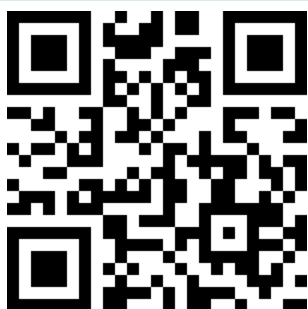


Drugs for solid cancer: the productivity crisis prompts a rethink

Daniel Rösel¹
Jan Brábek¹
Pavel Veselý²
Michael Fernandes³

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

→ Video abstract



Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: <http://dx.doi.org/10.2147/OTT.S45177>

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

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

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 questions¹¹ 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

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 AstraZeneca⁴⁹ 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.

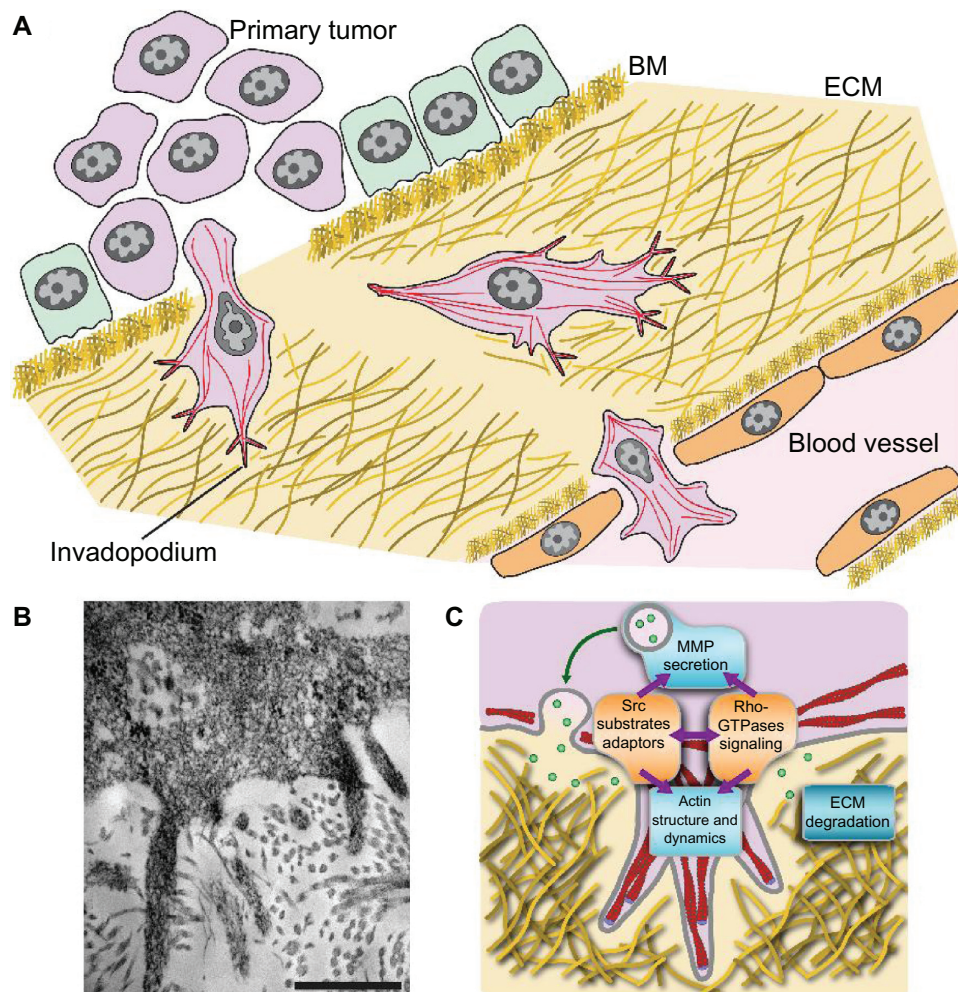


Figure 1 (A–C) Invadopodia in invasion. **(A)** Steps of the invasion/metastasis process. In most carcinomas, cells from the primary tumor undergo an epithelial–mesenchymal transition and gain a migratory phenotype that allows for degradation of the ECM. These modified cells then penetrate the BM barrier, 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.

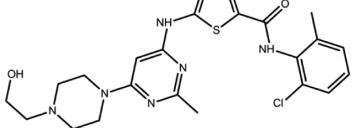
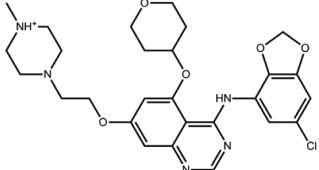
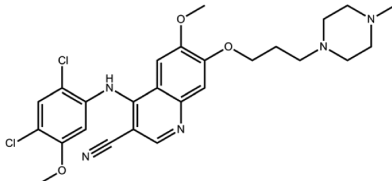
Abbreviations: BM, basal membrane; ECM, extracellular matrix; MMP, matrix metalloproteinase; GTPase, guanine nucleotide triphosphatase.

- 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 (Sprykel 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.

(IC₅₀ = 2.7 nM) and Abl kinase (IC₅₀ = 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 (IC₅₀ = 1.2 nM) and Abl kinase (IC₅₀ = 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 IC₅₀ 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” (*Zauberkegel*).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}

Acknowledgments

We thank Professor Jan Svoboda (Institute of Molecular Genetics, Prague, Czech Republic) for his fundamental insights into the early studies on Src in cancer, and M Sunil Kumar, PhD, of the Godavari Pharma Group, Hyderabad, India. We express deep appreciation to our reviewers. This work was supported, in part, by the Kellner Family Foundation Principal Investigator Grant and a grant of the Ministry of Education of the Czech Republic (MSM0021620858).

Disclosure

The authors report no conflicts of interest in this work.

References

- DeVita VT Jr, Rosenberg SA. Two hundred years of cancer research. *N Engl J Med*. 2012;366(23):2207–2214.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674.
- Javier RT, Butel JS. The history of tumor virology. *Cancer Res*. 2008;68(19):7693–7706.
- Scannell JW, Blanckley A, Boldon H, Warrington B. Opinion: diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov*. 2012;11(3):191–200.
- Pammolli F, Magazzini L, Riccaboni M. The productivity crisis in pharmaceutical R&D. *Nat Rev Drug Discov*. 2011;10(6):428–438.
- Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov*. 2004;3(8):711–715.
- Fernandes M. Judging a cancer drug: Avastin's story [letter]. *New York Times*. 2011;160(55423):section A.
- Brábek J, Fernandes M. Affordable cancer care. *Lancet Oncol*. 2012;13(1):2–3.
- Kuhn TS. *The Structure of Scientific Revolutions: 50th Anniversary Edition*. Chicago: University of Chicago Press; 2012.
- Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol*. 2011;12(10):933–980.
- Benowitz S. Provocative questions initiative to fund innovative cancer research. *J Natl Cancer Inst*. 2012;104(13):966–967.
- Weber GF. Why does cancer therapy lack effective anti-metastasis drugs? *Cancer Lett*. 2013;328(2):207–211.
- Sleeman JP, Christofori G, Fodde R, et al. Concepts of metastasis in flux: the stromal progression model. *Semin Cancer Biol*. 2012;22(3):174–186.
- Eckhardt BL, Francis PA, Parker BS, Anderson R. Strategies for the discovery and development of therapies for metastatic breast cancer. *Nat Rev Drug Discov*. 2012;11(6):479–497.
- Sleeman J, Steeg PS. Cancer metastasis as a therapeutic target. *Eur J Cancer*. 2010;46(7):177–180.
- Rous P. A sarcoma of the fowl transmissible by an agent separable from the tumor cells. *J Exp Med*. 1911;13(4):397–411.
- Weiss RA, Vogt PK. 100 years of Rous sarcoma virus. *J Exp Med*. 2011;208(12):2351–2355.
- Stehelin D, Varmus HE, Bishop JM, Vogt PK. DNA related to the transforming gene(s) of avian sarcoma viruses is present in normal avian DNA. *Nature*. 1976;260(5547):170–173.
- Martin GS. The road to Src. *Oncogene*. 2004;23(48):7910–7917.

20. Becsei-Kilborn E. Scientific discovery and scientific reputation: the reception of Peyton Rous' discovery of the chicken sarcoma virus. *J Hist Biol.* 2010;43(1):111–157.
21. Canel M, Serrels A, Frame MC, Brunton VG. E-cadherin-integrin crosstalk in cancer invasion and metastasis. *J Cell Sci.* 2013;126(Pt 2):393–401.
22. Zhang S, Yu D. Targeting Src family kinases in anti-cancer therapies: turning promise into triumph. *Trends Pharmacol Sci.* 2012;33(3):122–128.
23. Sirvent A, Benistant C, Roche S. Oncogenic signaling by tyrosine kinases of the SRC family in advanced colorectal cancer. *Am J Cancer Res.* 2012;2(4):357–371.
24. Tsuda M, Tanaka S. Roles for Crk in cancer metastasis and invasion. *Genes Cancer.* 2012;3(5–6):334–340.
25. Elsberger B, Stewart B, Tatarov O, Edwards J. Is Src a viable target for treating solid tumors? *Curr Cancer Drug Targets.* 2010;10(7):683–694.
26. Aleshin A, Finn RS. SRC: a century of science brought to the clinic. *Neoplasia.* 2010;12(8):599–607.
27. Lu P, Weaver VM, Werb Z. The extracellular matrix: a dynamic niche in cancer progression. *J Cell Biol.* 2012;196(4):395–406.
28. Bissell MJ, Hines WC. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. *Nat Med.* 2010;17(3):320–329.
29. Box C, Rogers SJ, Mendiola M, Eccles SA. Tumor-microenvironmental interactions: paths to progression and targets for treatment. *Semin Cancer Biol.* 2010;20(3):128–138.
30. Brábek J, Mierke CT, Rösel D, Veselý P, Fabry B. The role of the tissue microenvironment in the regulation of cancer cell motility and invasion. *Cell Commun Signal.* 2010;8:22.
31. Loboda A, Nebozhyn MV, Watters JW, et al. EMT is the dominant program in human colon cancer. *BMC Med Genomics.* 2011;4:9.
32. Savagner P. The epithelial-mesenchymal transition (EMT) phenomenon. *Ann Oncol.* 2010;21 Suppl 7:S87–S92.
33. Roussos ET, Condeelis JS, Patsialou A. Chemotaxis in cancer. *Nat Rev Cancer.* 2011;11(8):573–587.
34. Bravo-Cordero JJ, Hodgson LJ, Condeelis J. Directed cell invasion and migration during metastasis. *Curr Opin Cell Biol.* 2012;24(2):277–283.
35. Wirtz D, Konstantopoulos K, Searson PC. The physics of cancer: the role of physical interactions and mechanical forces in metastasis. *Nat Rev Cancer.* 2011;11(7):512–522.
36. Cukierman E, Bassi DE. Physico-mechanical aspects of extracellular matrix influences on tumorigenic behaviors. *Semin Cancer Biol.* 2010;20(3):139–145.
37. Guck J, Lautenschläger F, Paschke S, Beil M. Critical review: cellular mechanobiology and amoeboid migration. *Integr Biol.* 2010;2(11–12):575–583.
38. Panková K, Rösel D, Novotný M, Brábek J. The molecular mechanisms of transition between mesenchymal and amoeboid invasiveness in tumor cells. *Cell Mol Life Sci.* 2010;67(1):63–71.
39. Kumar S, Weaver VM. Mechanics, malignancy, and metastasis: the force journey of a tumor cell. *Cancer Metastasis Rev.* 2009;28(1–2):113–127.
40. Mierke CT, Rösel D, Fabry B, Brábek J. Contractile forces in tumor cell migration. *Eur J Cell Biol.* 2008;87(8–9):669–676.
41. Yamaguchi H. Pathological roles of invadopodia in cancer invasion and metastasis. *Eur J Cell Biol.* 2012;91(11–12):902–907.
42. Saltel F, Daubon T, Juin A, et al. Invadosomes: intriguing structures with promise. *Eur J Cell Biol.* 2011;90(2–3):100–107.
43. Tolde O, Rosel D, Vesely P, Folk P, Brábek J. The structure of invadopodia in a complex 3D environment. *Eur J Cell Biol.* 2010;89(9):674–680.
44. Destaing O, Block MR, Planus E, Albiges-Rizo C. Invadosome regulation by adhesion signaling. *Curr Opin Cell Biol.* 2011;23(5):597–606.
45. Wang Y, McNiven MA. Invasive matrix degradation at focal adhesions occurs via protease recruitment by a FAK–p130Cas complex. *J Cell Biol.* 2012;196(3):375–385.
46. Matsui H, Harada I, Sawada Y. Src, p130Cas, and mechanotransduction in cancer cells. *Genes Cancer.* 2012;3(5–6):394–401.
47. Styli SS, Kaye AH, Lock P. Invadopodia: at the cutting edge of tumour invasion. *J Clin Neurosci.* 2008;15(7):725–737.
48. Eckert MA, Lwin TM, Chang AT, et al. Twist1-induced invadopodia formation promotes tumor metastasis. *Cancer Cell.* 2011;19(3):372–386.
49. Plé PA, Green TP, Hennequin LF, et al. Discovery of a new class of anilinoquinazoline inhibitors with high affinity and specificity for the tyrosine kinase domain of c-Src. *J Med Chem.* 2004;47(4):871–887.
50. Lombardo LJ, Lee FY, Chen P, et al. Discovery of N-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl)-piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide (BMS-354825), a dual Src/Abl kinase inhibitor with potent antitumor activity in preclinical assays. *J Med Chem.* 2004;47(27):6658–6661.
51. Hennequin LF, Allen J, Breed J, et al. N-(5-chloro-1,3-benzodioxol-4-yl)-7-(2-(4-methylpiperazin-1-yl)ethoxy)-5-(tetrahydro-2H-pyran-4-yloxy)quinazolin-4-amine, a novel, highly selective, orally available, dual-specific c-Src/Abl kinase inhibitor. *J Med Chem.* 2006;49(22):6465–6488.
52. Boschelli DH, Wu B, Barrios Sosa AC, et al. Synthesis and Src kinase inhibitory activity of 2-phenyl- and 2-thienyl-7-phenylaminothieno[3,2-b]pyridine-6-carbonitriles. *J Med Chem.* 2005;48(11):3891–3902.
53. Jallat H, Valentino ML, Chen G, Boschelli F, Ali S, Rabbani SA. A Src/Abl kinase inhibitor, SKI-606, blocks breast cancer invasion, growth, and metastasis in vitro and in vivo. *Cancer Res.* 2007;67(4):1580–1588.
54. Vultur A, Buettner R, Kowolik C, et al. SKI-606 (bosutinib), a novel Src kinase inhibitor, suppresses migration and invasion of human breast cancer cells. *Mol Cancer Ther.* 2008;7(5):1185–1194.
55. Green TP, Fennell M, Whittaker R, et al. Preclinical anticancer activity of the potent, oral Src inhibitor AZD0530. *Mol Oncol.* 2009;3(3):248–261.
56. Pichot CS, Hartig SM, Xia L, et al. Dasatinib synergizes with doxorubicin to block growth, migration, and invasion of breast cancer cells. *Br J Cancer.* 2009;101(1):38–47.
57. Dong M, Rice L, Lepler S, Pampo C, Siemann DW. Impact of the Src inhibitor Saracatinib on the metastatic phenotype of a fibrosarcoma KHT tumor model. *Anticancer Res.* 2010;30(11):4405–4413.
58. Schweppe RE, Kerege AA, French JD, Sharma V, Grzywa RL, Haugen BR. Inhibition of Src with AZD0530 reveals the Src-focal adhesion kinase complex as a novel therapeutic target in papillary and anaplastic thyroid cancer. *J Clin Endocrinol Metab.* 2009;94(6):2199–2203.
59. Chan CM, Jing X, Pike LA, et al. Targeted inhibition of SRC kinase with dasatinib blocks thyroid cancer growth and metastasis. *Clin Cancer Res.* 2012;18(13):3580–3591.
60. Rabbani SA, Valentino ML, Arakelian AS, Boschelli F. SKI-606 (bosutinib) blocks prostate cancer invasion, growth, and metastasis in vitro and in vivo through regulation of genes involved in cancer growth and skeletal metastasis. *Mol Cancer Ther.* 2010;9(5):1147–1157.
61. Morton JP, Karim SA, Graham K, et al. Dasatinib inhibits the development of metastases in a mouse model of pancreatic ductal adenocarcinoma. *Gastroenterology.* 2010;139(1):292–303.
62. Ammer AG, Kelley LC, Hayes KE, et al. Saracatinib impairs head and neck squamous cell carcinoma invasion by disrupting invadopodia function. *J Cancer Sci Ther.* 2009;1(2):52–61.
63. Boyce B, Xing L. Src inhibitors in the treatment of metastatic bone disease: rationale and clinical data. *Clin Investig (Lond).* 2011;1(12):1695–1706.
64. Creedon H, Brunton VG. Src kinase inhibitors: promising cancer therapeutics? *Crit Rev Oncog.* 2012;17(2):145–159.
65. Puls LN, Eadens M, Messersmith W. Current status of Src inhibitors in solid tumor malignancies. *Oncologist.* 2012;16(5):566–578.
66. Burchill SA. What do, can, and should we learn from models to evaluate potential anticancer agents? *Future Oncol.* 2006;2(2):201–211.
67. Decaudin D. Primary human tumor xenografted models ('tumorgrafts') for good management of patients with cancer. *Anticancer Drugs.* 2011;22(9):827–841.

68. Ocana A, Pandiella A, Siu LL, Tannock IF. Preclinical development of molecular-targeted agents for cancer. *Nat Rev Clin Oncol*. 2011;8(4):200–209.
69. Caponigro G, Sellers WR. Advances in the preclinical testing of cancer therapeutic hypotheses. *Nat Rev Drug Discov*. 2011;10(3):179–187.
70. Teicher BA. In vivo/ex vivo and in situ assays used in cancer research: a brief review. *Toxicol Pathol*. 2009;37(1):114–122.
71. Céspedes MV, Casanova I, Parreño M, Mangués R. Mouse models in oncogenesis and cancer therapy. *Clin Transl Oncol*. 2006;8(5):318–329.
72. Singh M, Lima A, Molina R, et al. Assessing therapeutic responses in Kras mutant cancers using genetically engineered mouse models. *Nat Biotechnol*. 2010;28(6):585–593.
73. Francia G, Kerbel RS. Raising the bar for cancer therapy models. *Nat Biotechnol*. 2010;28(6):561–562.
74. Robles AI, Varticovski L. Harnessing genetically engineered mouse models for preclinical testing. *Chem Biol Interact*. 2008;171(12):159–164.
75. Carver BS, Pandolfi PP. Mouse modeling in oncologic preclinical and translational research. *Clin Cancer Res*. 2006;12(18):5305–5311.
76. Francia G, Cruz-Munoz W, Man S, Xu P, Kerbel RS. Mouse models of advanced spontaneous metastasis for experimental therapeutics. *Nat Rev Cancer*. 2011;11(2):135–141.
77. Baker BM, Chen CS. Deconstructing the third dimension – how 3D culture microenvironments alter cellular cues. *J Cell Sci*. 2012;125(Pt 13):3015–3024.
78. Li L, Lu Y. Optimizing a 3D culture system to study the interaction between epithelial breast cancer and its surrounding fibroblasts. *J Cancer*. 2011;2:458–466.
79. Harunaga JS, Yamada KM. Cell-matrix adhesions in 3D. *Matrix Biol*. 2011;30(7–8):363–368.
80. Krause S, Maffini MV, Soto AM, Sonnenschein C. The microenvironment determines the breast cancer cells' phenotype: organization of MCF7 cells in 3D cultures. *BMC Cancer*. 2010;10:263.
81. Yamada KM, Cukierman S. Modeling tissue morphogenesis and cancer in 3D. *Cell*. 2007;130(4):601–610.
82. Griffith LG, Swartz MA. Capturing complex 3D tissue physiology in vitro. *Nat Rev Mol Cell Biol*. 2006;7(3):211–224.
83. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline version 1.1. *Eur J Cancer*. 2009;45(2):228–247.
84. Tuma RS. Sometimes size doesn't matter: reevaluating RECIST and tumor response rate endpoints. *J Natl Cancer Inst*. 2006;98(18):1272–1274.
85. Diederich S. Imaging beyond RECIST: CT and MRI in molecular therapies. *Cancer Imaging*. 2012;12(2):347–350.
86. Bradbury P, Seymour L. Tumor shrinkage and objective response rates: gold standard for oncology efficacy screening trials, or an outdated end point? *Cancer J*. 2009;15(5):354–360.
87. Goldmacher GV, Conklin J. The use of tumour volumetrics to assess response to therapy in anticancer clinical trials. *Br J Clin Pharmacol*. 2012;73(6):846–854.
88. Sullivan DC, Gatsonis C. Response to treatment series: part 1 and introduction, measuring tumor response – challenges in the era of molecular medicine. *AJR Am J Roentgenol*. 2011;197(1):15–17.
89. Weber WA. Assessing tumor response to therapy. *J Nucl Med*. 2009;50 Suppl 1:S1–S10.
90. Mozley PM, Bendtsen C, Zhao B, et al. Measurement of tumor volumes improves RECIST-based response assessments in advanced lung cancer. *Transl Oncol*. 2012;5(1):19–25.
91. Birchard KR, Hoang JK, Herndon JE Jr, Patz EF Jr. Early changes in tumor size in patients treated for advanced stage nonsmall cell lung cancer do not correlate with survival. *Cancer*. 2009;115(3):581–586.
92. Sekine I, Kubota K, Nishiwaki Y, Sasaki Y, Saijo N. Response rate as an endpoint for evaluating new cytotoxic agents in phase II trials of non-small-cell lung cancer. *Ann Oncol*. 1998;9(10):1079–1084.
93. Weber WA, Czernin J, Phelps ME, Herschman HR. Technology insight: novel imaging of molecular targets is an emerging area crucial to the development of targeted drugs. *Nat Clin Pract Oncol*. 2008;5(1):44–54.
94. Desai IM, van Herpen CM, van Laarhoven HW, Barentsz JO, Oyen WJ, van der Graaf WT. Beyond RECIST: molecular and functional imaging techniques for evaluation of response to targeted therapy. *Cancer Treat Rev*. 2009;35(4):309–321.
95. Serkova NJ. Translational imaging endpoints to predict treatment response to novel targeted anticancer agents. *Drug Resist Updat*. 2011;14(4–5):224–235.
96. Garcia Figueras R, Padhani AR, Goh VJ, et al. Novel oncologic drugs: what they do and how they affect images. *Radiographics*. 2011;31(17):2059–2091.
97. Kang H, Lee HY, Lee KS, Kim JH. Imaging-based tumor treatment response evaluation: review of conventional, new and emerging concepts. *Korean J Radiol*. 2012;13(4):371–390.
98. Elvin P, Garner AP. Tumor invasion and metastasis: challenges facing drug discovery. *Curr Opin Pharmacol*. 2005;5(4):374–381.
99. Gerhardt H, Semb H. Pericytes: gatekeepers in tumour cell metastasis? *J Mol Med (Berl)*. 2008;86(2):135–144.
100. Cooke VG, LeBleu VS, Keskin D, et al. Pericyte depletion results in hypoxia-associated epithelial-to-mesenchymal transition and metastasis mediated by MET signaling pathway. *Cancer Cell*. 2012;21(1):66–81.
101. Páez-Ribes M, Allen E, Hudock J, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell*. 2009;15(3):220–231.
102. Ebos JML, Kerbel RS. Antiangiogenic therapy: impact on invasion, disease progression, and metastasis. *Nat Rev Clin Oncol*. 2011;8(4):210–221.
103. Shojaei F. Anti-angiogenesis therapy in cancer: current challenges and future perspectives. *Cancer Lett*. 2012;320(2):130–137.
104. Zhang S, Huang WC, Li P, et al. Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways. *Nat Med*. 2011;17(4):461–469.
105. Muthuswamy SK. Trastuzumab resistance: all roads lead to SRC. *Nat Med*. 2011;17(4):416–418.
106. Woodcock J, Griffin JP, Behrman RE. Development of novel combination therapies. *N Engl J Med*. 2011;364(11):985–987.
107. Esserman LJ, Woodcock J. Accelerating identification and regulatory approval of investigational cancer drugs. *JAMA*. 2011;306(23):2608–2609.
108. Kaiser D. In retrospect: the structure of scientific revolutions. *Nature*. 2012;484(7393):164–166.
109. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. *Nat Rev Cancer*. 2008;8(6):473–480.
110. Lord CJ, Ashworth A. Biology-driven cancer drug development: back to the future. *BMC Biol*. 2010;8:38.
111. Drews J. Case histories, magic bullets and the state of drug discovery. *Nat Rev Drug Discov*. 2006;5(8):635–640.
112. Andreeff M, Goodrich DW, Pardee AB. Cell proliferation, differentiation, and apoptosis. In: Bast RC Jr, Kufe DW, Pollock RE, et al, editors. *Holland-Frei Cancer Medicine*. 5th ed. Hamilton (ON): BC Decker; 2000:17–32.
113. Frame MC. Src in cancer: deregulation and consequences for cell behaviour. *Biochim Biophys Acta*. 2002;1602(2):114–130.
114. Dyson FJ. Is science mostly driven by ideas or by tools? *Science*. 2012;338(6113):1426–1427.
115. Drews J. Paul Ehrlich: magister mundi. *Nat Rev Drug Discov*. 2004;3(9):797–801.

OncoTargets and Therapy**Publish your work in this journal**

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic agents and protocols on

Submit your manuscript here: <http://www.dovepress.com/oncotargets-and-therapy-journal>

patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress