Precision Approaches in Radiation Synthetic combinations (PAIRS)

PAR Concept

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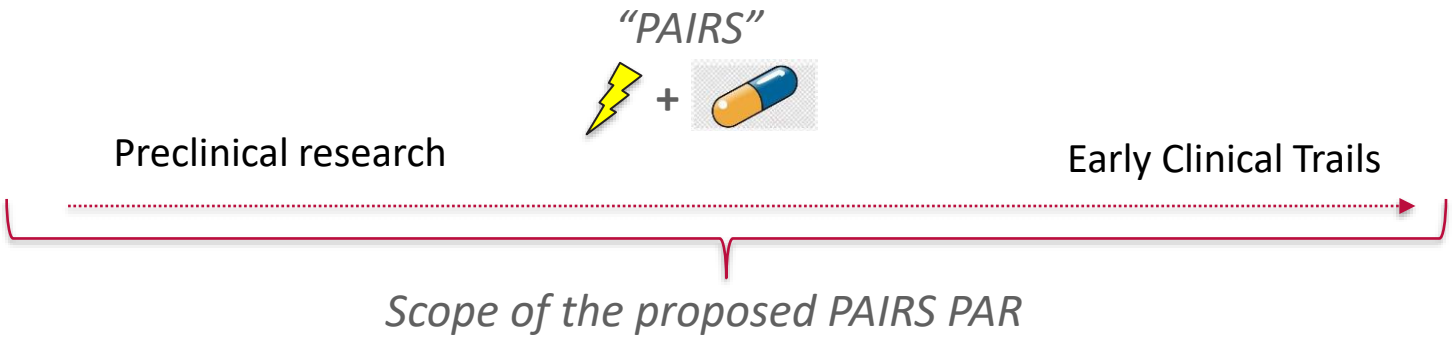
BSA concepts March 29, 2022

Precision Approaches in Radiation Synthetic combinations *(PAIRS)*

- Requesting a **PAR** to support research focused on targeting **vulnerabilities** created by **cancer reprogramming** associated with **responses to radiation-drug combination therapy**;
- Seeking to catalyze interdisciplinary research at the intersection between **precision medicine, pre-clinical cancer research,** and **radiation oncology**;
- Goal is to strengthen the **translation of pre-clinical research** that leverages the unique qualities of **radiation** working in tandem with **targeted** **synthetic combination strategies**.



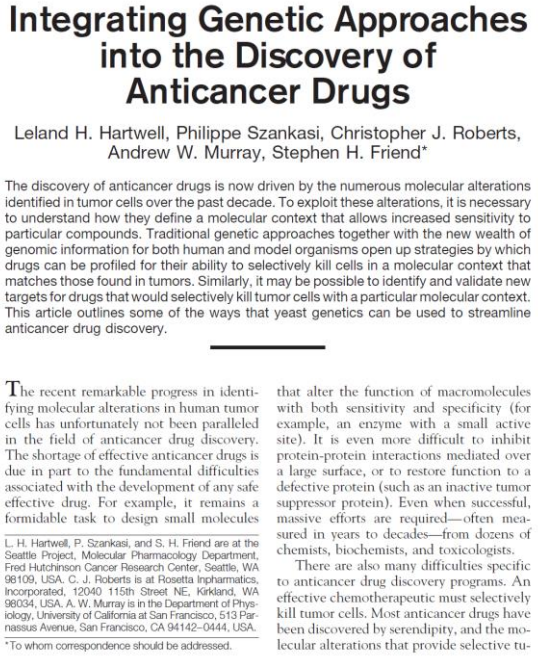
Synthetic Lethality (SL) *itself is not a new concept*

- In model organisms (*e.g.*, yeast), SL typically describes the scenario where mutation in 1 of 2 interacting genes is viable, but mutation of both results in lethality;
  (Bridges, 1922; Dobzhansky, 1946)

- SL was proposed as a strategy to exploit the presence of underlying cancer mutations; (Hartwell, 1997) →

- Potential to target Loss-of-Function mutation scenarios (archetypic *BRCA1/2* HR defect + PARPi);

- SL target discovery well suited to “essentiality” approaches (*e.g.*, RNAi, CRISPR, small mol. HTS, systems biology);



Integrating Genetic Approaches into the Discovery of Anticancer Drugs

Leland H. Hartwell, Philippe Szankasi, Christopher J. Roberts, Andrew W. Murray, Stephen H. Friend*

The discovery of anticancer drugs is now driven by the numerous molecular alterations identified in tumor cells over the past decade. To exploit these alterations, it is necessary to understand how they define a molecular context that allows increased sensitivity to particular compounds. Traditional genetic approaches together with the new wealth of genomic information for both human and model organisms open up strategies by which drugs can be profiled for their ability to selectively kill cells in a molecular context that matches those found in tumors. Similarly, it may be possible to identify and validate new targets for drugs that would selectively kill tumor cells with a particular molecular context. This article outlines some of the ways that yeast genetics can be used to streamline anticancer drug discovery.

The recent remarkable progress in identifying molecular alterations in human tumor cells has unfortunately not been paralleled in the field of anticancer drug discovery. The shortage of effective anticancer drugs is due in part to the fundamental difficulties associated with the development of any safe effective drug. For example, it remains a formidable task to design small molecules that alter the function of macromolecules with both sensitivity and specificity (for example, an enzyme with a small active site). It is even more difficult to inhibit protein-protein interactions mediated over a large surface, or to restore function to a defective protein (such as an inactive tumor suppressor protein). Even when successful, massive efforts are required—often measured in years to decades—from dozens of chemists, biochemists, and toxicologists.

There are also many difficulties specific to anticancer drug discovery programs. An effective chemotherapeutic must selectively kill tumor cells. Most anticancer drugs have been discovered by serendipity, and the molecular alterations that provide selective tu-

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SCIENCE • VOL. 278 • 7 NOVEMBER 1997 • www.sciencemag.org

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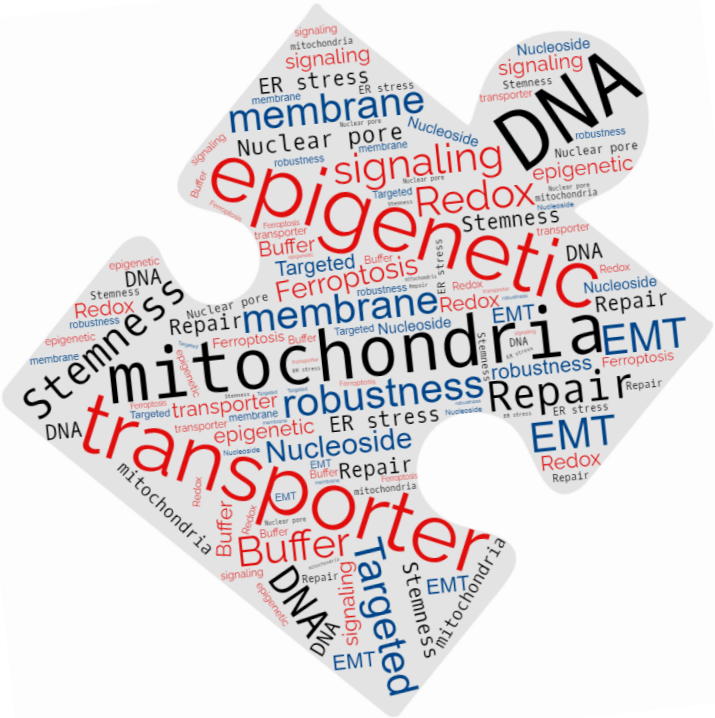
Reprograming in cancer

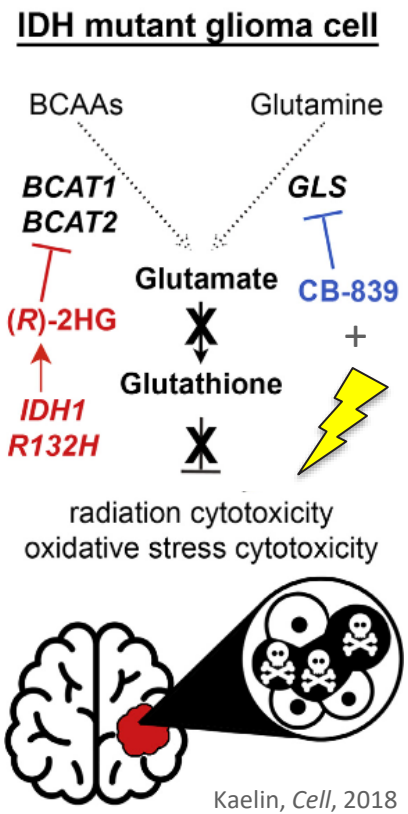
connection to radiation - synthetic combinations



- Buffers systems against underlying oncogenic mutations (e.g., workarounds);
- Fitness trade-offs winnow functional redundancies and create synthetic combination vulnerabilities
- Radiation responses place demands on nodes essential for repair and cell survival;
- Radiation can be precision tool to “set-up” conditional pairings (in time and space) with a targeted agent

RT – Conditional Synthetic Combinations

exploit intrinsic vulnerability

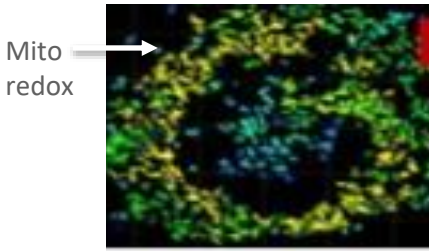


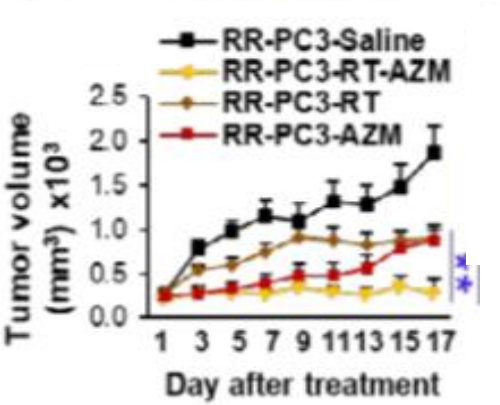
- IDHmut → oncometabolite 2HG ┤ glutamate from BCAA;
- RT ⚡ induces "conditional essentiality" for glutathione (GSH);
- Tx with GLSi CB-839 chokes off alt. route for glutamate → GSH synthesis, creates SL;
- RT + CB839 has moved thru Phase 1, poised for Phase 2 trial in glioma patients with IDH mutation;

Kaelin, *Cell*, 2018

BrigWH-MGH SPORE P50CA165962

RT – Conditional Synthetic Combinations





Luksana Chaiswing
U.Ky R01CA251663-A01
(data shown w/ permission)

exploit adaptive vulnerability

- Prostate ca. RT resistance dependent upon reprogramming for increased mitochondrial biogenesis;
- FDA approved antibiotic azithromycin (AZM) induces “conditional essentiality” by blocking mito-specific translation;
- Tx with RT + AZM creates mito-redox imbalance & SL;

RT – conditional synthetic combinations

Portfolio Analysis defines “the Gap”

- Majority of NCI’s active “SL” therapy awards are in DTP

  (e.g., R01 = 38);
- Very few radiation-treatment synthetic combination awards exist

  (e.g., R01 = 2)

Premise is to expand potential of RT + synthetic combination strategies

- Ionizing radiation (RT) is a SOC component for > 50% of cancers;
- RT can precisely trigger essentiality demands on cancer selective drug targets;
- Libraries of candidate agents exist for diverse synthetic-related targets

  molecular therapeutics, known MoA, rationale for combo w/ RT

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Priority areas of focus

- Epigenetic reprogramming factors
- Organelle-linked processes
  - Mitochondria
  - Nuclear pore complex, DDR
  - ER – stress
  - Lysosomes and autophagy
- Membranes
  - lipid peroxidation-ferroptosis
- Stemness-resistance pathways
- RNA processing - spliceosome
- TME targets
  - CAF
  - MDSC

Proposed Initiative

PAR to solicit applications that advance development and/or translation of strategies leveraging RT's unique precision targeting of synthetic combination vulnerabilities

- **Mechanism:** R01 (clinical trial optional) and R21
  - Scope: Pre-clinical to early clinical
  - Funding source: RPG pool, no set-aside
- **Projects focused on RT-drug synthetic synergies to target cancer-specific vulnerabilities**
  - RT precision medicine to induce select demands targetable by synthetic combination strategies
  - Couple existing SL libraries with radiobiology RT models to support the rationale for new clinical translational concepts
- **PAR justification**
  - Incentivize applications from SL-targeting labs to collaboratively investigate RT as a precision medicine tool
  - Increase the number of high-quality applications not seen with unsolicited route
  - Broaden the field, serving as a timely catalyst to drive potential to impact clinical adoption of RT + drug combinations.

BSA sub-com. comments & suggestions

- "Synthetic Lethality" terminology
  - Conditional v strict genetic SL terminology (*FOA glossary*)
  - To emphasize, "subpopulations of patients based on known genetic subtypes"
  - Types of interactions (*targeting of both primary (intrinsic) and acquired (adaptation-related) vulnerabilities)*
  - FOA title tweak (Precision Approaches in Radiation Synthetic **combinations**)

- Anticipated response: pre-clinical – early clinical trials?
  - Likely most projects will be on the pre-clinical R01 end of the spectrum
  - R21 is an option for early testing of novel RT-drug synthetic combination concepts
  - R01-"clinical trial optional" is available for teams that are at the point of proposing an early-stage clinical trial

- What does success look like?
  - Nucleate NCI portfolio with 6-8 meritorious proposals drive clinical adoption of new RT-drug synthetic combinations
  - Stimulate productive intersections between the drug dev. and RT communities