Brain metastasis may be the most devastating, and is certainly the most feared, consequence of breast cancer. It not only robs the patient of her life, it has the potential to rob her of her self, of her essence as a human being. It is also poorly studied. In the clinic, this dearth of research has been a function of the difficulty of obtaining tissue in those who suffer from it, and the lack of dedicated trials. In the laboratory, researchers have lacked model systems that allow them to dissect the mechanisms and effects of brain metastasis. This situation is now changing, as shown in the report by Lockman and colleagues in the current issue of *Clinical Cancer Research* (1).

What we know about brain metastasis in breast cancer is easily summarized. Although not the most frequent of clinical presentations, numerous autopsy studies have shown that occult brain metastases are exceptionally common (2). As many as 15% of patients with advanced breast cancer will have asymptomatic brain metastases visible on screening MRI or computer assisted tomography (CAT) scans (2).

Brain metastasis occurs relatively more commonly in patients with HER2-positive and triple-negative (basal) breast cancers than in patients with estrogen receptor–positive breast cancers (3, 4). Among patients with HER2-positive tumors, the frequency of brain metastasis may have increased recently as a function of the use of trastuzumab, of which the inability to penetrate the central nervous system, even as it controls other metastases, allows them to dissect the mechanisms and effects of brain metastasis. This situation is now changing, as shown in the report by Lockman and colleagues in the current issue of *Clinical Cancer Research* (1).

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Therapy for brain metastases has been divided into local control measures (both surgery and radiation therapy) and systemic therapy. Local control measures are palliative and generally ineffective, with median survivals following diagnosis generally fewer than 12 months (3, 6). More targeted radiation techniques (e.g., stereotactic radiation) have improved palliation and (in combination with whole brain radiation for patients with few lesions) modestly improved survival (6). Systemic therapies [both chemotherapy, hormonal therapy, and more recently HER2-targeted therapy with the small molecule receptor tyrosine kinase (RTK) inhibitor lapatinib] produce occasional responses of short duration (7, 8). All told, it is a gloomy story.

Why have we failed so miserably? Part of the failure, of course, represents our larger failure to cure metastatic breast cancer, a failure rooted in the development of drug resistance to all existing systemic therapy modalities. But there has always been a sense that brain metastasis poses specific challenges, rooted in normal neurophysiology, which must be addressed if we are to improve outcome. The existence of the blood-brain barrier, with efflux pumps in brain endothelium capable of preventing the penetration of many therapeutic agents (especially natural products such as anthracyclines and taxanes), has long been recognized, but also debated as a cause of therapeutic failure, given its disruption in the setting of brain metastasis (9). One recent clinical report has suggested that disruption of the blood-brain barrier is common in triple-negative breast cancers but rare in HER2-positive brain metastases (10).

It is in this context that we should view the contribution of Lockman and colleagues to the brain metastasis literature. This report represents the combination of separate technological approaches to the study of brain metastasis, and it is worth devoting some space to the examination of these techniques.

First, the authors used relatively newly developed murine models of breast cancer metastasis to the brain (11–13). These models (using the human xenograft MDA-MB-231 human breast cancer cell line and the murine 4T1 breast cancer cell line) involve the intracardiac injection of cells that have been serially passed through the brain to produce brain-tropic cell lines (Fig. 1). Such model systems are necessarily artificial, and the degree to which they are representative of the processes by which human brain metastasis occurs is open to question. But, they are undoubtedly an efficient means of producing brain metastases in rapid fashion, and this useful attribute provides the basis for this report. This metastasis model, in turn, has been married to novel quantitative imaging techniques allowing analysis of blood-tumor barrier (BTB) permeability of both size...
Miller K, Weathers T, Haney L, et al. Occult central nervous system metastases are remarkably heterogenous in permeability, with order-of-magnitude differences being noted between metastases. These differences are not obviously related to tumor size or morphology. Second, this heterogeneity in central nervous system penetration extends to the chemotherapeutic agents paclitaxel and doxorubicin, with up to 200-fold differences in uptake. Third, the “blood-brain barrier doesn’t exist in brain metastases” hypothesis turns out to be both right and wrong. Brain metastases typically undergo higher levels of drug penetration than surrounding normal tissue (i.e., the barrier is disrupted), but far lower levels of penetration than metastases to other organs in the same mice (i.e., there is enough of a barrier to have clinical consequences).

The therapeutic result of this heterogeneity in permeability is evident as well, with paclitaxel-induced tumor cell apoptosis only occurring in the small fraction of metastases having markedly elevated taxane penetration. and with little overall effect on metastasis number. As in every other aspect of cancer therapeutics, tumor heterogeneity forms a basis for drug resistance. Although these artificial models may vary from the human experience, it seems reasonable to assume that similar mechanisms are at play in human brain metastases. The brain is different than the lungs, the liver, and bones, and these differences have important therapeutic implications.

What are the implications of these results, and of the model systems from which they were derived, for the future brain metastasis agenda? First, as seems evident, major differences exist in drug uptake among brain metastases related to BTB permeability; it is possible to increase the uptake of existing agents through the use of drugs (e.g., vascular disrupting agents) that alter permeability? All agents have a dose-response curve, and if we are low on that curve, might we improve outcome through selective improvement of delivery to brain metastases? This concept is not new, but the existence of brain metastasis models with exquisite measures of permeability allows us to test such agents.

A second implication involves the search for new drugs. Can we use such preclinical models as a testing ground for new agents? In the past, investigators have looked at the physicochemical characteristics of new agents to predict CNS penetration. The report by Lockman and colleagues clearly shows that such analyses, although necessary, are not sufficient as predictors of BTB permeability. Arguably, we should routinely test novel agents for their BTB permeability, particularly targeted agents developed for cancers with a known propensity for brain metastasis. Palmieri and colleagues have recently used this model to evaluate the novel histone deacetylase inhibitor vorinostat (11). This research suggests a new definition of targeted therapy: not only targeting a particular molecule, but also having the capability of targeting a specific metastatic site. This tactic is an old story in bone metastasis (with RANK ligand inhibitors and bisphosphonates), of course, but it is high time that such an approach be applied to brain metastasis. The existence of experimental models for breast cancer brain metastasis, both murine and imaging technologies such as used in this report, suggests not only that we should take this problem seriously, but also that we finally can.

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**References**


Heading in a New Direction: Drug Permeability in Breast Cancer Brain Metastasis

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