mutation and *EGFR* mutation can be treated with tyrosine kinase inhibitors [70,71]. The HER2 proto-oncogene over expressed in breast cancer is also a tyrosine kinase receptor that can be treated with targeted therapy [1]. Another ideal target is the pathway deregulated by BCR-ABL1 that associates with estrogen receptor expression in chronic myelogenous leukemia [72]. For example, the kinase inhibitor targeting *BCR-ABL1* fusion gene has been demonstrated as an efficient approach to treat the chronic myeloid leukemia tumor and gastrointestinal stromal tumor.

**Target core pathway:** As previously reviewed, the global genomics analysis showed that a dozen core signalling pathways were deregulated in the progression to metastatic pancreatic cancer [1]. The Cancer Genome Atlas (TCGA) project has identified frequent genomic and epigenetic aberrations that deregulate the p53, retinoblastoma RB, PI3-kinase, receptor tyrosine kinase (RTK) core signalling pathways of glioblastoma multiforme [73]. It is found that angiogenesis, a process of neovascular formation during carcinogenesis, is found to correlate with vascular endothelial growth factor (VEGF), fibroblast factor, Notch, transforming growth factor- $\beta$ , Hedgehog, and Wnt signalling [4]. These findings indicate that it might be promising to treat cancer by targeting the deregulated core pathways regardless of the progression mechanisms of metastatic cancer. The development of common therapeutic approach by targeting core pathway relies on the integration of multi-level Omics analysis. For example, various powerful Omics data analysis tools, including KEGG, Pathway Commons, Ingenuity, and Pathway Recognition Algorithm using Data Integration on Genomic Models, have been developed [74]. It is worthy to point out that some regulatory pathways (e.g., MYC, KRAS and TP53) are remarkably resistant to therapeutic interventions due to genetic instability [61]. So, it is critical to develop a second line therapy to counteract the recurrent disease and improve the clinical



efficiency of cancer therapy.

**Regulate glycolysis:** Warburg effect is referred as the phenomenon that the high rate of aerobic glycolysis followed by anaerobic respiration producing lactic acid dominates the energy production in malignant tumor. Glycolysis is an important metabolic process that provides carbon and energy to maintain cell growth and cellular function. Multiple Omics studies show that the glycolysis in cancer cells is abnormal [10,61], so it will be effective to target glycolysis. As the terminal enzyme of glycolysis, pyruvate kinase is the key regulator that determines cellular energy level, redox homeostasis, and cell proliferation. A strong correlation between transcriptional activation of oncofetal M2 isoform of pyruvate kinase (PKM2) and cancer metabolism has been reported [75]. PKM2 switches metabolism to lactate fermentation and promotes tumorigenesis. Most PKM2 positive cancer cells are signalled by epidermal growth factor receptor (EGFR) at the early-stage of cancer development. Therefore, regulating PKM2 is essential to control cancer cell proliferation. The activity of PKM2 is tightly regulated and controlled at multiple Omics levels (i.e., transcript omics, proteomics and metabolomics), which responds to environmental stresses or toxins. PKM2 is a specific metabolism hallmark of cancer cells directly controlling cancer cell progression, so it is recognized as an attractive target for novel cancer therapy development.

**Target mitochondria:** Mitochondria are semi-autonomous organelles that generate more than 95% of cellular energy and control various cellular metabolic activities. Previous mitochondrial metabolomics study uncovered the correlation between tumorigenesis and multiple abnormal metabolic activities. For example, the production of reactive oxygen species, decreased oxidative phosphorylation, increased glycolysis, and deregulated cellular energetics are considered as typical metabolic biomarkers of cancer cells [10]. The mitochondrial genomics analysis showed that the D-loop (a common mtgenome mutation) is an excellent signature for early detection of solid tumours. All these exciting findings have increased the enthusiasm for designing or identifying novel cancer therapeutic agents directly targeting mitochondria. As Verschoor et al. reviewed, the numerous mitochondrial databases, including MitoInteractome, MitoP2, HMPDb, and MitoMiner, provide the platforms for new therapy development [76].

**Screen small molecule drug:** The leading small molecule drug compounds for pre-clinical studies can be screened by integrating transcriptomics data, toxic genomics data, and computational approach [77]. The available drug databases include Drug Bank

[78,79], KEGG, NCBI Pub hem, Connectivity Map [80,81], and Comparative Toxic genomics Database [82,83]. The Omics-based drug screening can overcome the disadvantages (i.e., expensive, time consuming and laborious) of traditional *in vivo* animal experiments and *in vitro* drug screening.

### Targeted anticancer biopharmaceuticals development

The public NIH Roadmap Epigenomics Mapping Consortium and the Personal Genome Project aim to create human genome maps integrated with highly comprehensive phenotype data [42]. The systems biology knowledge can provide insights into cancer cause and, therefore, guide the development of novel therapies. Scientists and clinicians are dedicated to providing the highest life quality for patients diagnosed with cancer by improving prevention, diagnosis and survivorship. Developing novel biopharmaceuticals and increasing the clinical efficiency of various therapeutic proteins represent an efficient way in cancer therapy.

The ever-increasing efficiency of cancer genomics has accelerated the development of targeted anticancer therapeutic biomedicines. Biopharmaceuticals represent a significant amount of targeted therapeutics, including monoclonal antibody (mAb), recombinant therapeutic protein, and nucleic acid-based biomedicine [84]. More than one hundred biopharmaceuticals have been approved by the FDA and are available on the market. Several dozen of pathway-targeted drugs have been applied for clinical treatment of breast, ovarian, colon, and other cancers. In addition, thousands of pipeline biopharmaceuticals are in the clinical trial stage.

mAb targets specific receptors of tumor cells to mediate cytotoxicity *via* antibody dependent cell cytotoxicity or complement dependent cytotoxicity. Table 1 highlights some mAbs for cancer treatment on market. Breast cancer is the second leading cause of death among women, which kills nearly 40,000 Americans in 2011, and an estimated 300,000 new cases of breast cancer are expected to be diagnosed each year [85]. The monoclonal antibody Trastuzumab (Brand name: Herceptin) developed by Genentech is the first commercially available biopharmaceutical to target HER2. It has been proved that humanized Trastuzumab improves the survival rate of breast cancer patients by interfering the oncogenes to which cancer cells addict [5]. The fusion protein MM-302 is a therapeutic protein candidate for HER2 positive breast tumor under clinical evaluation [14]. The patients with colorectal cancer, the fourth leading cancer death, can be treated by inhibiting VEGF receptor using chimeric antibody Cetuximab (Erbix, products of Bristol-Myers-Squibb, Merck and ImClone systems) [86]. Other cancers, such as head

**Table 1:** Example of therapeutic proteins for cancer treatment on US market.

Name / Brand name	Description	Company	Cancer treated
Bevacizumab / Avastin	Inhibit VEGF, humanized mAb	Genentech (Roche)	Colorectal cancer, non-small-cell lung cancer, breast cancer, glioblastoma, kidney cancer
Cetuximab / Erbitux	Inhibit EGFR, chimeric mAb	Bristol-Myers-Squibb, Merck and ImClone systems	EGFR expressing metastatic colorectal cancer, head cancer and neck cancer
Etanercept / Enbrel	Inhibit tumor necrosis factor, fusion protein	Amgen	Target tumor necrosis factor
Panitumumab / Vectibix	Inhibit EGFR, humanized mAb	Amgen & Pfizer	Metastatic colorectal cancer
Rituximab / Rituxan	Anti-CD20 IgG1, chimeric mAb	Biogen Idec	Leukemia, transplant rejection, and autoimmune disorders
Trastuzumab / Herceptin	Anti-Her 2, humanized mAb	Genentech (Roche)	Metastatic breast cancer

and neck cancers, can be treated by Cetuximab. The human mAb, Bevacizumab (Avastin) developed by Genentech, has been approved for clinical use in treating metastatic colorectal cancer by inhibiting VEGF. Also, Bevacizumab is used in the clinical treatment of NSCLC, breast cancer, ovarian cancer, and kidney cancer [4]. The anti-EGFR receptor therapeutic protein, Panitumumab (Vectibix), has been developed by Amgen and Pfizer to treat colorectal cancer.

It has been reported that some small molecules can promote the apoptosis of tumour cells by targeting the receptor signalling pathways or inhibiting intracellular enzymatic activity. For example, the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase was identified as a fusion type driver oncoprotein in about 5% of small cell lung cancer [87]. The Crizotinib (Xalkori), ATP-competitive small molecule ALK inhibitor, has been approved to treat NSCLC patients. The poly-ADP-ribose polymerase 1 inhibitor, i.e. Iniparib, developed to treat breast and ovarian cancer patients with *BRCA 1/2* aberrations, is currently under Phase III clinical evaluations.

### Personalized medicine

The traditional anticancer biopharmaceuticals are used for all cancer patients without considering the heterogeneity of individual patient's genetic information, thereby often resulting in some adverse effects. Therefore, the interest in developing individual therapy by performing personal cancer Omics profiling is recently increasing. The principle to define a suitable rational anticancer strategy is to investigate the patient cancer samples by integrating disease risk assessment, driver factor diagnosis, patient response to cancer drugs, individual habits, and clinical history [14,88]. It is critical to identify the altered genes and pathways in patient tumour cells and, therefore, elucidate the particular oncogenic roles.

In personalized therapy development, patients are monitored regularly; individual genetic disease risks are assessed; and personal profiles are collected, assembled and integrated. Specifically, the genome alterations, such as point mutation, insertion, deletion, copy number alteration, and structural differences [89], have been discovered using next-generation sequencing technology. The oncogene or oncoprotein can be identified by investigating a vast amount of high-resolution personal Omics profiling. The global human protein map launched by Human Proteome Organization enables the discovery of protein signalling marker. The advances in Omics can guide the rational design of personalized antitumor therapies, particularly the tumour cells caused by the well-known genetic instability.

The targeted therapies have been successfully developed and some examples are listed here: 1) Imatinib Mesylate (Gleevec) inhibiting Ab1 kinase for the control of chronic myelogenous leukemia caused by Philadelphia chromosome [42]; 2) Trastuzumab, a targeted therapeutic protein, for breast cancer caused by the amplification of HER2 and the resultant aberrant phosphorylation (predominance of receptor tyrosine kinase) [90]; 3) Dabrafenib (Tafinlar) for the treatment of melanoma caused by BRAF mutation V600E [91]; 4) Epireregulin, COX2 and MMP1&2 for the treatment of lung metastases [42]. With the high scale Omics analysis, the cancer patients can be profiled in timely manner and treated with specifically designed therapy. The personalized medicine is especially crucial to deal with

rare genetic or complex cancer disease. Taken together, the design of efficient individual medicine has great potential in future cancer therapy development.

### Omics in Anticancer Therapeutic Protein Production

CHO cells have been widely utilized in biopharmaceutical industry to produce cancer therapeutic proteins, such as mAbs and recombinant proteins. It is estimated that over 70% of therapeutic proteins in global market are produced using CHO cells. The continuing increase of the market of mammalian cell-derived biopharmaceuticals requires a highly efficient bio processing platform. The recent advances in CHOomics technologies (i.e. Omics in CHO cell) allow for the rational design of the specific bioprocess, such as host cell engineering, cell line development, and production process development, to produce CHO-based therapeutic proteins.

### Cell engineering to express anticancer biopharmaceuticals

With the developed CHO genomics knowledge, it is feasible to regulate the expression of anticancer biopharmaceuticals to improve protein productivity and manipulate post-translational modification through host cell engineering. The typical dosage of antibody for cancer patients is to maintain serum concentration over 10  $\mu\text{g}/\text{mL}$ , i.e. estimated weekly dosage of several hundred million grams [92]. The increased patient number and high dose requirement for therapeutic protein have driven the process development of mammalian cell culture to reach high-level protein production [93]. As shown in functional genomics studies, protein productivity can be improved by manipulating regulators involved in unfolded protein response and secretion bottleneck, such as X-boxing binding protein 1, activating transcription factor, N-ethylmaleimide-sensitive factor attachment protein receptors, and ceramide-transfer protein [94-96]. Additionally, direct metabolic engineering guided approaches have been applied to achieve desired cell phenotypes [97-99]. For example, CHO DG44 has been developed by deleting the dihydrofolate reductase gene to metabolically select the expression of a desired heterogeneous gene. Multiple commercialized biopharmaceuticals are produced by the metabolically engineered CHO DG44 cells.

### Post-translational modification

The enhanced bioactivity anticancer therapeutic protein with proper post-translational modifications directly contributes to cancer therapy by improving clinical efficiency. Of all post-translational modifications, galactosylation, sialylation and fucosylation are the most extensively evaluated ones [100,101]. CHO genomics analysis has been performed to evaluate the genes or regulators involved in metabolic pathways of post-translational modification [102]. The transcriptomics maps and proteomics profiling of multiple cell lines have been collected in CHOomics studies, generating a couple of CHO cell engineering targets. For example, the N-linked oligosaccharide structures synthesized by over expressing the  $\beta$ 1, 4-glycosyltransferases have resulted in greater homogeneity. The over expression of  $\alpha$ 2, 3-sialyltransferase has produced significantly increased sialylation branches [103-105].

### Cell line development

In addition to direct cell engineering, the construction of high anticancer biopharmaceutical producing cell lines can significantly

increase the productivity of a therapeutic protein. The CHO proteomics study showed that the expression of chaperones and cytoskeletal proteins correlates with the high production of mAb [106]. Both the stability and productivity of a therapeutic protein are affected by the insertion location of heterogeneous genes. CHONomics studies discovered site-specific integration elements, cis-acting elements, and multiple regulators for stable cell line development, including scaffold/matrix attachment regions, insulators, ant repressor elements, and ubiquitous chromatin opening elements [107].

### Anticancer biopharmaceutical production process

Rational process development through CHONomics investigation is a promising strategy to improve the productivity and control the quality of targeted anticancer biopharmaceuticals. The rational design of a specific production process is based on cell response to process parameters and extracellular metabolites. For example, the CHO metabolomics and proteomics analysis provides the in-depth understanding of cell growth and biopharmaceutical expression. The obtained Omics knowledge of CHO cell culture can guide the development of fed-batch process and lead to high-titer and high-yield biopharmaceutical production. The effects of production conditions can be optimized [108] because the intracellular and extracellular metabolite profiling collected in metabolomics study enables one to identify the critical process operation parameter [109]. Additionally, Omics analysis of bio processing is an effective tool to direct the scale-up of mammalian cell culture while maintaining consistent cell culture profiling and protein production [110].

### Conclusion and Perspective

Cancer Omics have improved the understanding of cancer driving mechanism. The accumulated knowledge allows for distinguishing the key molecular events, such as gene mutation and cellular pathway. The identification of cancer biomarkers contributes to clinical diagnosis, prognosis and treatment of cancer. The deciphering of cancer driving biological events finally leads to the specific design of targeted cancer therapies, anticancer biopharmaceuticals, and personalized medicines. The advanced CHONomics provide whole cell profiling and genome-scale understanding of cell culture to improve the bio processing efficiency of therapeutic proteins. Take together all the effective achievements in Omics technologies will benefit cancer diagnosis, new therapy development, biopharmaceutical production, and cancer treatment, which will extend the lives of millions of patients in cancer treatment.

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