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The American Thoracic Society's 105th International Conference, May 15 to 20, 2009



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News Release

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Mini-Symposium time: May 19: 1:30 p.m. to 4 p.m.

Presentation time: May 19: 3:15 p.m.

Location: San Diego Marriott Hotel & Marina, Marriott Hall 5-6 (Marriott Pavilion)

Genetically-Engineered MSCs Kill Metastatic Lung Cancer Cells in Mice

ATS 2009, SAN DIEGO—Researchers in London have demonstrated the ability of adult stem cells from bone marrow (mesenchymal stem cells, or MSCs) to deliver a cancer-killing protein to tumors.

The genetically engineered stem cells are able to home to the cancer cells, both in culture and in mouse models, and deliver TNF-related apoptosis-inducing ligand (TRAIL), destroying the tumor cells while sparing normal cells.

The research will be presented on Tuesday, May 19, at the American Thoracic Society's 105th International Conference in San Diego.

“Present oncological therapies are limited by host toxicity,” said Michael Loebinger, M.D., M.A., who, along with S. M. Janes, M.D., Ph.D., conducted the research at the Centre for Respiratory Research at the University College of London. “They are also limited by cancer resistance and may not destroy cancer stem cells.”

With these experiments, the investigators combined two disparate areas of research that they believed held promise for treating cancer. Studies had shown that MSCs can be used as vectors to deliver anti-tumor therapy, while other studies found that TRAIL killed cancer cells, but not normal cells.

For their experiments, Drs. Loebinger and Janes identified those cells likely to be resistant to therapies (cancer cells that have characteristics of stem cells) and found that they were just as likely to be destroyed as tumor cells by this novel therapy.

In culture, the stem cells caused lung, squamous, breast and cervical cancer cells to die (all $p < 0.01$), even at low stem cell/tumor cell ratios (1:16).

In mice, the researchers showed that the stem cells could reduce the growth of subcutaneous breast tumors by approximately 80 percent ($p < .0001$). The stem cells could also be injected intravenously as therapy for mice with lung metastases and could eliminate lung metastases in 38 percent of mice compared to control mice, all of which still had metastases ($p = 0.03$).

It is the first study to intravenously introduce MSCs that have been genetically modified to deliver TRAIL. Drs. Loebinger and Janes chose the breast cancer cells for both models because in their *in vitro* experiments, the MSCs “demonstrated a particularly strong homing to breast cancer cells.”

“Breast cancer tumors are a good model of metastases,” added Dr. Loebinger, “but our plan is to test the engineered stem cells with other models, including lung cancer.”

While not fully understood, Dr. Loebinger added, the homing of the engineered cells appears to be a characteristic of MSCs themselves.

The authors conclude that, “this is the first study to demonstrate a significant reduction in tumor burden with inducible TRAIL-expressing MSCs in a well-controlled and specifically directed therapy.”

They believe that human trials of TRAIL-expressing MSCs could begin in two or three years.

Funding for this research was provided by the Medical Research Council UK.

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Session # C96: “Lung Tumorigenesis: Insights from Animal Models”

Abstract # 505: “On the TRAIL of a Killer: TRAIL-Expressing Mesenchymal Stem Cells are Able to Target and Eliminate Lung Metastases”

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Abstract Number: 505

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Yes

Title: On the TRAIL of a Killer: TRAIL-Expressing Mesenchymal Stem Cells Are Able To Target and Eliminate Lung Metastases

M. R. Loebinger, MD MA¹ and S. M. Janes, MD PhD¹. ¹Centre for Respiratory Research, University College London, London, United Kingdom.

Background: Present oncological therapies are limited by cancer resistance and host toxicity. We engineered MSCs to deliver TNF-related apoptosis-inducing ligand (TRAIL), which causes selective apoptosis of tumour cells, to seek out and destroy cancer cells in a lung metastatic cancer model.

Methods: MSCs were transduced with a tetracycline-inducible lentivirus containing TRAIL and GFP (MSCTRAIL). Transgene activation in vitro was demonstrated with GFP and TRAIL expression using flow cytometry, Western blot, and ELISA. Apoptotic function of MSCTRAIL was established in co-culture with cancer cell lines using flow cytometry. Cancer side populations were flow sorted by Hoechst staining. Chemotaxis assays and in vivo cell tracking demonstrated homing. In vivo subcutaneous and systemically delivered metastatic lung xenograft cancer models were performed in NOD/SCID mice (MDAMB231 cells).

Results: MSCs were transduced with 80% efficiency. Transduced and doxycycline-activated MSCs caused A549 (lung), H357 (squamous), MDAMB231 (breast), and Hela (cervical) cell

apoptosis in co-culture (all $p < 0.01$). The cancer cell side populations, often resistant to chemotherapy, were equally sensitive to this therapy. Tumour cell death was maintained at low (1:16) MSC/Tumour cell ratios ($p < 0.001$) and reduced by a TRAIL neutralising antibody ($p < 0.001$). Tumour cells expressing dnFADD showed TRAIL induced death was via the extrinsic apoptotic pathway ($p = 0.02$). The MSCs homed to tumour cells in vitro, ($p < 0.001$), and in vivo to lung metastases. MSC-TRAIL reduced tumour growth in subcutaneous xenograft experiments ($p < 0.001$) and when used systemically were able to eliminate lung metastases in 38% mice compared to no controls ($p = 0.03$).

Conclusion: This is the first study to demonstrate a significant reduction in tumour burden with inducible TRAIL-expressing MSCs.