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PERSPECTIVES

Drugs for solid cancer: the productivity crisis prompts a rethink

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Daniel Rösel[1]
Jan Brábek[1]
Pavel Veselý[2]
Michael Fernandes[3]

[1]Department of Cell Biology, Charles University in Prague, Prague, Czech Republic; [2]Central European Institute of Technology, Brno University of Technology, Brno, Czech Republic; [3]Medbase, Chapel Hill, NC, USA

Abstract: Despite remarkable progress in cancer-drug discovery, the delivery of novel, safe, and sustainably effective products to the clinic has stalled. Using Src as a model, we examine key steps in drug development. The preclinical evidence on the relationship between Src and solid cancer is in sharp contrast with the modest anticancer effect noted in conventional clinical trials. Here, we consider Src inhibitors as an example of a promising drug class directed to invasion and metastasis and identify roadblocks in translation. We question the assumption that a drug-induced tumor shrinkage in preclinical and clinical studies predicts a successful outcome. Our analysis indicates that the key areas requiring attention are related, and include preclinical models (in vitro and mouse models), meaningful clinical trial end points, and an appreciation of the role of metastasis in morbidity and mortality. Current regulations do not reflect the natural history of the disease, and may be unrelated to the key complications: local invasion, metastasis, and the development of resistance. Alignment of preclinical and clinical studies and regulations based on mechanistic trial end points and platforms may help in overcoming these roadblocks. Viewed kaleidoscopically, most elements necessary and sufficient for a novel translational paradigm are in place.

Keywords: cancer, paradigms, Src inhibitors, metastasis, translation, drug resistance

Video abstract

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Correspondence: Jan Brábek
Department of Cell Biology, Faculty of Science, Charles University in Prague
Vinicna 7, 12843, Prague 2,
Czech Republic
Email brabek@natur.cuni.cz

Introduction

The mismatch between science and translation is best illustrated by advances in cancer research,[1,2] especially tumor virology,[3] and the dearth of novel, safe, and sustainably effective drugs for solid cancer introduced to the clinic.[4–6] This anomaly prompts the question: Where are we going wrong?[7,8]

Fifty years ago, Thomas Kuhn explained that science does not progress linearly, but through paradigmatic shifts; conventional and seemingly logical paradigms lose their utility when they cease to be fruitful.[9] In this context, "fruitful" refers to translational potential, and anomalies between preclinical expectations and clinical reality are signs that all is not well. In solid cancer, an abysmally low approval rate, ineffective drug performance, market recalls, and unaffordable prices complicate the problem.[8,10] In order to identify whether the cause lies in discovery, development, or in the approval process, which in a manner governs development, a rethink is in order.

Provocative questions[11] are the best starting point for a collective rethink, and we address three issues in solid cancer: nonpredictive preclinical models, the Response Evaluation Criteria in Solid Tumors (RECIST) framework for evaluating tumor response to intervention, and an under appreciation of the role of metastasis in morbidity and mortality. We question the operational assumption that tumor shrinkage is an index

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of overall survival/regression and a reduction in metastatic potential, especially since this assumption governs drug development and may direct attention away from local invasion and metastasis. Dissemination is the leading cause of mortality, and the most important improvements in morbidity and mortality will result from the prevention (or elimination) of metastasis.[12–15] Accordingly, using the knowledge of Src inhibitors in solid cancer, we review the gaps between preclinical expectations and clinical reality in the evaluation of Src inhibitors, and indicate areas that may need emphasis.

Src and invadopodia in cancer cell invasion and metastasis

The year 2011 marks the centenary of Peyton Rous's discovery of the chicken sarcoma virus.[16,17] Six decades after this discovery, the agent was identified as the viral *Src* gene (*v-Src*) and it was established that a host gene (*c-Src* or *Src*) was captured by the virus.[18] In 1966, at the age of 85 years, and 55 years after the publication of work on the tumor-producing virus, Rous was awarded the Nobel Prize. In 1989, Harold Varmus and Michael Bishop were awarded the Nobel Prize for their discovery of the cellular origin of retroviral oncogenes as exemplified by Src.[18] Martin chronicles events along the winding "road to Src" and the discovery of the first human protooncogene,[19] while Becsei-Kilborn details the multiple reasons for the delayed recognition of this discovery.[20] Today, Src is considered a key consideration in cancer cell invasion and metastasis.[21–26]

Src and related signaling mechanisms influence key elements in carcinogenesis, and invadopodia may represent the proximate mechanism related to local invasion and metastasis. But under current regulations, it is likely that Src inhibitors will recapitulate the experience of the matrix metalloproteinase inhibitors – failure. Today, mechanism-based drugs that do not decrease tumor size are declared clinically ineffective.

Invasion of adjacent tissue is an early step in the metastatic cascade and the key determinant of the metastatic potential of tumor cells. The invasion process is complex, and is best understood in the context of the cancer cells' interactions with their environment.[27–30] This includes signaling pathways involved in epithelial–mesenchymal transition (EMT),[31,32] chemotaxis,[33,34] and structural and biomechanical properties of the extracellular matrix (ECM) and surrounding cells.[35–40] About 90% of cancers originate from epithelial tissue. EMT describes the morphological change in a normal cell to an invasive and possibly metastatic one. This transition results in a migratory phenotype that is responsible for penetrating the basement membrane and invading adjacent tissue. Focal degradation of the ECM as well as invasion through the basement membrane is affected by the formation and activity of invadopodia. Invadopodia are actin-based protrusions of tumor cells that mediate proteolysis of ECM constituents[41–43] (Figure 1).

Cancer cells have been shown to generate sufficient actomyosin force to deform collagen fibers and push through the ECM. However, focal degradation of the ECM precedes invasion, and it is now established that the invasive and metastatic potential of the cancer cells is related to their ability to form invadopodia. Local invasion is driven by two invadopodial processes: EMT-facilitated motility and migration, and protease-mediated degradation of the ECM.[44–46] The Src family kinases are critical for invadopodial formation and function.

Targeting Src/invadopodia for the development of anti-invasive drugs

Broad, coherent, and consistent preclinical evidence indicates that Src plays a role in the advancement and metastasis of solid cancer, and that invadopodia are an important and proximate driver of local invasion in metastasis.[44–48]

Src inhibitors: rationale and preclinical evidence justifying development in solid cancer

Rationale

The rapidly emerging interest in invadopodia in cancer invasion and metastasis has placed the Src proto-oncogene and related signaling pathways at the focal point of anticancer drug discovery. The rationale for development of Src inhibitors in solid cancer is distinctive and differentiated, since it is not directed primarily to cell proliferation but towards progression of the disease, namely invasion and metastasis. In the context of preclinical studies, Plé and colleagues at AstraZeneca[49] have outlined elements supporting this strategy:

- Src kinase is overexpressed and upregulated in several human tumor types.
- Increased Src activity in tumor cells reduces cell adhesion, facilitates motility, and thereby promotes an invasive phenotype. Src kinase plays a key role in EMT and the conversion of epithelial tumor cells to an invasive phenotype.
- Increased Src kinase activity is linked with disruption E-cadherin-mediated cell–cell adhesion and the function of focal adhesions, which are critical for cell migration.

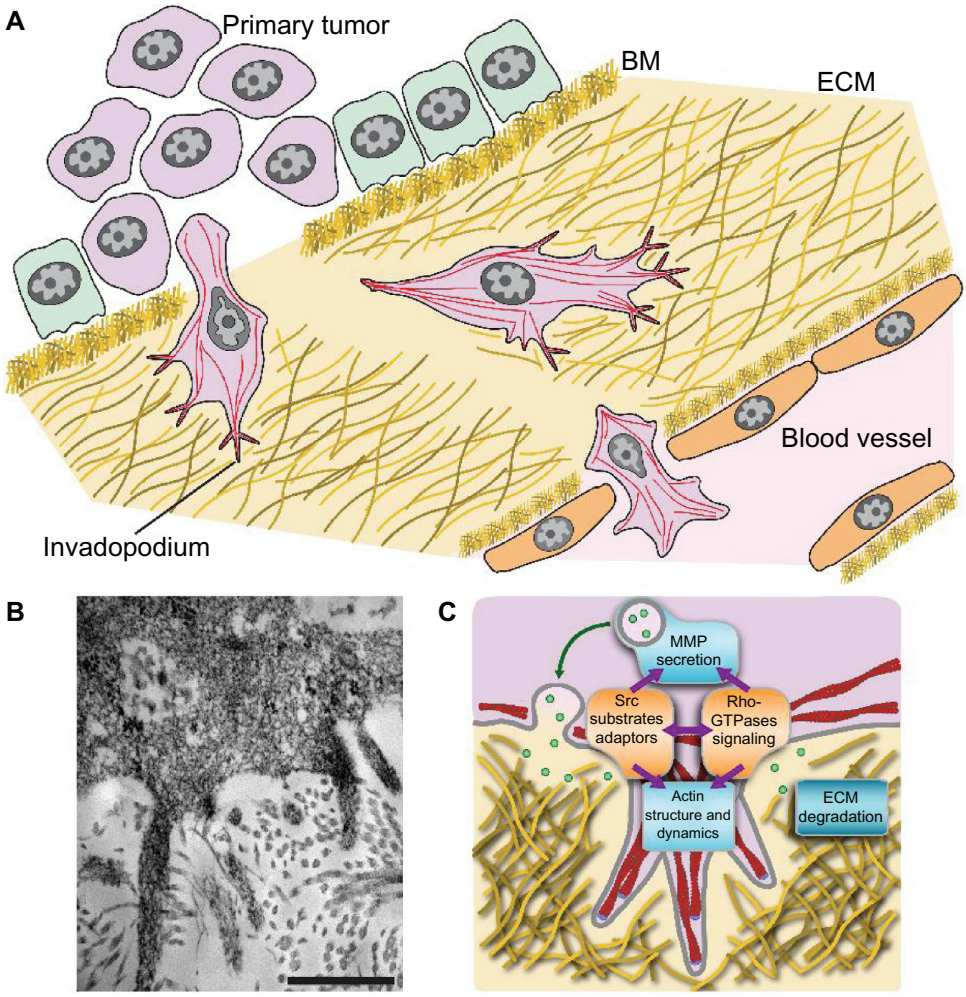


Figure 1 (**A**–**C**) Invadopodia in invasion. (**A**) Steps of the invasion/metastasis process. In most carcinomas, cells from the primary tumor undergo an epithelial–mesenchymal transition and gain a migratory phenotype that allows for degradation of the ECM. These modified cells then penetrate the BM barrier, invade adjacent tissue, and supply a vasculature. (**B** and **C**) Invadopodia are dynamic cellular protrusions with an ability to invade surrounding tissue via degradation of the ECM. (**B**) Transmission electron microscopy image of sarcoma cell section with invadopodia penetrating a dermis-based matrix; scale bar 500 nm.[43] (**C**) Schematic depicting the organization and key signaling components of invadopodia.

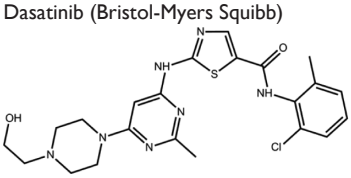
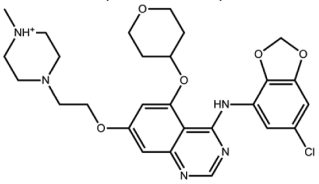
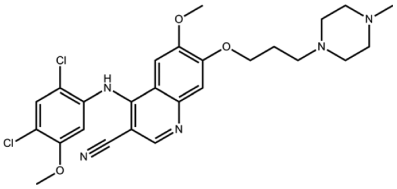
Abbreviations: BM, basal membrane; ECM, extracellular matrix; MMP, matrix metalloproteinase; GTPase, guanine nucleotide triphosphatase.

- Inhibition of Src kinase limits bone metastases.

  Three Src inhibitors are undergoing advanced clinical development in solid cancer:
- the thiazole carboxamide dasatinib (BMS-354825, SPRYCEL®, Bristol-Myers Squibb)
- the anilinoquinazoline saracatinib (AZD0530, AstraZeneca)
- the quinolinecarbonitrile bosutinib (SKI-606, Wyeth/Pfizer).

All are orally active, small-molecule, adenosine triphosphate (ATP)-binding, competitive inhibitors of tyrosine phosphorylation (Table 1). Dasatinib (Sprycel BMS-354825; Bristol-Myers Squibb, Princeton, NJ, USA) is an orally active, small-molecule (molecular weight [MW] = 488) multikinase inhibitor of several Src family kinases as well as c-Kit, platelet-derived growth-factor receptor, Bcr-Abl, and ephrin-receptor kinases. It is an ATP-competitive inhibitor and inhibits Src tyrosine kinase (half-maximal inhibitory concentration [IC_{50}] = 0.55 nM). Dasatinib was approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of adult patients with chronic myelogenous leukemia in the chronic phase resistant or intolerant to prior therapy that included imatinib (June 2006), and for the treatment of newly diagnosed adult patients with Philadelphia chromosome-positive chronic myelogenous leukemia in the chronic phase (October 2010).[50] Saracatinib (AZD0530; AstraZeneca, Reims, France) is an orally active, small-molecule (MW = 542), highly selective, dual-specific inhibitor of Src/Abl kinase inhibitor. It is an ATP-competitive inhibitor and inhibits Src tyrosine kinase

Table 1 Src inhibitors: specificity and clinical phase

Inhibitor/company	Specificity	Clinical phase
Dasatinib (Bristol-Myers Squibb) 	Broad: Src-family, c-Kit, PDGFR, Bcr-Abl, and ephrin receptors (IC_{50} cSrc = 0.6 nM)	Approved: chronic myelogenous leukemia by FDA and EMA Phase 2: breast, prostate cancer
Saracatinib (AstraZeneca) 	Dual-specific: Src/Abl (IC_{50} Src/Abl = 2.7/30 nM)	Phase 2: pancreatic cancer
Bosutinib (Pfizer) 	Dual-specific: Src/Abl (IC_{50} Src/Abl = 1.2/1 nM)	Phase 2: metastatic breast cancer

Notes: Dasatinib, *N*-(2-chloro-6-methylphenyl)-2-([6-{4-(2-hydroxyethyl)-1-piperazinyl}-2-methyl-4-pyrimidinyl]amino)-5-thiazole-carboxamide; saracatinib, *N*-(5-chloro-1,3-benzodioxol-4-yl)-7-(2-[4-methyl-1-piperazinyl[ethoxy]-5-([tetrahydro-2H-pyran-4-yl]oxy)-4-quinazolinamine; bosutinib, 7-alkoxy-4-([2,4-dichloro-5-methoxyphenyl]amino)-3-quinolinecarbonitrile.
Abbreviations: PDGFR, platelet-derived growth-factor receptor; FDA, Food and Drug Administration; EMA, European Medicines Agency.

(IC_{50} = 2.7 nM) and Abl kinase (IC_{50} = 30 nM).[51] Bosutinib (SKI-606; Wyeth/Pfizer, Pearl River, NJ, USA) is an orally active, small-molecule (MW = 530) dual inhibitor of Src/Abl kinase inhibitor. It is an ATP-competitive inhibitor and inhibits Src tyrosine kinase (IC_{50} = 1.2 nM) and Abl kinase (IC_{50} = 1 nM).[52]

Evidence

Overall, studies in in vitro and in vivo models of cancer have confirmed the ability of Src inhibitors to control tumor-cell motility and invasion. Cell proliferation and survival were unaffected at concentrations sufficient to block cell migration and invasion.[53–55]

Pichot and colleagues examined the effect of dasatinib in a drug-sensitive breast cancer cell line (MDA-MB-231), and demonstrated that dasatinib inhibited the formation of invadopodia and invasiveness in sensitive cells.[56] Furthermore, the combination of dasatinib and doxorubicin synergistically decreased proliferation and viability in the dasatinib insensitive MCF7 cell line, lowering the IC_{50} of doxorubicin by more than one log unit. Dong and colleagues examined the effect of saracatinib on the highly metastatic murine sarcoma cell line KHT. Saracatinib inhibited major elements in the metastatic cascade, including Src and focal adhesion kinase, and decreased cell migration and invasion. Pretreatment of KHT cells with saracatinib prior to injection markedly lowered lung colonies in mice in a dose-dependent manner, suggesting an antimetastatic effect.[57] Schweppe and colleagues examined the effect of saracatinib on cell lines from papillary and anaplastic cancer. In addition to noting inhibition of growth and invasion, they demonstrated the involvement and sensitivity of an Src–focal adhesion kinase complex in this cancer type.[58] They further examined the effect of dasatinib in an orthotopic metastasis mouse model of papillary thyroid cancer. Here, dasatinib blocked growth and metastasis.[59] Rabbani and colleagues examined the effect of bosutinib on the highly invasive human prostate cancer cell lines PC-3 and DU-145. Bosutinib pretreatment of PC-3 cells prior to injection markedly lowered skeletal lesions in mice.[60] Morton and colleagues demonstrated the effect of dasatinib in inhibiting the development of metastases in a mouse model of pancreatic ductal adenocarcinoma.[61] In head-and-neck squamous cell carcinoma cell lines, Ammer and colleagues demonstrated the effect of saracatinib in inhibiting cell growth, cell-cycle progression, and transwell Matrigel invasion.[62] Dose-dependent decreases in Src activation and phosphorylation of the invasion-associated substrates focal adhesion kinase, p130CAS, and cortactin were also observed. Further, saracatinib treatment displayed a dose-dependent inhibitory effect on invadopodia formation,

ECM degradation and matrix metalloproteinase 9 activation. They concluded that inhibition of Src kinase by saracatinib impairs the proinvasive activity of head-and-neck squamous cell carcinoma by inhibiting Src substrate phosphorylation important for invadopodia formation and associated matrix metalloproteinase activity. Because metastatic bone colonization consists of an initial latent phase mediated by an Src survival response and a later regrowth phase, there are opportunities to interrupt one or both phases of colonization. The relevance of Src activation in bone-specific metastasis in prostate and breast cancer is well established.[63]

Src inhibitors: success in the laboratory, and failure in the clinic

Despite the elegant case made for Src invadopodia in invasion and metastasis,[21–26,47–64] overall results of Src inhibitors as monotherapy and in conventional clinical trials in solid cancer have shown "little or modest activity."[65] We now review possible causes of this anomaly.

Preclinical models

Today, there is no ideal preclinical strategy that can predict the efficacy of agents in clinical trials. Preclinical models range from the simple, rapid, and convenient to the complex, delayed, and cumbersome (Table 2). In mouse xenograft models, size can be measured with calipers, but imaging is needed for genetically engineered mouse models (GEMMs). Although tumor cell lines and xenograft models are still in use today, the former do not address stromal interactions, while the latter are biased towards cytotoxic agents. In a superb perspective, Burchill concludes that complementary strategies are best used, and the selection of models should be based on a clear definition of the desired information.[66]

Tumor xenografts, unlike conventional xenografts, use the patient's tumor, not permanent cell lines. In an impressive treatise, Decaudin described advances in the primary human tumor xenograft model ("tumorgrafts") that appear quite promising but await validation.[67] Tumor xenografts in immunodeficient mice have the advantages of convenience and visualization of tumor growth, and may have the ability to predict clinical efficacy of candidate drugs.[68–71] GEMMs are created by allowing for overexpression of defined oncogenes, knock-in of genetic point mutations, and knockout of tumor suppressors. GEMMs address certain deficiencies of the tumor xenograft model, especially immunodeficiency, but introduce new concerns. Since predictive utility in a high-throughput system is a major roadblock in anticancer drug research, a clear demonstration of superiority over the tumor xenograft model may justify the effort and costs involved with GEMMs. The selection of models depends on the questions that need to be answered, and at this time tumorgrafts and GEMMs have the potential to provide prescriptive but limited information.[72–75]

Table 2 Preclinical cancer models – the quest for predictive utility and industrialization

	Advantages	Concerns
Cultured tumor cell line assays	Simple, rapid, convenient Inhibition of cell growth Similar drugs have similar inhibitory patterns High throughput	Selection pressure decreases dependence on defined oncogenic pathways Focused on cell stroma Immunodeficient state Poor predictability
Mouse-tumor xenograft models (subcutaneous/orthotopic)	Rapid, synchronized tumor development Tumor size measurement by calipers Minimal variability in tumor progression High throughput	Cell lines may not represent original tumor-repeated passaging Not characterized at genetic, molecular and histologic level Appropriate tumor-host interactions questionable Immunodeficient state Evaluation of antimetastatic potential difficult Rapid growth sensitive to cytotoxics, not cytostatics
Genetically engineered mouse models	Based on alterations of defined genes Immunocompetent state Characterized at the genetic, molecular, and histologic level Can replicate tumor-host interactions Evaluation of antimetastatic potential possible Evaluation of chemopreventive agents possible Study on early stage oncogenesis possible Study on acquired resistance and relapse possible Study on mechanistic biomarkers possible Potential for improved predictability	Complicated and laborious development/breeding protocol Tumor development not predictable Tumor size measurement requires complex imaging Patent concerns High cost Low throughput – obstacle to industrialization

According to Céspedes and colleagues, the ideal mouse model should show histopathologic features similar to the human tumor, progress through the same stages, and involve the same genes and biochemical pathways in its initiation and progression.[71] Further, the tumor response may reflect the response of the human tumor to a specific therapy, and thereby predict efficacy in clinical trials. Singh and colleagues systematically studied tumor growth and responses to treatment in two GEMMs involving non-small-cell lung cancer and a pancreatic adenocarcinoma, and compared the results to clinical trial data using erlotinib and bevacizumab.[72] In this retrospective analysis, they found encouraging correlations between outcomes in GEMMs and clinical trials.

Importantly, a clinically relevant animal model should be metastatic. In this context, Francia and colleagues describe various models of aggressive multiorgan spontaneous metastasis after surgical resection of orthotopically transplanted human tumor xenografts.[76] In solid cancer, the key differentiator is invasiveness, which depends on cell motility and the ability to cross tissue boundaries, and biomarkers and metastasis assays could direct the discovery of novel invasive agents. Although defined steps in the metastatic cascade can be studied in isolation and in vitro, a 3-D and lifelike in vitro model would be useful.[38,77–82] Griffith and Swartz have outlined "design principles" for the creation of 3-D in vitro models that can recreate the interwoven set of biochemical and mechanical cues in the cellular microenvironment that are relevant to invasion.[82] 3-D in vitro models, by mimicking features of the in vivo environment, span the gap between 2-D cell cultures and whole-animal systems, and can thereby further anticancer drug research.[78]

RECIST, and its limitations

In clinical trials, tumor shrinkage and prevention of new lesions is a standard measure of efficacy. According to the RECIST trial, the following definitions apply: complete response, the disappearance of all target lesions; partial response, at least a 30% decrease in the sum of the longest diameter of all target lesions; progressive disease, at least a 20% increase in the sum of the longest diameter of all target lesions or the appearance of new lesions; and stable disease, neither partial response nor progressive disease.[83] A key regulatory element for approval of a candidate agent in solid cancer is a RECIST-based response: tumor shrinkage is accepted as a surrogate measure for a beneficial and sustained effect on local invasion and metastasis. With RECIST, intervention in solid cancer with novel drugs targeting invasiveness of cancer cells may be declared (or even predicted to be) clinically ineffective, since they rarely reduce tumor size.[84–86]

Further, in the RECIST scheme, the categories are arbitrary and wide. It gets more complex when one realizes that terms such as "tumor size" and "tumor shrinkage" refer to volume and therefore require measurements in three dimensions. Changes in tumor size are more sensitive to volumetric rather than linear measurements, thus allowing for a much earlier detection of response and progression.[87]

In the context of targeted agents in solid cancer, the assumption that a decrease in tumor size is a surrogate index of improvement has not been validated.[88] Importantly, with cytostatic-induced necrosis and cavitation, evaluation based on tumor size alone, as is done in RECIST, is no longer an adequate method.[85] Accordingly, attempts to validate "predictive" biomarkers within a regulatory construct (RECIST) based on tumor size, especially with targeted agents, will be difficult to interpret, and for a simple reason: a mismatch in terms between the natural history of the disease, and tumor size, and the questionable assumption that "tumor shrinkage" is a surrogate index of improvement.

With good reason, Weber has stated that tumor response is a fundamental concept in clinical oncology, but perhaps the least understood.[89] Mozley and colleagues at Merck list the key concerns about RECIST-based response assessments: "tumors do not always expand or contract uniformly, changes in line lengths represent only a small fraction of the available information in the images, and the stable disease category is so broad that it is not always adequately sensitive to changes in tumor mass."[90] Birchard and colleagues studied 99 consecutive patients with advanced non-small-cell lung cancer using RECIST. There was no relationship between early tumor response and patient survival, and patients who had an initial reduction in tumor size did not have an improved survival compared with patients with initial disease progression. In addition, there was no particular percentage reduction in tumor size that was found to correlate with survival.[91] This study confirms the meta-analysis conducted by Sekine and colleagues in more than 50 trials in patients with non-small-cell lung cancer; the correlation coefficient between response rate and median patient survival was 0.5.[88,92]

In this context, imaging technologies based on signaling pathways and metabolism, not just tumor size, have the potential to extract in vivo mechanistic information in real time, generate longitudinal data sets in intact host environments, and directly translate from preclinical cancer models to the clinic.[93–97]

Src inhibitors: opportunities

Metastasis

The primary problem in drug research in solid cancer is that discovery studies, by definition, are mechanistic in nature, while clinical evaluation is empiric and is based on tumor shrinkage. Further, although the rationale and evidence for the use of Src inhibitors in metastasis is impressive, there is no clear regulatory route to demonstrate a clinical effect of a drug on tumor metastasis.[15,98] Interpretation and decision-making is limited to what we observe and measure. Since conventional preclinical development plans focus on the primary tumor, and not on metastasis, it is likely that the specific action of a candidate drug on metastasis – braking, acceleration, or a permissive effect – may be missed. A possible differential effect of a drug on the primary tumor and metastasis could be discordant on account of direct or indirect mechanisms. Pharmacologic-induced shrinkage of the primary tumor alone may not necessarily confer overall benefit, because deficient pericyte coverage of tumor vessels may facilitate metastasis via hypoxia-associated EMT and the MET signaling pathway.[99,100] As an example, preclinical studies suggest the beneficial effects of inhibition of tumor angiogenesis may be linked to an increase in local invasion and metastasis.[101–103] Accordingly, proposals to integrate preclinical and clinical programs on metastasis are self-evident.[12–15]

Drug resistance and tumor heterogeneity

The continuing resistance of solid cancer to therapy, especially with selective kinase inhibition, is an important and urgent concern. This is a likely consequence of tumor heterogeneity that allows for the emergence of preexisting low-frequency cancer cells that harbor resistant mutations. The initial clinical response is not sustained.

In breast cancer cell lines, Zhang and colleagues demonstrated that resistance to trastuzumab (Herceptin) was linked to hyperactivation of Src, and that this resistance could be reversed by Src inhibition using saracatinib.[104] Their data supports the conclusion that Src is a critical signaling node that is hyperactivated in various trastuzumab-resistance models. This discovery, that Src is a druggable node that may prevent resistance, has an important bearing on rational combination therapy using cytostatic drugs: trastuzumab + Src inhibitors (saracatinib). Based on a review of the preclinical database on Src inhibitors, Zhang and Yu conclude that Src inhibitor-containing combinatorial regimens have potential in overcoming resistance to current anticancer therapies and in preventing metastatic recurrence.[22] These translational initiatives promise both resistance prevention (or reversal), a separate beneficial effect on disease progression and metastasis, and also a lower predicted toxicity profile.[105] In this context, the repeated pattern of an initial response followed by a relapse and resistance consequent upon tumoral heterogeneity may be mitigated and/or delayed by the initial administration of defined combination therapy. The FDA has addressed these concerns and is now encouraging the development of combination therapies in cancer,[106] and has announced a pathway for the accelerated identification and regulatory approval of investigational cancer drugs.[107]

Why focus on regulations?

Regulations, not science, define and determine both the process of drug development and the specifications of the commercial product. Clinical and regulatory thinking are the key determinants of the quality and rate of the translational throughput from science to medicines. And in cancer, it is now evident that the surrogate measure of efficacy, a reduction in tumor size (also termed "response"), does not extrapolate to sustained clinical benefit. With targeted therapy, the emergence of resistance should be anticipated, and candidate combinations evaluated earlier in phase II trials.

Justification for a rethink

The productivity crisis in pharmaceuticals is multifactorial, and a simple and single strategy is unlikely to be successful. The prevailing paradigm in cancer drug development – tumor shrinkage leads to improved survival – is based on the central assumption that cellular proliferation (and mutations) is mechanistically related to invasive and metastatic capability. A failure in the productivity of this paradigm is the primary reason for a rethink.

Earlier, in 1962, Kuhn envisioned a thematic and sequential process to explain scientific progress,[9] and the steps are well explained by Kaiser:[108]

1. A mature scientific program is characterized by paradigms: guiding concepts, theories, and methods.
2. In experiments, anomalies sometime arise between results and expectations.
3. When accumulated anomalies cannot be co-opted into the existing paradigm, the field enters a state of crisis and productivity ceases.
4. Resolution comes only with the introduction of a new paradigm that addresses the anomalies.

   Ideally, a crisis in translational productivity should encourage paradigm rethinks.

The century-old productivity stream of targeted drugs can be traced to the concepts of Paul Ehrlich (1854–1915), namely his translational strategy for the development of safe and effective "magic bullets" (*Zauberkugel*).[109] Today, we face a translational roadblock; we have more attractive new drug classes for solid cancer in the laboratory than safe and effective medicines in the clinic,[110] and the locus of this anomaly is clearly at the interface between rational science and the empirical and outdated assessment of clinical efficacy. Drews has explained that it is risky to identify and develop drugs on the basis of incomplete and insufficiently validated hypotheses.[111] Specifically in cancer, tumor size (burden) is a consequence of the accumulation of clonal cells,[112] and this is unrelated to the mechanisms driving distant metastasis. Accordingly, tumor shrinkage, especially in trials with Src inhibitors, may not qualify as a surrogate measure of overall clinical efficacy.[113]

Interestingly, although science is driven by ideas and tools,[114] the life sciences may have been more receptive to new tools (the science-industry complex) rather than new ideas. Whether the primacy of new tools or new ideas is responsible for the advancement of science is a false choice; both are necessary, but the latter needs more emphasis. New tools have supported prevailing paradigms, but have also identified anomalies. Here, a Kuhnian mindset is essential for the advancement and reception of alternative ideas that address these anomalies.

Today, anomalies have brought us to a decision node: should the development, clinical evaluation, and regulatory criteria for the approval of anticancer drugs be modified to reflect the shift from an antiproliferative strategy based on the experience of cytotoxic agents to one based on pathophysiologic mechanisms? The reasoning, taken together, is that if the mechanisms determining cellular proliferation and local invasion and metastasis are separate and distinct, then a unitary and establishment mindset fixated on cellular proliferation and tumor size may be antithetical to clinical objectives.

Conclusion: homage to magister mundi

We have looked at Src and invadopodia, and have outlined integrative strategies to lift translational roadblocks in solid cancer. Looking back, we realize that a rethink would have been unnecessary had we followed the guidance of Ehrlich.[110,115] An Ehrlichian realignment between medicinal chemistry, cell biology, preclinical development, and clinical trials has the potential to redirect anticancer efforts towards anti-invasion and antimetastatic objectives, and operate towards the delivery of safe medicines with meaningful efficacy. If this approach is fruitful, the increase in productivity should also lead to affordable medicines for all.[8,10]

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