Communicating Research to the General Public

At the March 5, 2010 UW-Madison Chemistry Department Colloquium, Prof. Bassam Z. Shakhashiri, the director of the Wisconsin Initiative for Science Literacy (WISL), encouraged all UW-Madison chemistry Ph.D. candidates to include a chapter in their Ph.D. thesis communicating their research to non-specialists. The goal is to explain the candidate's scholarly research and its significance to a wider audience that includes family members, friends, civic groups, newspaper reporters, program officers at appropriate funding agencies, state legislators, and members of the U.S. Congress.

Over 50 Ph.D. degree recipients have successfully completed their theses and included such a chapter.

WISL encourages the inclusion of such chapters in all Ph.D. theses everywhere through the cooperation of Ph.D. candidates and their mentors. WISL is now offering additional awards of $250 for UW-Madison chemistry Ph.D. candidates.

Wisconsin Initiative for Science Literacy

The dual mission of the Wisconsin Initiative for Science Literacy is to promote literacy in science, mathematics and technology among the general public and to attract future generations to careers in research, teaching and public service.

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Finding the bottleneck in brain rejuvenation: mechanisms underlying neural stem cell quiescence exit

By

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A dissertation submitted in partial fulfillment of

the requirements for the degree of

Doctor of Philosophy

(Molecular and Cellular Pharmacology)

at the

UNIVERSITY OF WISCONSIN-MADISON

2021

Date of final oral examination: 6/29/2021

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Chapter 6

Chapter 6: Non-Scientist Accessible Summary of Thesis for the Wisconsin Initiative for Science Literacy

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6.1 Preface

The Wisconsin Idea suggests that every citizen should have the opportunity to learn about publicly funded research happening in Wisconsin. To this end, the Wisconsin Initiative for Science Literacy provides an annual award for PhD thesis chapters that are written to convey research to a non-science audience. Over the past 5 years I have been a graduate student working at the University of Wisconsin-Madison in the Department of Neuroscience in a stem cell biology laboratory. During this time I have contributed to the effort to help us live longer, healthier, happier lives by studying brain stem cells in a mouse. My predominant tasks were to 1) learn how to be an effective scientist, and 2) learn new things about how life works. In Chapter 6, I will convey my experiences to a non-scientist audience by discussing a couple of key experiments which illustrate some of the work I completed in graduate school. First I will provide an introduction to the topic I have been focused on in graduate school – brain stem cell aging. I will then discuss an example of experiments I performed to help us understand how to improve brain stem cell aging. Lastly, I will speculate next steps suggested by my findings.

6.2 An effort to live a long, healthy life

Is aging inevitable? Could we stop, or even reverse aging? Although people throughout history have strived to find the fountain of youth, up until only a few decades ago, these questions seemed so hard to answer that many scientists thought it was futile to even try. It wasn't until scientists discovered that you could make worms live as much as ten times longer by changing just one out of their roughly twenty thousand genes that people started to see aging as a process that we could control. While thinking about aging can seem depressing, by the time you finish reading this chapter I hope to convince you that it is well within our power to improve human aging and that human aging is emerging as one of the greatest biological and socioeconomic challenges of our time.

While living forever may on occasion seem attractive, there are several far more important reasons to study aging that have more practical applications. As modern medicine and technology has boomed over the past century, people are living longer than ever, but the gained years aren't the healthiest. As you get older, your risk of getting many major diseases increases, such as many types of cancer (Lopez-Otin et al., 2013). Modern medicine and public health has extended human lifespan (the number of years before dying), but has failed to comparably extend human healthspan (the number of years without being riddled by ailments). Thus, we are creating epidemics of age-related diseases with enormous social and economic consequences (Spector, 2018). If left unaddressed, the aging population will become a significant burden for future generations. Further, as your risk for getting most major diseases increases as you get older, aging provides a unique opportunity to understand many diseases at the same

time. If we can understand why you are at higher risk for these diseases as you age, we could make progress towards tackling all of these diseases simultaneously.

Studying aging in a comprehensive way is challenging due to the complexity of the aging process. Many things change as you age, such as your hair turning grey and your muscles weakening, and figuring out which things are causing you to age versus things that are just an effect of the aging process can be difficult. To make an effective dent, we had to narrow our focus to tangible goals. Our research group focused on one component of aging: stem cell aging (Lopez-Otin et al., 2013). Your body is composed of many different types of components, one of which is something called a cell. **Cells** are units of life that are responsible for "doing" things to keep your body functioning optimally. For example, you have red blood cells that travel through your blood to deliver oxygen from the air to different parts of your body. Your body has hundreds of different types of cells that all have different jobs that all function together in a coordinated system to make you who you are. **Stem cells** are cells in your body that have the potential to create many different types of cells in your body and to effectively regenerate select parts of your body. While stem cell activity largely declines after our childhood, adult humans still have stem cells in at least a dozen spots. The problem is that, as we age, the ability of stem cells to properly support us diminishes (Boyette and Tuan, 2014). Thus, many scientists are interested in trying to understand if rejuvenating adult stem cells throughout the body could be an effective strategy to slow, stop or even reverse aging.

Our group is interested in aging and stem cell aging broadly, but more specifically we are most interested in stem cells in the brain, called **neural stem cells** (which I will refer to here as **brain stem cells**). Brain stem cells are a cell type in the brain with the

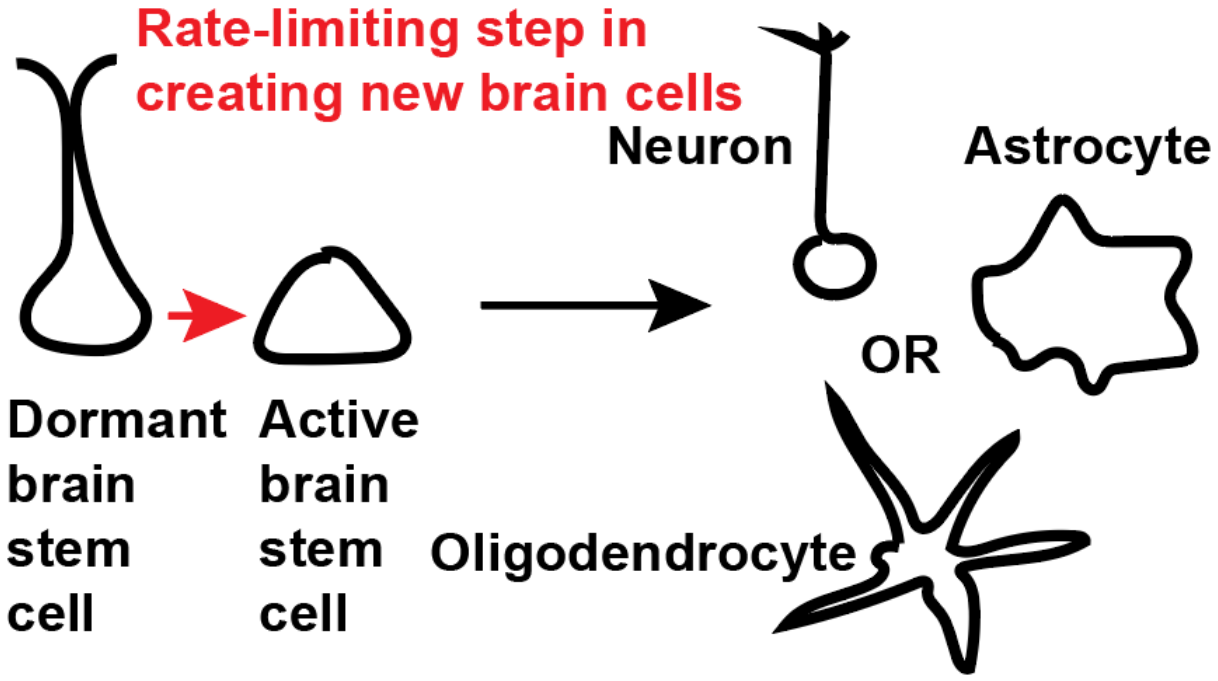

Figure 6.1 *– Schematic depicting how brain stem cells create new brain cells. White shapes outlined in black represent different cells. To make a new brain cell type, such as a neuron, astrocyte, or oligodendrocyte, dormant brain stem cells must first activate and become activated brain stem cells and then continue to mature into a specified brain cell type, such as the types of cells listed on the right. We think that a rate-limiting step in the production of new brain cells in adults is in the ability of dormant brain stem cells to become activated.*

capacity to make new brain cells. (Fig. 6.1) (Goncalves et al., 2016). The problem is that brain stem cells are largely dormant when you are an adult and are not producing new brain cell types at a rate which could substantially repair your brain when your brain would need them most (Kalamakis et al., 2019, Ibrayeva et al., 2021). For example, Alzheimer's Disease results, in part, from the destruction of brain cells (Cummings et al., 2014). Currently there are no effective ways to treat Alzheimer's Disease. If we could figure out how to help brain stem cells be more active we could potentially figure out ways to improve the prognosis for Alzheimer's Disease patients. Thus, many scientists such as myself have been focused on trying to understand how to make dormant brain stem cells become more active. To this end, I study brain stem cells in mice and brain stem cells in a petri dish that originate from mice and focus on trying to find ways to get them to be more active (Fig. 6.2).

During my time at the University of Wisconsin-Madison I learned many new things about brain stem cells. To convey a sample of what I learned, here I will discuss a few key experiments from one of the projects I completed where I found that brain stem cells use a cellular garbage can called the aggresome to keep themselves clean and leave the dormant state to make new brain cells and promote healthy aging.

6.3 A cellular garbage can that makes brain stem cells more efficient

In 2018, scientists found that dormant brain stem cells accumulate cell junk called protein aggregates and that they have to get rid of this junk to become activated and begin to make new brain cells (Leeman et al., 2018). Cells have many ways to get rid of junk. Therefore, we wanted to see if experimenting with different ways that cells have

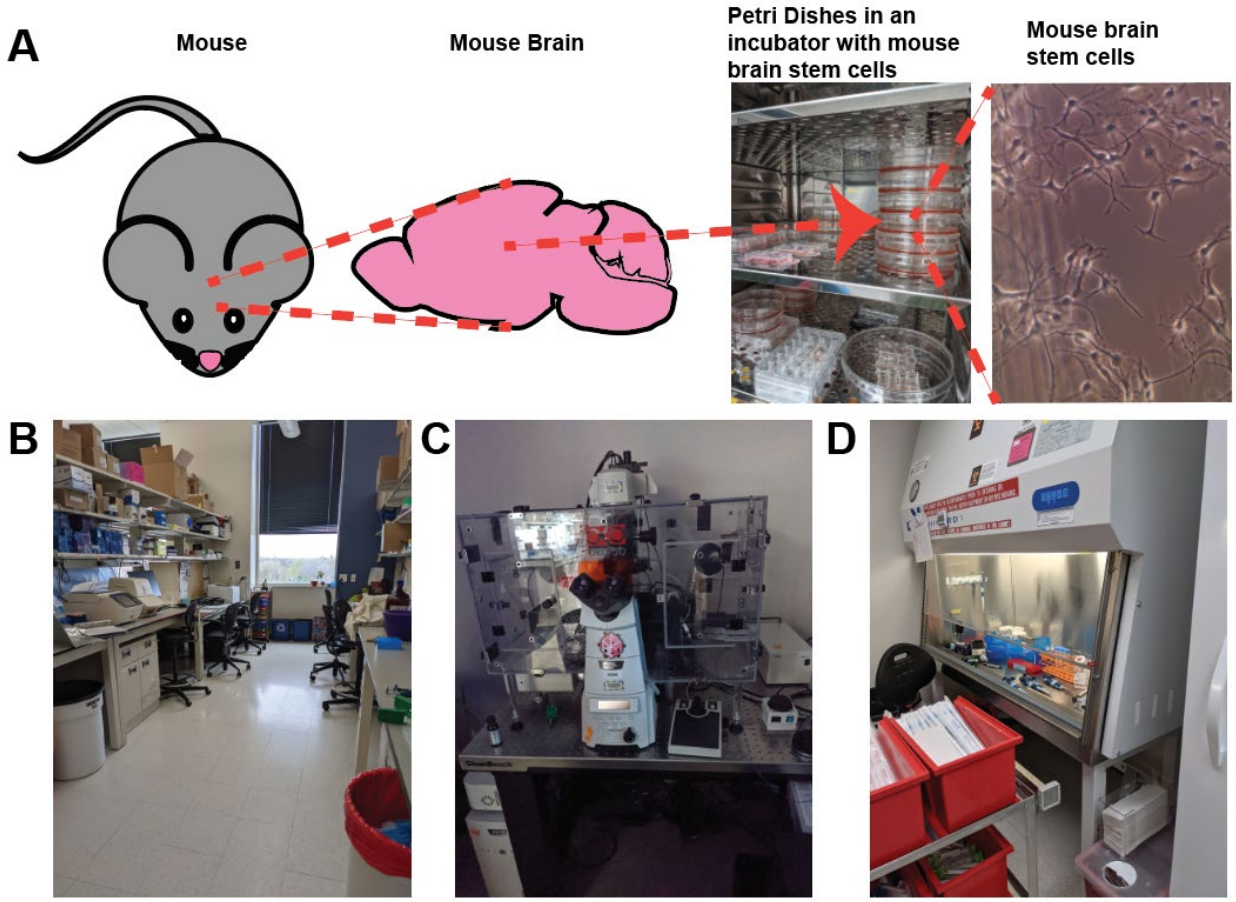

Figure 6.2 *– Pictures of the lab I work in and the cells I work with. A) Schematic showing the brain stem cells we work with. Brain stem cells are taken from a mouse brain and put in a petri dish in an incubator with cell food (the red liquid in the petri dishes). The far right image shows brain stem cells under a microscope. B) A picture of the lab space I work in. C) A picture of one of our fancier microscopes (confocal microscope). D) A picture of a "hood" – the sterile space we use to work with our brain stem cells where we can minimize the risk of contaminating them with microbes in the air.*

for getting rid of junk could be an effective strategy to increase or decrease the rate at which brain stem cells activate and make new brain cells.

One way that cells can get rid of junk is through a cellular garbage can called the aggresome. The **aggresome** is a garbage can cells have that could be thought of as a staging ground for the destruction of cell junk (Fig. 6.3) (Johnston et al., 1998). The cell takes junk that needs to be destroyed and takes its tools for destroying the junk and carefully organizes them in one spot. We think that this helps a cell in many ways, such as by keeping the junk organized so it isn't sprawling out across the cell interfering with other critical tasks a cell must complete to stay healthy. Imagine living in a house without a trash can where the trash gets randomly spread everywhere rather than nicely contained in one spot. **We wanted to know if brain stem cells used the aggresome to get rid of cell junk when they activate and begin to make new brain cells.**

To see if brain stem cells used the aggresome to keep themselves clean as they activate, we took brain stem cells from a mouse and put them in a petri dish and then used a microscope to see if we could observe the aggresome forming as brain stem cells activated. To look at the aggresome, we had to treat the brain stem cells with a set of chemicals that would allow us to see different parts of the aggresome. More specifically, we looked at one part of the aggresome, called **vimentin**, which is a part of the cell's skeleton that encapsulates the aggresome. You can tell a cell is forming an aggresome if you see a condensed ball of vimentin in the middle of the cell. Excitingly, when we performed this experiment, we found that aggresomes formed when brain stem cells activated (Fig. 6.4A-B). This result supports our hypothesis that brain stem cells use the aggresome to keep themselves clean and produce new brain cells. This result also

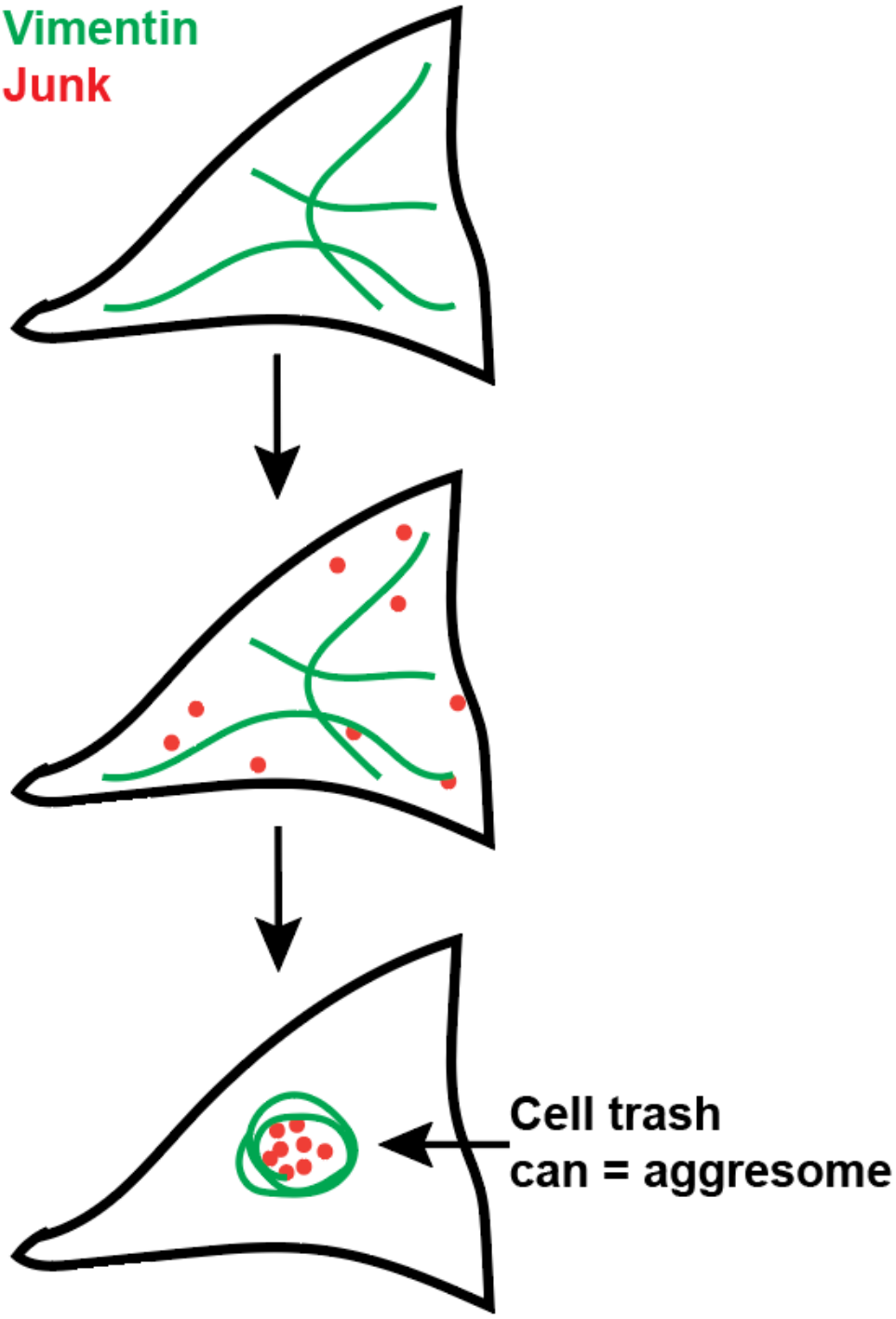

Figure 6.3 *– Schematic depicting how cells form a cellular trash can called the aggresome to get rid of cell junk (red). The white objects with a black outline are cells. During aggresome formation, a skeletal part of the cell called vimentin (green) forms a cage around the cell junk in the middle of the cell.*

suggests that we could use the aggresome as a target to increase or decrease new brain cell production in adults.

Although we had seen that the aggresome was used by brain stem cells as they activated, we still didn't know if the aggresome was important for this process. Think of it this way, all astronauts that have been to the moon have drank water, but drinking water doesn't mean you will end up on the moon. In other words, is the aggresome a part of what is causing brain stem cells to activate, or is the aggresome just a side-effect of other things that are happening that drive brain stem cell activation? To try and find an answer to this question, we examined brain stem cells which have an aggresome that doesn't work properly. We learned from other experiments that brain stems cells needed vimentin to efficiently degrade cell junk at the aggresome. Vimentin isn't important for forming the aggresome, but is important for getting rid of junk in the aggresome. You could think of a brain stem cell without vimentin as having a trash can that doesn't empty often enough. Therefore, to determine whether the aggresome is important for brain stem cell activation, we took mice that either had vimentin or mice that had vimentin removed and looked at their brains using a microscope to observe the rate at which dormant brain stem cells were activating. To our great excitement, we observed that brain stem cells without vimentin had a harder time activating (Fig. 6.4C). This result suggests that the aggresome is a junk clearance system that is important for a brain stem cell's ability to activate and produce new brain cells.

In conclusion, in this section I discussed key experiments from a project we completed in which we found a new way that brain stem cells keep themselves clean, a cellular garbage can called the aggresome, and that this cellular garbage serves

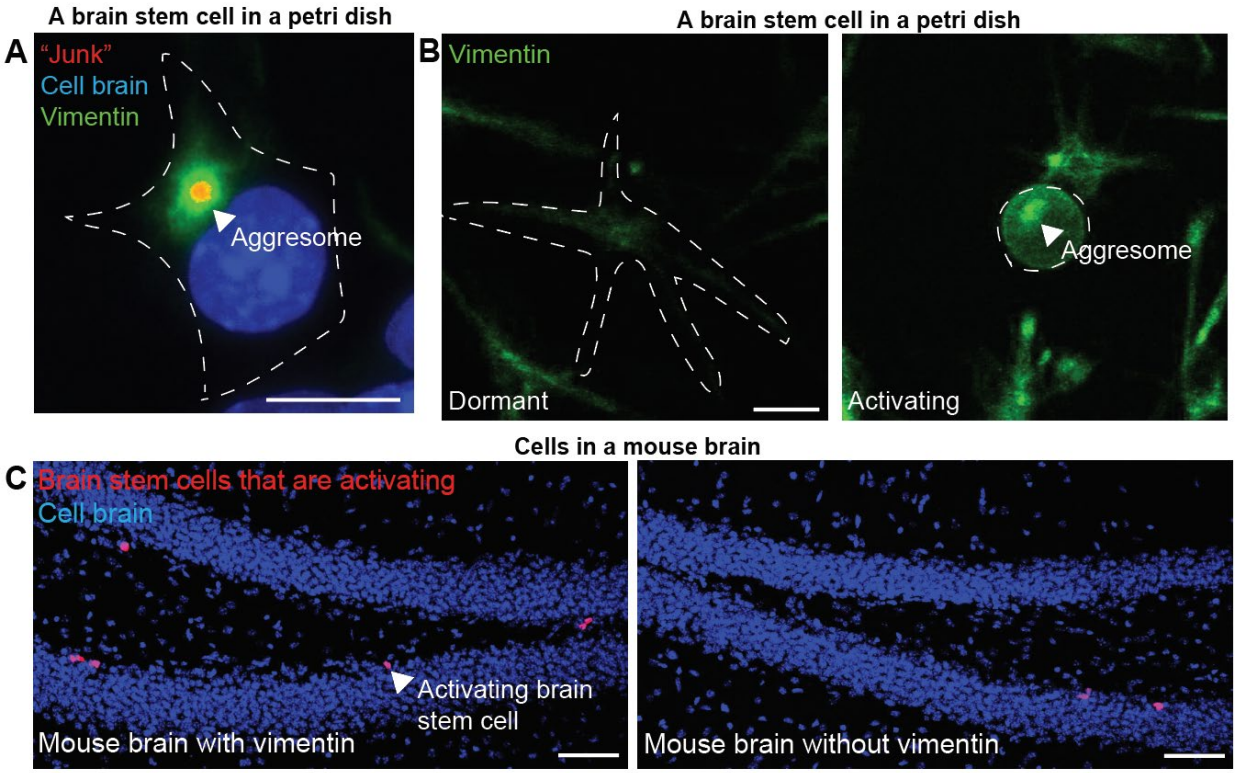

Figure 6.4 – *Data for section 6.4. A) Picture of a brain stem cell with an aggresome where we imaged junk (red), the cell's brain (nucleus; blue) and vimentin (green). Notice how vimentin forms a cage around the cell junk. This structure denoted by the white arrow is the aggresome. The cell is outlined with a white dashed line. B) Pictures of a brain stem cell in a petri dish making a vimentin cage (green) around the aggresome as it starts to activate out of a dormant state. The cell is outlined with a white dashed line. Notice how vimentin gets brighter and forms a smaller dot within the cell when activating – this is the vimentin cage. C) Pictures of a mouse brain from a mouse that either did or did not have vimentin where all nuclei were labeled (not just brain stem cells, but also other cells in the brain, like neurons) in blue and brain stem cells that are activating are labeled in red. Notice how when vimentin is in the brain there are more red cells – indicating vimentin is important for a brain stem cell's ability to activate in the mouse brain.*

important roles in the production of new brain cells. At a broader level, these experiments provide a framework explaining some of the rate-limiting steps in how the adult brain creates new brain cells which limit our brain's ability to repair itself.

6.4 Where we go from here

In this chapter, I first discussed the aging research field and discussed how scientists study stem cells to figure out whether increasing their activity can help us age more gracefully. More specifically, I discussed how scientists think a reason your brain is unable to regenerate sufficiently when suffering from brain degenerating diseases or injuries, such as Alzheimer's Disease, is tied to brain stem cells having a hard time getting out of a dormant state. In section 6.3 I summarized our work identifying a cellular garbage can called the aggresome as a critical component of a brain stem cell's ability to exit the dormant state on the path to making new brain cells. These experiments provide an example of the types of progress we have made in the laboratory towards improving brain stem cell aging. In addition to these key discoveries, we have also made new tools to identify dormant and active brain stem cells and learned more about how cells put the aggresome together. It is our ultimate hope that these advances in knowledge can continue to instruct the world-wide journey towards healthier aging.

While it may seem a bit abstract how the experiments I described above could cause you or your children to live longer, healthier lives, it might help to know that groundbreaking science almost always starts as what we have discussed in this chapter. Many of the most significant scientific discoveries were the result of "basic science" research, which was not specifically focused on directly curing a human disease. For

example, CRISPR/Cas9, the hot new gene editing technology that is arguably the discovery of the century, came from unsuspecting scientists who were studying what happens when bacteria are attacked by viruses. My point is not that my work is worthy of the title “discovery of the century,” but rather that everything we do, no matter how small it may seem, contributes to the betterment of the world, often in ways we could never fully anticipate.

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