

Anticancer Drug Development, Challenge from Historic Perspective

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Abstract

There are several millions new cancer cases each year in the world. Yet the cancer mortality rates reduce slowly due to a shortage of effective anticancer drugs. Despite cancer biological and therapeutic knowledge evolution during the past six decades, the progress of anticancer drug discovery, development and manufacture entered into a bottleneck stage over the past two decades-limited curable therapeutic drugs for wide-variety of cancer subtypes, especially the late-stage cancer patients. In searching a healthy progress of anticancer drug developments, the evolutions of anticancer drug development systems interactive with cancer etio-pathogenesis are introduced from past history and current advancements. From our own perspective, drug experimentally evaluation routines must be streamlined and clinically developed-including aspects of medical, pharmaceutical and economic considerations. In addition, global cooperation and regulatory network also needs to be carried out in the future.

Keywords: Anticancer Drug Development; Neoplasm Metastasis; Medicinal Chemistry; Animal Models; Toxicology; Individualized Cancer Therapy

Introduction

Cancer, a multi-step and highly malignant disease costs 7 - 10 million human mortality annually worldwide [1,2]. Six decades has been spent for this very pharmaceutical endeavor. Despite great advances, current cancer therapy still has many limitations and obstacles, especially a shortage of low cost and highly effective anticancer drugs [3-8]. Facing with this grim clinical situation, a systematic modification of cancer drug developmental system is worth to note. To attain a goal of completely managing cancer patients, past experience and current pharmaceutical limitations must be known first. After all, basic drug development systems under utility are introduced and discussed herein.

Key factors relating to anticancer drug development

Roles of different spectra of tumor models

Tumor models play essential roles in anticancer drug developments and marketing. Until now, tumor model selection and cellular/molecular mechanism discovery need to be subjected into more rigorous investigations. There are at least 3,000 established *in vitro* animal/human tumor cell lines and 500 formal *in vivo* animal/human tumor modalities throughout the world. These broad-ranges of animal/human tumor cell lines and models are the very basis of assessing and evaluating anticancer compounds or drugs in the first place. There are some kinds of mode transformation in current anticancer drug development study.

Mode transformation

The dawn of tumor model utility in systematic anticancer drug evaluation happened amidst 1950 - 1960 in the US. In that special period of time, modern drug developmental systems began to establishments in the US. At that time, molecular biology (DNA helix modality proposition in 1953) was shocking and shaping the world greatly. Amongst this golden period, a number of industry countries, especially in US and Soviet Union capture the opportunity of large-scale financial investments for building modern pharmaceutical industry and medical capability (from personal fund lab to governmental or large company fund lab/institute)-including drug developments and manufactures in modern ways.

Due to this industrial transformation, formalized and universal drug developmental chain is required-including fixation of tumor modality and relatively rigorous toxicity systems. The question of how we can adapt to modernization of drug developments, especially where and how we can take advantages of this very trend.

Aftermath of political turmoil

In order to adapt this industrialization of drug development system, significantly fund/investments must follow up. Sustain financial support is the key for industrial survival.

Due to this huge financial support, hundreds of hundreds of animal/human tumor cell lines or models were developed and linearly kept. Until the reign of President Nixon, US (AD 1968 - 1974), he even launched an ambitious plan of curing all cancer patients before 21st century. Everyone was excited after hearing this ambitious plan. But this drama plunged suddenly after his unexpected resign. Until now, we still do not know for sure that this crusade was defeated by the causality of politic turmoil (dramatic financial support cut-down) or a shortage of enough scientific knowledge (patho-therapeutic relations) and technological advances. Today, we are still struggling to find out an answer of which is the core of anticancer drug developments-the sized of financial investments or new ideas/qualified research talents [9,10].

Drug development pitfall and limitation

Tumor model sizes vs effective drug identifications

After this flood of animal/human tumor cell line and model establishments, scientists surprisingly found that this vast collection of tumor cell lines and models does not add noticeable chance for identifying effective anticancer drugs. This raises a lot of global attentions. Improvement however is in a small scale or even none for tumor model innovations. As a result, we highlight this issue by inviting further debating, ideas and renovation.

Financial situations on drug developments

Drug manufactory is a pillar industry for small number of world-leading countries in the past. However, it is also a highly competitive and adventurous one until now [7-13]. Drug discovery, development and manufacture face new pressure and challenge-productivity and successful rates of clinical drug evaluation and development decline every year in a global basis [11].

This phenomenon worsens the adventurous character of drug developments, especially anticancer drug developments. Look for an enduring anticancer drug development system is our new dream. This should not depend only on a small number of developed countries-a unilateral modality or effort from past global situation. Global cooperation and dialogues might be a new trend-multilateral modality [14].

Balanced systems for drug evaluation and developments

Since greater sum of money must be paid for initial drug screening, pharmacologically mechanistic studies, pharmaco-kinetics, overall toxicity investigation and high quality of clinical validations, it therefore results in growing treatment fee for patients with various cancers. Huge economic burden for social and medical insurance comes to a mixed feeling among drug developers and consumers worldwide. The whole process of each anticancer licensing need 1 - 2 billion USD in US and other developed countries [11-13]. Unfortunately,

cancer therapies improved slightly in clinical practice, especially for patients with neoplasm metastasis [3-6,15-21]. It raises a question of whether optimizations of resources of financial and talents, especially from a global basis may be helpful. Thus it faces a great challenge for a healthy progress of cancer treatment study in labs and preclinical/clinical evaluations [10].

Scientific significance in anticancer drug developments

Patho-therapeutic relations

There are a lot of patho-therapeutic information in anticancer drug developments is unclear to us until now. We thus must try to find out these unresolved issues for overcoming obstacles in anticancer drug study. Following questions need to be answered first.

1. What is the key for a great diversity of cancer subtypes (> 200 subtypes) and therapeutic difference against different types of cancer [21,22]. The rigid drug evaluation and regulatory network forbid a healthy progress of anticancer drug developments and manufacture [9,10].
2. Many biological or pathological properties of cancers, such as neoplasm metastasis, drug resistance, cancer stem cells, cancer heterogeneity and plasticity are unclear to us. As a result, new anticancer drugs have to be produced from random experimental screening and clinical validations. All these processes are very low-efficiency. This costs more money in drug discovery and off-targets in mechanistic study.
3. Since neoplasm metastasis is responsible for 90% cancer deaths worldwide, is there any difference between anticancer drugs and anti-metastatic drugs? [3-8,15-21].
4. Is current clinical therapeutics against neoplasm metastasis is on the right track? If it is not so, how can we adjust our future anti-metastatic therapeutics in the clinic? [5,6].
5. Why the natural chemotherapeutic drugs commonly have a higher therapeutic index? [23,24].
6. Owing to the shortage of high-qualified researchers and great economic investments in most developing countries, it is almost a franchise to a small numbers of developed countries [14]. The unbalanced revenues between drug developers (highly developed countries) and drug markets (developing countries) produce significant fracture worldwide.
7. How cancer genomic difference (somatic mutation, DNA methylation, sequence copy number changes and gene expression) changes with drug activity? [25,26].

Balanced tumor modality

Tumor-drug relationship

Anticancer drugs are divided into wide-spectra and narrow-spectra categories, which target on different types of cancer genetic, cellular and organ origins (Table 1) [27]. Obviously, different anticancer drugs often act onto different types of animal or human tumor models and oncogenic events and pathways (DNA methylation, sequence copy number changes and gene expression) in the clinic [25-28]. Tremendous work must be applied for verification of each possibility before clinical drug developments. Look for hidden law behind the cancer pathogenesis (especially genomic events) may facilitate these huge tasks [25-28]. Huge past literatures and biological work must be carefully analyzed for reaching pharmacologic knowledge of tumor-drug interaction and relationship. The understanding of tumor model diversity is the top priority.

Different categories of molecular target drugs	Major drug examples
Tumor genetic interactive	Binding and replication interferences
DNA repair inhibitors	PARP1 inhibitors
Metabolic antagonists	5Fu, MTX and others
Receptor tyrosine kinase inhibitors	Antibodies and small-molecular chemicals (gefitinib, lapatinib and others)
PI3K/AKT/mTOR	Small-molecule chemotherapeutic agents
Ras/Rat/MEK/MAPK	Small-molecule chemotherapeutic agents
Antiangiogenic agents	VEGFR antibody; bevacizumab VEGF inhibitors
Hormone therapy	Tamoxifen Aromatase inhibitors GnRH-analogues
Immune checkpoint inhibitors	Anti-PD-1 inhibitors
Other bio-agents	HER2 protein antibody; trastuzumab, pertuzumab, T-DM1
Cancer stem cell inhibitors	Many synthetic or natural compounds
Neoplasm metastasis treatments	MMP inhibitors, bisdioxopiperazines
Assistant therapies	Anticoagulants; Fibrinolytic agents Traditional Chinese medicine

Table 1: Major genetic and molecular target drugs.

Tumor model narrow-down or broad-up

Similarly, cancer is a series of different disease that shares the common pathologic character of unlimited growths. There are more than 200 tumor subtypes in the clinic until now [21,22]. Otherwise, at least six cancer hallmarks are present in different tumor cells and tissues [19] (Table 2). Generally speaking, different subtypes of tumors are sensitive to different compounds, drugs or therapeutic options. Facing this complicate tumor-drug relationship, future experimental or preclinical tumor models should be categorized into different series and screened by different types of anticancer agents and combinations. As mentioned above, present *in vitro* or *in vivo* animal or human tumor models for drug screening are enormously diversified in major drug developing countries [7-10]. For example, approximately 1,200 human tumor cell lines are stored for anticancer drug screening, verifications and mechanism explorations in America Tissue Culture and Collection (ATCC), USA. This phenomenon is a double-sword. The best part of this large-volume of tumor cell lines globally may possibly harvest more anticancer drugs in real clinical situation. The worst part of that is too cumbersome and costly in this period of financial restrain. As a result, tumor model narrow-down or broad-up may be decided from existing pharmaceutical situation and further benefit the patients in the future.

Hallmarks of cancer	Possible molecular or pathological mechanisms
Sustaining proliferative signaling	Oncogene mutation, cell or proliferative signal over working, environmental alteration etc.
Resisting cell death	Apoptosis (caspases, Bcl-2, Bax etc.) and autophagy
Inducing angiogenesis	Vascular or inflammatory factors (VEGF, TNF) etc.
Evading growth suppressors	Tumor growth suppressors (RB, TP53) etc.
Enabling replicative immortality	Telomerase
Invasion and metastasis	Tumor stromal or matrix (MMP), Immunological factors and function, angiogenesis, glycoproteins, blood coagulation, neoplasm plasticity

Table 2: Schematic outlook on biology and pathology mechanisms of cancer [27].

However, the utility of different tumor origin and tissues may be important in anticancer drug evaluations. It is quite usual and necessary. Previously, we compare the IC₅₀ of bisdioxopiperazines (probitmane) against 13 human tumor cell lines. It is shown that there is a positive relation between drug efficacy (IC₅₀ value reduction) and sensitive tumor types (leukemia and lung cancer cells) in the clinic [29,30]. Stay in a wide-size/spectrum of tumor models in drug evaluation is an indispensable.

Present tumor model characters and deficit

According to previous data, there seems an association between volume of tumor models and quality of anticancer drug evaluation, yet most of these animal or human tumor models have lost their original genotypes or phenotypes by long passages *in vitro* or *in vivo*, which make relatively less quality and originality of preclinical drug activity studies via an addition of more tumor models [3-10]. The understanding of the diversity and similarity of tumor models will promote drug development capability and industrial competitive in a long run.

Tumor metastasis models and future innovation

Anti-metastatic drug developments need to be updated with times because 90% cancer mortality is caused by neoplasm metastasis, especially for aged cancer patients. Until now, few anti-metastatic agent or drug exhibits any therapeutic survival benefits for patients with neoplasm metastases [3-6]. This is the most important failure of cancer drug treatments in the clinic. The unnoticed causality must be found out lately.

Neoplasm metastasis occurs by at least 4 different routes, such as transelomic, lymphatic, hematogenous and canalicular pathways in the clinic. Future innovation should focus on these different pathways step by step. Certainly, some tumor spread models and biology (seed and soil hypothesis. Invasive-metastatic cascades and others) need to be intensively followed up in the future.

Currently, many compounds that can greatly inhibit tumor metastasis in animal models fail to show any therapeutic survival benefits in cancer patients clinically. It is probably caused by lack of good animal tumor models for anti-metastatic drug developments [21]. Present available tumor metastatic models (Lewis lung carcinoma and B16) are observed for tumor colony in lung (pulmonary metastasis). However, there are a lot of human organs that can host metastatic cells and colony. Human brain, liver, bone and abdominal areas are all vulnerable to tumor invasion and metastasis [21]. As a result, a lot of other good metastatic models (seeking lodging on tissues of bone, brain, liver and others) must be utilized in anticancer drug evaluations. This process might need larger mammal animal tumor models (such as dogs, monkey and so on)

Durg evaluation protocols and schedules

Transplantation routes

Different patterns of tumor inoculation routes, drug dose or schedules in experimental or preclinical studies may affect the outcomes of new compound responses/efficacy among various tumor models and biomedical/pharmacological data statistics. Initially, *in vivo* tumor transplanting models were mostly inoculated unto subcutaneous locations (sc), intraperitoneal (ip), intravenous (iv) and lately hollow-fiber (HF). Figure 1 shows the evolution of tumor models across the history in the US.

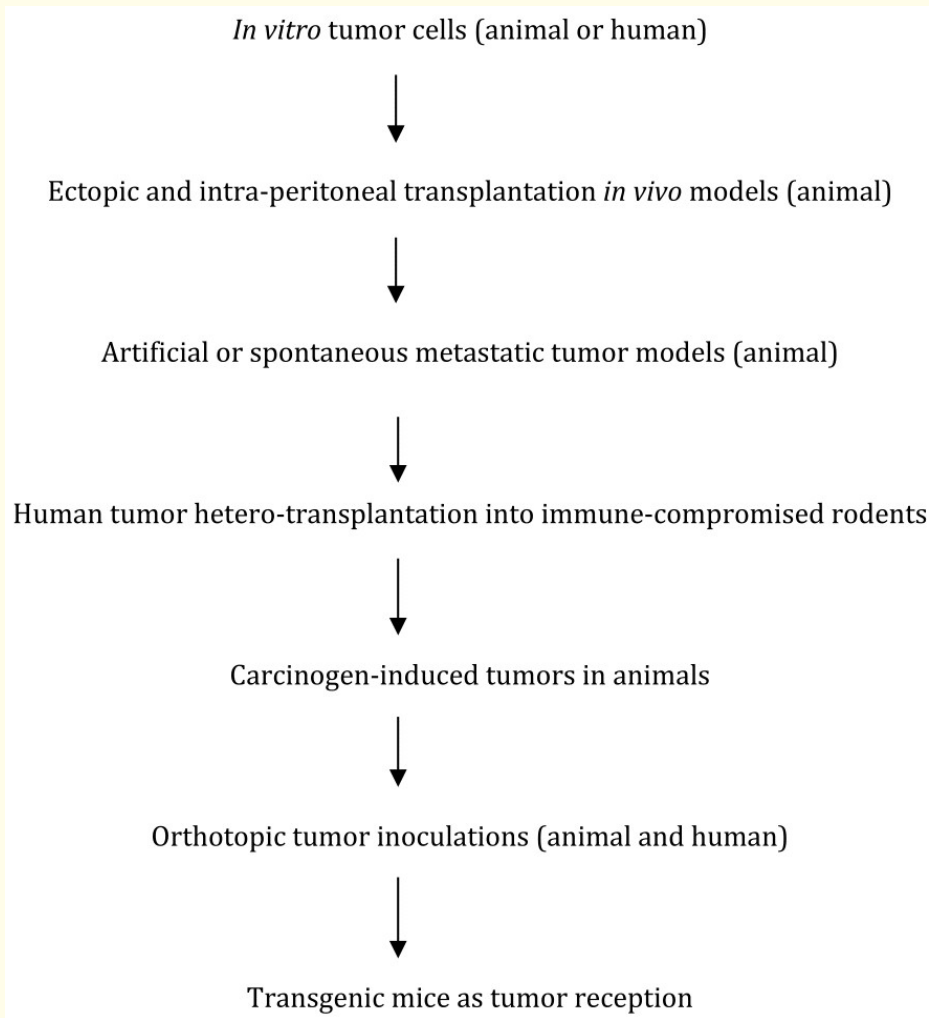


Figure 1: Timescales and progresses of tumor inoculation models for anticancer drug developments [14].

Hosting tissues and tumor origin

After such pharmacologic study of human conditions more represented to cancer patients in the clinic, wide-spectrum, highly effective anticancer drugs will be discovered. For example, murine tumor tissues subcutaneously transplanted might be superseded by murine tumors induced by different types of carcinogens [13].

From these forms of tumor model progresses, the new *in vivo* tumor models may help us to develop new drugs.

Natural chemotherapeutic drug developments

Mechanistic study

Along with other types of drugs, natural chemotherapeutic drugs often exhibit higher therapeutic index against tumor growths and metastasis [23,24]. From our perspective, two questions must be explored first.

Why natural chemotherapeutic drugs show higher therapeutic index comparing with synthetic drugs?

How to create a new drug screening system that is more suitable for natural chemotherapeutic agents identification?

Without answering these two questions, natural anticancer drug development will still be in slow-pace.

Modern techniques in drug developments

Relationship between drug developing fee and lab equipment costs

New techniques are always the major driving-force for updating drug developments. Certainly, more money must be paid off. New techniques are not always losing money. For example, human genome drafting expenditure can reduce from 3 billion USD before 2000 (Human Genome Projects) into approximately 6,000 USD after 2010 (the utility of next generation sequencing, NGS) [31,32]. This looks like to save a great fortune. But the required experimental instruments must also be expensive than the costs of single electrophoresis device alone. Similar examples can be found everywhere in recent decades. Balanced systems must be established.

Lab facilities and equipments

After 2000, building of a single modern drug evaluating lab must need at least one million USD [13]. This is very difficult for many developing countries. The high-threshold condition for drug development still exists nowadays. This capital-oriented effort is a great challenge for the willingness of developing countries and triggers our early arguments of core of anticancer drug developments-a matter of money or a matter of idea [9,10]? This is why only small number of industrial countries can survive in this ever-changing and highly competitive world.

Apart from animal or human tumor models, avant-garde experimental equipments and lab facilities, scientific investigations on patho-therapeutic relation have long way to go. Given the rapidly instrumental revolution, it is supposed that the qualities of drug therapeutic efficacy and toxicity evaluations might be more objective and scientific. But it is not always the truth. Many times, it does not benefit the study from high-throughput technology utilities. The pathologic or therapeutic knowledge improvements may be more useful and long-lasting. This character requires talented researchers that needs the training of decades and nature-borne.

Mathematicians and computational network

Since money and techniques play important roles in drug developments, the disciplinary that needs less financial investment or facilitate cumbersome experiments by less biomedical exploration are new trends. Money is always easier to collect than prodigal person engagements. But money collection is an indispensable move in initial stages of dramatic changes and highly talented person recruiting [9,10]. Not only for highly talented medicinal chemists and pharmacologists, mathematic/physics-majored students and scholars might also create a great deal of benefits globally and make a great difference in anticancer drug developments/marketing [33-35]. These kinds of mathematic/physics-majored students and scholars ought not only to play assistant roles as usual, but also significantly change the landscapes of anticancer drug developments/marketing. They can do a lot of things in cancer etiological/pathological studies.

Mathematics and computational network are only twin technology that need no great money invests. Previously we discuss this issue from our past experience [33-35]. Overall, mathematics in pharmaceutical industry can be concluded in figure 2.

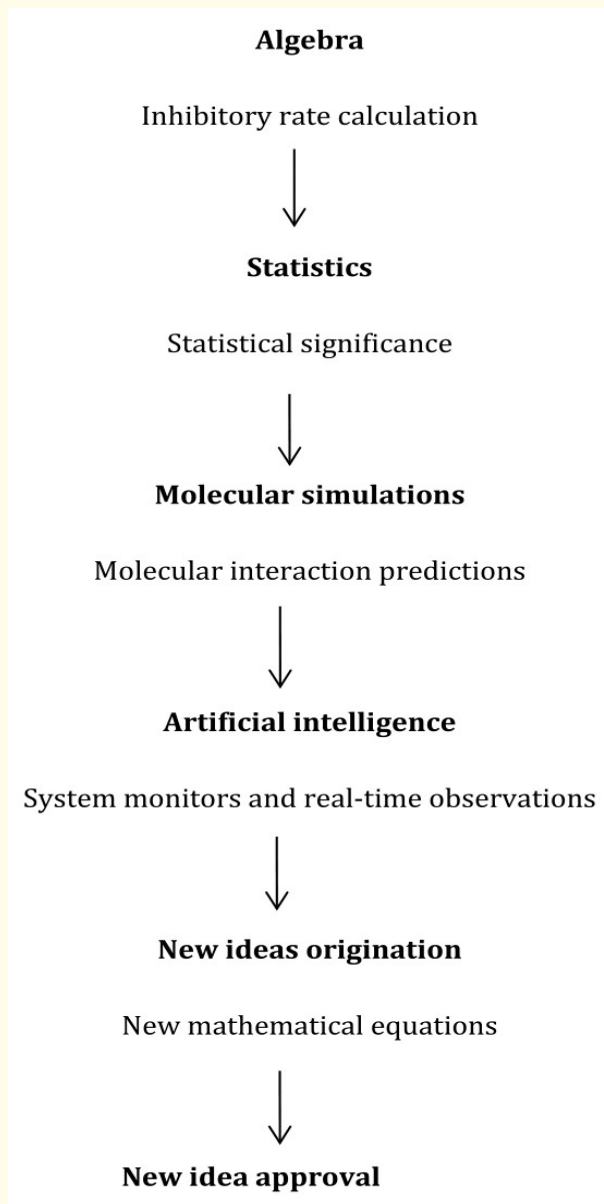


Figure 2: The evolution of mathematics in pharmaceutical science.

Governmental regulatory network

Interests contradiction and potential threats

Good governmental regulatory policy and network should provide the solid supports of high quality drug developments and intellectual property rights. However, real of these assets are at the hands of a few developed countries. How you can expect the enthusiasm of

developing countries on this matter? Every country has its own policy. This financial fracture globally create current adventurous situation of drug developments. This is the key of current country-to-country confrontation in this matter. If we cannot find a solution of that, global turmoil will continue.

Possible revision

BRICS or large or median-sized industrial countries (such as France, Japan, Italy, Canada, Australia, Austria, Spain and so on) must pay especial attentions on this matter so that expanding countries can equally join drug developmental campaigns that will benefit their countries forever. For medicinal chemists and pharmacologists in BRICS, large or median-sized industrial countries, they should not satisfy only with publishing articles in highly impact factor international journals, creative ideas on new drug developments are more important and noteworthy rather than following the other's work and pathways [14]. World forum on drug developments and multilateral ties are inevitable.

Regulatory network in China

Pharmaceutical science in China seems improved (doubling its number of pharmaceutical colleges nationwide over the past three decades). Since anticancer drug developments require both money and high-talented scientists. Countries like China, as we can see need to change their policy of money distributions from short goal (publish as much as possible). In the past three decades, in order to receive grant-money, a lot of non-original articles have been published in international journals while new discoveries do not change. As we can see that financial support in drug developments are not suitable for high competitive grant application system. These pharmaceutical short-term projects lead to growing publications and long-term scientific exploration neglects. We think global drug development paradigm and cooperation should seek revision from this negative experience and regulatory network.

Drug combination updating

Question generations

Cancer is a malignant disease that is often difficult to be completely managed. Despite great advances, current cancer chemotherapy has still many limitations from the shortages of highly effective anticancer drugs, especially anti-metastatic drugs and so on [3-10,36,37]. To overcome this obstacle, drug combination is a useful way to improve overall therapeutic outcomes in clinical cancer trials [36,37].

Current scenario

Systematically evaluating the therapeutic efficacy of drug combinations is a new possibility of anticancer drug studies but have long way to go-study for every possibility in the future [38-40]. After these kinds of efforts, anticancer drug combinations can be translated from preliminary experimental data into clinical paradigms [37]. Through these kinds of experimental study, we can understand of both therapeutic benefits and undesired outcomes against cancer growth, invasion and remote metastasis. Overall, drug combination study has a lot of thing to do in drug development stage. To enhance this clinical study, new drug screening systems for drug combinatorial mechanisms must be carried out.

Modern drug delivery systems

Drug delivery systems are unavoidable avenues to improve cancer therapeutic outcomes so far. Different pharmaceutical forms of anticancer drugs may vary in therapeutic efficacy against both primary tumor growth and remote disseminations, such as nano-technology [41,42] or chemical ligands to biologic agents. Yet, some of literatures exaggerate their therapeutic efficacy and clinical applications. Higher immune system toxicities of nano-particle anticancer drug treatments may compromise their therapeutic outcomes in clinical cancer trials [41,42]. If we pay no heed on these exaggerations, government funding or healthy financial investments will be damaged. At this moment, nano-therapeutic technique alone is unable for curing cancer patients in the clinic. Overcome this deficiency in the clinic by new strategies, such as drug combinations are highly expected.

Landscape in anticancer drug development in modern era

Outlines of drug development system

Anticancer drug developments evolved across the history (start from 1970s). Their developmental chain is outlined in figure 3. Too familiar with this anticancer drug developmental chain, we may find out new anticancer drugs of high quality and large quantity. It contains the experts of mathematicians, chemists, biochemists, technicians, pharmacologists, toxicologists, pathologists and medical doctors. How to integrate systems of multidisciplinary is a great future challenge. Excellent teamwork should always be pursued.

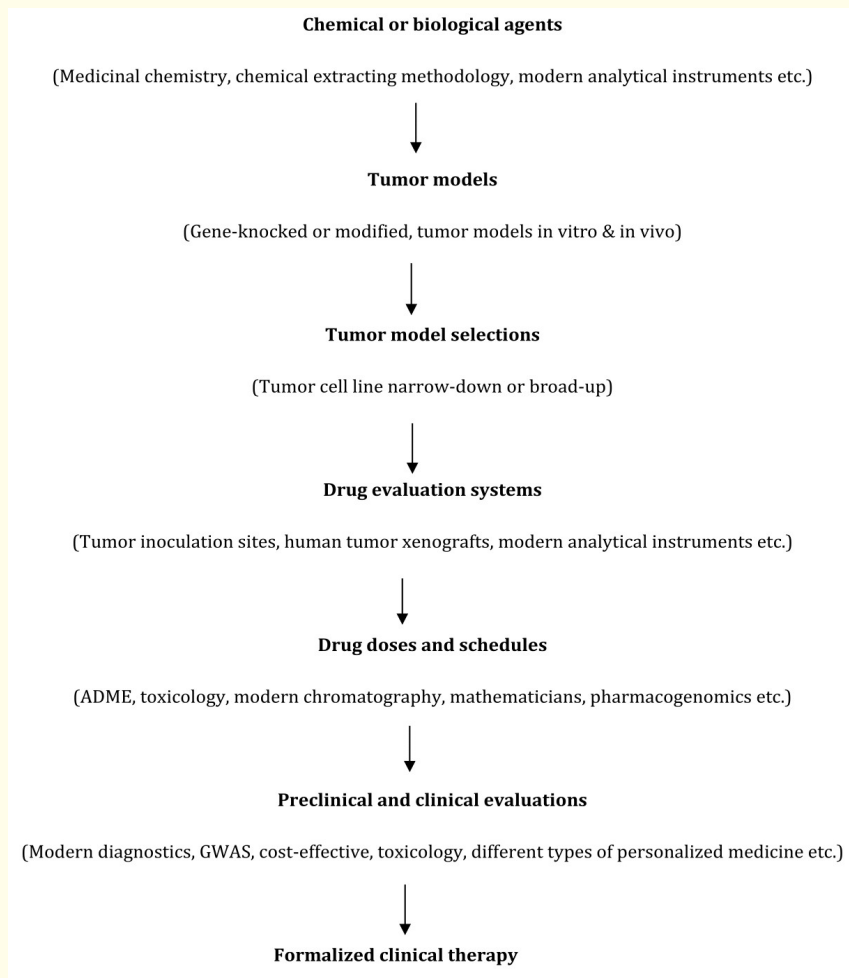


Figure 3: Major pathways to update anticancer drug development chain.

System updating

The highly efficient determination of drug activity, dose ranges, administered schedules, tumor inoculating route and therapeutic durations in animal models and in humans are theoretically very difficult to optimize. But they can be improved by further rigorous scientific integrations and tight budget control. Possible future avenues are given as followings.

Patho-therapeutic relation

An understanding of patho-therapeutic relationship can be promoted by modern diagnostic and therapeutic approaches. This can be a golden rule for improving clinical cancer therapy and drug developments. However, cancer is diversity in oncology origin and long course of onco-genesis progresses started from somatic mutations in normal cells. It could be classified to more than 100 cancer subtypes [22], or even classified into 200 subtypes in the clinic [21]. As a result, modern diagnostics is an useful route for making experimental, preclinical and clinical drug evaluation more specify and competitive (smarter systems).

Future Directions

Several useful steps for the promotion of anticancer drug screening protocols and systems are discussed in following sectors-including major obstacles and future approaches for renovation.

System optimization for reducing costs and finding new drugs

To optimally use animal or human tumor models can not only reduce research funds but also find out more effective anticancer drugs. Efforts must be made to reduce anticancer drug evaluations and development costs and find out highly active anticancer drugs. Concrete action of this system updating would benefit cancer study and clinical therapeutics from modern science and technology utilities. Drug developmental budget and cost-effective considerations in the clinic might be reduced by global cooperation and benefit larger population of cancer patients.

Wider spectra of drug targets

The establishment of patho-therapeutic relationship needs to look for wider spectra of drug targets, which is the fundamental issue for anticancer drug developments. Currently, anticancer drug target study is far from satisfactory and fruitful enough [3-10]. Future actions on this matter (drug target discovery) will be the top priority. Pharmaceutical, pharmacologic and toxicological study may all be available in new drug developments. Implementing high quality drug tolerability/toxicity and PD/PK study in both animals and humans must continue to be encouraged, which are important building-blocks of anticancer drug development and clinical transformation. Nevertheless, this is an endless enterprise and can be varied among different individuals. Rational and balanced design and standardize basic toxicity evaluating systems and protocols in clinical circumstances needs to be well carried out in the future.

Tumor stroma and blood coagulation

Apart from tumor cells, tumor stroma and blood coagulation can also be an important drug targets against tumor growth and metastasis [43-46]. These kinds of drugs can not only be direct targets against primary tumor growth, but also as an assistant agents for survival benefits for patients with lung and other organ metastasis via tumor-stroma or tumor coagulant mechanisms [45,46].

Anti-metastatic drug developments

Anticancer drugs against neoplasm metastasis [3-6,13-21,47-49] and cancer stem cells [50-52] are unsettled question in clinical cancer trials. Modifying tumor models for adapting this unfavorable condition, such as biotherapy or immunotherapy is warmly welcome in this series of anticancer drug development. Biotherapy or immunotherapy, though highly cost nowadays has been emerging powers to combat cancer growth and remote metastases in clinical trials. Nonetheless, they are inappropriate to be evaluated by conventional drug screening and verification systems. More effective tumor models must be utilized for evaluating biotherapy, immunotherapy and so on. We should not neglect this issue in the future.

Genetic-modified tumor models

Genetic modifying animal tumor models to quickly obtain useful information about therapeutic efficacy and outcomes at genetic levels might be a useful future option [53,54]. They must be widely invented and utilized in anticancer drug screening and preclinical studies with the mature of genetic technology. Cancer genomic study is exponentially growing [25-28]. These kinds of cancer genomic study may change the landscape of anticancer drug developments.

Cancer stem cell inhibitors

Cancer stem cells can relapse from drug or surgery treatments. However, it is difficult to find new therapeutic solution in the clinic [50-52,55]. Future work is desperately needed.

Global cooperation

Currently, global anticancer drug developmental systems are derived from National Cancer Institute, National Institute of Health, (NCI, NIH), US [14]. Its development speed is hindered by this limitation of small-range of experts. As a result, the highly risky property of anticancer drug development and licensing is existed worldwide. Joint-ventures between world-leading pharmaceutical companies in leading industry countries, emerging economic entity (BRICS), large or median-/small sized industrial countries must work together in anticancer drug development and manufactures in the future [14]. Governmental or drug regulatory authority/network may provide new stipulations for smooth progresses of drug licensing and clinical utility according to the country conditions of their own. This might receive unexpected feedback through global cooperation and therapeutic standardization.

Categories	Methodology
Experimental screen <i>in vitro</i>	Tumor cell narrow-down Tumor cell specification Genetic-knockout cells Genetic-modified tumor cells Drug screen routine updating Tumor genomic study (NGS)
Experimental screen <i>in vivo</i>	Tumor inoculation sites Therapeutic schedules Survival benefits Drug metabolisms Tumor metastatic model updating Analytic chemistry Toxicity study in animals Cost-reductions
Pre- and clinical study	Drug tolerance and toxicity in animals and humans Absorption, metabolism, distributions and excretions Modern diagnostics GWAS Bioinformatics Analytical chemistry Tumor category specificity Budget control Medications of multidisciplinary Neoplasm metastasis treatment Meta-analysis Personalized medicines (Different choice) Global cooperation

Table 3: Future directions of anticancer drug developments.

Conclusion

To improve anticancer drug development, more practical and balanced tumor models or screening routines must be carried out. In future, higher efficient tumor growth or metastasis models in the state of experimental work and good regulatory network must be implemented by modernizing lab facilities and establishing smarter clinical paradigms worldwide. We sincerely welcome global participations in a new era of anticancer drug discovery and developments.

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