New Anticancer Agents Targeting the Tumor-Specific Microenvironment

(OTT ID 1277)

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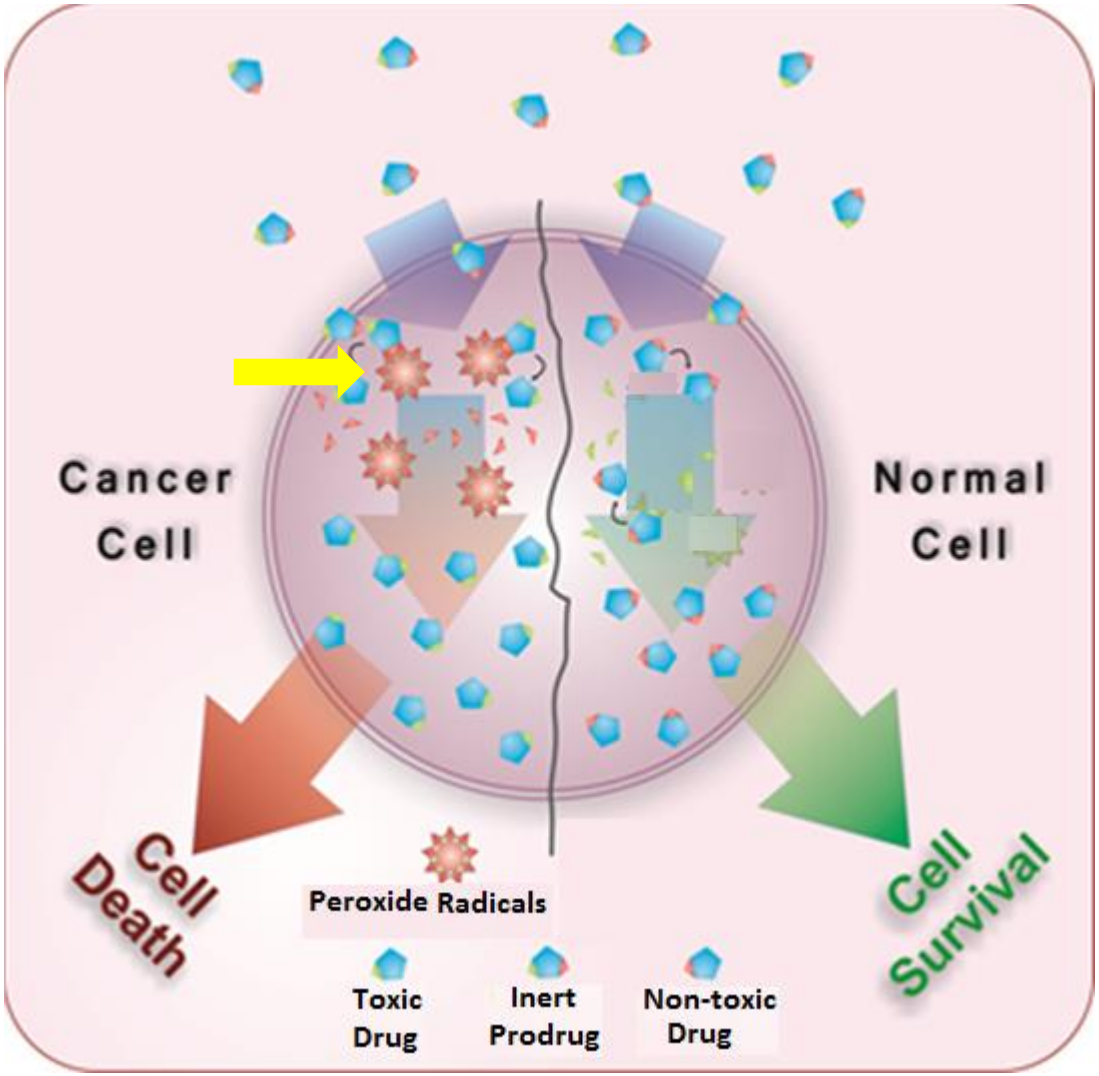
Current Problems with Cancer Therapies

- **Goal: Improve the selectivity of cancer therapy**
- **Problems/Unmet Needs:**
  - **Severe side effects, attack healthy cells**

  - **Prodrug approach: drugs in an inactive or significantly less active form, metabolized to active form**
  - **Previous prodrug approach: low selectivity**
    low levels of activators in necrotic tumor tissue

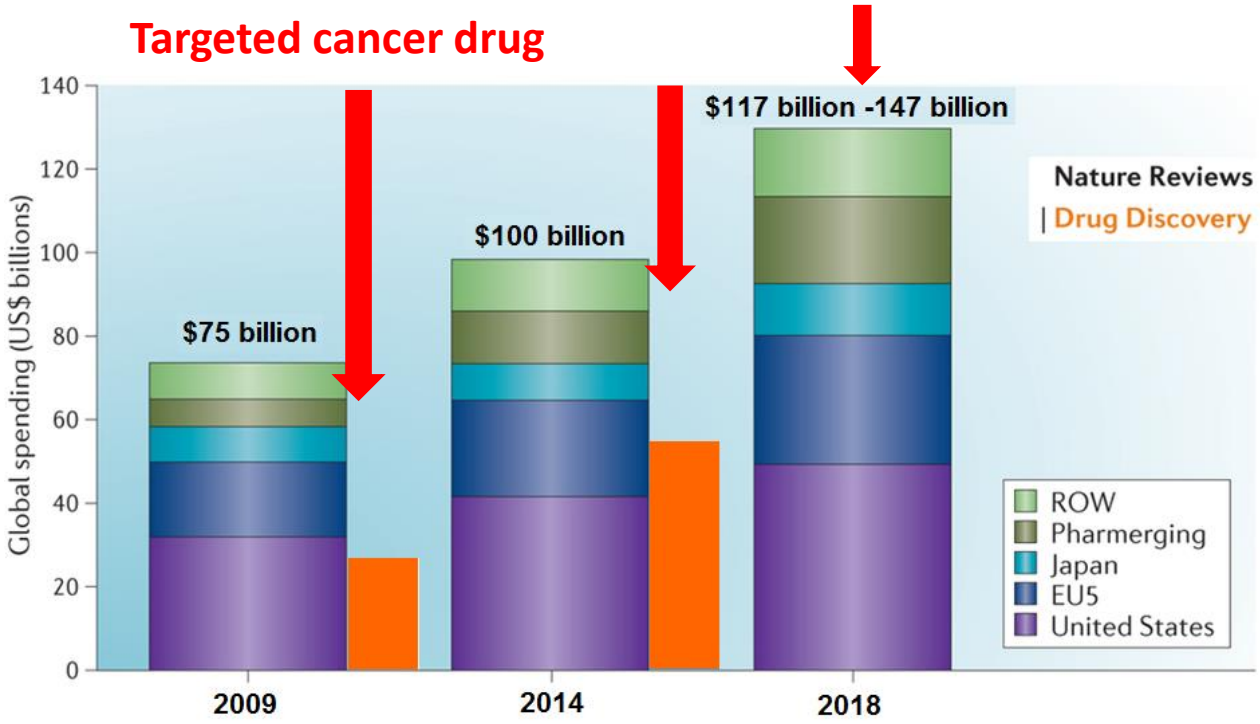
Pro-drugs Targeting Tumor Cells

- Prodrugs are only activated by **unique features** inside cancer cells
- Selective release of toxic drug in cancer cells
- U.S. Utility Patents Issued
  - Anti-Cancer Agents: 8,637,490
  - Anti-Cancer Agents: 8,962,670



Market Size

- The global oncology market is expected to reach $112B by 2020
- Targeted cancer drugs now make up 46% of cancer sales
- The Agency for Healthcare research and Quality (AHRQ) estimates that the direct medical costs (total of all health care costs) for cancer in the US in 2014 were $87.8 billion



http://www.thepharmaletter.com/article/targeted-cancer-drug-market-set-to-reach-51-billion-by-2015-led-by-pfizer-barriers-to-use-of-oral-cancer-drugs-identified

Market Potential

Applications for our compounds

- **Inhibiting cancer cell growth or causing cell death in leukemia, non-small cell lung cancer, colon cancer, breast cancer, and renal cancer cell lines (tested in NCI 60 assays)**

- **Reducing tumor size in animal models for renal cancer cell lines and breast cancer cell lines**

- **Our tumor-targeting prodrug platform approach can be applied to thousands of other drugs**

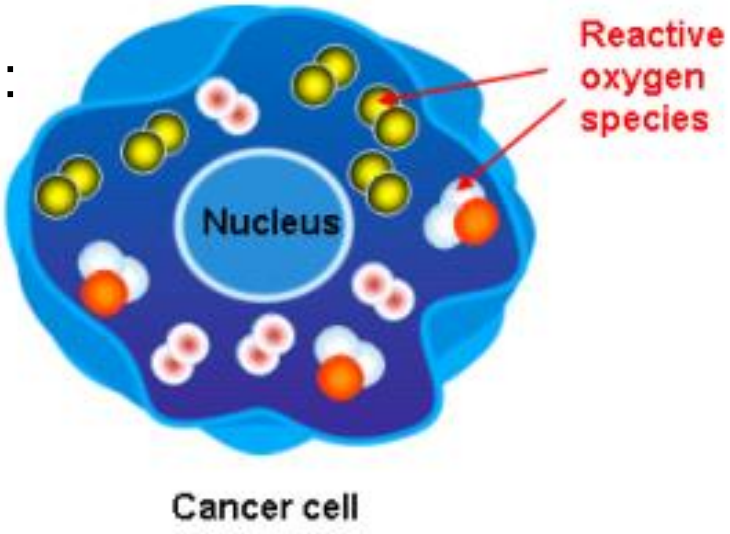
High Level of Hydrogen Peroxide in Cancer Cells

CANCER CELLS:

- Contain **reactive oxygen species (ROS)**:

  hydrogen peroxide and free radicals

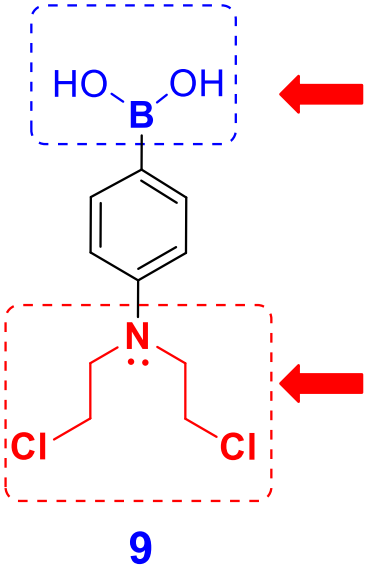
- Rapidly divide and grow
- Have increased active metabolism
- Show decreased free radical scavenging enzymes



***Prodrugs activated by hydrogen peroxide can selectively kill cancer cells**

Designing Prodrugs That Target Tumor Cells

- **Non-toxic** until located in cancer cells
- **Hydrogen peroxide trigger**



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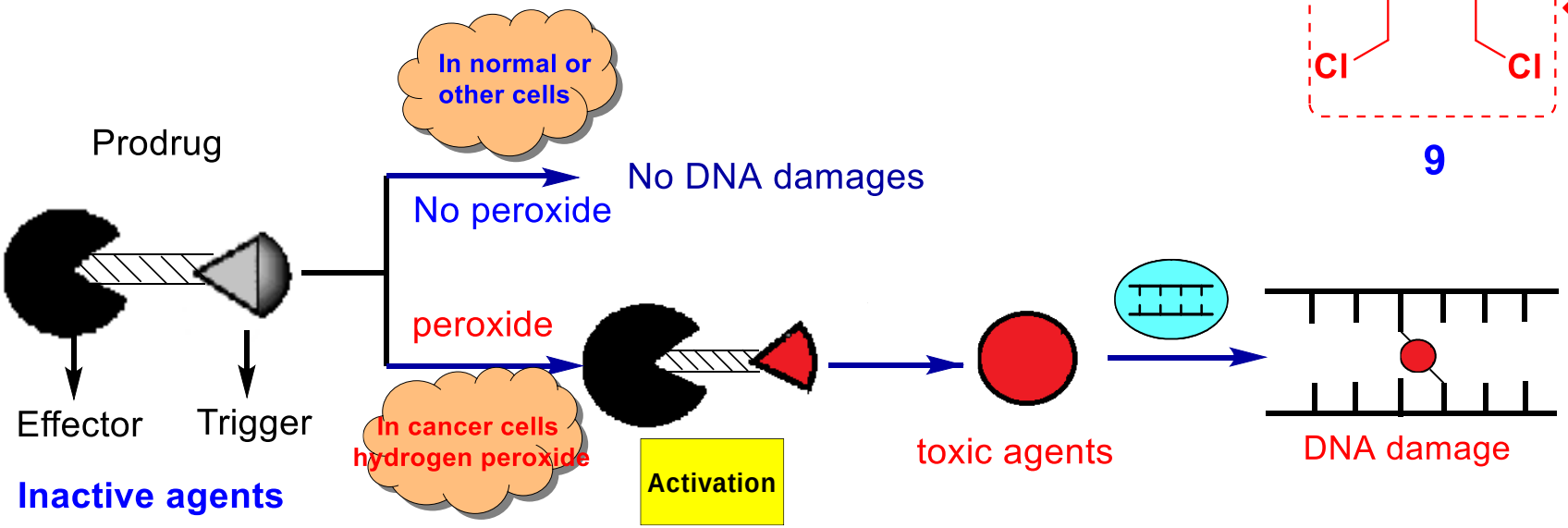
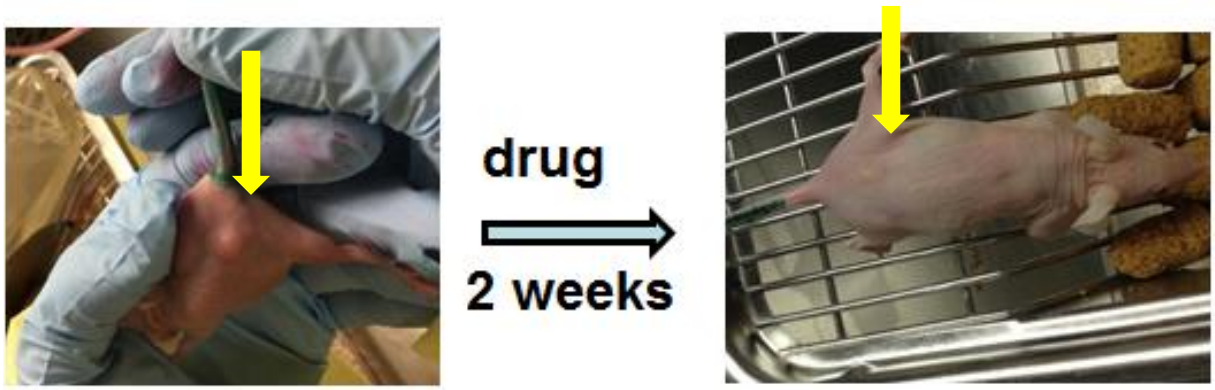
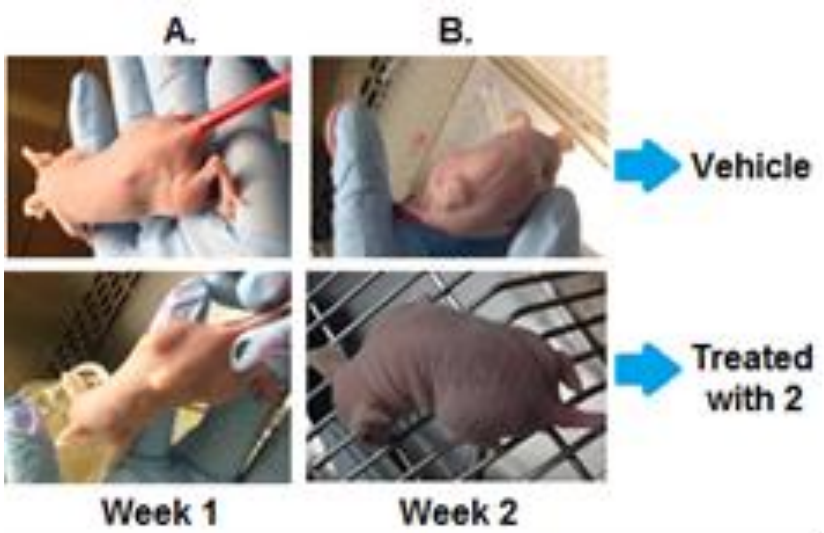


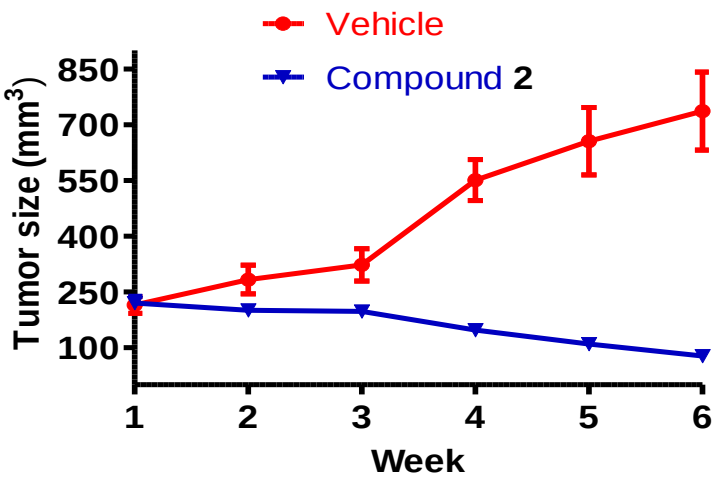
Our Drugs Work *in vivo*

- They are safe to mice: no obvious toxicity, no weight loss
- Reduce tumor size (breast cancer)
- Drug used during entire treatment



Our Drugs Also Shrink Established Tumors





- **Compound 2 induces genes involved in apoptosis and cell cycle**
- **P21, P53, Bcl2, and CyclinD1 RNA levels were induced**
- **Microarrays showed genetic modulation in DNA binding, DNA repair, and DNA ligation**

*Manuscript submitted; related data Wang et al. 2017. EJMC. 133: 197-207.

Moving the Program Forward

Pharmacological proof of concept (PK/Tox/ADME)

- **Animal model studies ($500,000)**
  - **Toxicity test (√)**
  - **Xenograft mice model study (√)**
  - **Transgenic mice model**
- **Lead optimization ($300,000)**

  ***metabolic stability (√)**
  ***oral availability**
  ***bio-distribution**
  ***function of mechanism: *in vivo* target selectivity**

Next Steps Needed

Looking for industry partners

- **Transition to clinical/commercial development**
- **Further funding required**
- **Conducting clinical trials for effective lead compounds**
- **Licensing of our technology**

Partnering with industry on sponsored research

- **Applying this platform technique for developing novel pro-drugs**

In Summary

- **The Peng lab has designed and synthesized a series of novel ROS-activated aromatic nitrogen mustards which selectively kill tumor cells with minimal effects on normal cells**

- **Mouse xenograph tumor models using breast cancer show tumor prevention and regression with lead compounds**

- **Lead compounds are not prohibitively toxic to normal cells**

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