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Motivation for launching a Cancer Metastasis Inhibition (CMI) program

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Abstract

Metastatic cancers impose significant burdens on patients, affecting quality of life, morbidity and mortality, and even during remission, microscopic metastases can lurk. Few therapies directly target tumor cell metastasis. Agents that interfere with this process would represent a new paradigm in cancer management, changing the ‘waiting game’ into a time of active prevention.

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Compliance with Ethical Standards

Conflicts of interest: Dr. Bernard is a shareholder in Cumberland Pharmaceuticals, Inc., which is developing CPI211, a pharmacological antagonist of the thromboxane A₂/prostaglandin endoperoxide receptor, a class of drugs mentioned in the manuscript as a possible therapy for metastasis prevention. No other competing financial interests exist.

These therapies could take multiple forms based on the pathways involved in the metastatic process. For example, a Phenome Wide Association Study showed that a single nucleotide polymorphism in the gene *TBXA2R* is associated with increased metastasis in multiple primary cancers ($P = 0.003$), suggesting clinical applicability of *TBXA2R* antagonists. Emerging data related to the role of platelets in metastasis are concordant with our sense that these pathways present significant opportunities for therapeutic development. Before real progress can be made towards clinical targeting of the metastatic process, however, foundational work is needed to define informative measures of critical elements such as circulating tumor cells and tumor DNA, and circulatory vs. lymphatic spread. These challenges require an expansion of team science and composition to obtain competitive funding. At our academic medical center, we have implemented a Cancer Metastasis Inhibition (CMI) program investigating this approach across multiple cancers.

1. Introduction

In many ways, cancer remains the “Emperor of all Maladies.”¹ There has been a steady decline in mortality from many types of cancer over the past 20 years. However, cancer-related death rates have not changed materially for several malignancies, including non-small cell lung, pancreatic, and bladder cancers². Mortality rates for some cancers, such as uterine cancer, are on the rise³. Cancer remains a leading cause of morbidity and mortality globally⁴. For the majority of cancers, cytotoxic chemotherapy has been the standard of care for decades, although emerging advances in targeted therapies and immunotherapeutic strategies are altering the reliance on chemotherapy for some cancers. Despite advances in how some cancers are treated, cancer metastasis and recurrence are universal concerns across all solid cancers diagnosed in early stage; in fact, this concern is so prominent that it often occurs in people’s health-related thoughts *even when they do not have cancer*⁵. Metastatic and/or recurrent cancer diagnoses impose a significant emotional, social, and economic burden that impacts quality of life for each patient, in large part because these diagnoses generally associate with early death. Even when a cancer is in remission (a clinically silent state), microscopic metastases, even single cancer cells, can lurk clinically undetectable throughout the body for variably long periods of time, depending on the type of cancer⁶. These potentially dangerous cells remain unseen, even to the most sensitive imaging modalities, until they grow to a level that becomes clinically apparent.

Here, we advocate for a parallel avenue of investigation in the field of oncology – the development and refinement of strategies specifically targeting the metastatic process – and share ongoing work as one illustrative example; we also summarize key knowledge gaps that are in need of bridging through pre-active research initiatives.

2. Metastasis as the target of a treatment paradigm

The “hallmarks of cancer” were first described in 2000 and along with the expanding knowledge base have been updated in the years since⁷. Treatment strategies targeting the many hallmarks of cancer have been employed to destroy cancer cells, shrink or eliminate tumors, or slow their growth. Recent advances in genomic and molecular tumor profiling

have led to treatment strategies that exploit unique characteristics of tumor cells. Some specialized targeted therapies are aimed at blocking tumor angiogenesis, and emerging breakthroughs in immunotherapy have identified new avenues of treatment, intended to stimulate the patient's own immune responses to eradicate tumors. Like molecularly targeted treatments, many immunotherapies counteract the molecular targets produced by cancer cells that would otherwise inhibit the patient's anti-tumor responses, although many other immunotherapies are designed to actively stimulate specific components of anti-tumor responses. However, it is difficult to find treatment breakthroughs aimed specifically at the inhibition of the metastatic process. Despite a range of intriguing preclinical work conducted since the 1980s suggesting that some strategies (e.g. calcium channel blockers,^{8–10} antithrombotics,¹¹ beta blockers¹², ERK inhibitors¹³) may have therapeutic potential related to the metastatic process, relatively few therapies directly target tumor cell invasion and/or metastasis and none are currently in FDA-approved clinical use for this indication. Deliberate approaches to *specifically prevent metastases* by neutralizing or thwarting the problematic dispersion of tumor cells would be important, and could manifest in a number of different forms: containment of cells to the primary site, disabling cancer cell survival in the circulation, reducing evasion of immune surveillance, preventing platelet/tumor cell aggregates that may enable extravasation at secondary sites, and/or making secondary sites inhospitable to metastatic seeding. Agents that are FDA approved to specifically affect the metastatic process across cancers would thus represent a new paradigm in cancer management, addressing an unmet medical need and aimed ultimately at blocking lethal dissemination of cancers – focusing beyond the primary tumor.

3. Benefits in metastasis blockade

In a review of cancer metastasis, Talmadge and Fidler delineate 10 steps in the metastatic process¹⁴. These steps can be leveraged to support new avenues of research aimed specifically at reducing the metastatic spread of cancer. Blockade of metastasis may have additional indirect benefits as well. For example, agents that thwart the spread of cancer might allow conventional chemotherapies to be used at reduced doses or for shorter durations. This is an important consideration, since chemotherapies often target fast-growing healthy cells in addition to fast growing tumor cells, causing treatment-associated toxicity, tissue damage, and morbidity. Further, treatments aimed at preventing metastatic dissemination might be used in combination with molecularly targeted anti-tumor agents. In this scenario, it should be noted that acquired resistance to molecularly targeted agents often arises at sites of metastatic recurrence. Thus, inhibition of metastatic dissemination may reduce the incidence and/or rate of acquired resistance, improving the clinical success of precision cancer therapeutics. Importantly, by paying attention not only to the primary tumor, but also to the metastatic process, we can focus additional resources towards innovations that will improve detection and quantification of circulating tumor cells (CTCs), build predictive models to determine which cancers are still localized and curable with surgery versus which have disseminated micrometastases, and pinpoint molecular vulnerabilities in the metastatic process that can be targeted safely and efficaciously.

4. The potential for active prevention

Patients diagnosed with solid cancers might receive any one or a combination of treatments, including surgery, radiation, chemotherapy, or molecularly targeted therapies. After the treatment course, including the treatment of any micrometastatic disease with adjuvant systemic therapy, a patient may have no additional clinical evidence of cancer. In these cases, the cancer is considered to be ‘in remission’. These patients, their families, and their physicians rely on watchful waiting until the time clinical evidence of cancer returns. Prevention of initial or secondary metastatic spread of any remaining tumor cells - by targeting the metastatic process itself - could replace watchful waiting with proactive prevention. The goal would be to find a treatment window in which targeted blockade of the metastatic process could be used adjuvantly – and/or following any standard of care therapies. If successful, these novel strategies would reduce metastatic disease across a variety of solid cancer types, while potentially providing emotional value to the patient.

While there could eventually be many strategies to prevent metastatic spread, we focus on one illustrative example in particular herein – the use of strategies affecting components within the arachidonic acid signaling pathway.

5. Therapeutic rationale for targeting metastasis

Some cancers – even cancers of common origin – can spread at different rates and employ distinct molecular and cellular pathways in one patient as compared to others. Some of this variability may be attributable to a host environment that is more or less conducive to metastatic spread. As just one example, data from a Phenome Wide Association Study (PheWAS)^{15,16} show that a single nucleotide polymorphism (SNP) in the gene *TBXA2R*, causing a gain-of-function arising from a single amino acid substitution, is associated with increased tumor metastasis ($P = 0.003$). These statistically significant observations span *multiple primary cancers* as well as *multiple metastatic sites*, suggesting the intriguing possibility of inherent requirements for thromboxane A₂ (TXA₂) and TBXA₂R in the basic mechanism of metastasis, and the potentially widespread clinical applicability of TBXA₂R antagonists as adjuvant therapy in multiple cancers. Given the complexity of thromboxane receptor pharmacology and related ligands within a range of biologic pathways,¹⁷ further investigations will be required to explore possible explanations for these effects. Preclinical work is currently underway at our institution.

Other promising work in this field includes: initial data showing potential applications for use of platelet mRNA in early diagnosis of metastasis;¹⁸ work demonstrating that platelets (one rich source of TXA₂, adhesion molecules, and growth factors) mediate cancer metastasis through a range of pathways^{19,20}; detection of CTCs extensively cloaked by platelets;²¹ approaches to genetically engineering platelets to kill tumor cells and reduce their spread²²; and exploration of the use of agents such as aspirin, an irreversible inhibitor of platelet TXA₂ synthesis, to limit cancer metastasis²³. One trial assessing a related (but significantly different) drug’s ability to prevent recurrence is the currently-enrolling Add-Aspirin study²⁴ (NCT02804815), which aims to determine whether aspirin use after standard curative therapy can prevent recurrence and improve survival in individuals with

non-metastatic tumors (breast, colorectal, gastroesophageal, and prostate). Study participants are randomized (double-blind) to either aspirin 100 mg, aspirin 300 mg, or a matched placebo, to be taken daily for at least 5 years. Outcome measures will include: recurrence and survival, adherence, toxicity, and other potential effects of aspirin (e.g., cardiovascular). While this trial is important, valuable, scientifically sound (it includes 11,000 participants) and has great potential to improve lives, the estimated completion date for the study is almost 10 years away (2026). Additionally, while aspirin and related drugs such as CPI211 both affect the coagulation pathway, they have substantially different pharmacological properties. Aspirin is a covalent enzyme inhibitor of cyclooxygenases and also affects platelet biosynthesis of prostaglandin E₂, posited to contribute to the inhibition of the immune system's response to cancer and implicated in the induction of epithelial mesenchymal transition.^{23,25} CPI211 is a receptor antagonist of the thromboxane A₂ (TP) receptor. The TP receptor's position deeper within the arachidonic acid signaling pathway may allow for a more specific response to pharmacological modulation by CPI211. Thus, there remain rich opportunities for exploring the effects of these and perhaps other agents in preventing or altering metastatic processes.

These emerging data are also concordant with our sense that these pathways are plausible and present significant opportunities for therapeutic discovery and development. In contrast to local tissue invasion by cancer cells, metastasis requires the transport of cancer cells to distant sites via the blood and/or lymphatic system; perineural invasion can also play an important role in a number of cancers.^{26–28} Indeed, the many roles platelets play in metastasis have been described extensively¹⁹. Selected platelet-mediated steps in metastasis that may be possible to target via pharmacological agents include: detachment and embolization of platelet-containing tumor cell aggregates; circulating tumor cells protected from host immune responses by aggregated platelets; and tumor embolus colonization facilitated by P-selectin-mediated tumor cell-platelet interactions.

While a number of investigations indicate involvement of platelets in the path to cancer metastasis (see Figure 1), research exploring the manipulation of these connections (using therapeutic approaches such as aspirin) to inhibit platelet activation with the goal of preventing or interrupting metastatic disease remains at a fairly early and heterogeneous stage. The diverse ways in which platelets interact with tumor cells and the complex directionality of those effects are yet incompletely understood and Figure 1 is not intended to be an exhaustive representation of this field; for example, much remains unexplored regarding interactions between platelets and tumor cells, the role that other factors such as tumor exosomal integrins may play in the overall disease process,²⁹ and the potential benefit of antiplatelet therapeutics, including factors such as intercellular transfer of mitochondrial DNA and various observed epigenetic changes.^{30–33} Results from preclinical studies of antiplatelet drug classes other than TBXA₂R inhibitors such as P₂Y₁₂ receptor antagonists and glycoprotein IIb/IIIa antagonists suggest a potentially broad role for antiplatelet drugs in metastasis prevention. However, the results have been mixed, with some clinical evidence indicating that long term use of antiplatelet drugs may promote tumor growth or facilitate metastatic dissemination.^{34,35}

Fortunately, randomized controlled trials of multiple aspirin doses across select different cancers are getting underway. However, despite the potential of these reasonable approaches and ongoing growth in the relevant evidence base, current real world clinical strategies still remain far away from implementation of a new class of medications targeting the metastatic disease process, agents that may eventually function as an armamentarium of “metastasis inhibitors.”

6. Challenges and issues in metastasis blockade

Importantly, pivotal groundwork is required before many of these approaches can be successfully implemented. For example, increased preclinical work is urgently required to determine if *different cancers spread differently* (between the vasculature/circulatory system and the lymphatic system), and if so, *how* can this variability be leveraged into novel therapeutic strategies. Further, it is not well-known how to reliably measure CTCs and use these data in treatment planning, with only one FDA approved technique and large heterogeneity in CTC values³⁶. Specific CTC values that reproducibly associate with key outcomes, such as progression-free survival (PFS) and overall survival (OS), have not been established across various cancers. These measures have not been successful thus far when used as endpoints in randomized controlled trials of antiplatelet therapies, perhaps because of issues with the sensitivity of CTC assays³⁷. In addition, CTC clusters, which represent less than 10% of total CTCs but have extremely high metastatic potential,^{38,39} remain very challenging to detect or measure³⁶. There is a related need for improved imaging modalities to detect rare but highly prognostic (and likely dangerous) microscopic cell clusters. A range of other issues related to the translation of findings into human implications will need to be explored, including selection of the ideal treatment window for this novel therapeutic strategy, considering how the TBXA2R profile should affect plans in combination with traditional hallmarks of metastasis, and feasibility of tracking more granular disease characteristics (e.g. tagging tumors to follow micrometastases⁴⁰).

Another potential measure of molecular recurrence, cell-free circulating tumor DNA (ctDNA), is a source of tumor genetic information and accepted as a prognostic measure, suggesting that ctDNA could be a highly sensitive marker for post-surgical residual disease, identifying individuals at risk of recurrence who may benefit from proactive blockade of the metastatic process. Yet, ctDNA carries many challenges: lack of rigorous studies with early-stage cancers, low concentrations of ctDNA, and sensitivity of available approaches for analyzing ctDNA. Finally, biopsies of any kind can reflect only the properties of that particular sample of tumor mass; it is entirely possible that different masses metastasize at different rates.

It is a complex, long, and expensive process to test and ultimately validate either CTC or ctDNA as a surrogate marker of metastatic disease across cancers. While progression-free survival (PFS) would be the optimal endpoint, the length of time likely required to see meaningful changes in PFS might preclude its use in many, but not all, cancers. These challenges, and certainly others, will need to be addressed before real progress can be made towards clinical targeting of the metastatic process. High-priority foundational questions include:

- Do any cancers spread primarily or disproportionally through the vasculature, as compared with another route such as the lymphatic system?
- Can distinct therapeutic strategies target different stages of the metastatic dissemination process?
- Should platelet level or activation state be a patient screening tool for selection of therapies focused on metastatic processes?
- Can clusters of CTCs be reliably measured through clinical testing, and are these prognostic?
- When should therapies focused on metastatic processes be given during the course of illness?

This last question has prompted consideration of several related challenges within our program. Tumor cells can enter the circulation long before a cancer diagnosis is made,⁴¹ and standard procedures such as biopsy and surgical removal of the primary tumor may increase tumor cell shedding into the circulatory system.^{42,43} There is also growing evidence that primary tumors begin conditioning distant metastatic sites to encourage the growth of secondary tumors before metastatic dissemination has even occurred.⁴⁴ This suggests that many patients clinically diagnosed with Stage I cancer could already be in the midst of the beginning phases of metastasis. While the approach described herein attempts to address this issue by targeting the process prior to clinical detection of metastatic disease, one pitfall is that perhaps the period of ‘watchful waiting’ is still not early enough. Unfortunately, there are safety issues prohibiting the use of TBXA2R antagonists earlier in the disease course than after surgical therapy and/or chemotherapy have been completed. These include the increased risk of bleeding associated with administering antiplatelet medications during surgical procedures and the potentially harmful interactions with chemotherapeutic agents that are currently unknown. Further, conflicting data regarding the possibility of increased risk for development solid tumors during long-term antiplatelet therapy warrants careful consideration as we design the next steps in our program.^{34,35} A decades-long prospective trial in cancer-free individuals to determine and better understand the long-term effect of TBXA2R antagonists on cancer prevention and overall survival is neither financially feasible for our program nor the fastest path to helping patients. Given these realities, we hope that this treatment strategy can, at a minimum, slow down or delay the metastatic process that is already underway and provide some valuable insights into the role of platelets in metastatic dissemination.

Generating answers to a series of platelet-related questions would also elucidate key aspects of the metastatic process and ultimately aid the development of therapies specifically targeting the platelet-mediated aspects of the metastatic process. These questions include:

- Does the absolute number of discrete metastatic sites, when analyzed among primary tumor types and between patients, suggest anything about individual platelet-related receptivity to or resilience against metastasis?

- Would platelet related strategies be more likely to show efficacy in preventing metastasis in primary tumors with greater *TBXA2R* expression and/or thromboxane A₂ synthesis?
- Would platelet related strategies be more efficacious in individuals with elevated baseline platelet levels or platelet-to-lymphocyte ratios at the time of resection (see Table 1)?

7. Parallel approaches in targeting metastasis

Research exploring the effectiveness of cyclooxygenase/arachidonic acid pathway inhibition for metastasis prevention remains at a fairly early and heterogeneous stage although some large, prospective clinical trials are getting underway. The underlying biology responsible for driving different tumor types is diverse. Consequently, there are likely to be tumor types that will respond better or worse to COX inhibition or thromboxane receptor antagonism. The NCI funding pathway and the significant potential of research exploring the Provocative Questions⁴⁵ present an exciting opportunity to both complement and move beyond the more traditional investigations. Perhaps these high reward activities can be funded by major initiatives, such as Stand Up to Cancer or the NCI Moonshot Initiative. However, it is woefully insufficient to simply call for changes to paradigms; in fact, that is always the easy part. It is far harder to design and conduct *breakthrough science*, to seek and obtain federal or other funding for highly novel approaches, and to successfully complete well-designed and executed human clinical trials for therapies leveraging these new models. But these are the necessary steps to make real progress. As a community of stakeholders (patients, industry, academics, government, providers, foundations) we need to put our most precious assets behind the support, sponsorship, and conduct of the needed investigations of therapies intended to prevent the metastatic spread of *those cancers we cannot yet kill for good*. At the very least, this will require the expansion of team science and composition, changing expectations for relying on traditional approaches in making funding determinations, and altering eligibility for funding (say, a platelet biologist with no experience in oncology successfully applying to NCI).

At our academic medical center, we have implemented a **Cancer Metastasis Inhibition (CMI)** program investigating this treatment approach across multiple cancers, beginning with a clearer understanding of foundational knowledge. Our program is in the early stages. A first step was bringing together researchers across cancer areas, whereas many have traditionally focused on a specific cancer type. A major goal of the initiative is to raise awareness of what is not currently known. Ongoing work includes a number of preclinical investigations, as well as parallel translation-focused discussions within this multidisciplinary team to work through the many issues related to future investigations in humans.

Cancer itself is known to cause a number of hematologic derangements; given increasing evidence regarding the range of ways in which tumor cells manipulate biologic processes to grow and spread, as well as evade detection⁴⁶, learning more about how to counteract these effects may lead to revolutionary approaches for helping the human body maintain and

restore its defenses in the context of a cancer. The metastatic process represents a complex and incompletely understood target within the larger spectrum of cancer therapeutic strategies. It is encouraging that the current literature reflects a number of intriguing paths under investigation for more directly targeting this process, despite the many challenges of finding and evaluating approaches for preventing metastatic disease. We are hopeful that the research community also working on CMIs can immediately work together to collaboratively share relevant foundational knowledge and collectively determine the most promising approaches that can help specific groups of patients in the shortest amount of time.

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Key Points

- We advocate for a new paradigm in cancer management; this approach would focus beyond the primary tumor and specifically address the metastatic process.
- A Phenome Wide Association Study revealed an association between a single nucleotide polymorphism in the *TBXA2R* gene and multiple secondary malignancies, supporting existing evidence related to the role of platelets in metastasis and suggesting that these pathways present opportunities for therapeutic development.
- We are developing a **Cancer Metastasis Inhibition (CMI)** program to investigate how the clinical targeting of arachidonic acid signaling pathway components may inhibit the metastatic process across multiple cancer types.

Fig 1. The role of platelets in metastatic disease

Platelets are a key in the development of secondary neoplasms, primarily through their role in shielding circulating tumor cell (CTC) clusters from host immune responses as they travel through the circulatory system to other parts of the body. Targeting platelet aggregation in order to prevent the formation of these clusters may be a more effective therapeutic approach than existing strategies that target tumor cells.

Table 1
Platelet measures may predict prognosis across multiple cancer types

There is a growing body of evidence that the level of platelets alone in relation to the level of lymphocytes may accurately predict a variety of cancer outcomes. More work is needed to further validate these platelet measures, characterize how they are impacted by platelet-related therapies, and determine their utility as clinical trial endpoints

Platelet measures	Cancer types	Associated prognostic variables
Elevated platelet levels	Breast (HER+)	Shorter PFS ⁴⁷⁴⁷
	Liver	Recurrence ⁴⁸⁴⁸
	NSC Lung	Elevated risk of disease progression and death ⁴⁹⁴⁹
	Ovarian	Shorter PFS and OS ⁵⁰⁵⁰
	Pancreatic	Tumor progression, metastasis, and OS ⁵¹⁵¹
Elevated platelet-to- lymphocyte ratio	Breast (HER+/ER+/PR+ subtypes)	Distant metastases and higher mortality rate ⁵²⁵²
	Colorectal	Shorter RFS, DFS, and OS ⁵³⁵³
	Liver	Recurrence ⁵⁴ and metastasis ⁵⁵⁵⁴ and metastasis
	NSC Lung	Shorter OS ⁵⁶⁵⁶
	Ovarian	Shorter PFS and OS ⁵⁷⁵⁷
	Prostate	Shorter MFS, CSS, and OS ⁵⁸⁵⁸

PFS: Progression-free survival; OS: Overall survival; DFS: Disease-free survival; RFS: Recurrence-free survival; MFS: Distant metastasis-free survival; CSS: Cancer-specific survival