

# Influence of methotrexate and cisplatin on tumor progression and survival in the VM mouse model of systemic metastatic cancer

Leanne C. Huysentruyt, Laura M. Shelton, Thomas N. Seyfried

Department of Biology, Boston College, Chestnut Hill, MA

We recently identified a new tumor (VM-M3), which arose spontaneously in the brain of an inbred VM mouse. When grown outside the brain, the VM-M3 tumor expresses all major biological processes of metastasis to include local invasion, intravasation, immune system survival, extravasation, and secondary tumor formation involving lung, liver, kidney, spleen and brain. The VM-M3 tumor also expresses multiple properties of macrophage-like cells similar to those described previously in numerous human metastatic cancers suggesting that the VM-M3 model will be useful for studying most types of metastatic cancer, regardless of tissue origin. VM-M3 tumor cells, expressing firefly luciferase (VM-M3/Fluc), were grown subcutaneously in the immunocompetent and syngeneic VM mouse host. The antimetastatic effects of methotrexate (MTX; 25 mg/kg) and cisplatin (10–15 mg/kg) were evaluated following i.p. injections administered once/wk for 3 weeks. Bioluminescent imaging was used to measure VM-M3/Fluc growth and metastasis. All (12/12) control mice developed systemic cancer within 21 days of subcutaneous VM-M3/Fluc implantation. Although methotrexate did not inhibit VM-M3/Fluc primary tumor growth, it reduced lung and liver metastasis by 50% and completely inhibited metastasis to kidneys, spleen and brain. Cisplatin significantly reduced primary tumor growth, blocked metastasis to lung, liver, kidneys, spleen and brain, and significantly increased survival in all treated animals. Our findings show that the response of the VM-M3/Fluc tumor to MTX and cisplatin is similar to that reported in humans with metastatic disease. These findings indicate that the VM-M3/Fluc tumor is a reliable preclinical model for evaluating antimetastatic cancer therapies and underlying control pathways.

Metastasis is the process by which cancer cells disseminate from the primary tumor, invade surrounding tissues and distant organs and is the primary cause of morbidity and mortality for cancer patients.<sup>1,2</sup> The metastatic cascade involves a series of sequential and interrelated steps to include cancer cell detachment from the primary tumor, intravasation into the circulation, evasion of immune attack, extravasation at a distant capillary bed and invasion and proliferation in distant organs.<sup>2–5</sup> Although many primary tumors can be treated with conventional therapies, few treatments are effective against metastatic disease.<sup>1,5,6</sup> Consequently, preclinical models that can accurately predict the therapeutic efficacy of antimetastatic drugs in patients would be useful for new drug development.

The management of metastatic cancer can be improved with *in vivo* models that represent the complete pathophysio-

logy of the human disease.<sup>1,7–10</sup> However, most available metastatic models including those that metastasize to brain have various shortcomings and limitations. For example, experimental metastatic models often require injection of tumor cells directly into the host's circulation, thus bypassing the early stages of metastasis before local invasion and intravasation.<sup>1,11,12</sup> Although spontaneous models express more steps of metastasis than experimental models, many of these models require implantation of tumor cells as xenographs into immune compromised animals. This is a limitation because evasion of the host's immune system is a key rate-limiting process for the spread of metastatic tumor cells.<sup>1,2,11,13,14</sup> Spontaneous metastasis models also do not reliably produce secondary lesions, whereas genetically engineered models have spontaneous tumor development with variable penetrance and long latency, making it difficult to obtain sufficient numbers of animals for comprehensive analysis of antimetastatic therapies.<sup>1,11,15,16</sup> These shortcomings and limitations have hindered progress in developing new therapies for metastatic cancer.

We recently described a new mouse model of systemic metastatic cancer that overcomes many of the shortcomings and limitations of current *in vivo* metastasis models.<sup>17</sup> The VM-M3 tumor arose spontaneously in the brain of the inbred VM mouse strain, which has a high incidence of spontaneous tumors.<sup>18,19</sup> The growth behavior of the VM-M3 cells in brain is similar to that seen in human glioblastoma

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**Correspondence to:** Thomas N. Seyfried, Department of Biology, Boston College, Higgins Hall, 140 Commonwealth Avenue, Chestnut Hill, MA 02467, USA, Fax: +617-552-2011  
E-mail: thomas.seyfried@bc.edu