Co-infection and Cancer

New Program Announcement with Review (PAR) Concept

Division of Cancer Control and Population Sciences
Division of Cancer Biology
Division of Cancer Prevention
Center for Global Health
Center to Reduce Cancer Health Disparities

June 10, 2019
Board of Scientific Advisors
National Cancer Advisory Board
13th Joint Meeting
Purpose

- Enhance mechanistic and epidemiologic research in co-infection* and cancer.
- Identify markers for early detection and prevention.

*Co-infection: the occurrence of infections by two or more infectious (pathogenic or non-pathogenic) agents—either concurrently or sequentially and includes both acute and chronic infections by viruses, bacteria, parasites, and/or other microorganisms.

For the purpose of this FOA, we exclude co-infection with HIV.
Cancer-causing Pathogens: 15% New Cancer Cases*

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr virus (EBV)</td>
<td>Lymphoma, nasopharynx, leukemia</td>
</tr>
<tr>
<td>Hepatitis B and Hepatitis C viruses</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>Anal, cervical, head and neck, oral, penile, vaginal, vulvar</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HIV)</td>
<td>Kaposi sarcoma, AID-related lymphomas</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helicobacter pylori (H.pylori)</td>
<td>Stomach</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parasites</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver flukes</td>
<td>Biliary, cholangiocarcinoma, gallbladder, pancreas</td>
</tr>
<tr>
<td>Schistosoma haematobium</td>
<td>Bladder</td>
</tr>
</tbody>
</table>

* Plummer, Lancet Global Health 2016
## Global and U.S. Prevalence of Carcinogenic Agents

<table>
<thead>
<tr>
<th></th>
<th>EBV</th>
<th>H. pylori</th>
<th>HPV</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>World</strong>¹</td>
<td>≥90%</td>
<td>~50%</td>
<td>~12%</td>
<td>~4%</td>
<td>~2%</td>
</tr>
<tr>
<td>**U.S.**²</td>
<td>~80%</td>
<td>~30%</td>
<td>~23%*</td>
<td>≤0.4%</td>
<td>~1%</td>
</tr>
</tbody>
</table>

¹WHO; ²CDC; *High-risk HPV types

### U.S. Population

<table>
<thead>
<tr>
<th>Population</th>
<th>H. pylori prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>20%</td>
</tr>
<tr>
<td>Black</td>
<td>50-80%</td>
</tr>
</tbody>
</table>

---

### Proportion of H. pylori+ over time

*Source: Epplein M*
Infection-Driven Carcinogenesis

- Most infected individuals are chronic carriers and rarely develop the associated cancer
- Infection-driven cancer initiation and progression may require additional co-factors
  - What factors act cooperatively with the pathogens to produce cancer?
  - What are the mechanisms that underpin that cooperation?
- Co-infection
  - What is the involvement of other pathogenic agents and non-pathogenic agents in the development and/or progression of cancer?

Prevalence of Co-infection: Likely High
▪ Evidence on co-infection and cancer risk is suggestive.
▪ Direct role in causation is unknown.
▪ Mechanisms are speculative.
Mechanisms of Infection-driven Carcinogenesis

Potential Mechanism

- Inflammation
- Host immune responses
- Immune evasion
- Genomic instability
- Altered tumor niche
- Changes in viral integration into hosts’ genome
- Episome maintenance

Co-infection: Unclear
Mechanism Examples

- Burkitt’s Lymphoma + P. falciparum
- c-myc translocation
- Gastric Cancer + H. pylori
- Head & Neck Cancer + HPV
- Breast Cancer + HPV
- Non-Hodgkins Lymphoma + HBV
- Breast Cancer + HPV
- Non-Hodgkins Lymphoma + HBV
Infection with another infectious agent(s) may be the necessary co-factor for infection-related cancer initiation and progression.

- Etiologic role of co-infection in cancer risk is suspected but largely unknown.
- Mechanisms of co-infection in carcinogenesis is unclear.
- Identification of risk profiles may lead to targeted interventions and prevention strategies.
PAR Co-infection and Cancer: Area of Warranted Research

- Responses from Request for Information (NOT-CA-16-067)
- Discussions across NCI
  - Disparities/Inequities
  - Global Health Implications
  - Encourage investigations of co-infection with certain infectious agents (e.g., EBV and H.pylori)
  - Exclude Co-infection with HIV

- Identify role(s) of co-infection in cancer susceptibility.
- Investigate mechanisms underlying co-infection and carcinogenesis.
- Determine the effect of timing and type of initial infection and secondary infection(s) on susceptibility to cancer.
- Develop of new models to test mechanisms of co-infection driven cancer etiology.
- Identify molecular signatures of co-infection that distinguish cancer susceptibility.
Proposed Characteristics of PAR and Portfolio Analysis

- Funding Opportunity Announcement: PAR
- Mechanism: R01, R21

**NCI coinfection-related grants* (n=40)**

<table>
<thead>
<tr>
<th>Category</th>
<th>HIV-related coinfection</th>
<th>Other coinfection</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCB</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>NCI OD</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>DCCPS</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DCP</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>DCTD</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Active grants only; search date: 3/2019
THANK YOU

- Divi Rao
- Danielle Carrick
- Gary Ellison
- Mukesh Verma
- Phil Dashner
- Betsy Read-Connole
- Jo Ann Rinaudo
- Sudha Sivaram
- Vidya Vedham
- Anil Wali
A higher proportion of cancer cases are due to infection in lower income countries, particularly in Asia and Sub-Saharan Africa.

Fraction of new cancer cases attributable to infection (by region, 2008)
Invasive Cervical Cancer: Co-infection with HPV

Epstein Barr Virus and *Helicobacter pylori* Co-Infection Are Positively Associated with Severe Gastritis in Pediatric Patients

Source: Smith JS, JNCI 2002
HPV: A Necessary but Insufficient Cause

- Established cofactors: tobacco smoking, high parity, long-term hormonal contraceptive use, co-infection with HIV
- Probable cofactors: coinfection with Chlamydia trachomatis, herpes simplex virus type-2, immunosuppression, certain dietary deficiencies
- Likely important: genetic and immunologic host factors and viral factors other than type (i.e., variants of type, viral load, viral integration)
- High number of sexual partners increases acquisition of oncogenic HPV infections
Are people harboring different bacteria based on genetic origin or heritage?
Beyond Established Carcinogenic Infectious Agents

ARTICLE
Antibodies Against Chlamydia trachomatis and Ovarian Cancer Risk in Two Independent Populations
Britton Trabert, Tim Waterboer, Annika Idahl, Sally B. Coburn, Patricia Hartge, Katrin Hufnagel, Alexander Mentzer, Beata Peplonska, Mark E. Bibbo, Michael Pawlita, Nicolas Wentzensen

Prospective seroepidemiologic study on the role of Human Papillomavirus and other infections in cervical carcinogenesis: Evidence from the EPIC cohort
NIH-wide Portfolio Analysis: Infections & Cancer

**INFECTION-RELATED GRANTS**
(N=90)

**CO-INFECTION GRANTS**
(N=11)

- HIV-related Coinfection
- Non-HIV-related Coinfection

Legend:
- NIAID
- NIDCR
- NIDDK
- Others
NCI INFECTION-RELATED GRANTS* (N=295)

INFECTION-RELATED GRANTS, BY INFECTIOUS AGENTS (N=295)

Others: cytomegalovirus, adenovirus, Vesicular Stomatitis Virus, Human T-cell leukemia virus type