Meeting minutes: SCLC Consortium WebEx

October 4, 2018 @ 1:00pm ET

Announcements/Updates

- Three more grants funded through the U01!
  - Mark Krasnow-Stanford
  - Kwon Park-UVA
  - Alissa Weaver and Christine Lovly-Vanderbilt
- Detection and Prevention PAR is no longer active

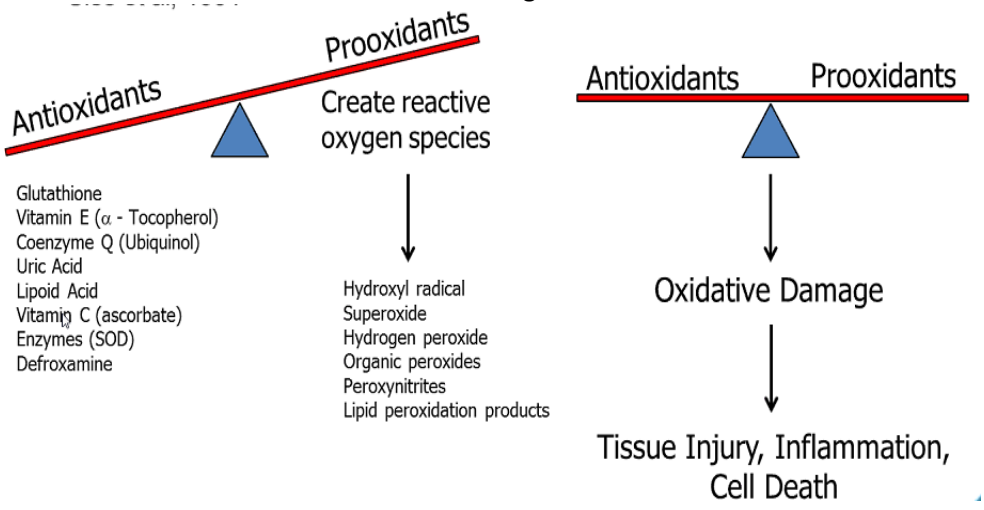
Title: Enhancing Small Cell Lung Cancer Therapy with Pharmacological Ascorbate

Dr. Bryan Allen- Dept of Radiation Oncology, University of Iowa

- Small Cell Lung Cancer
  - Epidemiology
    - 29,654 estimated cases in the US in 2018
      - 14% of lung cancer
    - Incidence is decreasing with smoking prevention
      - 95% of cases are attributable to cigarette smoking
      - Incidence in women is increasing with a male to female incidence ration of around 1:1
  - Median age at presentation: 64 years old
  - Screening with LDCT
    - Currently deemed not useful per NCCN guidelines
      - Aggressive: Develop of symptomatic disease in between annual scans
  - Presentation
    - Imaging-large hilar mass with bulky mediastinal lymph nodes
      - Symptoms: cough and shortness of breath
    - Associated paraneoplastic syndrome
      - Lambert Eaton Syndrome: 1-2%
        - Proximal leg weakness due to antibodies against voltage gated calcium channels
    - Ectopic Hormone Reduction
      - Antidiuretic hormone (vasopressin)-10%
        - Hyponatremia: fatigue, headaches, seizures
      - Adrenocorticotropic hormone (ACTH)-2-5%
        - Hirsutism, hypertension, hyperpigmentation, glucose intolerance, abdominal obesity
- Staging
  - Historical VA Lung Study Group
    - Limited stage (1/3): disease confined to the ipsilateral hemithorax
      - May include contralateral mediastinum and ipsilateral supraclavicular disease
    - Extensive stage disease (2/3): beyond the ipsilateral hemithorax to other lung, lymph nodes on other side of chest, or distant organs
  - AJCC TNM Staging System
    - Limited stage correlates to stage I-III (any T, any N, M0) that can be safely treated with definitive radiation and chemotherapy
    - Extensive stage correlates to stage IV disease and T3-T4 disease due to multiple lung nodules that are too large or extensive to be treated with definitive radiation and chemotherapy

Meeting minutes: SCLC Consortium WebEx

- Traditional Treatments and Outcomes
  - Limited stage
    - Chemo-RT→prophylactic cranial irradiation (PCI)
      - Cisplatin + Etopiside + Radiation
        - Chemo-responsive: response rates of 80-90%
          - Rarely sustained (median 6-8 months)
        - Radiation dosing
          - QD: 60-70 Gy at 1.8-2 Gy/fx
          - BID: 45 Gy at 1.5 Gy/fx
      - Timing
        - Begin RT as soon as possible (cycles 1-2)
          - 50-60% relative improvement in 3 years overall survival compared to starting RT after cycle 2 (oncologist 2004;9;665)
    - Surgery option for early stage
    - Outcomes
      - Median OS: about 24 months
      - 5 year OS: 26%
      - Thoracic failure rate: 35%
    - Extensive Stage
      - Typically managed with chemo (Cisplatin+etop)
      - Palliative radiation for symptom management and consolidation (?)
      - Outcomes
        - Median OS: 5-9 months
        - 5 yr OS <5%
- Hypothesis
  - We can manipulate the metabolic oxidative stress differences between cancer cells and normal cells to improve small cell lung cancer therapeutic response
- Oxidative Stress
  - Disturbance in the prooxidant-antioxidant balance in favor of the former that potentially leads to an accumulation of oxidative damage to critical biomolecules



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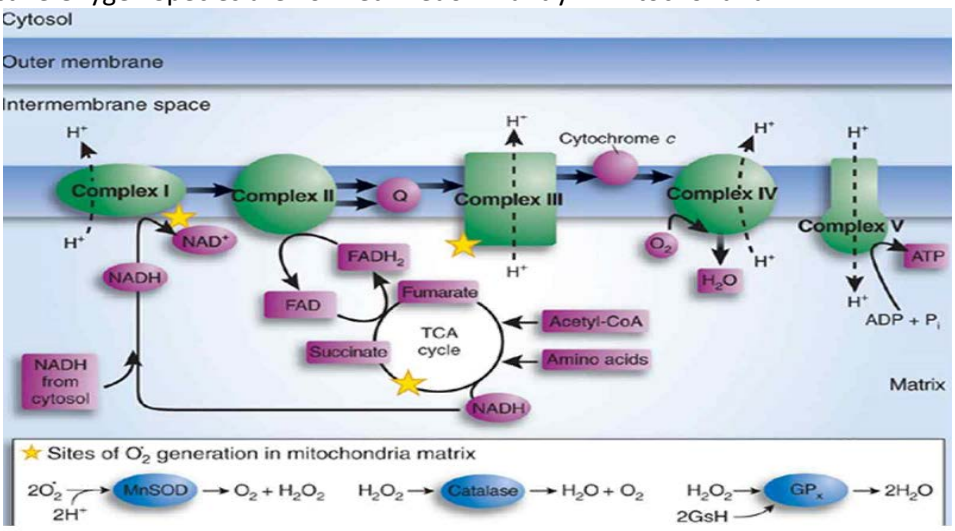
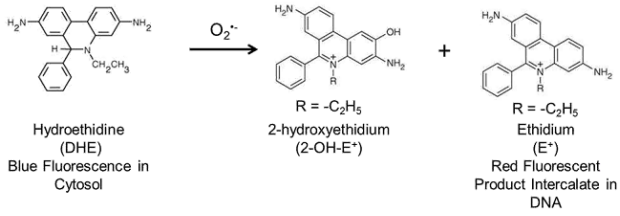
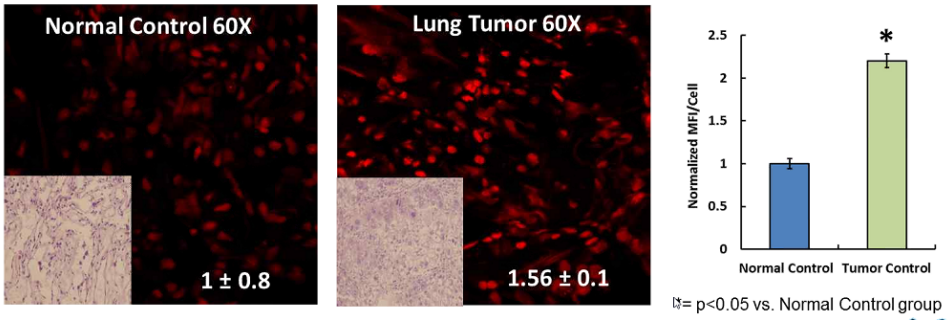
- Reactive Oxygen Species are Formed Predominantly in Mitochondria



Nature.com

- Cancer Cells have Increased Oxidative Stress Relative to "Normal Cells"

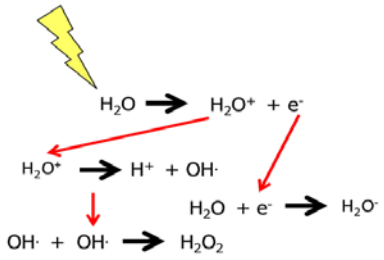




- Radiation and Chemotherapy also Induce Oxidative Stress

OXIDATIVE STRESS AND CHEMOTHERAPY	
High	Anthracyclines
	Pt-complexes Alkylating agents Epipodophyllotoxins Camptothecins
	Purine/Pyrimidine Antimetabolites
Low	Taxanes Vinca alkaloids

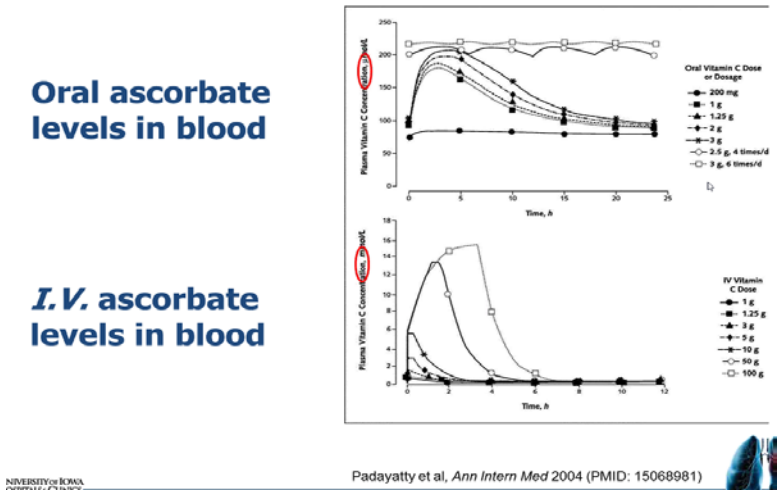
Conklin KA, 2004



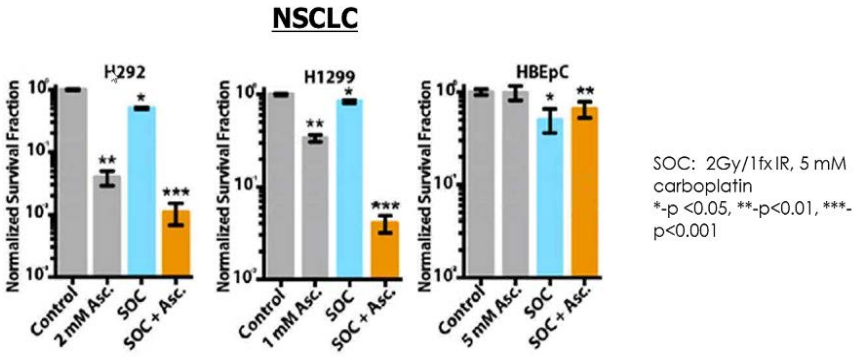
- History of Vitmain C as a Cancer Therapy
  - 1970's: Linus Pauling showed that high dose ascorbate (10g IV then 10g PO) increased survival 4x in a variety of cancers

- 1985: Two randomized trials demonstrated no difference in survival between patients received placebo or 1g oral ascorbate
- 1985: Two randomized trials demonstrated no difference in survival between patients receiving placebo or 10g oral ascorbate
- 1990's: Hugh Riordan demonstrated *in vitro* that many tumor cell types die when exposed to high concentrations of ascorbate (400mg/Dl) while normal cells are unaffected
- 2005 Mark Levine (NIH) demonstrated that effective concentratinos of ascorbate could not be achieved by oral administration alone

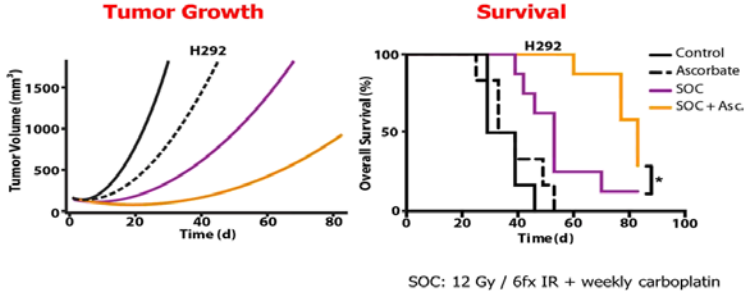
- Oral vs. IV Ascorbate



- Pharmacological Ascorbate Increases NSCLC Sensitivity to Radiation and Chemotherapy *in vitro*



- Pharmacological Ascorbate Enhances NSCLC Radiation and Chemotherapy Sensitivity *in vivo*



- Ascorbate Levels are Increased in Plasma and Tumor
  - Humans and hamsters are the only mammals that do not make their own Vitamin C, so mice already have a background concentration of Vitamin C in their plasma

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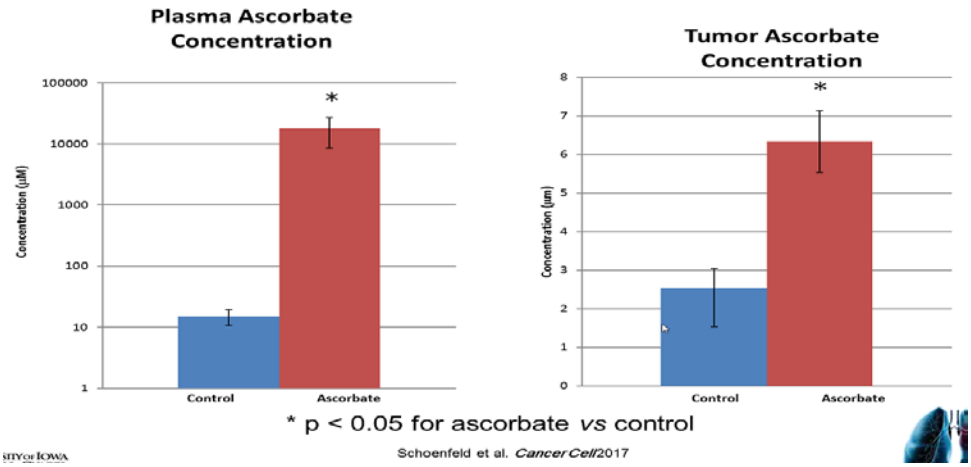
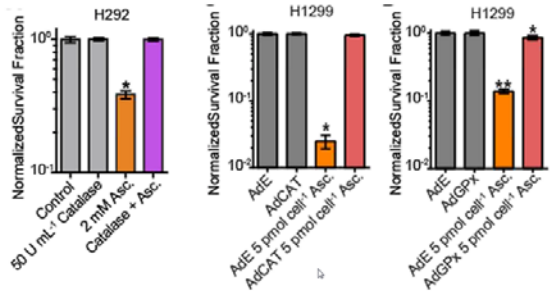
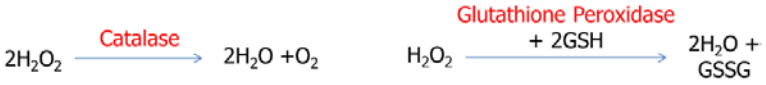
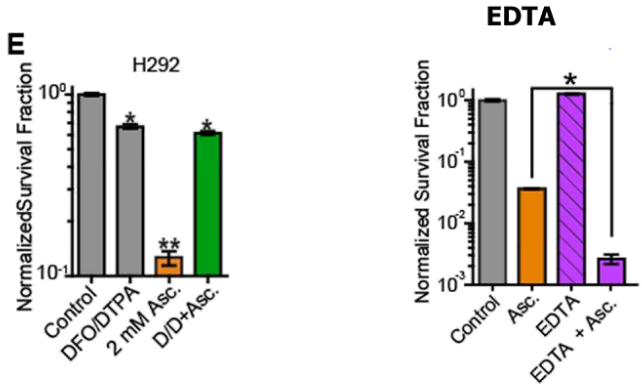


- H202 Mediates Ascorbate Cancer Cell Toxicity





- Redox Active Metal Ions Mediate Ascorbate Cancer Cell Toxicity



- Chelator (D/D) for 3 hours prevents redox cycling
  - 1 mM DETAPAC
  - 200 μM Deferoxamine
- 2 mM ascorbate and chelator for 1 hour

1 mM EDTA enhances Fe redox cycling

Schoenfeld et al. *Cancer Cell* 2017

- Iron Metabolism and the Redox Active Labile Iron Pool
  - Lung tumors have increased labile iron pools relative to adjacent normal lung tissue

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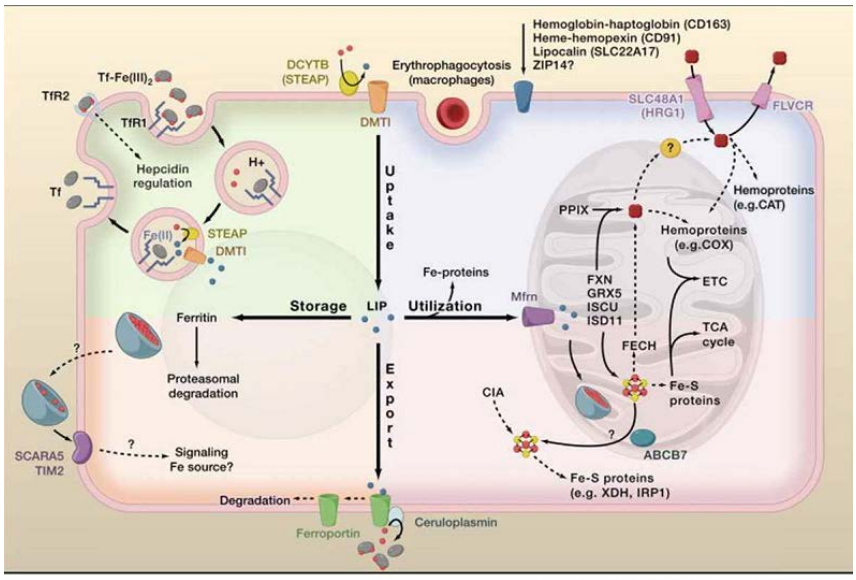
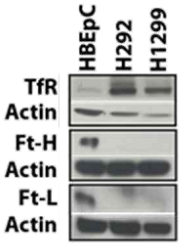
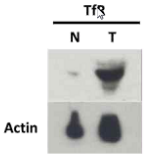


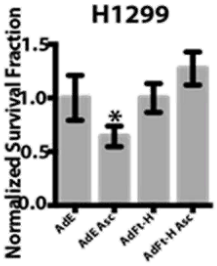
Hentze et al *Cell* 2010 (PMID 20603012)

- Iron Regulation Influences the Differential Susceptibility of Cancer vs. Normal Cells to Pharmacological Ascorbate

Cellular Expression **Patient Samples** **Clonogenic Rescue**

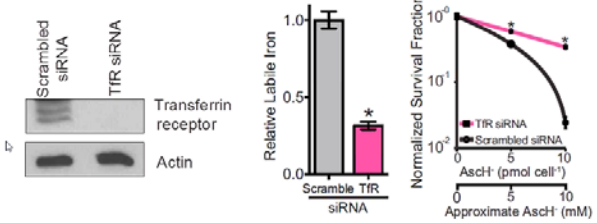




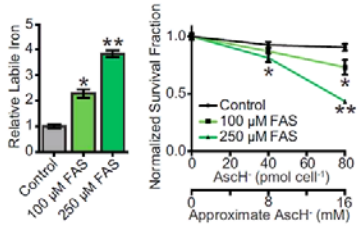


- Available Labile Iron Pools Influence Cell Sensitivity to Pharmacological Ascorbate
  - Knock down transferrin receptor to make cells that are sensitive to Vitamin C, resistant to Vitamin C

Reduce available LIP by siRNA



Increase available LIP by Ferrous Ammonium Sulfate



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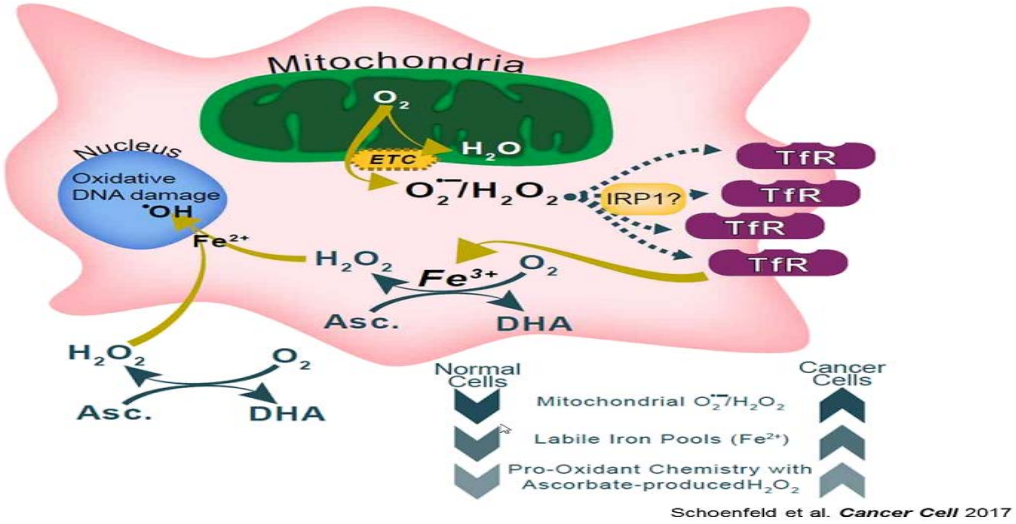
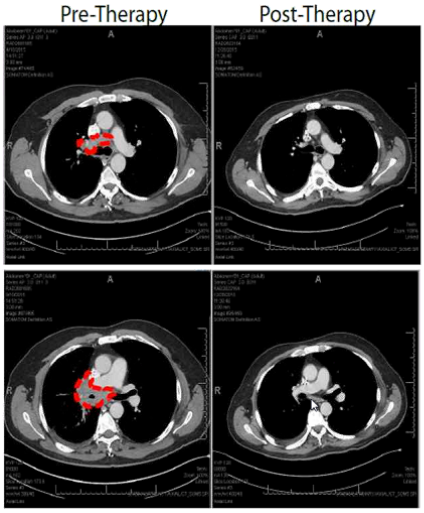
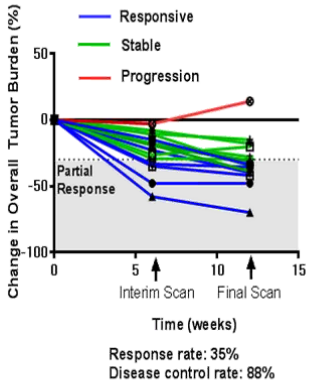
- Pharmacological Ascorbate Cancer Cell Selectivity Model



Schoenfeld et al. *Cancer Cell* 2017

- Phase 2 Clinical Trial of Pharmacological Ascorbate in Stage IV NSCLC
  - Give carbo+etop every three weeks (standard therapy) AND ascorbate IV twice a week
- Interim Results of Pharmacological Ascorbate Lung Trial

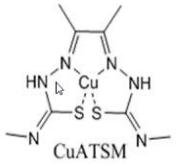




Response rate: 35%
Disease control rate: 88%

Historical objective response rate: ~15-19%
Historical disease control rate: ~40%

- Redox Active Copper
  - Transition metal ions like copper (Cu) and Iron (Fe) can participate in oxidation reactions
    - $M^{(-n)}+H_2O_2 \rightarrow M(+n)+OH^-+HO\bullet$
  - Cooper ATSM (copper(II)bis(thiosemcarbazone): previously used in clinical trials to treat ALS and Parkinson's disease



    - CuATSM preferentially concentrates in hypoxic tissues releasing its copper atom after entering cells
- Overview of CuATSM Uptake
  - Hypoxic conditions: Cu(II)ATSM is reduced to Cu(I)ATSM is reduced to Cu(I)ATSM
    - The complex becomes unstable and copper is released and may participate in oxidation reactions

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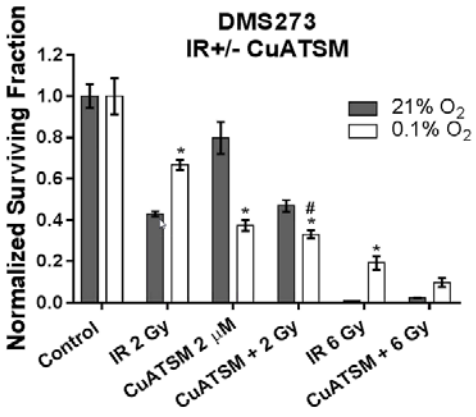
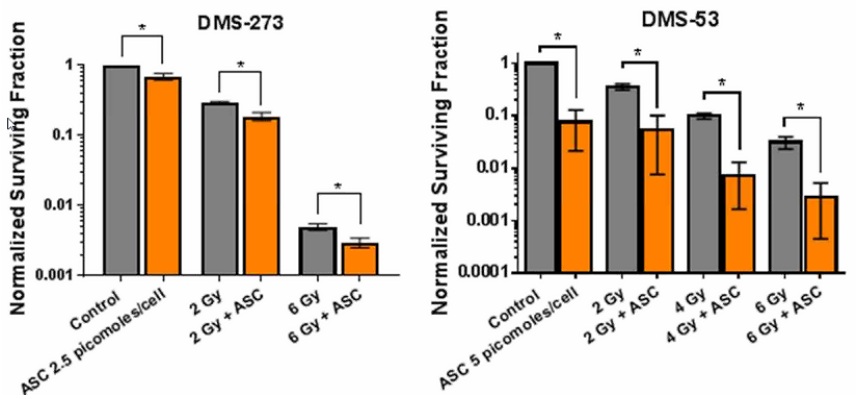
- CuATSM Enhances SCLC Radiation Sensitivity in Hypoxic Conditions

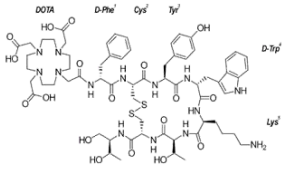


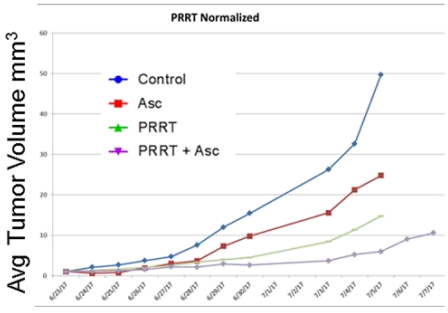
- Pharmacological Ascorbate Enhances SCLC Sensitivity to Radiation

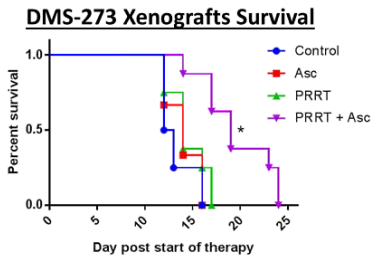


- Pharmacological Ascorbate Enhances Survival in SCLC Xenografts Treated with ^{90}Y-DOTATOC

DOTATOC: DOTA-D-Phe1-Tyr3-Octreotide
Somatostatin analog
SCLC cells express somatostatin receptors







Control: 1 M NaCl
Asc: 4 g/Kg mouse weight /day
^{90}Y-DOTATOC 20 MBq on Day 1

- Future Directions
  - SCLC xenograft studies assessing combinations of CuATSM, radiation therapy, chemotherapy, and pharmacological ascorbate
  - Clinical trial in SCLC combining pharmacological ascorbate with cisplatin and etoposide in extensive stage and pharmacological ascorbate combined with radiation, cisplatin and etoposide in limited stage

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- Questions:
    - What was the rationale for choosing DOTATOC for combination therapy for SCLC?
        - May not be the most active agent but it was available from a collaboration with the nuclear medicine department.
    - NCI did large number of combined radiotherapy/chemotherapy studies. Helped with local disease but the problem was with metastatic disease. What is the appropriate pre-clinical model to look at metastatic disease? Does it look like there is any other evidence that this could deal with metastatic disease?
        - For metastatic disease, combine chemo and ascorbate. For overcoming resistance to chemo, would have to do initial animal studies combining chemo with Vitamin C and combining chemo with radiation.
    - Why in some cases does the ascorbate seem ok and then in other cases not. What are the underlying factors of why it is not consistent?
        - Some cell lines are not sensitive. Believe it is related to amount of redox active metal inside the cell.
    - Thoughts on effects of radiation generating immune response and how can it be evaluated in a preclinical fashion to see if whether combining this would lead to a SCLC immune response?
        - World Lung result was without radiation but there are multiple models that show there is synergy between radiation and immune response.

Reminders:

- Next Call: November 1st from 1:30-2:30pm
    - Dr. Christopher Vakoc-Cold Spring Harbor Laboratory
- Annual Spring Meeting will be evening of April 3rd–April 5th 2019
    - Planning committee: Charles Rudin, JT Poirier, Trudy Oliver, Julie George and Taofeek Owonikoko