Cellular Localization of RAD51D Mutant Proteins and the Application of Art to Increase Scientific Literacy in America

Claire L. Chabot

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Cellular Localization of RAD51D Mutant Proteins and the Application of Art to Increase Scientific Literacy in America

By

Claire Lillian Marie Chabot

Submitted in Partial Fulfillment of the Requirements for Graduation with Honors from the South Carolina Honors College

May, 2019

Approved:

[Signature]
Dr. Douglas L. Pittman
Director of Thesis

[Signature]
Dr. Holly Crocker
Second Reader

Steve Lynn, Dean
For South Carolina Honors College
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“In purity and according to divine law will I carry out my life and my art.”

– The Hippocratic Oath (Hippocrates, 5th century B.C.)
Thesis Summary

When I first entered college, I scoffed at statistics that most students change their majors within their first year. There’s no way that I would be one of those people, I thought to myself, I have the next ten years of my life mapped out and nothing will get in the way of that. Little did I know how very, very wrong I was. My first semester as a pre-pharmacy student was spent pouring over every possible activity, and course, I could take to be ready for the intensive application process. Of those activities included attending meetings for the Carolina Association of Pre-Pharmacy Students (CAPPS). However, after extensive pharmacy shadowing I decided to no longer pursue a pharmacy degree but one of my friends convinced me to attend one last CAPPS meeting. It was here that I heard Dr. Doug Pittman speak about research linking chromosome integrity and potential chemotherapy targets in ovarian cancer genes. The future of personalized medicine drew me in. Once the meeting was over, I went right up to Dr. Pittman and asked if I could swing by sometime to see his lab. A week later, he gave me a tour of the lab, where I also met Dr. Nicole Reilly (then graduate student and one of my future mentors). I asked if it might be possible for me to come and work on a research project as an undergraduate. After discussing how many hours I would commit a week and other specifics, my training started! I’ve never considered myself to be an especially direct individual but I am truly glad that I took the risk in asking Dr. Pittman for an undergraduate research position.

When I initially decided to switch from pre-pharmacy to pre-medicine, I believed that doing research was a transient (but necessary) process that every
undergraduate should do to round out their application; I never believed that I would enjoy it too much. I never knew how much my time in the Pittman Laboratory would change my perspective on that. I soon found out that research requires patience, a lot of it. When I began in the lab, I didn't believe it when Dr. Pittman told me that research was “99% troubleshooting.” I thought he was joking until the entirety of the spring semester was spent trying to figure out why nothing was working despite my careful execution of established protocols. It was difficult not being able to dive right into a project but I understood why once I became somewhat independent with my own project. With the help of Dr. Pittman and Dr. Reilly, I decided on conducting localization studies of the RAD51D protein and correlating those results to the susceptibility observed in certain cancer patients to chemotherapeutics. As straight-forward as it would seem to simply follow the cloning procedures, seemingly pop the DNA into cells and snap some photos the process was never that streamlined. It wasn’t until a year and a half into my research project that I was finally able to visualize any data under a microscope, and it was one of the most rewarding things that I have done throughout my undergraduate career. Looking back it is satisfying to realize how much I have grown.

Research takes patience, research requires an independent mindset, and research certainly requires a creative mindset. This last part surprises most people including myself. But scientists are required to jump through a multitude of hoops before they even get a project started: creating the outline of their project, predicting results, and writing multiple grant proposals to be read by
different audiences. If someone had told me freshman year that I would be using these creative skills to also develop my data into an art project I probably would not have believed them. One rainy day between experiments though I found myself applying, albeit at the last minute, to the Honors College Artist in Residence Program. Somehow, my initial proposal was accepted and over the next few months I would meet with the project advisors and other artist to help develop my idea into something deeper than simply printing off my photos. Art, I discovered, can be used for advocacy and advocacy is very needed in the sciences these days with an abundance of fake facts floating around social media and an increasingly scientifically illiterate public.

Just as I have come to realize creativity is necessary for effective research, it is also beneficial to incorporate this trait into medical practices. Physicians treat dozens of patients every day and it is quite improbable any of those patients’ cases are carbon copies of each other; each case should be approached as an individual event. Not only is ingenuity and creativity required in the diagnosis and treatment of a patient but also the communication to establish the patient-physician relationship needed for effective treatment. The United States in particular is a melting pot of cultures and if I do practice medicine here, then I want to be able to incorporate the creative thinking I have developed in the Pittman laboratory into my future practice. There is no singular path to medical school but I feel as if I have been fortunate to having been able to have the Pittman laboratory as a part of my journey.
Abstract

Ovarian cancers are the leading cause of death from cancer of the female reproductive system. Approximately 50% of ovarian cancers have defects in the homologous recombination (HR) DNA repair pathway that is required for the repair of DNA double-stranded breaks. The status of HR genes, such as BRCA1, BRCA2, and the RAD51 family, contributes to ovarian cancer development as well as treatment decisions regarding chemotherapy, radiation, and immunotherapy. The overarching goal of this project is to identify new insights into HR that can integrate with Precision Medicine Initiatives and align with the goals of the Cancer Moonshot 2020 Program. I have hypothesized that specific RAD51D mutations disrupt RAD51D cellular localization since the absence of RAD51D from the nucleus is expected to increase DNA damage and chromosome instability. Mutant constructs were generated and fused to the Green Fluorescent Protein (GFP) gene so that fluorescent localization studies of RAD51D could be conducted. The data were quantified to determine if the protein constructs were localized to the nucleus or the cytoplasm. In this paper, the lysine to arginine mutant K298R was analyzed and compared to RAD51D WT. Current data suggest that RAD51D-K298R appears to have a statistically significant decrease of GFP expression in the cytoplasm compared to WT. In future experimentation, transfected cells will be treated with DNA crosslinking agents to determine the effect on RAD51D localization. If the mutated regions along the RAD51D protein alter localization in either the cytoplasm or nucleus,
they can provide a potential target site to block RAD51D function and sensitize or re-sensitize cells to chemotherapeutic agents.

With my cross-disciplinary art project, I want to spread awareness and understanding of how the genetics of ovarian cancer works as it is the fifth most prevalent cancer amongst women and, according to the American Cancer Society, women have a one in seventy-five chance of being diagnosed with ovarian cancer during their lifetime. I want to engage people in scientific research whom may not be otherwise interested in it; to show others that there can be beauty in laboratory research work and that it is not just pipetting and statistics. When examined closely, we can see the universe everywhere, even under a microscope. Each piece in my work has been named after historical or contemporary female scientists who I find extremely fascinating or have influenced me personally. I chose to do this not only to represent women in science but also to represent the female population that is heavily impacted by ovarian cancer.
Introduction

Over the past four years, this thesis project developed into something more than my work at the lab bench. As a result, I have divided this undergraduate honors thesis into two parts: one centering on the localization studies of RAD51D and the second, a cross-disciplinary art project I created with the Honors College. Until now, science and art have existed as separate entities to me but in bridging them, a new platform of communication can be achieved. Throughout this thesis, I will explain not only the importance of the genetic research being conducted in the Pittman Laboratory but I will also illustrate through art the significance of creating a forum for discussion that almost anyone can relate to and its potential impact on scientific literacy in the United States.

It is estimated that over the past several years that there have been 12.3 new cases of ovarian cancer per 100,000 women per year, and 7.9 of these cases will result in death.1 Risk for ovarian cancer, along with many other cancers, is increased if a patient has a mutation in certain genes, especially the DNA repair genes RAD51D, BRCA1, and BRCA2.2,3 Studies show that at least fifty percent of patients with high grade serous ovarian cancer have mutations in DNA repair genes.4 The protein encoded by the RAD51D gene is vital for the repair of DNA double strand breaks (DSBs) through the homologous recombination (HR) pathway. Cells that do not express RAD51D have high levels of chromosome instability and are hypersensitive to DNA damaging agents (Figure 2).5 Previous work in the Pittman laboratory identified a direct interaction
between RAD51D and an E3 ubiquitin ligase, RNF138. RNF138 promotes ubiquitination of RAD51D, a modification that typically occurs along lysine residues, and two specific lysine residues – K235 and K298 - along RAD51D are required for cell survival in response to DNA damage. A possible mechanism for the sensitivity is disruption of nuclear localization of the RAD51D protein. The importance of the lysines being observed, K235 and K298, comes from previous studies that demonstrated how a mutation at these lysine residues confer sensitivity to DNA crosslinking agents (see Figure 1).

Figure 1. A RAD51D schematic shows the positions of the lysine residues. The lysine residues in bold were used to generate RAD51D-EGFP constructs. Lysine to arginine substitutions K298R and K235R is suggested to express hypersensitivity to chemotherapeutics in ovarian cancer patients. The domains shown include the Walker Box motifs and a helix-hairpin-helix motif.
The localization of RAD51D lysine mutants is performed to help understand whether these mutations cause the RAD51D protein to be absent in the cells’ nuclei. These mutants would eventually result in cell death after being treated with DNA damaging agent. This would occur from a failure in inter-strand cross-link repair. An important impact of studying RAD51D mutations is that they provide insight into mechanisms that can potentially provide alternate paths to disrupt cancer cell division. This certainly makes it an area of science that deserves attention. Over the course of this project, my research work was presented twice at Discover USC (2017 and in 2018) where it was awarded 2nd
place in the Biological Sciences in 2018, at the National Conference for Undergraduate Research in Edmonton, Oklahoma (2018), and Posters on the Hill on Capital Hill in Washington D.C. (https://www.cur.org/what/events/students/poh/) where I represented USC and South Carolina to discuss support for undergraduate research work with congressional representatives (2019).

Yet, how did these studies translate into an art project?

As important as it is to submit abstracts to scientific conferences and explain the research in terms relevant to the biological sciences community, I find myself explaining this project more often in layman's terms to my non-science friends and family. My passion for this research compelled me to tell more and more people about it as these past three years in the Pittman Laboratory have flown by. What began the bridging of science and art in my research project, however, was when I observed the fluorescing images under a microscope and thought them to be beautiful. It was more than just data; the images were stunningly exquisite. Once the Honors College opportunity for the Artist in Residence Program appeared, I decided to take advantage of it in order to express my thoughts to a broader audience. Each of the images I constructed were then lasered onto glass to not only create a glossy appearance but also a more interactive exhibit as the viewer can see the image along with a reflection of themselves. My ultimate goal is to engage people in scientific research that may
not otherwise be interested and to show others that there can be beauty in lab work.

Over the course of this project, the art work was presented at the Artist in Residence Gallery in the USC Honors College, the National Conference for Undergraduate Research (2018) in Edmonton, Oklahoma, Discover USC (2018) where it was awarded 1\textsuperscript{st} place in Arts and Humanities, and Posters on the Hill on Capital Hill in Washington D.C. Most of this section of the Honors Thesis was published in Caravel, an undergraduate research journal for USC students.
Materials and Methods

*Site Directed Mutagenesis*\(^7\)

Specific mutagenesis with lysine to arginine codon substitutions was performed at the RAD51D 235 and 298 sites. The previously made K235R and K298R mutants were cloned into a pEGFP expression vector using *KpnI* and *BamHI* restriction enzymes for a double enzyme digest. This fusion of the pEGFP to the lysine mutants created an in-frame EGFP fusion protein verified by DNA sequence analysis. This fusion protein allowed for the visualization of the RAD51D protein within the cell and for the determination of RAD51D localized in the cell.

*Mammalian Cell Transfection*\(^8\)

Mouse embryonic fibroblasts (MEFs) and HeLa cell lines were maintained at 37°C with 5% CO\(_2\) in Dulbecco’s Modified Eagle’s Medium (DMEM; HyClone) supplemented with 10% newborn calf serum (Atlanta Biologicals), 1% penicillin/streptomycin, and 1% glutamine. The MEF cell line used was MEF258 (*Rad51d*\(^{-/}\) *Trp53*\(^{-/}\)). Plasmid constructs were transfected using Lipofectamine Reagents (Invitrogen) or Mirus TransIT-LT1 according to manufacturer’s instructions.

*EVOS Microscope*

Twenty-four hours post-transfection, the cells’ nuclei were stained with 4',6-diamidino-2-phenylindole (DAPI), and detection was performed using an EVOS
microscope (See Figure 3). Images of the EGFP detection of the RAD51D protein were captured first. Next, images of the DAPI staining that was done to locate the nucleus of the cell were capture. Finally, an overlay of the two images was created.

Figure 3. EVOS Microscope in Dr. Jason Stewart’s research laboratory used to take photos of the GFP fluorescent cells.

Processing of overlayed images using ImageJ

The photos were processed using ImageJ and the program would automatically select the DAPI stained nuclei. An Intuos Touch Tablet (Wacom) was then used to draw around the cytoplasm so that data could be analyzed as well. The cytoplasm and nucleus were selected using the free-hand loop tool. In the selected areas, the number of GFP pixels were quantified in ImageJ (https://imagej.net/Welcome) and recorded in an excel sheet. The background of
the image was also measured for GFP pixel detection and this number was subtracted from the total cytoplasm and nucleus results to ensure the quality of the data. The Chi Squared test was used to determine statistical significance.
Results & Discussion

This section is divided into the Research Project and the Art Project. The research project will be discussed first and will outline the generation of the constructs, transformation, and image analysis. The art project will further discuss the use of cross-disciplinary mediums to convey complex scientific topics and the historic and contemporary importance of women in science.

Research Project

1. Generating the constructs

The first goal was to insert the cloned RAD51D lysine mutants into EGFP expression vectors. The previously made K235R and K298R mutants made through site-directed mutagenesis were cloned into a pEGFP expression vector using KpnI and BamHI restriction enzymes (Figure 4). This fusion of the pEGFP to the lysine mutants created an EGFP fusion protein. This fusion protein allowed for the visualization of the RAD51D protein within the cell and the determination of RAD51D localized to the nucleus and the cytoplasm. Figure 4 displays the WT RAD51D cut in a double enzyme digest using BamHI and KpnI. A double enzyme digest using the enzymes KpnI and BamHI was successfully performed in order to excise the RAD51D fragment. These validity of the constructs’ and WT’s presence were then tested through double enzyme digests (Figure 5 and 6) and DNA sequence analysis (Figure 7).
Figure 4. Experimental design to clone RAD51D (wild type and mutant) using the restriction enzymes *KpnI* and *BamHI* into a pEGFP vector.

Figure 5. Gel electrophoresis was used to excise fragments of RAD51D WT and the K298R lysine mutant. Both were digested using *KpnI* and *BamHI*. The fragments were located at 981 base pairs, indicated by the arrow.
Figure 6. Agarose gel of RAD51D-WT-EGFP in a pEGFP vector after *KpnI/BamHI* double digest. Lane 1 – 1Kb DNA Ladder, Lane 2 – RAD51D WT uncut control, and Lane 3 – RAD51D-WT-EGFP clone. The confirmation of the clone is a 981 base pair fragment indicated by the arrow.

Figure 7. This is a chromatogram of RAD51D K298R-EGFP sequence. Top image is a four-colour chromatogram that shows the results of the sequence run. The different base pairs are designated their own colour: green for A, black for G, red for T, and blue for C. This illustrates the overall quality of the data obtained from the sequencing. The evenly spaced peaks with minimal baseline noise exhibit good quality data. The bottom sequence confirms the lysine to arginine point mutation of K298R. The single letters represent amino acids in the genetic code and the black dot is where the point mutation was successfully introduced.

2. Measuring RAD51D-EGFP cellular localization

To determine if lysine substitution affects RAD51D localization, the constructs were expressed in mouse embryonic fibroblasts (MEFs) that were *Rad51d-*
deficient and HeLa cells. Fluorescence microscopy was then used to detect the localization of each construct. Using lipofectamine, each construct was transiently expressed in the MEFs. The DAPI stained nuclei of the cells fluoresced blue and the RAD51D-EGFP proteins fluoresced green. To detect localization within the nucleus, the overlay image of the stained nuclei and the EGFP-tagged proteins were merged. In Figure 8, the nuclear localization of RA5D51D-WT is demonstrated with different staining techniques in MEFS cells.

![Figure 8](image)

**Figure 8.** These images represent the detection of RAD51D-EGFP in *Rad51d-deficient* MEFs and HeLa cells. *Rad51d*<sup>−/−</sup> MEFs and HeLa cells were used for the transfection. Twenty-four hours post-transfection, the cells were stained with DAPI, and detection was performed using an EVOS microscope. The image on the left presents the EGFP detection of the RAD51D protein. The center image represents the DAPI staining that was done to locate the nucleus of the cell while the image on the right represents overlay of the two images.
**Figure 9.** The images and graphs above represent the detection of RAD51D-EGFP in *Rad51d-deficient* MEFs. Pixel analysis was done using the NIH-ImageJ program. Using a Wacom drawing tablet, the cytoplasm and nucleus were selected and the number of GFP pixels were quantified in ImageJ. The GFP pixel count inside and outside the nucleus were quantified and added to this graph. Background was subtracted from the final pixel count.

<table>
<thead>
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<th>WT Trial 1</th>
<th>K298R Trial 1</th>
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<tr>
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<tr>
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<td><strong>Avg Nucleus</strong></td>
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<tr>
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</table>
Figure 10. Shown here is a sample of the calculations performed using the number of GFP pixels collected through ImageJ (subtracting background noise) and comparing the cytoplasm to the nucleus of the different trials.

3. Conclusions

I have generated and confirmed RAD51D-EGFP and mutant fusion constructs. Current data suggests that compared to RAD51DWT, K298R appears to have a statistically significant decrease of GFP expression in the cytoplasm compared to WT. In future experimentation, transfected cells will be treated with DNA crosslinking agents to determine the affect on RAD51D localization.
Cross-Disciplinary Discussion

The work described below was previously published in USC’s undergraduate research journal *Caravel*. The manuscript was titled “The Universe Under a Microscope.” And is available at the following website:

https://sc.edu/about/offices_and_divisions/research/news_and_pubs/caravel/archive/2019/2019_microscope.php

My ultimate goal is to engage people in scientific research that may not otherwise be interested and to show others that there can be beauty in lab work. It is not just statistics and pipetting. Art is an accessible way to communicate with broad groups of people, and this is one of the reasons I chose this medium. Taking the project a step further, each piece in my work has been named after historical or contemporary female scientists I find extremely fascinating or have personally influenced me. I chose to do this not only to represent women in science but also to represent the female population heavily impacted by ovarian cancer. When examined closely, we can see the universe everywhere, even under a microscope.

The importance of this art project stems beyond the need for the transparency of female contributions to science, it extends to the need for ethical and responsible visual scientific communication. There has always been a strong focus on increasing scientific literacy within the general population. In 2015, however, students in the United States ranked 24th out of 71 countries in scientific literacy. What’s important to remember as well is that not all students
learn the same way, so understanding how to reach a larger group of people is important. To gain public support for genetic cancer research, it is important that the general population has a solid grasp of science, as ignorance can lead to fear, and fear of the unknown is dangerous to the advancement of science.

As important as it is to have ethical and responsible scientific communication, I believe that it is equally important to have a deeper artistic meaning to draw in the public. To me, it seems almost improbable that empirical data can ever translate into an emotional understanding of the human experience with illness. How other people process their diagnosis and disease is very subjective to the individual, and how people process art is equally subjective. With this in mind, I wanted to bridge this subjective experience with the objective experience of research. When this gap can be bridged is when we can finally connect the importance of ovarian cancer research to the general public, even to those who may not have directly been affected by cancer. I think art has the capacity to reach that higher level of understanding by bringing out emotions in the viewer, depending upon how they respond to the contrasting colours and mutated cells. In her book “Illness: The Cry in the Flesh”, Dr. Havi Carel discusses how the medical field should not be objective about the human experience with illness; that to empathize as well with the sick person’s first-person subjective experience with the living body. This, I believe, is often lost on the side of the scientific researcher, and creating an artistic platform for easier communication will reinforce the importance of their work and how it reflects upon those individuals the scientists are striving to help.
The naming of each piece after contemporary and historical female scientists was also an important aspect of this project. This was done for two reasons: to highlight the importance of their work and contribution to scientific research or because of their influence towards me becoming the researcher that I am today. Two of the more contemporary female scientists are Dr. Nicole Reilly and Lana Hatt (the former being a previous graduate student in the Pittman Laboratory and the latter being my Mother). For three years of my undergraduate research experience, Dr. Reilly (Supplemental material, Figure 1) trained me and encouraged my ambitions inside and outside the research laboratory. Currently, Dr. Reilly is a Postdoctoral Research Fellow at the Candiolo Cancer Institute in Italy and is absolutely thriving in her position. As for my Mother (Supplemental material Figure 2), ever since I began to express my curiosity for the world around me as well as different areas of science, she has encouraged me to pursue my passions. She worked extremely hard to put herself through college and graduated from Acadia University (Nova Scotia, Canada) with a major in Biology and a minor in Chemistry. I have always admired her resilience and passion for the sciences, and those are traits that she has passed down to myself, making me who I am now becoming. My Mother’s unwavering support through my decisions to major in Biochemistry and Molecular Biology as well as focus on medical school as my career choice is something I will be forever grateful.

Four other female scientists are included in this project: Hypatia of Alexandria, Marie Curie, Rosalind Franklin, and Barbra McClintock. These
women were chosen to represent my art not just because of the importance of their scientific contributions but also because of the historical significance the advancements brought about. Hypatia of Alexandria (Supplemental material Figure 3) was a phenomenal mathematician, scientist, and philosopher in Egypt who was an extremely educated woman. With the three art pieces named after her, I wanted to represent her tragic murder by a mob of Christians in the streets of Alexandria. The more that her life progressed, the more intense the series of colours used in the series with an eventual eruption of orange, yellows, and reds. Marie Curie (Supplemental material, Figure 4.) sacrificed her health to discover radiation and its properties. Amongst many other awards, Dr. Curie’s establishment as a Nobel Prize winner in Physics in 1903 was historically important as she was a woman in her field. I have always been equally fascinated by her work since reading about her, wanting to connect her to my research as the “RAD” in RAD51D stands for radiation. Rosalind Franklin (Supplemental material, Figure 5) and Barbra McClintock (Supplemental material, Figure 6.) also generated leaps and bounds in the field of genetics that led to modern day clinical applications and diagnostics. Franklin’s photographs of the structure of DNA laid the foundation for the understanding of modern genomics. Without her work in the field Watson and Crick could not have come to the scientific conclusions that won them the Nobel Prize after her death. I have always found it a shame that she was not included in the Nobel Prize posthumously and it is equally tragic that she passed from ovarian cancer. However, this further links Franklin to my research and art project and another
reason why I wanted to include a piece named after her. Barbra McClintock, however, was awarded the Nobel Prize in Physiology and Medicine for her discovery of “jumping genes.” These transposable elements eventually led to the development of the revolutionary CRISPR-Cas9 system currently being used for tailoring genomes just as Dr. Jennifer Doudna pioneered.

There may be many ambitious points to this project yet, it was my intent to create something that everyone could learn from. Not just cancer patients, not just ovarian cancer researchers but something for everybody. If anyone has viewed this project and taken away a new piece of information, a new understanding or appreciation for cancer research or empathy for cancer patients, I have then accomplished my goal of humankind to see “The Universe Under a Microscope.”
Acknowledgements

I want to especially thank my Mom, Dad, and Sister for supporting me throughout my undergraduate career; I could not have graduated and completed this project without them. This project was made possible under the tutelage of Dr. Douglas Pittman and Dr. Nicole Reilly. Special thanks to Dr. Ed Munn Sanchez and Olaf Toffleson in the AIR program as well as Dr. Jason Stewart for lending me the EVOS microscope. Funding was provided through the National Institutes of Health under Award Number R15GM110615, the Magellan Research Grant, the SURF Grant, the USC Honors College Senior Thesis Grant, the Foley Thesis Project Grant, the USC Honors College Artist in Residence Program, and the USC Honors College Travel Award. My research has previously been presented at the Artist in Residence Gallery in the USC Honors College, the National Conference for Undergraduate Research (Edmonton, Oklahoma), Discover USC, and Posters on the Hill on Capital Hill in Washington D.C.
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Supplementary Figures

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Figure 5. Franklin
Figure 6. McClintock