

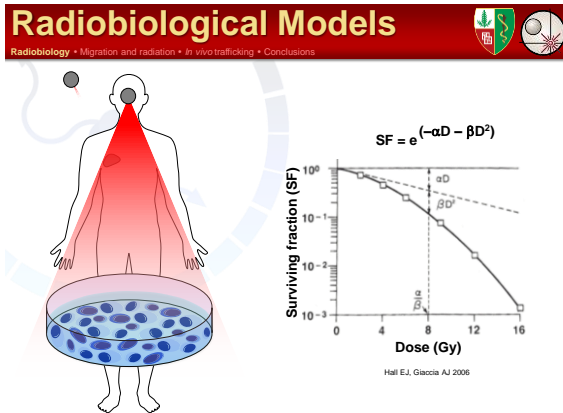
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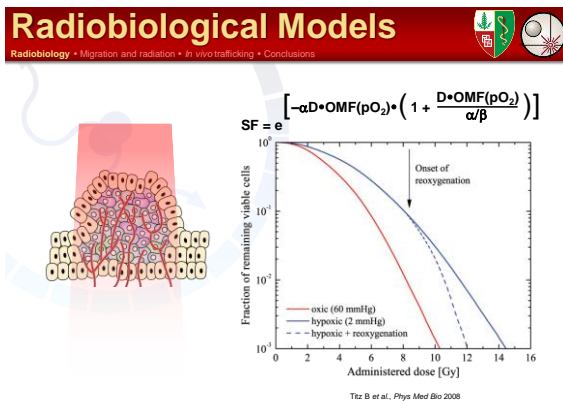
Radiation-Induced Long Distance Tumor Cell Migration Into and Out of the Radiation Field and Its Clinical Implication

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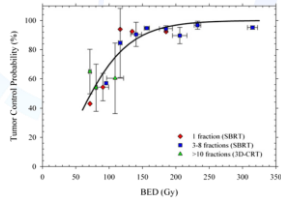
Tumor Control Models

Radiobiology • Migration and radiation • In vivo trafficking • Conclusions



$$TCP = e^{-D_c \cdot V \cdot e^{(-\alpha \cdot BED)}}$$

O'Rourke SFC et al., J Math Biol 2009



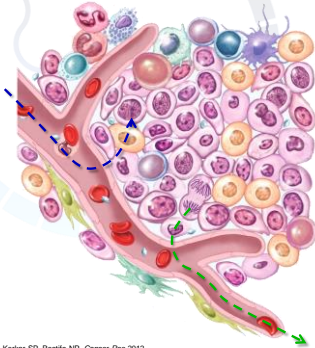
Brown JM et al., Int J Radiat Oncol Biol Phys 2013



Stamatatos G et al., Proc IEEE 2002

Tumor Microenvironment

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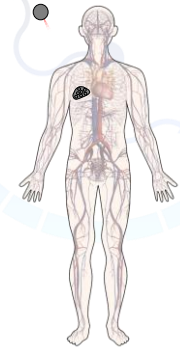


In addition to the myriad of recognized molecular, cellular, and tissue-specific influences on tumor radiation response, one that has not received significant attention is **transit of tumor cells into and out of the radiation target**.

Kerkar SP, Restifo NP, Cancer Res 2012

Tumor Cell Migration

Radiobiology • Migration and radiation • In vivo trafficking • Conclusions



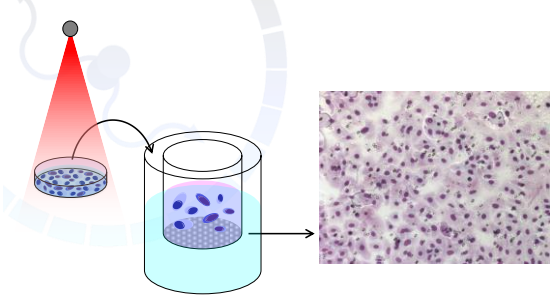
It is well known that cancer cells disseminate throughout the body in a process known as metastasis.

The vast majority of cells that undergo metastatic spread will die, while some will lay dormant and a small fraction will give rise to secondary cancers.

We are interested in "reverse metastasis", in which metastatic cells return to their parent tumor, and how this process could affect the control of cancers treated with radiation.

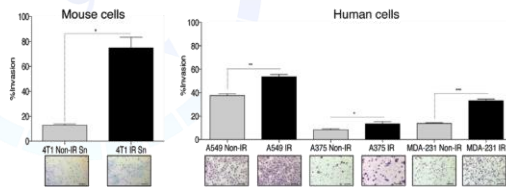
Transwell Migration Assay

Radiobiology • Migration and radiation • In vivo trafficking • Conclusions



In Vitro Migration

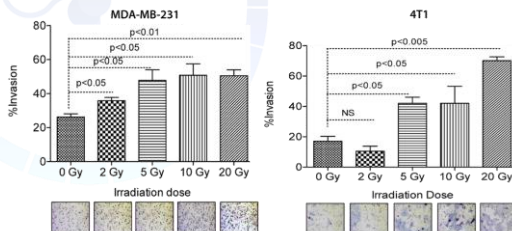
Radiobiology • Migration and radiation • In vivo trafficking • Conclusions



Vilalta M et al., Cell Reports 2014

In Vitro Migration

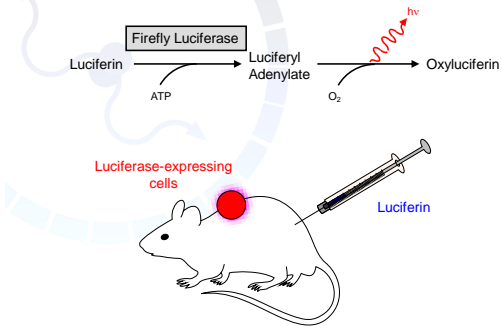
Radiobiology • Migration and radiation • In vivo trafficking • Conclusions



Vilalta M et al., Cell Reports 2014

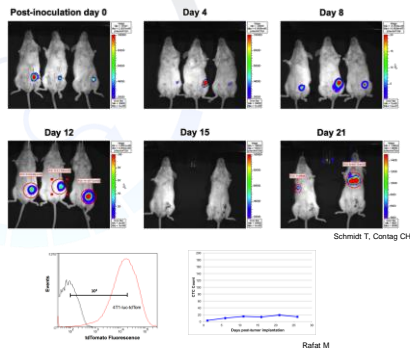
Bioluminescence Imaging

Radiobiology • Migration and radiation • **In vivo trafficking** • Conclusions



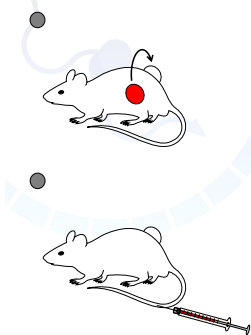
Orthotopic 4T1 Model

Radiobiology • Migration and radiation • **In vivo trafficking** • Conclusions



Donor-Recipient Model

Radiobiology • Migration and radiation • **In vivo trafficking** • Conclusions



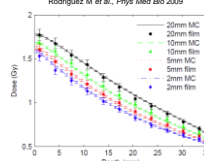
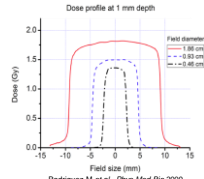
- Implant an unlabeled, non-bioluminescent tumor into a mouse (the "recipient")
- Create a population of luciferase-labeled, bioluminescent CTCs through creation of a second luciferase-expressing tumor or by direct injection of luciferase-expressing cells into the circulation (the "donor")
- Irradiate the recipient tumor and compare the level of bioluminescent signal relative to untreated recipients.

Small Animal Radiotherapy

Radiobiology • Migration and radiation • **In vivo trafficking** • Conclusions



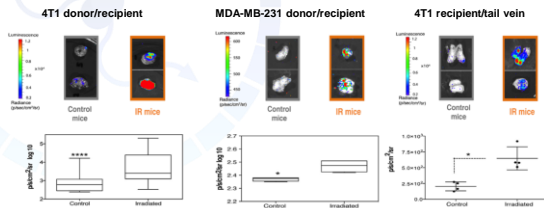
Zhou H et al., *Int J Radiat Oncol Biol Phys* 2010



Bacalova M et al., *Med Phys* 2009

In Vivo Migration

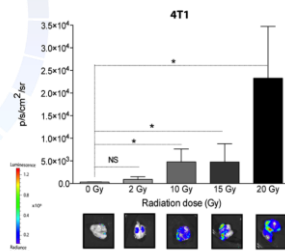
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Vilalta M et al., *Cell Reports* 2014

Dose Response

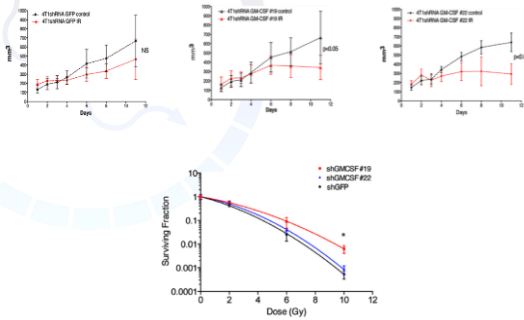
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Vilalta M et al., *Cell Reports* 2014

Migration and Recurrence

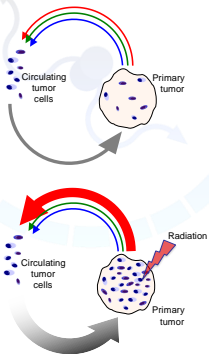
Radiobiology • Migration and radiation • *In vivo* trafficking • Conclusions



Vilalta M et al., Cell Reports 2014

Conclusions

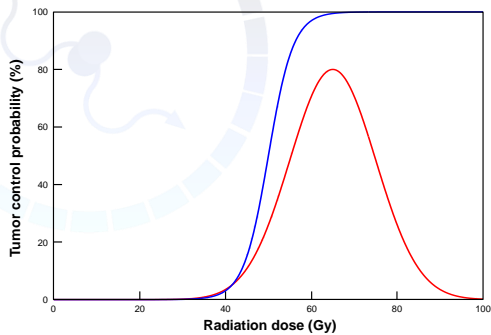
Radiobiology • Migration and radiation • *In vivo* trafficking • Conclusions



- Irradiation of tumor cells attracts migrating tumor cells
- *In vitro* and *in vivo* data demonstrate a dose response for this process
- BLI can monitor trafficking of tumor cells to irradiated sites

Consequences

Radiobiology • Migration and radiation • *In vivo* trafficking • Conclusions



Consequences

Radiobiology • Migration and radiation • In vivo trafficking • Conclusions



Radiobiological models must be recast from "surviving fraction" to a measure of both surviving and trafficking tumor cells.

$$N = N_0 f(D) + \frac{dN_{CTC}}{dX}(D)$$

Clearly the functional form of $\frac{dN_{CTC}}{dX}(D)$ is complex and will depend on a variety of physical and biological factors. Considerations for this function include:

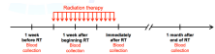
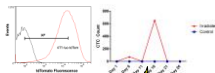
- It is likely not monotonically increasing with dose
Tissues in the CTV/PTV receiving intermediate doses may be preferentially sensitive
- It will reflect interactions between tumor and stromal cells
Immune cell responses may play a role in tumor cell migration
- It may reflect both a local tumor response as well as a systemic organism response
Molecular and cellular factors outside the radiation target may modulate cell trafficking

Future Directions

Radiobiology • Migration and radiation • In vivo trafficking • Conclusions

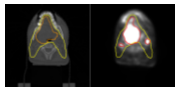
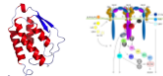


- Characterize CTC levels and dynamics before and after radiation therapy



- Measure tumor cell migration and its role in radiation response in human cancer patients

- Elucidate the molecular and cellular mechanisms driving this process



- Develop clinical trials to adapt radiation therapy targeting, fractionation, and chemotherapy to inhibit this process

Acknowledgements



Imaging Radiobiology Laboratory
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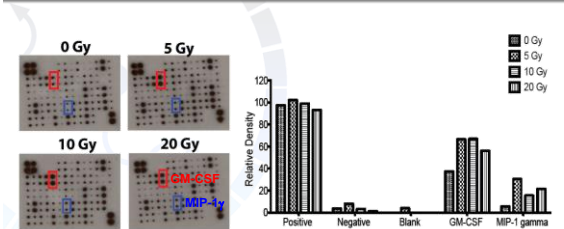
Collaborators



Funding: NIH NCI, CBCRP, Stanford Bio-X



Mechanism

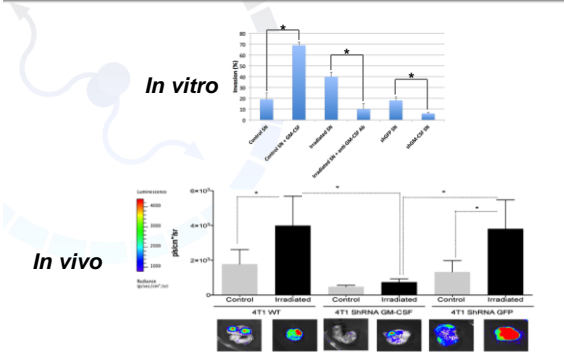


Granulocyte-macrophage colony stimulating factor (GM-CSF)

- A conserved cytokine that functions as a white blood cell growth factor.
- Used in cancer patients to stimulate the production of white blood cells during and after chemotherapy.

Vitala M et al., Cell Reports 2014

GM-CSF and Migration



Vitala M et al., Cell Reports 2014
