From Trash to Treasure:

The Lysosome's Role in Cancer, Aging, and Neurodegenerative Disorders

INTERVIEW WITH: DR. ROBERTO ZONCU

BY: GRACE ZHOU, SAMIKA ARUN, BRANDON BOSCH, AND SANIA CHOUDHARY

Dr. Roberto Zoncu is a professor of Molecular Therapeutics in the Department of Molecular and Cell Biology of UC Berkeley. He is also the co-director of the newly founded Molecular Therapeutics Initiative at UC Berkeley. After studying molecular biology at the University of Pisa in Italy, Dr. Zoncu earned a PhD in Cell Biology at Yale University. In 2008, he moved to the Whitehead Institute at MIT as a postdoctoral fellow before finally joining UC Berkeley staff in 2014. The Zoncu lab studies how lysosomes help cells sense nutrients and control growth. Their work shows lysosomes play an important role in keeping cells healthy and understanding diseases like cancer.

BSJ: Lysosomes are now recognized as signaling hubs rather than just cellular trash cans or recycling bins. How has this new understanding impacted your field and your lab's approach to identifying therapeutic targets?

RZ: Lysosomes were taught in high school and in college biology to be these cellular trash cans, which they are, but in recent years, several labs, including my own, actually discovered that the lysosome has many other properties. In fact, when I was a postdoc at MIT, I discovered that the lysosome is a site where this master regulator, mTOR kinase can initiate cell signaling. We also discovered that from the lysosome, there are actually programs that propagate all the way to the nucleus, where they can affect gene expression. This discovery has completely turned the lysosome upside down and made the field very exciting. All of a sudden, everybody wants to study the lysosome because it is such an interesting organelle that talks to other organelles in the cell. People began to discover why the lysosome is implicated in so many diseases; in many diseases, such as neurological cancer and diabetes, it is not just the issue of degrading things properly, but also a question of sending the wrong instructions to the cell. When I started my lab at Berkeley in 2014, 11 years ago now, this field was still in its early days, but I decided to really dedicate the [Zoncu] lab to studying this aspect of the lysosome as a computer for the cell that can instruct the cell to do certain things. We have been studying the lysosome since then, both from a fundamental viewpoint, to understand all the parts that make up the lysosome, how they talk to each other and other parts of the cell, as well as what happens when they go wrong. Our lab has been investigating neurodegeneration and cancer, which are two important directions, but I think there are more. Certainly, in immunology, there is a huge involvement of the lysosome and hat is something we are interested in studying too. Ultimately, we want to make cures for various diseases, and I think that this is a really promising era of investigation.

BSJ: Could you tell us a bit about lysosomal remodeling and how enhancing lysosomal repair and adaptation could play a role in neurodegenerative conditions like Alzheimer's or Parkinson's?

RZ: Before, lysosomes were taught to be these boring organelles that never change. It is like your trash can that sits in the kitchen and you just toss things in there. Now we know that lysosomes can change. For example, the cell can make more on demand in certain tissues. In the liver, in the adipose tissue, and in the muscle, there is more need for catabolism, and actually, in the brain as well. Cells can produce more lysosomes that can take care of all these things that need to be degraded, whether this is food coming from the extracellular space, or a damaged component that needs to be cleared out. This is important for a brain cell, because brain cells do not divide, so as they accumulate molecular trash over their lifetime, they cannot just pass it on to their progeny, so they grind it up right then and there. Now, we understand that there are certain transcription factors, so proteins that bind to the DNA, that activate this whole program that the cell requires to make a new lysosome from scratch. We know that these transcription factors can be activated by stress, starvation, drugs and things like that. On demand, the cell can make fresh lysosomes and use them. That is the good side. The bad side is that lysosomes do change with age. In fact, as we get older, unfortunately, lysosomes, particularly in our brain cells, which are one of the most sensitive, fill up with stuff that can no longer be degraded. If you put more stuff in these recycle bins, some proteins and lipids become highly concentrated, oxidized, unbreakable, and that eventually saturates the lysosome itself. Eventually the cell is unable to continue degrading which is a triggering factor for dementia. For example, it can be one of the contributors, or it can worsen certain mutations that you have in your genome that might predispose it to Alzheimer. Maybe the mutation by itself is not sufficient, but a mutation plus a worn out lysosome can actually speed up this process in the brain. What can we do about it? Can we actually make lysosomes better for aging or for the therapy of Alzheimer or Parkinsons? Now we understand how this pathway that makes new lysosomes for the cell works. By we, I mean, the field, and my lab as well; we use small molecule drugs that can activate this program. Another strategy is to supply the lysosome with fresh proteins that can be used, like fresh enzymes that could be used to degrade insoluble material or harmful material. This is also something that has been explored experimentally. Then there is gene therapy. In some cases you have mutations in your lysosomal genes. Then in that case you want to come in with cas9 and fix the problem, end of story. A lot of excitement about keeping lysosomes healthy or making them even stronger for various disease therapies.

BSJ: In your paper on mTORC1 signaling inhibition, you discuss an interplay between mTORC1 signaling and lysosomal function. Could you explain how this connection modulates mitochondrial activity in Friedreich's Ataxia models?

RZ: This relates to the theme of organelles talking to each other. The lysosome does not exist in isolation, but actually, it is highly coordinated with the mitochondria. We think of the lysosome as an excellent town center. Still, sitting in the center of the cell, the mitochondria are the power plants, the organelle that produces ATP but also produces many building blocks to build a new cell and nucleotides. In some cases, mitochondria can also degrade macromolecules to generate energy or other things. This organelle can work in conjunction. The best data that do that, for example, whenever

"mTORC1 is what we call the masterchef of the cell. It is a protein kinase that can make the cell do many things required for growth, proliferation, etc. When you block it, you are gonna block a lot of processes that happen."

you have mutations in autosomal genes, the mitochondria also suffer, like in all these neurological disorders in, you know, Parkinson's disease where the lysosome is affected, the mitochondria there are also affected. You can take electron microscopy slides of the patient's brain, for example, when you see that they are both significantly compromised. How did these two organelles talk to each other, and can the alternate one fix the other essentially? We are doing both, so this paper was the case where we look at the mitochondrial disease and then ask, "Is the mitochondria affected?" Can we do something to the lysosomes? Can we apply feedback to the mitochondria? Fixing mitochondria could be tricky but fixing the lysosome might be easier. If you have a disease that starts in the lysosome, perhaps you could fix mitochondria to make it better. Friedreich's Ataxia is a disease where mitochondria cannot make molecules called autosomal clusters, essential for respiration. For example, mitochondria aspired to use oxygen to transfer electrons to create ATP, right? Without autosomal clusters, you cannot do that. These people have a devastating both neurological and muscle condition. This was known for a long time. The protein kinase is one

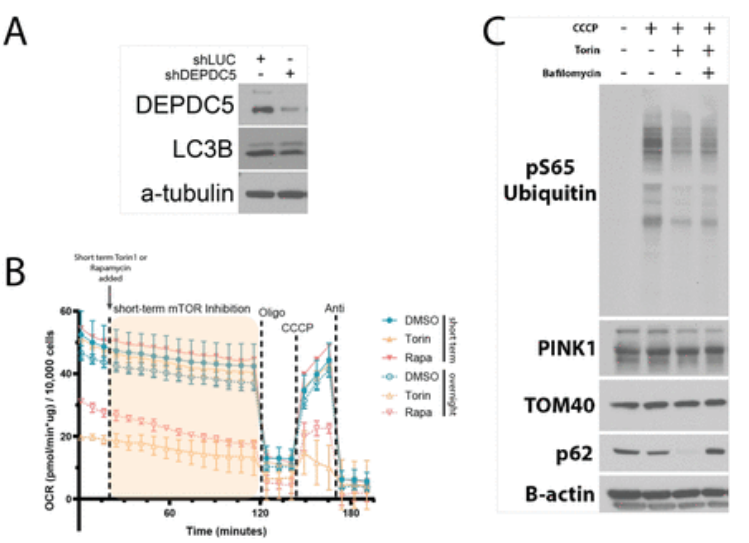

Figure 1: Affects of mTORC1 inhibition that influence mitochondrial function are the result of a longer term inhibition rather than immediate signaling effect. (A) DEPDC5 shRNA test for Fig1A control; (B) Western blot for mitophagic and mTORC1 signaling markers after either long- or short-term Torin1 treatment followed by CCCP challenge; (C) Western blot for mitophagic markers after treatment with Torin1 for 20hr, BafilomycinA1 for 12hr, and CCCP for 5hr; (D) OCR analysis of U2OS cells treated with vehicle, Torin1, or Rapamycin either overnight or for 1.5hr after taking basal measurements.[2]

of the single proteins from the south. There was evidence for why in the literature that mTORC1 came from mitochondria, but exactly how it does that is not clear. Take this disease of three Friedreich's Ataxia made in cell lines, and this was not done in mice, or you know, in sophisticated organisms, your cell lines, because we do not understand the basics, right? We took out this Frataxin, which was mutated in the disease, and then we started to manipulate mTORC1 using drugs, so there is this molecule, Rapamycin, that is a blocker. Then, we block mTORC1 in the lysosome, and then we look at another mitochondria It is really interesting, and evident, that this mitochondria prevents mTORC1 so that you can compensate for the defect that they have by acting on the lysosome. There are drugs available for mTORC1; we do not need to render in the wheel from any case the perspective if you just try this and heat those things potentially. You have to be careful when you do these things. A more advanced disease may be the mouse or something like that. This was just the first explanation, but I think it was very encouraging. Some questions came from this paper: What happens to mitochondria when you mess around within mTORC1 and the lysosome? What kind of changes happen there? We do not have the full list, and so we are using technologies called spectrometry, proteomics, and epitomics to really see how these mitochondria are changing, and that is it. It is still continuing.

BSJ: What are the potential therapeutic implications and concerns of mTORC1 inhibition for mitochondrial diseases, considering its diverse effects on cellular processes such as respiration, membrane potential, and overall metabolic homeostasis?

RZ: mTORC1 is what we call the masterchef of the cell. It is a protein kinase that can make the cell do many things required for growth, proliferation, etc. When you block it, you are gonna block a lot of processes that happen. While some of these could be beneficial, some of them could be harmful. The question is, how do we block mTORC1 in a way that is beneficial but leaves out the bad side effects? The reality is we do not know yet. We need to look at different disease models and see what happens. In each one, whether the benefits outweigh the risk, we think in general mTORC1 inhibitors are safe and nobody will die of them. However, there are some effects that could overcome the therapy. It also depends on how you communicate. Small molecule inhibitors are on impact, so mTORC1 does maintain and optimizes, for example, blocks only some, but not others. This other molecule they use called "tuning" blocks everything. So you want to locate everything for something, can we block this but not that? An important direction of the investigation, and not like the others, is to find that so-called input specific or output specific blockers of mTORC1, instead of blocking the whole thing, and can you only block one input or the second input or a third input or one output or the second output to a third output or any combination, it is. I think there are new chemical tools, then we will be able to precisely assess how to make it beneficial leaving aside the potential side effects.

BSJ: How does acute pharmacological inhibition of mTORC1 signaling differ from chronic inhibition in its effects on mitochondrial function, composition, and cellular metabolism, and has your lab explored the risks and differences in the mechanisms underlying these different methods of inhibition?

RZ: Usually to distinguish between acute versus chronic inhibition, you would compare the effect of the drug that you give acutely to cells or to an animal. Or using a so-called RNAi reagent we can track down mRNA or block mRNA, and that prevents the protein from being produced, versus making a mouse smaller, like a knockout mouse, where you completely knock out that particular gene. The mouse is like a bomb without that gene so we can ask, "What

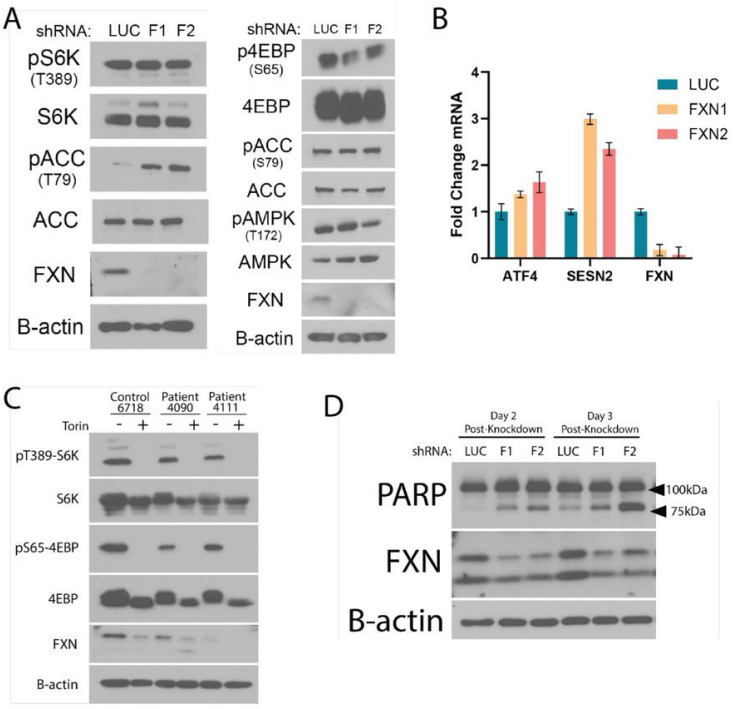

Figure 2: Model of FXN deficiency by shRNA knockdown induces mitochondrial stress markers without inhibition of mTORC1. (A) Western blot for mTORC1 and mitochondrial stress signaling markers in shLUC or shFXN cells; (B) qPCR for ATF4 and SESN2 activation in shLUC or shFXN cells. (C) Western blot of mTORC1 signaling markers in patient FA fibroblasts; (D) Western blot for cleaved PARP accumulation for two- and three-days post-shRNA mediated knockdown in U2OS cells.[2]

happens if I let the mouse grow and develop the disease, and then I acutely block mTORC1, versus I let this mouse be born without that mTORC1 gene to begin with?" Those are very different things. In fact, they are very different, so-called paradigms, because in one case, you do not give a chance for the mouse or the cells to adapt, because you hit them right then and there. You will see acute effects. In the other case, because the mouse is born without the gene, there are many ways in which it can adapt and compensate, so maybe the effects will not be as strong. However, the mouse has the ability to adapt to the lack of this gene and the side effects would not be as bad, right? One might get less of a benefit but also less harm. In evaluating this tool we need to decide what is more important for the disease we are studying. For example, if you are studying a progressive genetic disease that starts in children, there are many neurological diseases, where children of just a few months of age are symptomatic. Then, you probably want to treat them with something more long term, such as gene editing. That is the earliest possibility given the lifetime of these kids; you can use the defect, right? If it is something that happens with old age, then we need to come up with something acute and this is an issue—you need to be

on a drug. Then you need to ask, "If I keep taking this drug for months or for years, what are the consequences?" To make a long story short, it depends on the disease that is attacking. and you need to weigh the benefits of different manipulations.

BSJ: In your paper "LyLAP enables lysosomal degradation of membrane proteins" you mention using combined functional genomics screens and lysosomal proteomic profiling to identify LyLAP. Could you discuss the advantages and challenges of this multi-omics approach in discovering novel therapeutic targets?

RZ: The sort of diseases we have been talking about so far are neurological diseases where, typically, lysosomes are dysfunctional—they have not degraded things properly or are sending the wrong signal to the cell. This is a cancer study though, particularly pancreatic cancer. Pancreatic cancer is a tumor that relies on so-called "super lysosomes"—that is how we think about them. It is a tumor that grows in very challenging conditions where normal tissues and cells would not grow and proliferate. For example, a tumor in the pancreas is surrounded by a capsule of fibrotic tissue that protects it from the immune system, so it grows undisturbed, but this tissue also makes the tumor very hypoxic and hypervascularized, so there are very few blood vessels surrounding it. This tumor is basically challenged from the very beginning. So what does it do? It makes a lot of lysosomes and uses them as scavengers to grab as much food as it can from the surrounding environment. These pancreatic tumors can eat dead cells and the extracellular matrix—they are really professional scavengers. By the time the tumors emerge and metastasize across the body, it is already too late. These tumors are very, very hard to treat because they are extremely aggressive. We know that the lysosomes are important, and we know that there must be something in these lysosomes that make them so effective. Can we find what that something is, and can we then come up with a way to block it? How do you discover something that you do not know? You need to use a so-called unbiased method. The lysosome is probably about three to 400 different proteins and depending on the cell type, you might not know which ones they all are. To use an unbiased method, we took pancreatic cancer lines which are patient derived that we can culture in the lab and compared them to non cancer control cell lines. Using affinity tags we can pull lysosomes out of cells and purify them from all the other materials in the cell. These are pure and the lysosomes are actually intact, so they do not break, and the process is actually super, super clean. Then we use mass spectrometry to compare the composition systematically between the control non cancer cells and the cancer cells. We then asked, "What is higher in the cancer cell?" The answer: super lysosomes. If there is a protein, or some proteins that are very high in cancerous cells, we can hypothesize that perhaps, those proteins might be the drivers of this behavior and maybe we can develop a drug against this particular protein. However, we found that there were probably 150 proteins that were higher in the cancer lysosomes. That was not sufficient to pinpoint a single interesting one. So we took this mass spectrometry list of highly expressed proteins and we combined it with a bioinformatic pipeline. We asked: "Which one of these 150 proteins are also highly expressed in cancer patients?" There are all these databases of gene expression, so we can cross reference these with our list and see which one of them is also correlated to survival. For example, if you have a lot of this protein, your survival chances are lower. This enabled us to narrow our list down to 16 proteins—a much smaller pool. Then we asked, "Out of these 16 proteins, which one looks to be the most interesting and promising?" We realized that, although the others were known, people kind of know what they do, this one protein called PLBD1, or LyLap, nobody knew anything about it. We thought that could be a hidden treasure, something that, if we can figure out what it does, could be important or even a target. We started very broadly using these omics technologies. By combining many omics approaches, we were able to really narrow down to one candidate. I believe this is more and more the way to go about diseases. There are thousands of different proteins in the cell and you need to be able to prioritize them, because understanding any one of them is a lot of work, so you need to make sure that you put your eggs in the right basket.

BSJ: Although LyLAP is upregulated in PDA cells, they are still present in and critical for healthy cells. Do you see this as a significant cause for concern in the development of LyLAP targeting therapeutics? Have you investigated if there are ways to increase the specificity of this target?

RZ: When we started to study LyLap, we realized that if you block it in pancreatic cancer cells, the cells die. When looking at the cells using electron microscopy, we saw the lysosomes balloon up and become gigantic, which is what they look like when defective in neurological diseases. We are essentially giving cancer a neurological disease. Figuring out what LyLap does was an incredibly hard process and took some real detective work, but once we determined its function,

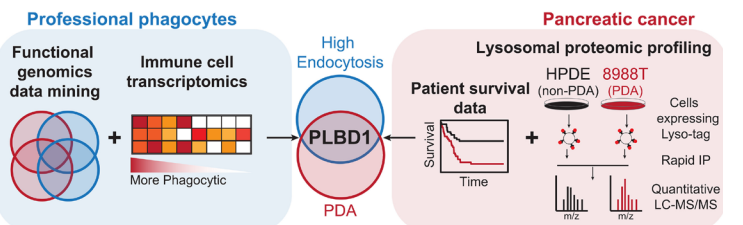

Figure 3: LyLAP is a highly enriched lysosomal hydrolase required for PDA growth. Bioinformatic pipeline combining functional genomics screens for endocytosis regulators and transcriptomics in immune cells with lysosomal proteomic profiling from 8988T (PDA) versus HPDE (non-PDA) cells and patient survival data from cancer-associated lysosomal hydrolases.[1]

it was very easy to devise a small molecule screen to find a blocker. In fact, we have already found several blockers for LyLap. Then we asked, "What could be the side effects?" We found that LyLap is not highly expressed in every cell type, but there are some cell types that have a lot of it; for example, immune cells and macrophages. Macrophages are like the cleaners of the body that go around killing bad cells. The question is: by developing an inhibitor against LyLap, could we also compromise the immune system, which is what sometimes keeps cancer at bay? There are two ways that we are going about this. One way is to make a mouse model where we specifically block the enzyme, either in the cancer, in the immune cells, or both. Then we ask, "What are the results if you block it everywhere, versus only here or only there? The second factoris timing. My gut feeling—this is just a hypothesis for now—is that if you give a LyLap inhibitor too soon, when the tumor is still small, you might actually block the immune system from acting on it, which may not be ideal. However, if you intervene later, when the tumor is

growing very actively and spreading around the body, that is when the maximum window of efficacy could be. We do not know this for sure yet and we still need to do the experiments. So far, we are really excited about this protein as a new target, but with every target, you need to do your homework to figure out risk versus benefits. I should also say that since pancreatic cancer is incurable at this point, almost anything that can prolong survival is acceptable, as long as the side effects are not overwhelming. It could just be a question of finding the right timing, the right dose, and the right setting where we use these inhibitors.

BSJ: Given that increased LyLAP levels help lysosomes maintain their integrity under high proteolytic loads and various stressors, could this mechanism be beneficial in other diseases characterized by lysosomal stress or dysfunction?

RZ: Absolutely, we are thinking that in conditions where the lysosome is defective, such as in brain diseases like Alzheimer's and Parkinson's, supplying cells with LyLap could be helpful. Again, this enzyme is not normally high in neuronal cells, but it is very potent in breaking down things that are potentially damaging. There are already technologies such as enzyme replacement therapy for people who have mutations in certain lysosomal enzymes and are given the corrected protein recombinant. We can inject the enzyme in various forms in the body so that the tissues can pick it up, and since the lysosomes can communicate with the outside world through endocytosis, we can always deliver things elsewhere. What if we now use LyLap to make a super lysosome, a better lysosome in conditions where the lysosomes are not degraded properly, like in these brain diseases? That is definitely a possibility.

BSJ: Is making a "super lysosome" something your lab is working towards?

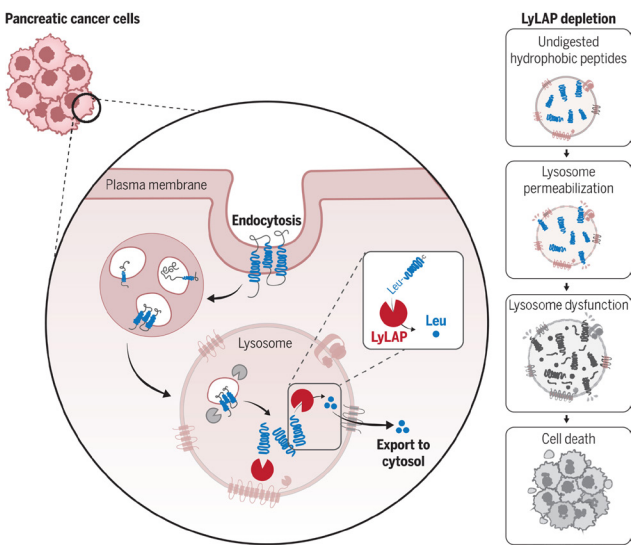

Figure 4: LyLAP enables membrane protein degradation in highly endocytic cells. Integral membrane proteins at the plasma membrane are internalized and trafficked to the lysosome, where LyLAP mediates the complete degradation of hydrophobic transmembrane domains. In highly endocytic pancreatic cancer cells, LyLAP depletion triggers the accumulation of undigested hydrophobic peptides, inducing lysosomal permeabilization and dysfunction, in turn leading to cell death.[1]

"...we saw the lysosomes balloon up and become gigantic, which is what they look like when defective in neurological diseases. We are essentially giving cancer a neurological disease."

RZ: Yes, we are definitely trying to do that. First of all, we are thinking that discovering new enzymes –like LyLap with new functions –could provide tools we can give to other lysosomes. The other source of enzymes that is really interesting is the prokaryotic world. Bacteria and archaea, for example, live in very challenging environments and they have many different enzymes that can degrade almost anything, while us humans can not. Imagine that we took a bacterial enzyme that does not exist in our bodies, engineered it so that it is not recognized as a foreign body, and adapt it to the specific pH and conditions of the lysosome. Then, you could imagine using it as a tool to increase the lysosome's efficiency. We are really excited about this possibility—it is not trivial, but I think it is something to pursue.

BSJ: What is the difference between gene editing to increase the expression of an enzyme versus directly injecting it through enzyme replacement therapy?

RZ: It is a question of what is easier and more beneficial. If you think about the brain, the first major issue is the blood brain barrier, which will prevent almost anything from crossing into the brain. There are actually biotech companies nowadays that are making very efficient vectors, like Denali Therapeutics and Cisco, which are making molecular tags that can help an enzyme cross the blood brain barrier. Assuming that you can do that, now the question is, should you just put back the missing enzyme or should you put in a Cas9 that goes in and fixes the problem? Both options have advantages and drawbacks. Cas9 is going to be hard, because firstly you need to get it to go into the cell, and usually it will go into the endosomes and lysosomes first. Then, you have to cross into the cytoplasm, get into the nucleus, find the right gene that it has to edit while making sure it does not edit anything else. Otherwise, this may result in cancer or some other disease. But if successful, then it is done and you do not need to do any intervention again. On the other hand, if you directly provide the missing enzyme, the advantage is it is easier to get it where it needs to get, because it will go to the lysosome directly, and it can act there. However, you need to inject a lot more of the enzyme because you need to supply it to cells that do not have the right gene or a mutated version. It would be a very temporary benefit which you would need to keep repeating. I would say that nowadays, neither approach really cures the disease. They can give improvements, but I think it is still early days and people are very careful about gene editing in the brain.

BSJ: You recently took on the role of co-director of the Molecular Therapeutics Initiative (MTI) which launched in March of 2024. What about MTI are you most excited for? And how will MTI tie into and support your current research?

RZ: As you might already know, Berkeley does not have a medical school. But, Berkeley has made some of the most important revolutionary discoveries in biomedicine, which includes CRISPR

Cas-9 by Jennifer Doudna and Cancer Immunotherapy by James Allison, both of whom received a Nobel Prize for these discoveries. Because we do not have a hospital and a clinic and patients, we are at a disadvantage in terms of testing these things therapeutically, putting them into people, and really demonstrating that they work. So, there is quite a movement, particularly in the Molecular and Cell Biology department, to do more translational science. We want to keep the basic science just as strong, but make it more immediately translatable. How do we do it without a medical school? The MTI is one of the answers that we are trying to give. The MTI is basically the fundraising and entrepreneurship arm of a new division within the department, which is also called Molecular Therapeutics. There is a Molecular Therapeutics division, which the faculty belong to, and where the teaching goes on. We teach a drug development class and we

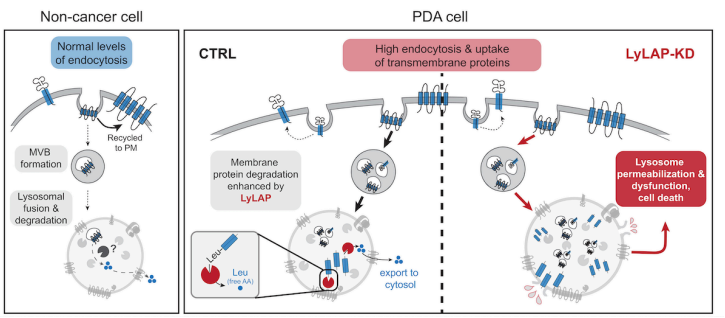

Figure 5: Loss of LyLAP activity triggers lysosomal membrane permeabilization. Model of LyLAP-mediated membrane protein degradation in highly endocytic cells. (Left) In nonmacropinocytic/nonphagocytic cells, housekeeping mechanisms (yet to be fully elucidated) enable lysosomes to process transmembrane protein substrates. (Middle) In PDA cells (and possibly phagocytic noncancer cells), LyLAP upregulation enables complete degradation of hydrophobic transmembrane domains derived from integral membrane proteins that are trafficked to the lysosome. (Right) Loss of LyLAP triggers accumulation of undigested hydrophobic peptides, leading to lysosomal permeabilization and dysfunction and ultimately PDA cell death.[1]

are setting up a drug discovery lab. The MTI is a fundraising arm, it can do its own fundraising, and it can launch its own initiatives to speed up this more translational aspect of science at Berkeley. We already raised the first chunk of money that we are using for several initiatives. One of them is an innovation grant program, which means that PIs and students and postdocs who have an idea about developing new drugs can apply for about $100,000 a year for a couple of years to basically put a crazy idea to the test. We give you resources, we give you the money, and we give you access to the drug screening facility, and you can try to come up with your new molecule. Also, if you are successful, we can link you up to companies that do what is called medicinal chemistry. When you do a drug screen in a university, the chemical hits you get are very far away from being a drug. You need to do so much more chemical evolution and improvement. We usually cannot do these things in a university, so you end up doing nothing with it, or shelving it, or maybe it gets forgotten. Medicinal chemistry is the art of turning a chemical heat into something that is much closer to a drug. Then the question is, what do you do with this drug? If you have something that could be a drug, we can help you start a company. One of the initiatives of MTI is to promote this interchange between Berkeley trainees and faculty and local VCs, venture capital firms, that come here, listen to our ideas, make proposals, and network together. From there, there can be a proposal to actually start a company. For example, a grad student, for example, that then becomes the CSO of a company. As part of that, we also promote a lot of these events, like our annual symposium where we invite major companies in the Bay Area like Genentech and Amgen to come to Berkeley and give a science presentation. It is a two day event; the first day the company comes to Berkeley, the second day we go to the company site and there is a poster session where our trainees show the work they are doing. We decided to really accelerate this intermixing between academia and industry, which can lead to drugs more rapidly. We either start our own companies or we establish alliances with existing biopharma. In general, we also provide UC Berkeley students with more access to these professional outcomes. After students graduate from Berkeley, they might want to become an entrepreneur, a drug hunter, or a consultant. The MTI gives them this early exposure so they can get that sort of experience. This is also open, of course, to undergrads working in MTX labs and those who are taking our drug discovery class, MCB 120.

BSJ: What are you looking forward to the most in your field of translation research and lysosomal discovery?

RZ: Making super lysosomes. I think super lysosomes are going to be really a new direction in many diseases: neurological, metabolic, or even aging. Since I am aging myself, I should give myself some super lysosomes! Now that we understand how this really fascinating organelle works and all the parts that make it tick, or at least some of them, we know what is possible using both small molecules, gene editing, or biologicals like recombinant proteins and enzymes to make it more efficient. If you think about it, evolution has not equipped us to deal with damage and dementia and degeneration, because those things happen much later in life, after the window of natural selection has passed. I think there is a huge opportunity here to correct those evolutionary distractions that leave us vulnerable to all these diseases. I think the lysosome is a great place to start, because it controls so many things in the cell, and also because it communicates with the outside world, unlike the nucleus or mitochondria, which are protected by additional membrane and transport systems. The lysosome is accessible, so we can go there first and try to correct the problem or make it better than what nature gave us, which is something I am very excited about.

REFERENCES

1. Jain, Aakriti, et al. "Leucine Aminopeptidase LyLAP Enables Lysosomal Degradation of Membrane Proteins." bioRxiv, Jan. 2024, p. 2024.12.13.628212, https://doi.org/10.1101/2024.12.13.628212.
2. Lehmer, Madison, and Roberto Zoncu. "mTORC1 Signaling Inhibition Modulates Mitochondrial Function in Frataxin Deficiency." bioRxiv, Jan. 2024, p. 2024.08.06.606942, https://doi.org/10.1101/2024.08.06.606942.
3. Zoncu, Roberto. Zoncu Lab Website. University of California, Berkeley, www.robertozonculab.org/.