Improving Treatment for Cervical Cancer: What Can Tumor Biology Tell Us?

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NIH Cervical Cancer Funding

Cervical Cancer – RCDC Official Public Category

Basic Research - Translational Research - Clinical Research
Pre-Malignant - Malignant - Invasive
Prevention - Screening - Detection - Diagnosis - Treatment
HPV - Vaccines - Vaccination

Data from RCDC Categorical Spending Reporting
https://report.nih.gov/funding/categorical-spending#/

2017: $113,602,958
2018: $111,566,327
2019: $105,989,895
2020: $113,490,444

Funding by Percentage of ICO budget, FY 2020

- NCI: 1.42%
- NIMHD: 0.91%
- NIAID: 0.20%
- NICHD: 0.15%
- All other ICs: 0.02%
Projects were assigned to ICRP Common Scientific Outline (CSO) classifications using a Dimensions Machine Learning process.
Individual projects can be assigned to multiple categories.
Not all projects are classified and those have been excluded from the data shown.
Cervical Cancer Treatment

- Pelvic irradiation and concurrently administered cisplatin chemotherapy
Our approach

Patient data

New therapies

Model systems

Tumor biology

Functional imaging
FDG-PET/CT

**SUV** = tissue radioactivity concentration (nCi/mL) / injected dose(mCi)/patient weight (g)
$SUV_{\text{max}}$ and cervical tumors

Survival outcomes and $\text{SUV}_{\text{max}}$
Complete Metabolic Response

Schwarz JK et al, JNM 2009
Partial Metabolic Response

Schwarz JK et al, JNM 2009
Our approach

- **Patient data**
- **New therapies**
- **Functional imaging**
- **Model systems**
- **Tumor biology**

- **2007**
- **2012-2017**
- **2017-2020**
Radio-resistant cervical cancers respond to metabolic drugs

Rashmi R et al Mol Cancer Ther 2020
Can genomic biomarkers be used to personalize treatment?

- Cervical Cancer TCGA
- HPV genotype and HPV gene expression
  - Not all HPVs are created equal!
- mRNAs, miRNAs, IncRNA
  - GARD – gene expression derived from cancer cell lines + linear quadratic modeling
    - Scott, JG et al *Lancet* 2017
- Proteomics
  - Rader, JS et al *Gyn Onc* 2019
Prospective evaluation of host and viral biomarkers in cervical cancer

Tumor Profiling
- Mutational landscape
- Transcriptome - Viral and host
- HPV genotype

Clinical parameters of interest
- Recurrence status
- Overall survival outcome

Analysis
- Univariate Cox regression for features correlated with survival outcomes
- Kaplan-Meier survival curves
- Differential expression of viral and host transcripts
HPV genotype and outcome after chemoradiation in cervical cancer

Ruiz, F et al JCI Insight 2021
Relative expression of HPV E6*I and outcome after chemoradiation

Ruiz, F et al JCI Insight 2021
HPV E6* overexpressing cancers are resistant to chemoRT
- senescence
- role for senolytics?

HPV E6 overexpressing cancers are also resistant to chemoRT
- DNA repair
- role for DDRi?

Ruiz, F et al *JCI Insight* 2021
**SUV** = tissue radioactivity concentration (nCi/mL) / injected dose (mCi)/patient weight (g)
Floberg, JM et al Clinical Cancer Research 2021
Future Directions

• New Targets:
  • DNA Damage Response Inhibitors
  • Metabolism/ROS
  • Inflammatory pathways

• Better Model Systems
  • 2D Co-Culture
  • 3D culture
  • PDX
  • GEMMs

• Personalized medicine approaches to better suit our patients
  • Genomics
  • Imaging
What can we do to shorten the timeline to get new approaches to our patients?

- **Funding, funding, funding!**
  - Especially as it pertains to local control for solid tumors
    - Gynecologic oncology
    - Radiation oncology

- **Faster path to establish safety for lead drug + RT combinations (Phase I)**
  - Support for generation of key preclinical data
    - Monotherapy + drug combinations
    - RT alone
    - SOC CRT – needs to reflect current paradigms
      - Clinically relevant drug concentrations
      - RT dose, fractionation and image guidance
  - Better model systems (in vitro and in vivo)

- **Collaboration across centers within the US and globally**
  - Team Science and resource sharing rather than competition
Opportunities

- Training grants to support research workforce development in Gyn Onc/Rad Onc
  - NIH K12 BIRCWH
- Group Grants to improve innovation in treatment approaches for cervical cancer
  - SPORE, P, U level grants
- Increase R01 level funding for investigators working on tumor biology and treatment
  - Gyn Onc specific study section that prioritizes needs
    - cervical cancer treatment innovation
- Sample RFAs
  1. Improving Preclinical Models for Treatment Assessment in HPV Associated Cancers
  2. Novel Imaging and Genomic biomarkers for Outcome Prediction in Cervical Cancer
  3. Optimizing technology to improve outcomes in resource poor settings
  4. Novel targeted therapy approaches +/- RT in cervical cancer
    - DNA Damage Response Inhibitors (DDRis)
    - Metabolic therapy (drugs and diet)
    - Immunotherapy
  5. Personalized treatment to improve outcomes in cervical cancer

DNA Damage Response Inhibitors (DDRis)
- Metabolic therapy (drugs and diet)
- Immunotherapy
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