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# Anti-Metastatic Drug Developments: Work Out towards New Direction

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**Abstract**

Neoplasm metastasis is a multiple-step and multi-level feature that is resistance to current norm of anticancer drugs. More seriously, current anticancer drugs are commonly derived from *in vitro* tumor cell line data or animal models of primary tumors rather than workable metastatic models reflecting clinical situations. This article provides different aspects of pathologic/pharmacological information and study against neoplasm metastasis.

**Keywords:** Neoplasm metastases; Cancer chemotherapy; Cancer plasticity; Drug combination; Clinical cancer trial; Metastatic cascade; Cancer stem cells; Personalized medicine

## Background

### Medical significance

Neoplasm metastasis is a multiple-step and high plasticity phenotype that is resistance to current conventions of drug therapeutics. Previously, chemotherapeutic benefits against cancer growths and metastasis were usually derived from experimental models and data of *in vitro* tumor cell lines and volume of primary tumors. Accordingly, antimetastatic drugs (several types available) are often used as assistant agents to cancer therapy.

### Problem origination

Generally speaking, cancer patient's survival has hardly been improved in patients with overt metastasis (late-pathologic stage) from current therapeutic conventions and shortage of antimetastatic drugs in the clinic [1]. Therefore, any small breakthrough for drug developments in this area will achieve therapeutic benefits in clinical cancer trials [2-9]. In order to achieve this goal, the patho-therapeutic relationship must be analyzed by literature survey, our past experimental data and existing biological theories.

## Current Therapeutics Against Neoplasm Metastasis

### Therapeutic mechanisms of current antimetastatic drugs

Antimetastatic drugs have been developed over half a century worldwide [10,11]. The therapeutic targets under investigations are approximately ten categories (Table 1). We will discuss them in details next sectors.

## Detail Information of Antimetastatic Drugs

### Bisdioxopiperazine compounds

Bisdioxopiperazine compounds (Biz), including ICRF-154, Razoxane (ICRF-159, Raz), ICRF-186 and ICRF-187 (two stereo-isomers of Raz) and ICRF-193, developed in the UK, have been a series of serendipitous agents found to be significantly effective against a model of spontaneous metastasis (Lewis lung carcinoma, 3LL) [11,12]. Ever since their development (1969), new analogs Probimane and Bimolane were synthesized at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China [35,36]. Early mechanistic studies of Biz compounds were reported in China and UK [37-39].

### MMP inhibitors (tumor matrix)

Primary tumors are embedded in surrounding matrix. Tumor cells and their surrounding matrix can secrete a spectrum of proteinases that can break up these surrounding matrixes and make tumor cells penetrable through these surrounding matrixes and finally intrigue invasion-metastasis cascade. These proteinases are composed of matrix metalloproteinase (MMPs). MMPs inhibitors are those agents proposed to inhibit tumor metastases in early metastatic-stage [13].

### Angiogenesis inhibitors

Metastatic cells, after extravasation to remote organs, need new blood vessels to offer nutrients to transform the dormant/micrometastatic tumor to metastatic outgrowth (overt metastatic colony) in distant tissues. Drugs (commonly antibody against these series of vascular factors/promoters) are generally known as anti-vascular anticancer drugs [14,15,40,41]. However, several weeks/months survival benefits are far from our requirement of long-term disease control (>5 years) or even cure patients with neoplasm metastasis.

### Bisphosphonates (BP) in the treatment of osteolytic metastases

BP has a long history of being used in treating osteoporosis. It was already licensed to treat osteolytic metastasis. Others suggest that BP can influence from oncogenes to metastatic-related genes in treating metastases of many organs.

### Immune system promoters (Plant extracts or chemicals)

Treatment of neoplasm metastases by plant extracts or chemicals seems to be a future trend. Now, growing numbers of plant extracts, chemicals and alkaloids have been found to inhibit tumor metastases in animal models [16]. These polysaccharides are proposed to enhance immune response in animals and humans.

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| Drug categories | Involving molecules & pathways | References |
|---|---|---|
| Bisdioxopiperazine compounds | Tumor cell detachments | [10,11] |
| MMP inhibitors | Tumor stroma (extracellular matrix, ECM) | [12] |
| Angiogenesis inhibitors | Tumor blood & nutrition | [13,14] |
| Bisphosphonates | Bone metastasis | [15] |
| Various drugs | Invasion-metastasis cascade | [16,17] |
| Probimane & polysaccharide | Aberrant sialylation in tumors | [18-22] |
| Immune promoters | Tumor cells/cluster in vasculatures | [23,24] |
| Assistant therapy | Blood coagulants | [25-27] |
| Cancer stem cell inhibitors | Difficult to define currently | [28-30] |
| Next generation | Seed and soil | [24] |
| New generation | Cancer plasticity state | [31-33] |
| Traditional Chinese medicine | Human body and organ functionality | [34] |

**Table 1:** The evolution of anti-metastatic targets and drugs.

## Invasive-metastasis cascade

Present antimetastatic therapy treats patients equally. No specific attentions are paid according to clinical situations of patients.

From this pathologic point of view, since a metastasis must travel more than one body-organ, the obvious different anatomic organs may possibly trigger different molecules and pathways linking neoplasm metastases. This reasonably results in being affected or inhibited with different types of drugs in different stages of metastatic processes [17].

In general, it was proposed that the MMPs inhibitors might be more active in preventing tumor cells from detaching primary locations [13]. Immuno-modulators might promote the activity of macrophages in killing tumor cells during the vascular and lymphatic circulations [16]. Angiogenesis inhibitors might be used as the substage of attaching of tumor cells to metastatic outgrowth to distant organs. However, highly cytotoxicity agents might be more effective in the treatment of formed metastatic colony and preference-organs [42-45] (Figure 1).

## Circulating tumor cells and clusters for drug targets

In invasive-metastatic cascade, tumor cells/clusters must circulate in human blood or lymphatic vessels seeking refuge in distant organs [33].

The neoplasm metastasis is a mechanically dynamic process in human body. Tumor cells/cluster circulating in vascular system (blood or lymphatic) is one of the most noticeable one. In the past, it has been found that tumor cells in vascular systems have higher ratio of mesenchymal state that can be cleared by human immune systems. It is found that agents of immune promotion can reduce the number of tumor cells/clusters floating in human vasculature. The circulating tumor cells (mesenchymal type-rich) in human vasculatures are a different one comparing with in primary/metastatic colony (epithelial type-rich) in human body [32-34]. As a result, this is an interesting drug targets for metastatic control and managements. Certainly, it should not be restricted in drug type of immune system promotions.

## Tumor stroma and assistant therapy

Cell adhesion molecules (CAM), such as E-cadherin, p-cadherin, integrin, selectin, play key roles in cancer progression, metastasis in distant tissues and colony formation in varying way (invasive-metastatic cascades). Cell-cell and cell-matrix interactions of cancer cells with environments determine the metastatic spread (linear or parallel mechanisms) [7]. Alterations in these molecules are observed during tumor progression and metastasis [40,41]. Heparin can inhibit CAM related metastatic processes and improve therapeutic outcomes in patients with solid tumors, especially in lung cancers [45,46].

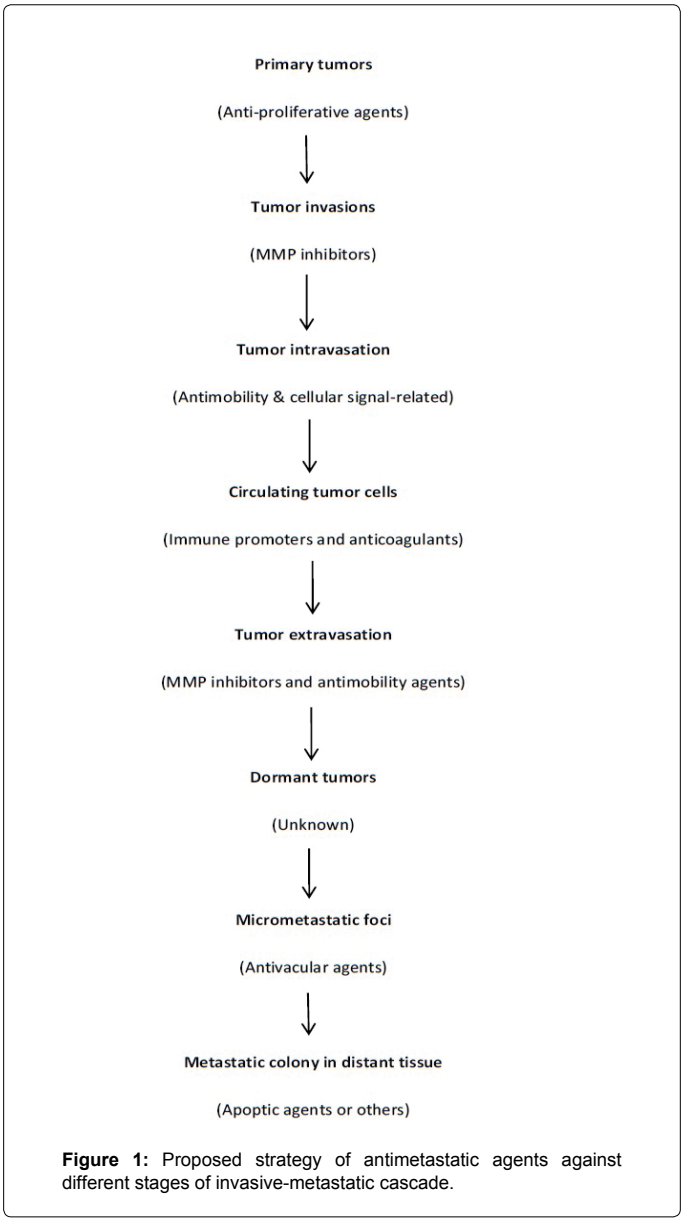


**Figure 1:** Proposed strategy of antimetastatic agents against different stages of invasive-metastatic cascade.

### Cancer stem cell inhibitors

Cancer stem cell (CSC) is still an enigma for modern biomedical scientists. Its character is very tricky-tumor renewable after operations and drug therapy [28-30]. This tumor renewal itself is closely related to neoplasm metastasis and drug resistance. Presently, CSC is commonly resistance to conventional drug therapy, even anticancer drug combinations. Future therapeutic study, as we can guess, must rely on its biological characters first. Only after fully understanding the biology of CSC, effective therapeutics can be expected.

### Cancer plasticity (EMT/MET)

One of the greatest advances in cancer biological/pathologic study over the past decade is the linkage between EMT/MET and adaptive phenotype of neoplasm tissue [47,48]. The therapeutic interventions against tumor plasticity have been carried out widely [31,33]. We hope some effective therapeutic options might be stood out in the following decades.

### Sialic acid-related drugs and therapies

The earliest work tackling the phenomenon of a positive relationship between sias and tumors can be traced back to Kimura et al. from 1958. Their discovery is tumor cells might excrete and contain more sialyl glycoproteins or glycolipids. These characteristics later have been found to be linked with highly metastatic tumor types, organ origin, site preference and targeted therapies [20-22]. Since 1990s, a great number of researches have also showed diagnostic and therapeutic utility patients with tumors of high levels of sialylations. Many patho-therapeutic relationships can be found out and promoted by sialylation changes in clinical cancer diagnostics and treatments. These types of experimental and therapeutic models are reflected in Figure 2 and Table 2.

### Combinations of western medicine with TCM in cancer treatments

Cancer treatment by TCM is one of hot-spots in modern China and even earns growing popularity worldwide. In most cases of cancer treatments, seeking strengthening upright air therapy rather than expelling outside damaging air therapies is proved to be higher utilities and therapeutic outcome improvements [49,50]. Additionally, expelling exogenous wind-heat recipes are also utilized for cancer therapies by TCM.

### Other therapeutic targets

Beside drugs mentioned above, other new types of drug targets are also available worldwide [51-60]. They are cell-signal inhibitors, AMF, HGF/c-Met, TGF-β inhibitors, β-catenin inhibitors [59], cell movement inhibitors [60] and newly discovered targets globally. Most of these metastatic-related targets and inhibitors have not been licensed but have a great potential for future clinical utility. The more these targets are studied, the more useable drugs could be expected.

### Targeting the formed metastatic foci in the clinic

Most people die of cancer with formed metastatic cancer and organ failures. In these patients, MMPs inhibitors or antivascular agents or other therapeutic options usually do not work at all. Given this grim situation, high active drugs targeting to neoplasm metastasis that can greatly control physiological conditions for patients need to be developed.

It might broaden present customs of finding antimetastatic drugs only into clinical drug option strategy as a complementary and perfection of individualized cancer therapy/personalized cancer therapy (ICT/PCT) [61-65].

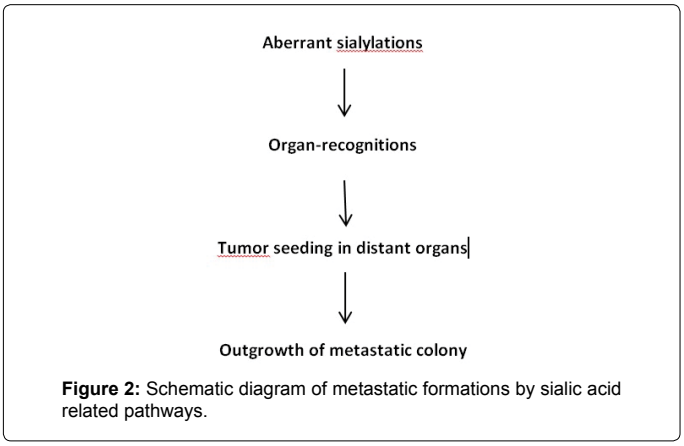


**Figure 2:** Schematic diagram of metastatic formations by sialic acid related pathways.

| Therapeutic modality types | Characters |
|---|---|
| Therapeutics of multi-disciplinary (Teamwork of different experts) | Oncologists<br>Surgeon<br>Pharmacologists<br>Technicians<br>Mathematician<br>TCM doctors<br>Computer-network (artificial intelligence) |
| Precision medicine | Modern diagnosis-based Therapeutic formalizations |
| Drug combination strategy | Multi-steps of neoplasm metastasis<br>Intermediate states of tumor<br>Heterogeneity of tumor cells in one nodule |
| Personalized medicine | Drug sensitivity testing<br>Pharmacogenetics/pharmacogenomics<br>Tumor biomarkers<br>Tumor bioinformatics<br>Cost-effective |

**Table 2:** Modern therapeutic modality for neoplasm metastases.

### Animal tumor models and anti-metastatic drug developments

Currently, many compounds that can greatly inhibit tumor metastasis in animal models fail to show any therapeutic benefits in cancer patients clinically. It is probably caused by lack of good animal tumor models for that [33]. As a result, a lot of other good metastatic models must be utilized in anticancer drug evaluations.

## Modern Therapeutic Modalities

Besides the promotion of anticancer drug developments, cancer therapeutic study in the clinic is also important route to improve cancer metastatic medications and managements.

In these items of clinical cancer therapeutic options, drug combinations and personalized medicine deserve further explanations because these two topics are developing rapidly more recently;

### Drug combination

Anticancer drug combinations many times can receive unexpected therapeutic benefits in the clinic. Yet, anticancer drug combination needs to transform from doctor's experience into scientific-based investigations [66]. In our recent study, this kind of scientific research has large things to do [67,68], including experimental study of every possibility and global cooperation among clinical doctors.

## Future Directions

### Global participations

Anticancer drug development is entering into bottleneck stage [8-10,69,70]. Currently, anticancer drug development (including antimetastatic drugs) should not solely rely on small number of most advanced countries in medical/pharmaceutical science and technology. Global participation is indispensable.

## Conclusion

Cancer metastasis is the main cause of cancer patient mortality worldwide. We thus need to pay more attentions on these patho-therapeutic relationship researches and enhance our horizon on this matter. As the large population of global cancer patients (approximately 15 million) occur every year, if we adhere and improve in metastatic therapy, we might save life of millions each year. In this regard, let's do it as early as possible.

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