The role of neural stem cells in cerebellar development, regeneration and tumorigenesis

Reporting Period: Year 1

The goal of our studies is to determine the role of neural stem cells in the development, regeneration and tumor formation in the cerebellum. By understanding the role of stem cells, we hope to learn to use them for repair of neurological damage and to develop more effective treatments for patients with brain tumors. The aims of our studies are: (1) To identify the cell types generated by cerebellar stem cells during normal development; (2) To determine the capacity of cerebellar stem cells to repair damage caused by radiation or disease; and (3) To determine whether cerebellar stem cells can give rise to the pediatric brain tumor medulloblastoma. We have made significant progress toward our goals over the last year. In particular, we have identified genetic markers that allow us to trace the fate of cerebellar stem cells during normal development. In addition, we have demonstrated that cerebellar stem cells carrying cancer-causing genes can give rise to medulloblastoma. Importantly, this finding has allowed us to create stem cell-based models of medulloblastoma that can be used to test drugs that may be useful for treating the disease. Over the next few years, we hope to use this information to develop more effective therapies for children suffering from medulloblastoma.

Reporting Period: Year 2

The goal of our studies is to determine the role of neural stem cells in the development, regeneration and tumor formation in the cerebellum. By understanding the role of stem cells, we hope to learn to use them for repair of neurological damage and to develop more effective treatments for patients with brain tumors. The aims of our studies are: (1) To identify the cell types generated by cerebellar stem cells during normal development; (2) To determine the capacity of cerebellar stem cells to repair damage caused by radiation or disease; and (3) To determine whether cerebellar stem cells can give rise to the pediatric brain tumor medulloblastoma. We have made significant progress toward our goals over the last year. In particular, we have identified genetic markers that allow us to trace the fate of cerebellar stem cells during normal development. In addition, we have demonstrated that cerebellar stem cells carrying cancer-causing genes can give rise to medulloblastoma. Importantly, this finding has allowed us to create stem cell-based models of medulloblastoma that can be used to test drugs that may be useful for treating the disease. Our screening efforts over the past year have begun to identify compounds that inhibit the growth of human medulloblastoma tumor cells. Over the next few years, we hope to use this information to develop more effective therapies for children suffering from medulloblastoma.

Reporting Period: Year 3

The goal of our studies is to determine the role of neural stem cells in development, regeneration, and tumor formation in the cerebellum. By understanding the role of stem cells, we hope to learn to use them for repair of neurological damage and to develop more effective treatments for patients with brain tumors. We have made significant progress towards our goals during the past year. We have identified new drugs that potently inhibit the growth of medulloblastoma, the most common malignant brain tumor in children. This work could lead to development of new, more effective therapies for medulloblastoma in patients. In addition, we have developed new models for several types of brain tumors, including one that resembles the most aggressive form of medulloblastoma, and several that model choroid plexus tumors. These models are valuable resources for studying the biology and therapeutic responsiveness of these diseases. Over the next few years, we will continue in our efforts to develop more effective therapies for children suffering from aggressive brain tumors.

Reporting Period: Year 4

The goal of our studies is to elucidate the role of neural stem cells in development, regeneration, and tumor formation in the
cerebellum. By understanding the role of stem cells, we hope to learn to use them for repair of neurological damage and to
develop more effective treatments for patients with brain tumors. We have made significant progress towards our goals in the past
year. Using animal models developed in our lab, we have uncovered new mechanisms and pathways that drive the growth and
metastasis of medulloblastoma, the most common malignant brain tumor in children. In addition, we have identified molecular
pathways that are de-regulated in choroid plexus carcinoma, a rare brain tumor with a poor prognosis that occurs most frequently
in children. Our work has also led to the identification of new drugs that inhibit the growth of medulloblastoma and choroid plexus
carcinoma. In the coming year, we will continue in our efforts to understand these aggressive cancers and develop new, more
effective therapies for children who suffer from them.

Reporting Period: Year 5

The goal of our studies is to elucidate the role of neural stem cells in development, regeneration, and tumor formation in the
cerebellum. By understanding the role of stem cells, we hope to learn to use them for repair of neurological damage and to
develop more effective treatments for patients with brain tumors. We have made significant progress towards our goals in the past
year. Using animal models developed in our lab, including those that propagate patient-derived primary tumors, we have
uncovered new mechanisms and pathways that drive tumor growth and metastasis. In addition, we have identified pathways that are altered in choroid plexus carcinoma, another rare and frequently lethal pediatric brain tumor. Finally, by using tumor cells to screen
thousands of drugs, we have identified therapeutic agents that may be effective against medulloblastoma and choroid plexus
carcinoma, and are testing them in our models of these diseases. In the coming year, we will continue in our efforts to understand
these aggressive cancers and develop new, more effective therapies for children who suffer from them.

Reporting Period: Year 6

The goal of our studies is to elucidate the role of neural stem cells in development, regeneration, and tumor formation in the
cerebellum. By understanding the role of stem cells, we hope to learn to use them for repair of neurological damage and to
develop more effective treatments for patients with brain tumors. During the last year, we have made important progress in several
areas. Using animal models of medulloblastoma, the most common malignant brain tumor in children, we have uncovered new
mechanisms and pathways that drive tumor growth and metastasis. In addition, we have identified pathways that are altered in
choroid plexus carcinoma, another rare and frequently lethal pediatric brain tumor. Finally, by using tumor cells to screen
thousands of drugs, we have identified therapeutic agents that may be effective against medulloblastoma and choroid plexus
carcinoma, and are testing them in our models of these diseases. In the coming year, we will continue in our efforts to understand
these aggressive cancers and develop new, more effective therapies for children who suffer from them.

Reporting Period: Year 7 NCE

The goal of our studies has been to elucidate the role of stem cells in development, regeneration and tumorigenesis in the
cerebellum. We have made significant progress towards this goal during the course of our work. Our studies have provided
insight into the types of cells derived from cerebellar stem cells during development, and shown that cerebellar stem cells can
serve as cells of origin for pediatric brain tumors. Moreover, we developed several new stem cell-based animal models of pediatric
brain tumors, and used them to study mechanisms driving tumorigenesis and metastasis. Importantly, we also used these models
to screen for compounds that might be effective inhibitors of tumor growth, and identified a number of promising candidates. Our
long-term goal is to move these agents toward clinical trials, to improve outcomes for pediatric brain tumor patients.

The role of neural stem cells in cerebellar development, regeneration and tumorigenesis

Grant Type: Research Leadership

Grant Number: LA1-01747
Project Objective: To understand the role of neural stem cells in cerebellar development, regeneration and tumorigenesis. The proposed studies approach the above goal through multiple strategies which trace the fate of cerebellar stem cells and determine their role in regeneration of normal tissue and in the development of brain tumors.

Investigator:

<table>
<thead>
<tr>
<th>Name</th>
<th>Robert Wechsler-Reya</th>
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</thead>
<tbody>
<tr>
<td>Institution</td>
<td>Sanford-Burnham Medical Research Institute</td>
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<tr>
<td>Type</td>
<td>PI</td>
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</tbody>
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Disease Focus: Brain Cancer, Cancer, Solid Tumors

Cell Line Generation: Cancer Stem Cell

Award Value: $5,226,049

Status: Closed

Application Title: The role of neural stem cells in cerebellar development, regeneration and tumorigenesis

Public Abstract: Stem cells have the remarkable ability to renew themselves and to generate multiple different cell types. This allows them to generate normal tissues during development and to repair tissues following injury, but at the same time, renders them highly susceptible to mutations that can result in cancer. Only by understanding the signals that control growth and differentiation of stem cells can we learn to harness their regenerative capacity and restrain their malignant potential. The research described in this proposal is aimed at elucidating the role of neural stem cells in development, regeneration and tumor formation in the cerebellum. Our previous studies identified a population of neural stem cells in the developing cerebellum. We now propose to use genetic approaches to mark these cells and identify the cell types that they generate during normal development. In addition, we plan to examine the capacity of these cells to regenerate the cerebellum following radiation. Finally, we propose to study the ability of these cells to give rise to brain tumors, and use the models that result from these studies to develop and test novel approaches to therapy. These studies will pave the way towards use of stem cells for repair of neurological damage and help develop more effective treatments for patients with brain tumors.
Statement of Benefit to California:

We have previously identified a novel population of neural stem cells in the cerebellum. This proposal is focused on understanding the role of these cells in normal development, regeneration and tumor formation. It has the potential to benefit California in a number of important ways.

1. Treatment of Brain Damage: Radiation is the most commonly used treatment for brain tumors, and children who receive this treatment often suffer severe side effects, including a progressive loss of intellectual function. By studying the ability of cerebellar stem cells to repair brain tissue, we will advance the treatment of patients suffering from brain damage due to radiation therapy. The knowledge we gain may also be more broadly applicable, advancing the use of stem cells to repair damage due to congenital brain disorders, trauma and stroke.

2. Treatment of Brain Tumors: Medulloblastoma and astrocytoma are the most common brain tumors in children. By examining the role of stem cells in development of these tumors, we will deepen our understanding of how brain tumors form, and develop novel approaches to treating them. Moreover, we will create new model systems that can be used to test these therapies, with the hope of moving the most effective ones forward towards trials in patients.

3. Technology: Our research will culminate in the invention and generation of new drugs and approaches to therapy that will be made available for licensing by the academic institutions in California, such as [REDACTED] and its collaborators, and developed by pharmaceutical companies based in the State.

4. Collaboration: Our work is multidisciplinary and translational in nature. As such, it will require collaboration with other investigators, including stem cell biologists, neurobiologists, cancer biologists and chemists involved in experimental therapeutics. Once discoveries are made that may be of benefit to patients, we will also work with clinicians to move these discoveries towards the clinic. Californians will be the likely first beneficiaries of these therapies because the clinical trials will be conducted here and we will make an effort to make sure that Californians have immediate access to these therapies when they become standard. By bringing together investigators from various fields and focusing their attention on clinically relevant problems, our studies will advance the translational potential of stem cell research in California.

Source URL: https://www.cirm.ca.gov/our-progress/awards/role-neural-stem-cells-cerebellar-development-regeneration-and-tumorigenesis