NOVEL DRUG DEVELOPMENT AT ANTICANCER IN SOI (MetaMouse ®) MODELS

1. The metalloproteinase inhibitor Batimastat: Active against a SOI human-patient colon tumor model [1] including:
   a. Inhibition of primary tumor growth
   b. Inhibition of metastatic events
   c. Extension of survival.

2. The metalloproteinase inhibitor CT1746: Active against a SOI human colon tumor xenograft model [2] :
   a. Arrest of primary tumor growth
   b. Inhibition of metastatic events, and
   c. A large increase in survival.

3. IFN-γ: Active against a patient pleural cancer SOI model [3]:
   a. Elimination of metastatic events
   b. Decrease in cachexia, and
   c. Extension of survival.

4. Angiogenesis inhibitor TNP-470: Active in patient colon and stomach tumor SOI models [4-8]:
   a. Inhibition of liver metastasis in colon cancer
   b. Minimal or no effect on primary tumor.

5. Anti-VEGF antibody: Active in SOI model of colon and stomach cancer [7, 9, 10]:
   a. Inhibition of liver metastasis in colon cancer
   b. Minimal or no effect on primary tumor.

6. Antisense phosporothionate oligionucleotide specific for VEGF-receptor active in SOI model of stomach cancer [11]:
   a. Inhibition of peritoneal tumor dissemination
   b. Increased tumor cell apoptosis
   c. Microvessel density (MVD) in tumor nodules.

7. New platinum analogs {Pt(cis-dach)(DPPE)·$2NO_3$} and {Pt(trans-dach)(DPPE)·$2NO_3$} active in SOI model of bladder and stomach cancer [12, 13]:
   a. No metastases in either of the high- or low-dose platinum-analog-treated groups in SOI model of bladder cancer.
   b. No mesenteric lymph node metastases in the groups treated with the high or low doses of both new platinum analogs with SOI model of colon cancer.

8. Liposomal doxorubicin (Doxil) [14].
   a. Inhibition of MDA-MB-231 human breast tumor xenografts, which were resistant to free doxorubicin.

9. Camptothecin analog DX-8951f: Active in SOI models of pancreatic cancer [15].
   a. DX-8951f showed efficacy against two human pancreatic tumor cell lines in the SOI-GFP model. DX-8951f was highly effective against primary and metastatic growth in the two models and showed significantly higher efficacy than gemcitabine, the standard treatment of pancreatic cancer.

10. Cytosine analog, CS-682: Active in SOI model of pancreatic cancer [16,17,34].
    a. CS-682 showed efficacy on inhibiting pancreatic cancer growth and metastasis in a RFP orthotopic nude mouse model of human pancreatic model.
    b. CS-682 showed efficacy in an adjuvant treatment orthotopic model of human pancreatic cancer suggesting possibility of chronic use of CS-682 to control pancreatic cancer.

11. Estrogen analog 2-methoxyoestradiol-bis-sulphamate: active in MDA-MB-435 SOI model of breast cancer [18].

12. Truncated galectin-3 (galectin-3C) was found active in an orthotopic breast cancer xenograft nude mouse model imaged with green fluorescent protein [19].

13. The agonistic anti-LTBR monoclonal antibody (mAb) CBE11 inhibited tumor growth in xenograft models and potentiated tumor responses to chemotherapeutic agents[35].

14. Additive effects of glufosfamide and gemcitabine in fluorescent orthotopic mouse models of human pancreatic cancer[36,37].

15. A monoclonal antibody to the chemokine receptor CXCR2 was effective against pancreatic cancer in the SOI model[38].

16. TSU68 prevents liver metastasis of colon cancer xenografts by modulating the premetastatic niche[39].

17. Type II PDGFRβ/B-RAF inhibitor disrupts angiogenesis and tumor growth[40].

18. A small molecule inhibitor of SDF-1/CXCR4 inhibits vasculogenesis, but not angiogenesis, and prevents the recurrence of glioblastoma following irradiation in mice[41].

19. HER-2 therapy inhibits metastasis of esophageal cancer[42].

20. Metronomic gemcitabine therapy greatly inhibits metastasis of pancreatic cancer[43].

21. Bisphosphonate olpadronate inhibits bone metastasis in prostate cancer[44].

22. Knockdown of the β_1 integrin subunit reduces primary tumor growth and inhibits pancreatic cancer metastasis[45].

23. High antimetastatic efficacy of MEN4901/T-0128, a novel camptothecin carboxymethyldextran conjugate[46].

24. Imaging the inhibition by anti-β1 integrin antibody on lung seeding of single cells in live mice[47].

25. Traditional Medicinal Herb Celastrus orbiculatus Thunb on human hepatocellular carcinoma in an orthotopic fluorescent nude mouse model[48].

26. Real-time imaging of induction of apoptosis of human breast cancer cells by the traditional Chinese medicine herb Tubeimu[49].

27. Paclitaxel nanosuspensions for targeted chemotherapy – nanosuspension preparation, characterization, and use[50].

28. Therapeutic effect of 1 M tegafur-0.4 M 5-chloro-2,4-dihydroxypyridine-1 M potassium oxonate (S-1) on liver metastasis of xenotransplanted human colon carcinoma.[32]

29. Efficacy comparison of traditional Chinese medicine LQ versus gemcitabine in a mouse model of pancreatic cancer.[53]

30. Comparison of efficacy and toxicity of Traditional Chinese Medicine (TCM) herbal mixture LQ and conventional chemotherapy on lung cancer metastasis and survival in mouse models.[54]

31. Traditional Chinese medicine herbal mixture LQ arrests FUCCI-expressing HeLa cells in G0/G1 phase in 2D plastic, 2.5D Matrigel®, and 3D Gelfoam® culture visualized with FUCCI imaging.[55]

32. Photoimmunotherapy lowers recurrence after pancreatic cancer surgery.[58]

33. Nanoparticle albumin-bound-paclitaxel: a limited improvement under the current therapeutic paradigm of pancreatic cancer.[59]

Feasibility for the drug discovery in the SOI models has been demonstrated with colon, pancreatic, stomach, bladder, and lung cancer where chemotherapy has resulted in dose-response, differential sensitivity of primary and metastatic tumors, reproducibility, and correlation to historical clinical activity of the drugs including 5-FU, CDDP, mitomycin-C as well as the new agents listed above [1, 4-8, 11-13, 20-33,51,52,56,57].

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