AWARD NUMBER:  W81XWH-16-1-0271

TITLE:  Somatic Mosaicism for Cancer Predisposition Genes and Pancreatic Cancer

PRINCIPAL INVESTIGATOR:  Christine A. Iacobuzio-Donahue

RECIPIENT:  Sloan Kettering Institute for Cancer Research
            New York, NY 10065

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TYPE OF REPORT:  Annual

PREPARED FOR:  U.S. Army Medical Research and Materiel Command
                Fort Detrick, Maryland  21702-5012

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Somatic mosaicism refers to the occurrence of two genetically distinct populations of cells within an individual, derived from a postzygotic mutation. Unlike inherited mutations in which the variant allele is present in all cells in the body, somatic mosaic mutations may affect only a subset of cells and may not be passed on to their progeny. Somatic mosaicism is a clinically relevant phenomenon for a variety of human diseases, including rare and common cancers. However, the extent to which somatic mosaicism for PDA cancer predisposition genes accounts for PDA incidence is unknown. In this proposal we propose two specific aims to address this topic. First, we will determine the extent to which driver genes are somatically mutated in multiple matched normal tissues previously collected from >100 clinically annotated PDA patients who underwent rapid autopsy. Second, we will determine the extent to which somatic mosaicism for driver gene mutations are associated with pancreatic carcinogenesis. Towards these goals we have extracted genomic DNA of 772 normal tissues from 103 individuals, the majority of which died of pancreatic cancer or had a strong family history of cancer. Thus far all tissues from 21 of these patients have undergone targeted sequencing using a 468 gene panel and are currently undergoing bioinformatics analysis.
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Somatic mosaicism refers to the occurrence of two genetically distinct populations of cells within an individual, derived from a postzygotic mutation. Unlike inherited mutations in which the variant allele is present in all cells in the body, somatic mosaic mutations may affect only a subset of cells and may not be passed on to their progeny. Somatic mosaicism is a clinically relevant phenomenon for a variety of human diseases, including rare and common cancers. Our work being performed under this award aims to derive a better understanding of the prevalence and influence of somatic mosaicism in PDA incidence and recurrence. Should somatic mosaicism account for a subset of PDA it could dramatically change screening approaches, patient management and genetic counseling.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

pancreatic cancer, mutation, genetics, screening, somatic mosaicism, hereditary cancer

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

Our goals are to determine the extent to which driver genes are somatically mutated in multiple matched normal tissues previously collected from >100 clinically annotated PDA patients who underwent rapid autopsy and to determine the extent to which somatic mosaicism for driver gene mutations are associated with pancreatic carcinogenesis.

What was accomplished under these goals?

Thus far we have extracted genomic DNA of all 772 normal tissues from all 103 patients. All samples were analyzed for quality and quantity using a LINE assay. Thus far we have submitted 152 samples from 21 patients to the MSKCC Genomics Core for library preparation and sequencing using the IMPACT targeted sequencing panel. This panel covers the entire coding sequence of 468 known genes as well as several introns involved in common rearrangements. SNPs scattered throughout the panel also allow for copy number analyses such as homozygous deletions and amplifications. Thus far sequencing has been completed and the data is currently under initial analysis in the MSK bioinformatics pipeline.

What opportunities for training and professional development has the project provided?
In the course of this work a high school student worked with the postdoctoral fellow in charge of this project and learned how to extract and quantify genomic DNA from tissues.

**How were the results disseminated to communities of interest?**

Nothing to report.

**What do you plan to do during the next reporting period to accomplish the goals?**

In the next reporting period we will complete sequencing of the sample dataset and analyze the genomic data of all 103 patients to determine the extent that they are somatic mosaic for a known cancer driver gene, the extent that that same gene is inactivated in the matched tumor (evidence that the variant was selected for), and ultimately determine the frequency of somatic mosaicism in pancreatic cancer and the genes most commonly attributed to this finding.

**4. IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

**What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report.

**What was the impact on other disciplines?**

Nothing to report.

**What was the impact on technology transfer?**

Nothing to report.

**What was the impact on society beyond science and technology?**

Nothing to report.
5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them.

Nothing to report.

Changes that had a significant impact on expenditures.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use of biohazards and/or select agents

Nothing to report.
6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”

- **Publications, conference papers, and presentations**
  
  Nothing to report.

- **Books or other non-periodical, one-time publications.**
  
  Nothing to report.

- **Other publications, conference papers, and presentations.**
  
  Nothing to report.

- **Website(s) or other Internet site(s)**
  
  Nothing to report.

- **Technologies or techniques**
  
  Nothing to report.

- **Inventions, patent applications, and/or licenses**
  
  Nothing to report.

- **Other Products**
  
  Nothing to report.
7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change.”

<table>
<thead>
<tr>
<th>Name:</th>
<th>Christine A. Iacobuzio-Donahue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Researcher Identifier:</td>
<td>orcid.org/0000-0002-4672-302</td>
</tr>
<tr>
<td>Nearest Person Month Worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Dr. Iacobuzio has overseen all sample processing and submission to the Genomics Core.</td>
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<table>
<thead>
<tr>
<th>Name:</th>
<th>Peter Allen</th>
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<tbody>
<tr>
<td>Project Role:</td>
<td>Co-Investigator</td>
</tr>
<tr>
<td>Researcher Identifier:</td>
<td>not available</td>
</tr>
<tr>
<td>Nearest Person Month Worked:</td>
<td>1</td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Dr. Allen has worked with Dr. Iacobuzio to select samples for initial submission to the Genomics Core.</td>
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<tr>
<th>Name:</th>
<th>Hitomi Sakamoto</th>
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<tr>
<td>Project Role:</td>
<td>Postdoctoral Fellow</td>
</tr>
<tr>
<td>Researcher Identifier:</td>
<td>not available</td>
</tr>
<tr>
<td>Nearest Person Month Worked:</td>
<td>6</td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Dr. Sakamoto has performed all genomic DNA extractions of all tissues, created a database of all samples to track their findings, and submitted the first batch of samples to the</td>
</tr>
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Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.
What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to https://ers.amedd.army.mil for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

Not applicable.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

None.