Background
Radiotherapy and chemotherapy are the current standards of care for most cancers. While these treatment methods eradicate the tumor, they also initiate accelerated repopulation. Accelerated repopulation causes surviving tumor cells to rapidly proliferate, repopulating the irradiated area at a significantly accelerated pace. Further complicating cancer treatment, radiation and chemotherapy regimens incorporate necessary recesses from treatment, allowing for the recovery and repopulation of normal cellular tissue. These breaks in treatment, when paired with accelerated repopulation, allow for rapid growth of tumor cells. Tumor cell repopulation is a common cause of failure for cancer treatments (see Nature Reviews Cancer 5, 516-525, July 2005).

Technology
At the University of Colorado Cancer Center, Dr. Chuan-Yuan Li has discovered a molecular signaling pathway integral to accelerated repopulation and developed an approach to prevent tumor repopulation and metastasis, enhancing the effectiveness of cancer treatment.

Dr. Li has shown that apoptotic cells release growth signals that stimulate the proliferation of progenitor cells (see Science Signaling reference below), identifying Caspase-3 as a key factor in the signaling. Using in vitro and in vivo models, Dr. Li has discovered that activated Caspase-3 is integral to the rapid proliferation of surviving cancerous tumor cells. More specifically, Dr. Li has found that irradiation activates Caspase-3 and, by decreasing Caspase-3 expression using small hairpin RNA, cellular growth of irradiated tumor cells can be significantly attenuated in vitro.

Using an in vivo approach, Dr. Li irradiated cells genetically deficient in Caspase-3 and subsequently injected them into nude mice. Compared to controls, tumor cell-growth was decreased in the Caspase-3 deficient group by as much as 1000 fold. Further supporting the role of Caspase-3 in stimulating cellular growth, Dr. Li has shown that Prostaglandin E2, a promoter of cell proliferation and tissue regeneration, acts downstream of Caspase-2 to facilitate stem cell activity and neovascularization.

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Applications
Dr. Li’s work points to the promise of using Caspase-3 inhibitors to prevent tumor repopulation and metastasis following radiotherapy and chemotherapy, potentially reducing patient radiotoxicity and increasing sensitivity to chemotherapy dosage.

Partnering Needs
- Access to small molecule libraries for identification of caspase inhibitors optimal for radiosensitization and prevention of accelerated repopulation.
- Evaluation of downstream pathway modulators: iPLA2 (Calcium independent Phospholipase A2) and Prostiglandin E2.
- Evaluation of the therapeutic concept in orthotopic solid tumor models.

Data Update
In vivo proof of concept has been conducted in the following models:
- Breast cancer
- Colon cancer
- Melanoma.
- Mouse xenograft: Breast cancer, colon cancer, and melanoma using bioluminescence to monitor cell proliferation in vitro and in vivo.

Key Documents
Apoptotic cells activate the "phoenix rising" pathway to promote wound healing and tissue regeneration. Science Signaling. 2010 Feb 23; 3(110):1-10. PDF available upon request.
Caspase Modulators and Methods of Use. Provisional patent application filed Jan. 6, 2010, available under CDA.