FROM PARTHANATOS TO PAANIB-1: A MULTIMEDIA EXPLORATION OF CELL DEATH MECHANISMS AND THERAPEUTIC STRATEGIES FOR PARKINSON'S DISEASE

by
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Abstract

Recent discoveries in molecular biology have shed light on a potential therapeutic treatment for Parkinson's disease (PD)—a progressive neurological disorder marked by the gradual loss of dopaminergic neurons in the brain.[1] This treatment involves selectively intervening in the parthanatos pathway, a preventative cell death mechanism that normally helps restrict the cell-to-cell spread of disease.[2] This cell death pathway is characterized by its distinctive breakdown of the cell's DNA into fragments that escape from the nucleus into the cytoplasm prior to degrading.[3]

In addition to parthanatos, the cGAS-STING pathway is another molecular mechanism that produces a rapid microglial immune response upon detection of cytosolic DNA fragments.[4] Thus, the cGAS-STING pathway is linked to the elimination of infected cells by sensing and responding to foreign DNA, as well as self-DNA fragments created through parthanatos.[5] In neurogenerative diseases such as PD, both pathways become excessively engaged and overactivated—perpetuating a cycle of widespread inflammation and cell death.

Traditionally, it has been believed that blocking the initial stages of parthanatos would be the most effective in preventing DNA fragmentation and cell death.[6] However, targeting the early steps of parthanatos has drawbacks, as this inadvertently hinders essential DNA repair. Therefore, new research has shifted focus downstream to prevent parthanatos-induced DNA cleavage without interfering with important upstream DNA repair processes. In particular, Macrophage Migration Inhibitory Factor (MIF) nuclease has been identified as the critical molecule for initiating self-DNA cleavage in cells, thereby triggering the decisive step of parthanatos.[3,6]

Exciting new research has unveiled PAANIB-1, a first-in-class MIF inhibitor that prevents this final step of parthanatos, thus also preventing the generation of DNA fragments that over-activate the cGAS-STING pathway.[8,9] Targeting MIF using PAANIB-1 therefore shows promising potential in its ability to slow or prevent inflammation and neuronal damage in PD.[8,9] As further testing for PAANIB-1 viability proceeds, it is crucial for researchers, students, donors, and patients to understand both PD pathogenesis and this novel, highly-targeted intervention strategy. I aim to transform these findings into a didactic, highly engaging 3D animation and interactive web module, catering to both scientific and lay audiences.

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Introduction

Parkinson's Disease (PD)

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized in part by the degeneration of dopamine-producing neurons in the substantia nigra region of the midbrain, as well as other neuronal systems throughout the brain.[10] The hallmark symptoms of PD are defined by a combination of motor and non-motor symptoms, such as resting tremor, muscle rigidity, bradykinesia, and cognitive impairment, as well as certain autonomic dysfunctions.[10] PD is primarily associated with the formation of neuronal cytoplasmic inclusions called Lewy bodies, formed by the misfolding and toxic aggregation of the presynaptic neural protein Alpha-Synuclein.[11] However, mounting evidence points to the substantial involvement of the immune system in the pathogenesis of Parkinson's disease, such as overactive inflammatory processes or autoimmune responses.[4,5,12] Such immune hyperactivation could be the underlying contributor of neuronal loss, rather than merely a subsequent response to it.[12]

Parthanatos Pathway

In addition to well-known cell death pathways such as apoptosis, necroptosis, and autophagy, another significant mode of cell death, known as parthanatos, is highly involved in neurodegenerative disorders such as PD.[13] As DNA damage and oxidative stress may gradually overwhelm the cellular self-defense system, the subsequent parthanatos response is first initiated by the overactivation of Poly-ADP Ribose

Polymerase (PARP-1), a nuclear enzyme that normally facilitates DNA repair.[9,13] Hyperactivity of PARP-1 in turn triggers an overproduction of a DNA-scaffold polymer called Poly-ADP Ribose (PAR), which exits the nucleus in excess to prompt the release of the mitochondrial protein Apoptosis Inducing Factor (AIF).[3,9,13] As the PAR-AIF complex detaches from the mitochondria and travels through the cytoplasm, AIF subsequently binds to a critical cytosolic protein called Macrophage Migration Inhibitory Factor (MIF). [3,9,13] This AIF-MIF complex translocates to the nucleus, where it binds to the cell's DNA. While MIF serves several important cellular functions, it is MIF's nuclease activity that initiates fatal DNA cleavage and fragmentation, triggering the decisive step of parthanatos and ultimately inducing cell death. [3,9,13]

cGAS-STING Pathway

The cGAS–STING pathway is another protective mechanism in the body that provides a robust immune defense against infection.[5,14] It activates upon the detection of foreign or suspicious cytosolic DNA such as viruses or bacteria, as well as damaged fragments of the cell's own DNA.[14] This inflammasome response thus normally facilitates neuroprotection from pathogens and provides intrinsic antitumor immunity.[15] However, excessive activation of the cGAS pathway by self-DNA can also lead to autoimmune and inflammatory disease.[15,16] Such is the case in PD, where aberrant self-DNA cleavage by the overactive parthanatos pathway can trigger excessive inflammation by the cGAS-STING pathway, resulting in a perpetual cycle of inflammation, stress, and cell death upon neurons and supporting microglial cells.[4,16]

PAANIB-1: an Avenue for Therapeutic Invention

Exciting new research has unveiled PAANIB-1, a groundbreaking brain-penetrant MIF-inhibitor that prevents the last step of the parthanatos cell death pathway.[7,8] PAANIB-1 specifically blocks MIF's nuclease activity to prevent the generation of harmful DNA fragments without interfering with the molecule's other functions.[7,8,17] MIF's unique structure differentiates it from other nucleases in the body, ensuring that PAANIB-1 safely and selectively inhibits MIF nuclease without indiscriminately disrupting other nuclease activity throughout the body, thus minimizing adverse effects.[8,17,18] Targeting MIF using PAANIB-1 shows promising clinical potential and provides hope for finding a treatment to halt or reverse the progression of neuronal damage that causes the symptoms of Parkinson's Disease.

Project Objectives

- **Craft an engaging 3D animation** that improves public understanding of the Parthanatos pathway and its relationship to the cGAS-STING pathway in PD.
- **Raise awareness of PAANIB-1,** a previously unvisualized first-in-class MIF-inhibitor, as a novel potential therapeutic target for PD.
- **Design an interactive web module** for graduate students that expands on the molecular mechanisms of PD pathogenesis and interventional strategies.

Learning Theories

Cognitive Load Theory states that when too much information overwhelms working memory, learning efficiency decreases and encoding information into long-term memory becomes more difficult.[19] Therefore, it was important to portray the 3D animation as linearly as possible to reinforce an easy-to-follow storyline.

Dual Coding Theory advocates the use of both visual and verbal representations when presenting information, as associating words with imagery aids in information retention.[20] I thus incorporated frequent text labels in the animation to supplement the voiceover and emphasize key information.

Minimalist Theory promotes self-contained and self-directed learning, particularly relevant for interactive learning modules and website design.[21] These principles were utilized when iterating the layout and content flow for my online interactive web module to be as intuitive and self-directed as possible.

Intended Audience

The primary audience for the 3D animation will be the general public, including patients and donors interested in supporting clinical research, and a secondary audience of investigators and graduate students who study neurodegenerative disease. The interactive web module is specifically geared towards onboarding students and researchers who may be working closely on the topic in an academic setting.

Potential Contribution to Biocommunication

To date, no 3D visualizations exist to teach the detailed pathways related to PAANIB-1 research. Existing educational materials found in molecular biology research and publications are often uni-faceted, complex 2D diagrams that prompt cognitive overload, disinterest, and poor comprehension. To address this, my two-part project centers on the design and development of a 3D animation that presents PD pathogenesis as a clear, linear storyline for use in scientific presentations to researchers, donors, and patients. Additionally, I will develop an interactive web module for researchers and students that provides more in-depth information about the concepts depicted in the animation, and that can be easily updated to incorporate future developments in research.

Materials and Methods

Research, Planning, and Design Overview

Cellular and molecular research was conducted in close collaboration with the Dawson Lab at the Johns Hopkins Institute of Cell Engineering. An extensive literature search was conducted, and the following 6 primary topics were studied:

i. The parthanatos pathway

ii. CGAS-STING inflammasome pathway

iii. DNA damage across nervous system disorders

iv. Role of MIF as a PARP-1–dependent nuclease required for parthanatos

v. Mechanisms of pathologic a-synuclein misfolding and Lewy body formation

vi. PAR-dependent cell death in neurodegenerative diseases

From the research data, a voiceover script was drafted alongside several iterative storyboards and wireframes using Adobe Photoshop and After Effects. The material was reviewed by members of the Dawson Lab and faculty advisor for clarity, accuracy, and functionality. All 3D models were created using Cinema4D 2024 (C4D), PyMOL, and embedded Python Molecular Viewer (ePMV) plug-in. All 2D assets were created using Adobe Illustrator and Photoshop. All 3D scenes were rendered using Maxon Redshift, and all assets were subsequently imported into Adobe After Effects for post-processing. The interactive web module was built using WordPress.

Script and Narration Development

In developing the script, the primary aim was to seamlessly guide viewers from the broader concepts of PD to its more technical and detailed molecular mechanisms and relationships, as outlined in **Figure 1.** This required being judicial in deciding which details to include—the script needed to provide ample context without overwhelming the audience, while also not being overly broad and vague.

Additionally, wherever possible and appropriate, scientific terms were explained and accompanied by on-screen text and repetition of abbreviations to increase retention and reinforce names and concepts used throughout the animation.

Lastly, one of the main challenges during the script-writing process was to keep the narration as short and succinct as possible. Since this was a priority, the script remained flexible well into the post-production process to allow for progressive editing as needed. This flexibility allowed continued assessment of what narration was essential. The initial script of 547 words (approx. 5 min reading time) was ultimately edited and shortened to 462 words (approx. 3 min reading time).

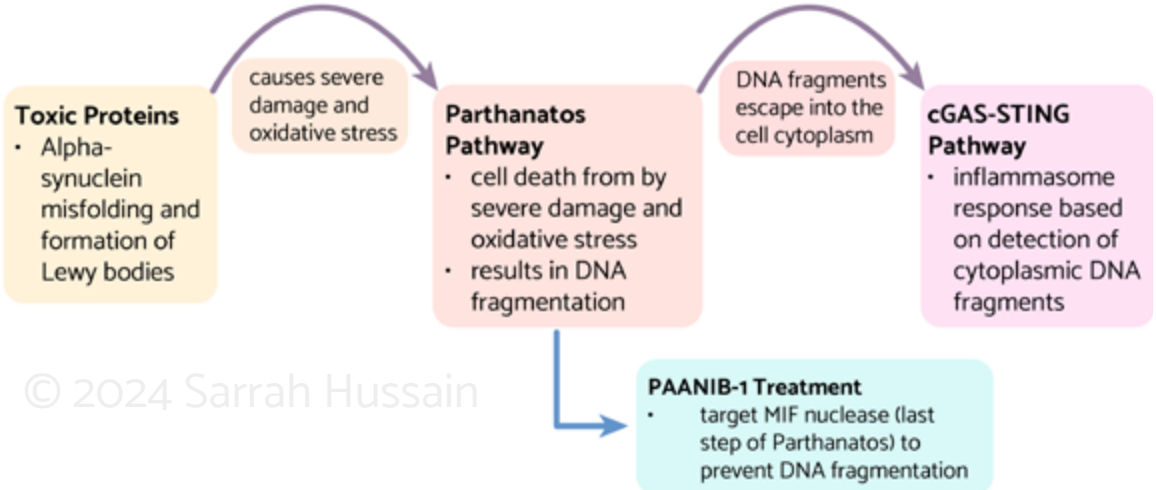


Figure 1. Flowchart for 3D animation script.

Storyboard Development

a. Interactive website

The original intent of the webpage was to serve as an information repository for the molecules and pathways discussed in the project, as depicted in the initial—now obsolete—wireframe concept **(Figure 2).** However, as the 3D animation neared completion, the interactive web module underwent significant development, departing significantly from this original wireframe. The initial idea of three separate page tabs was discarded in favor of a single-page comprehensive visual timeline of PD pathogenesis, which more effectively connected the relationships between neuronal damage, cell death, and inflammation. Additionally, the Parthanatos molecules were reorganized into a more engaging and interactive semi-circular timeline. Finally, a section on PAANIB-1 was added, detailing how this therapeutic treatment could effectively mitigate PD symptoms. These layout decisions emerged concurrently during the webpage development process and were greatly influenced by experimenting with the capabilities of WordPress.

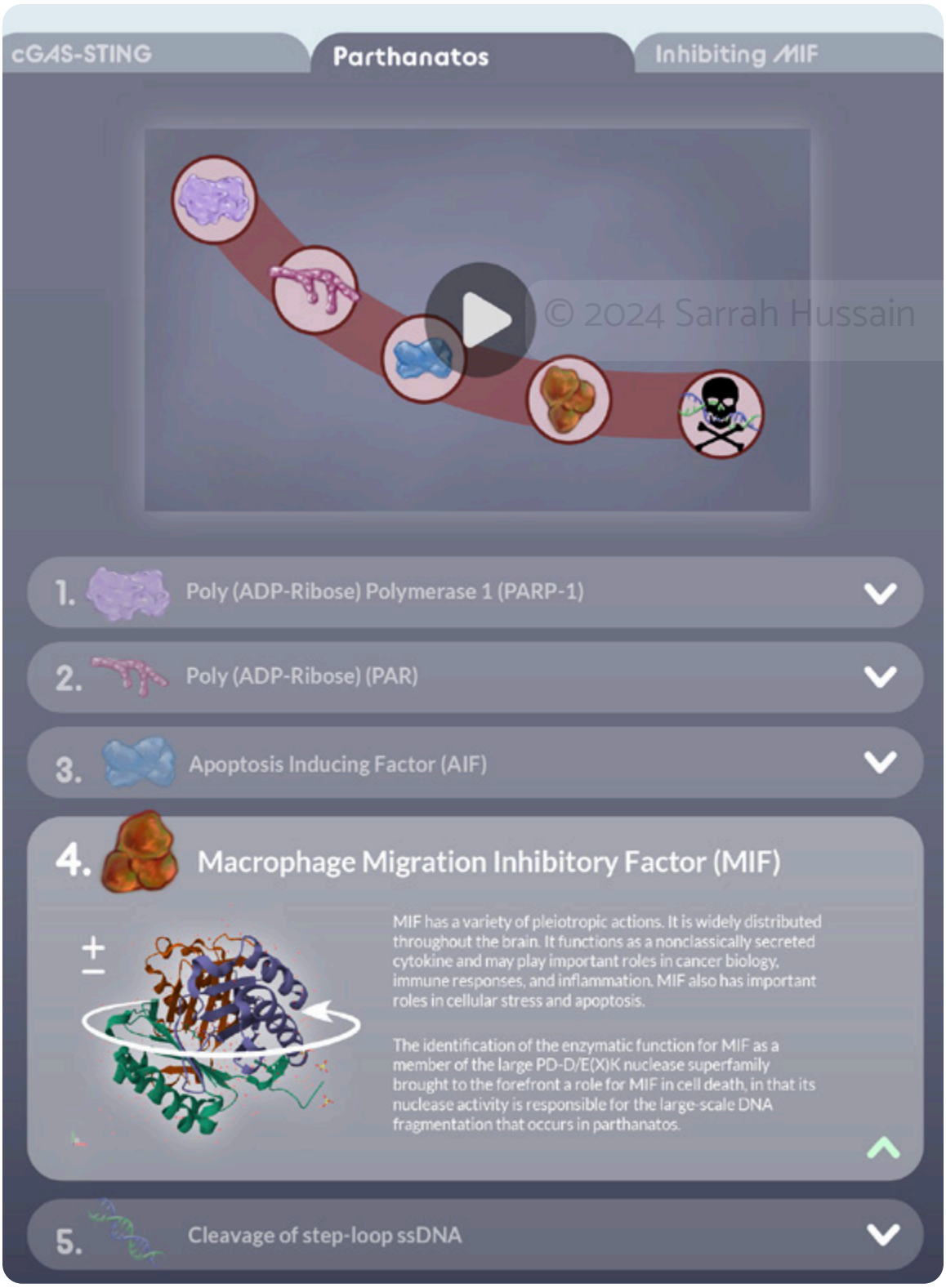


Figure 2. Initial (obsolete) wireframe of interactive webpage. Text not intended to be read.

b. 3D animation

Thumbnail sketches for the animation were first developed in pencil **(Figure 3)** and revised into a complete preliminary storyboard **(Appendix B)**. These storyboards were subsequently scanned, cleaned and further developed digitally using Adobe Photoshop to create concept art **(Appendix C)** that reflected the intended look of the final visuals. Using these thumbnails, concept illustrations, and a rough recording of the voiceover script, a preliminary animation, or *animatic*, was drafted in Adobe After Effects. This served as the creative blueprint or "skeleton" off which the final 3D animation would be built.

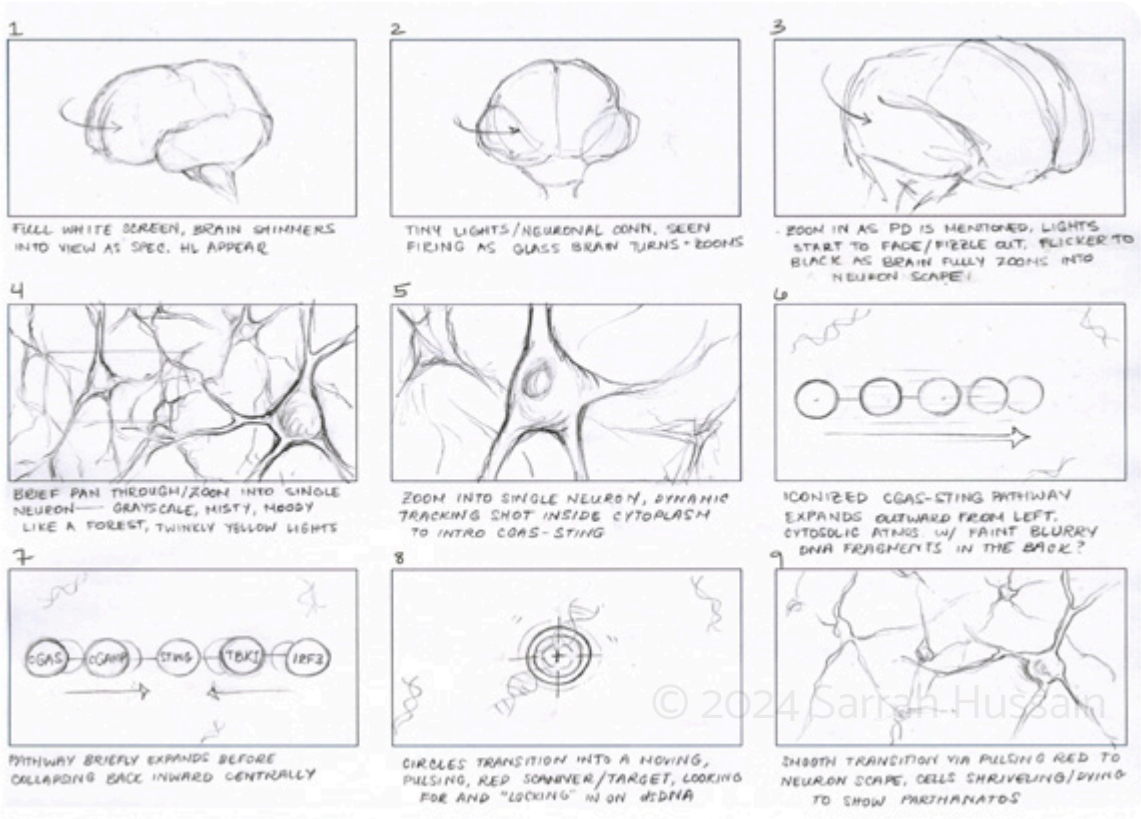


Figure 3. Select thumbnail sketches for 3D animation storyboard. Text not intended to be read. Full storyboard available in Appendix B.

Asset Creation

a. Interactive Web Module

Visual content for the interactive web module was derived from the animation except for a few newly added assets such as the atomic structure of PAANIB-1, which were introduced to provide in-depth information for web delivery.

b. 3D animation

Throughout the animation process, several creative and logistical decisions were made to prioritize the overall visual impact of the product while optimizing efficient production and delivery of the desired scenes and effects. For example, I opted to fully render cytosolic DNA fragment scenes in C4D instead of using alpha channels for transparent DNA and creating the environment in After Effects. Although the latter approach offered potential stylistic flexibility during post-processing, my small-scale experiments showed that this flexibility was not significant or particularly advantageous in this instance. Instead, focusing on perfecting the environment within C4D was a more time-efficient route and allowed for a more convincing final product. For instance, it enabled realistic interactions of "God-rays" with scene objects, producing authentic refraction and shadows.

Additionally, to achieve the effect of synaptic activity in my neuron-scape scenes for example, I utilized Maxon Red Giant Universe in After Effects rather than manually producing an electrical pulsing light effect in C4D. Manual manipulation and keyframing of materials within C4D would have been tedious and would have

significantly increased render time. Instead, reserving this effect for post-production offered remarkable flexibility to fine-tune in real-time without the need to re-render assets after each revision.

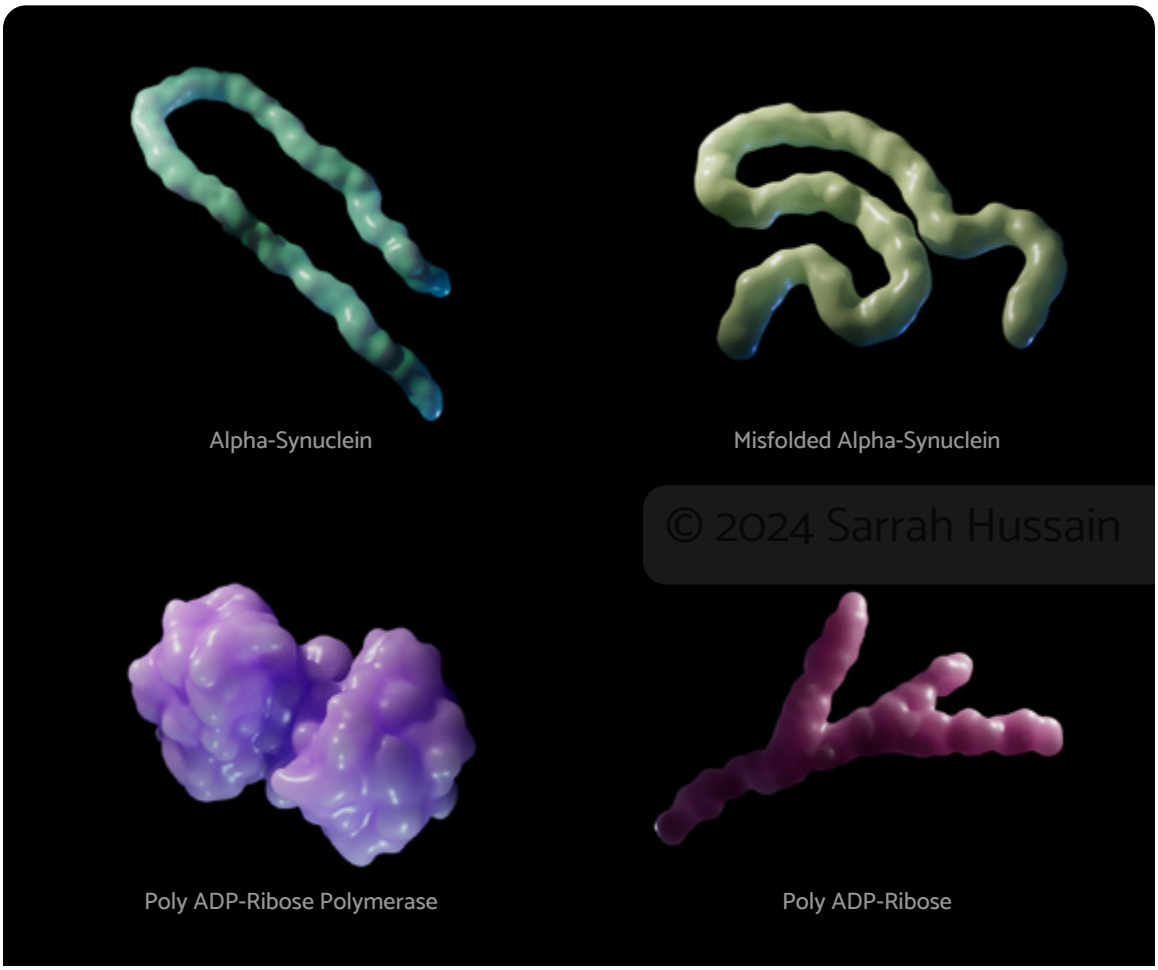
Lastly, given the abundance and variety of molecules or "characters" in the animation, it was crucial for viewers to be able visually differentiate molecules and easily recognize and interpret contextual changes in environmental scenes, especially in areas where molecules and locations were not explicitly restated. I therefore organized all my material color and texture assignments into a chart I could consistently reference during the modeling process to maintain clarity and visual contrast across my assets.

c. Modeling molecules in Cinema4D

The RCSB Protein Data Bank (PDB), Alpha-Fold, and ChemDraw were utilized to retrieve and reconstruct accurate 3D models based off PDB codes **(Figure 4).** Because PAANIB-1 research is currently ongoing, I worked with principal investigators from the Dawson Lab to manually construct a PDB file of the atomic and molecular surface structures of PARP-1 and PAANIB-1. Additionally, there was little data available on the exact structure of the carbohydrate polymer PAR. This molecule was therefore manually constructed using a series of cloned spheres aligned along a spline in Cinema4D. Each molecule was indivually refined and rendered in C4D **(Figure 5)**, and additionally imported and stored into a single 3D project file for convenient asset retrieval.

Molecule:	PDB Code:
Alpha-Synuclein	1xq8
Misfolded Alpha-Synuclein	6peo
Apoptosis Inducing Factor (AIF)	1m6i
Macrophage Migration Inhibitory Factor (MIF)	1gdo
Human Nuclear Pore Complex (NPC)	5a9q
Poly ADB-Ribose Polymerase 1 (PARP-1)	File supplied by Dawson Lab
PAANIB-1	File supplied by Dawson Lab
Poly ADP-Ribose	Manually constructed

Figure 4. PDB source material for 3D structure of each molecule structure.



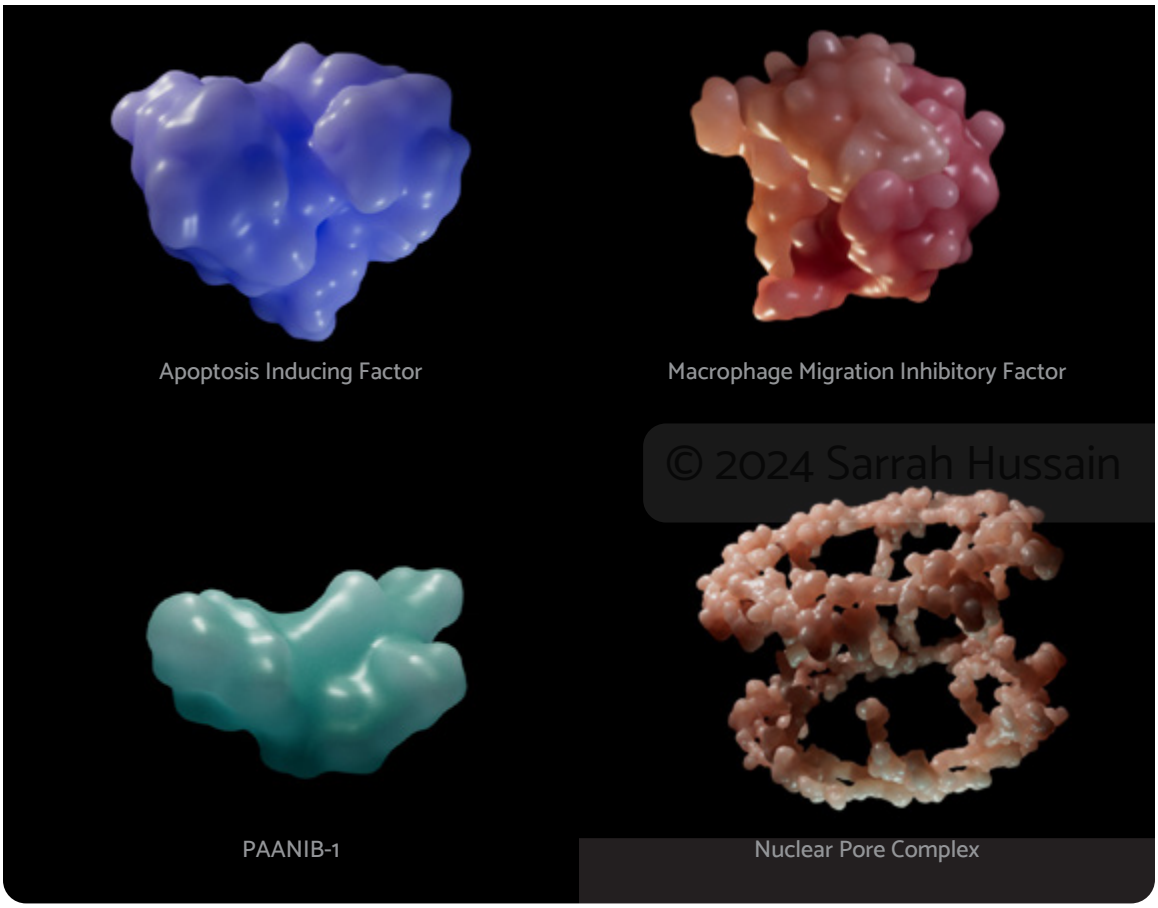


Figure 5. Rendered 3D models of all PDB-specific molecular structures using Cinema4D.

i. *Creating a stylistic depiction of DNA fragmentation*

During the last scene of the parthanatos pathway when MIF nuclease binds to DNA inside the nucleus, I used Cinema4D to create a stylistic depiction of DNA cleavage that emulated glass shattering. To achieve this, I first used the **Lasso tool** on point-select mode to isolate point groups, and then used the **Split** function to divide the DNA strand into 3 separate objects. Therefore, while the DNA still appeared as a single strand, I could isolate the middle segment and apply a fracture effect to that segment only. I then created a **MoGraph Voronoi Fracture** and parented it to the middle DNA segment. Within the Voronoi Point Generator

Distribution, I refined the **Point Amount** to 37 to achieve a convincing fracture output **(Figure 6).** After adjusting **Gravity** metrics to zero, I then added **Random** and **Push Apart** effectors to manipulate the fracture physics to my desired explosion effect. I keyframed the Push Apart effector to increase in strength immediately after the molecule moved away from the strand. Lastly, I manually keyframed the two flanking DNA pieces to have some subtle outward movement and rotation during fragmentation.

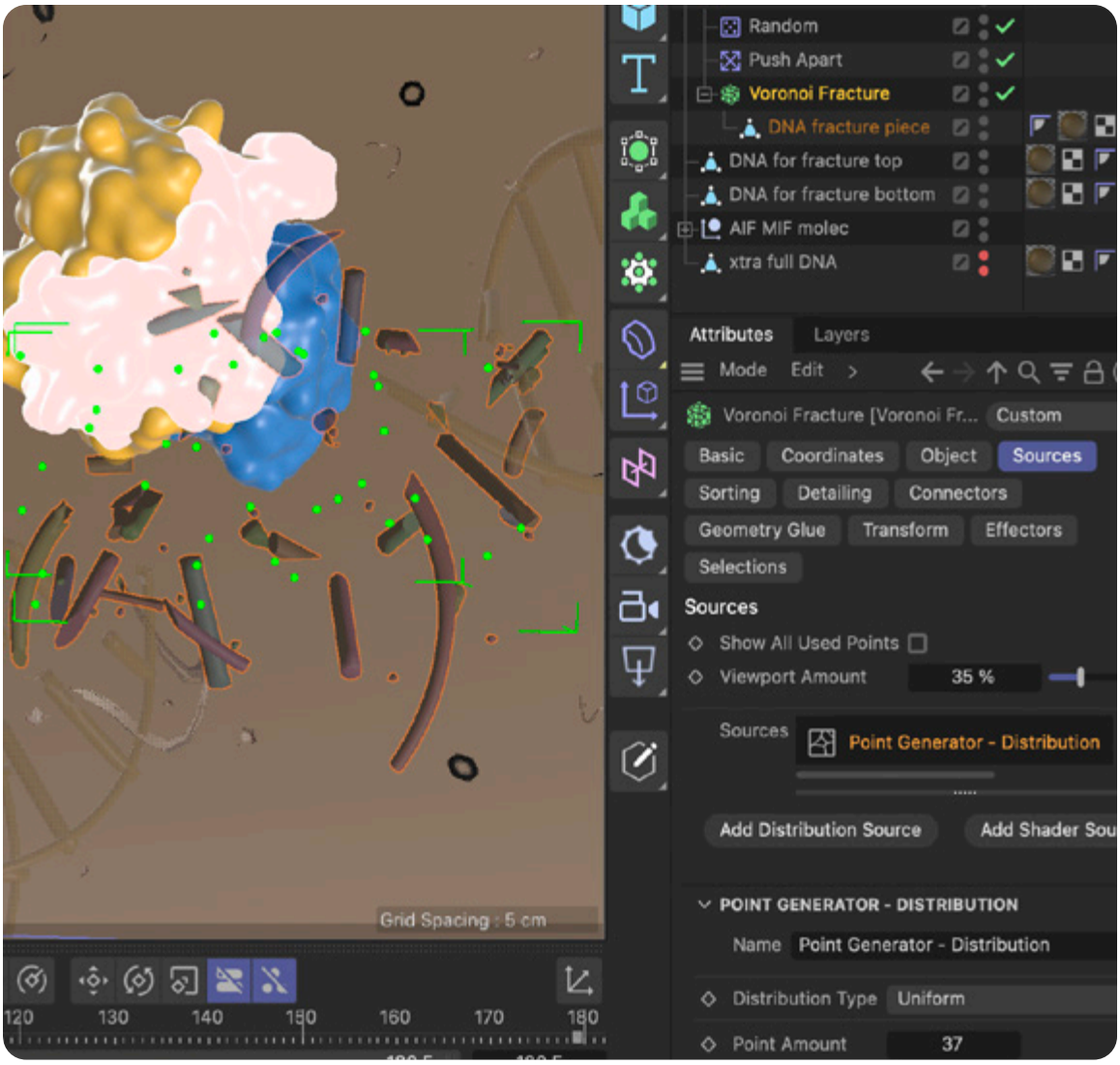


Figure 6. MoGraph Voronoi Fracture Point Generator Distribution setup in C4D.

ii. *Creating Mitochondrial cristae*

Mitochondria were necessary to provide environmental context to several scenes in the animation. I therefore strove to model them in a way that was stylistic yet still recognizable and representative of their characteristic structure. To achieve this, I began with two identical **Capsule** objects in C4D, each representing the outer and inner mitochondrial membranes. Identical **Bend** deformers were applied to each to create a bean-like shape, after which the inner capsule was scaled down to sit centered inside the outer capsule.

I then shifted to **sculpt layout** in C4D to begin refining the inner capsule into a more realistic cristae structure. I used a variety of tools such as **Wax, Draw, Inflate,** and **Smooth** to sculpt a series of organic folds and undulations to represent the extensive surface area **(Figure 7)**. During this process, I incrementally increased the number of **Sculpting layers** on the base object to 5 to increase polygon count to allow for more nuanced surface manipulations.

Figure 7. Using Wax tool to sculpt mitochondrial cristae in Cinema4D.

I then created two separate Redshift materials for the inner and outer membranes. I strove for the outer membrane to have a glassy, almost jelly-like appearance that allowed the inner cristae to be seen. For the inner membrane I created a powdery, snow-like Redshift material by layering a **Noise shader** (Naki) in the **Bump map (Figure 8A)** and adjusting subsurface scattering settings. Lastly, I incorporated a **Cloner** object of stylized proteins to appear embedded in the jelly-like outer membrane of the mitochondria **(Figure 8B)**.

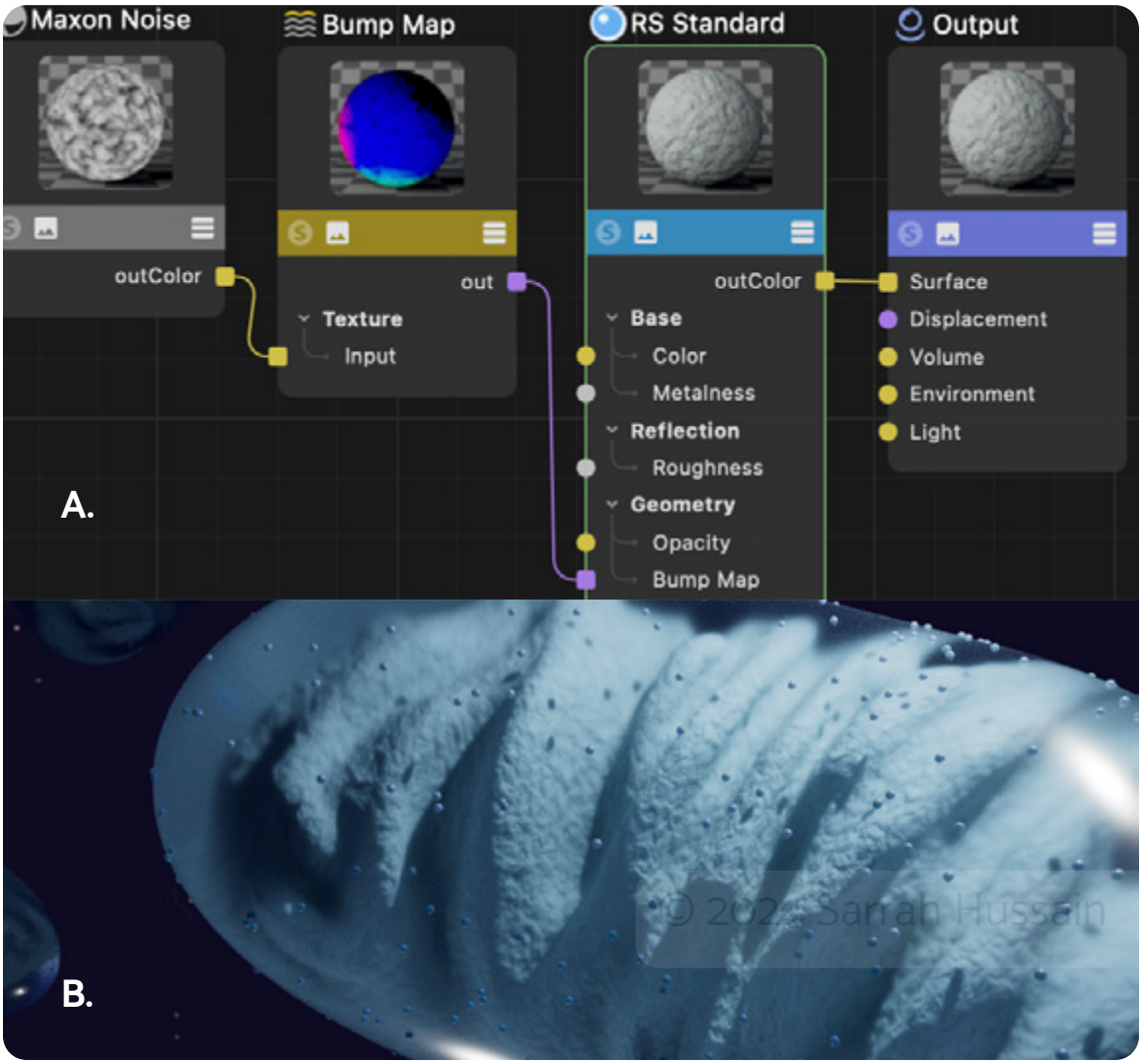


Figure 8. (A) Mitochondria Redshift material node editor showing Bump map setup. (B) Final Redshift render output for double membrane mitochondria textures.

iii. *Creating the nucleus and nuclear pore complex (NPC)*

There are two primary scenes in my animation which involve molecules entering or leaving the nucleus. I built the framework for these scenes using **Sphere** objects and a series of cloners. To first create a hollow spherical shell, I used the **Boole** tool (A without B) to subtract one "inner sphere" (80 cm radius, 12 segment icosahedron) from an "outer sphere" (100 cm radius, 12 segment icosahedron). I converted this shell into an **editable object** (Object > Current State to Object). Next, I created a **Cloner** object of 6 cm spheres, with **Mode set to Object,** and used my shell as the reference object. With **Align Clone** checked and Distribution set to **"Vertex,"** the spheres were evenly distributed across my shell to represent the location of each nuclear pore. I converted this cloner into an object and repeated the **Boole** process (A without B) with the shell and converted cloner object to create a nucleus with several holes **(Figure 9)**. I again converted this into its own object called "nucleus," and nested it under a **Thicken** generator. This allowed me to fine tune the desired thickness of my nucleus (3 cm).

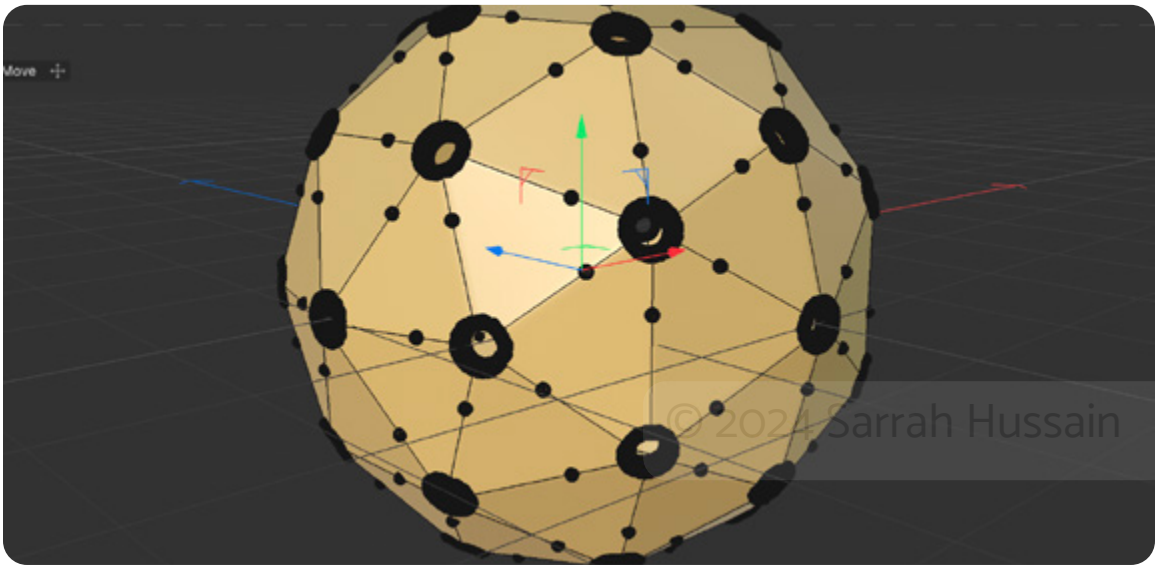


Figure 9. Distribution of nuclear pore Cloner object across vertices of nuclear shell.

From this point, I began refining the aesthetics of my nucleus by embedding stylistic surface proteins and filaments using various cloners. Within my Redshift (RS) Materials for the nuclear surface and pore complex, I utilized a **Maxon Noise** through a **Displacement TexMap** to achieve a distorted, proteinaceous surface texture **(Figure 10)**. PDB data was also utilized to achieve a realistic NPC structure. This NPC model was refined in a separate C4D file, then imported into my nucleus

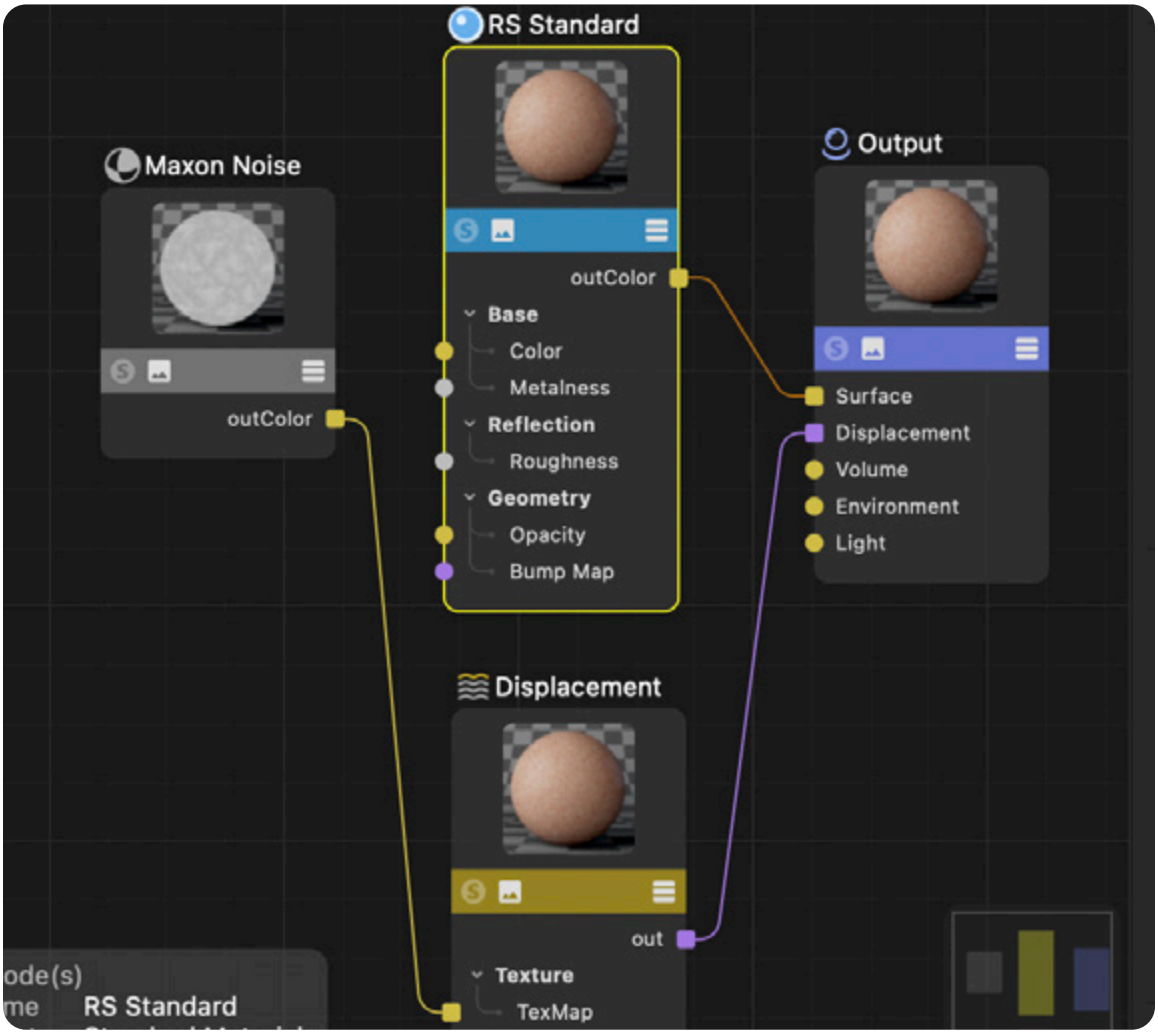


Figure 10. Redshift material node editor showing Displacement TexMap setup for nuclear surface and pore textures.

structure, scaled, and embedded into place at the pore site **(Figure 11).** Lastly, using RS Environment object and a RS Point light centered inside the nucleus, I adjusted various fog, scattering, attenuation, and volume light parameters to achieve a glowing light source that emanated through the pores.

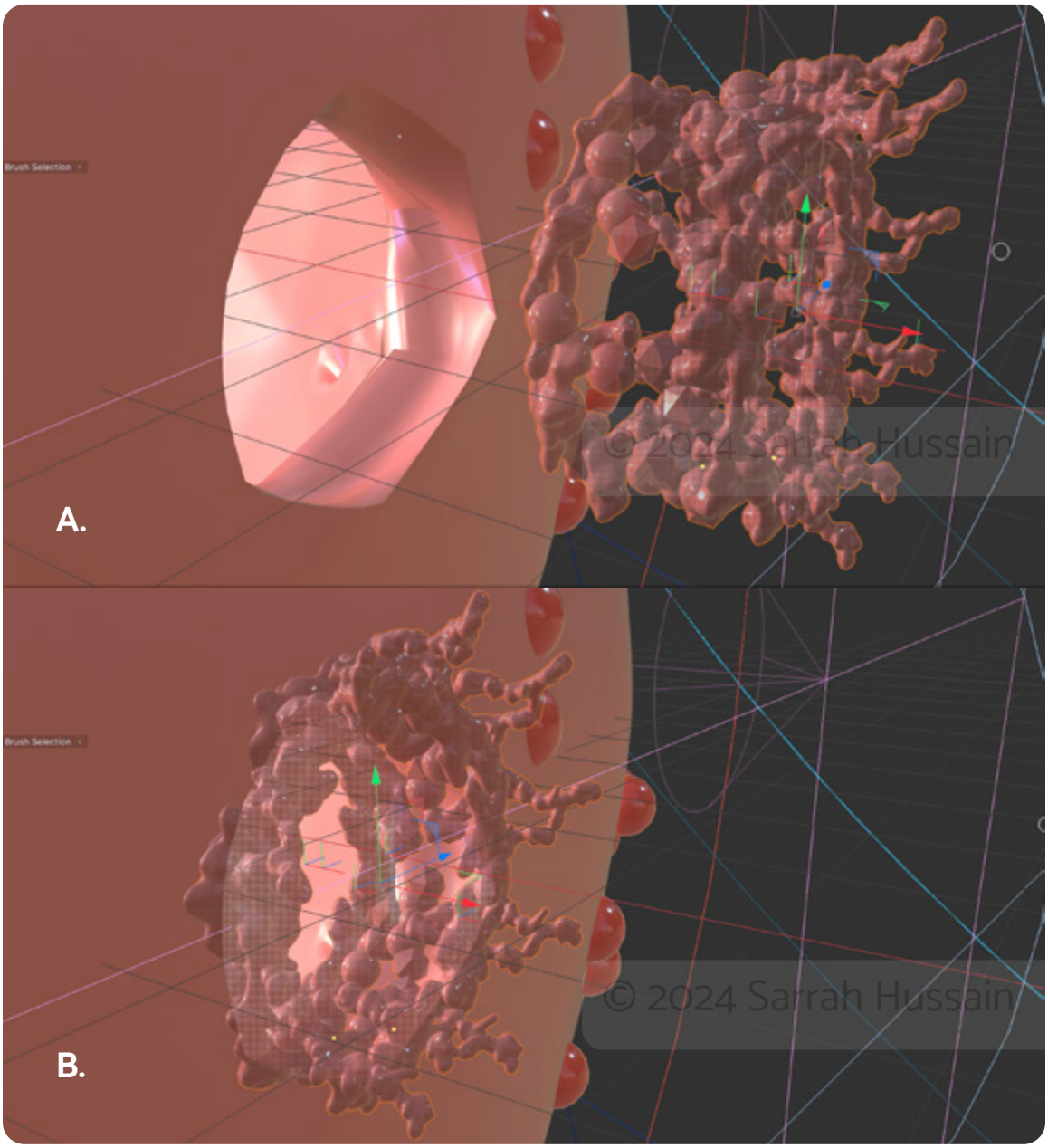


Figure 11. (A) NPC model imported and scaled to nucleus model. (B) NPC model positioned and nested inside nucleus model to complete the pore site.

Post-Production

Rather than waiting until all assets were fully rendered, I began the post-production process as soon as C4D footage was available. This allowed simultaneous progress in 3D modeling and editing to avoid project delays or bottlenecks. In several cases, exporting low-resolution **.MOV** renders served as effective placeholders for scene testing and reviews by preceptors. This approach allowed for swift adjustments and circumvented the need for laborious high-quality renders after each iteration.

It is worth noting that for certain post-production effects, additional exports of specific file types were necessary. For example, separate **.OBJ** files of the PAANIB-1 introduction scene were required for Trapcode Suite to produce 3D model-based Particular dynamics.

i. *Creating holographic MIF effect*

During the portion of the animation which addresses the unique structure of MIF, I aimed to create a glitchy, holographic "body-scan" effect that visually emphasized the molecule's topography. To achieve this, I first duplicated the desired footage, pre-composed it, and set the blend mode to "screen" to allow all further manipulations to the pre-comp to appear overtop the original footage. I then added **Find Edges** effect, set it to "invert," and set "Blend to Original" to a low value. I next added a **Tint** effect. The "Map White To" controls the color of the holographic body scan, which I set to a characteristic tech-style neon green color. I then added both the **Glow** and **Curves** effects to adjust style and degree of visibility of hologram **(Figure 12)**. I lastly layered a **uni.Holomatrix II** effect,

found within Maxon Red Giant Universe. I kept this very low by setting “Blend with Original” to 88%. Within this pre-comp, I created a rectangular mask with approx. 30 px. feather blur, and keyframed the **Mask Path** to sporadically pan across the screen to emulate a scanning effect **(Figure 13)**.

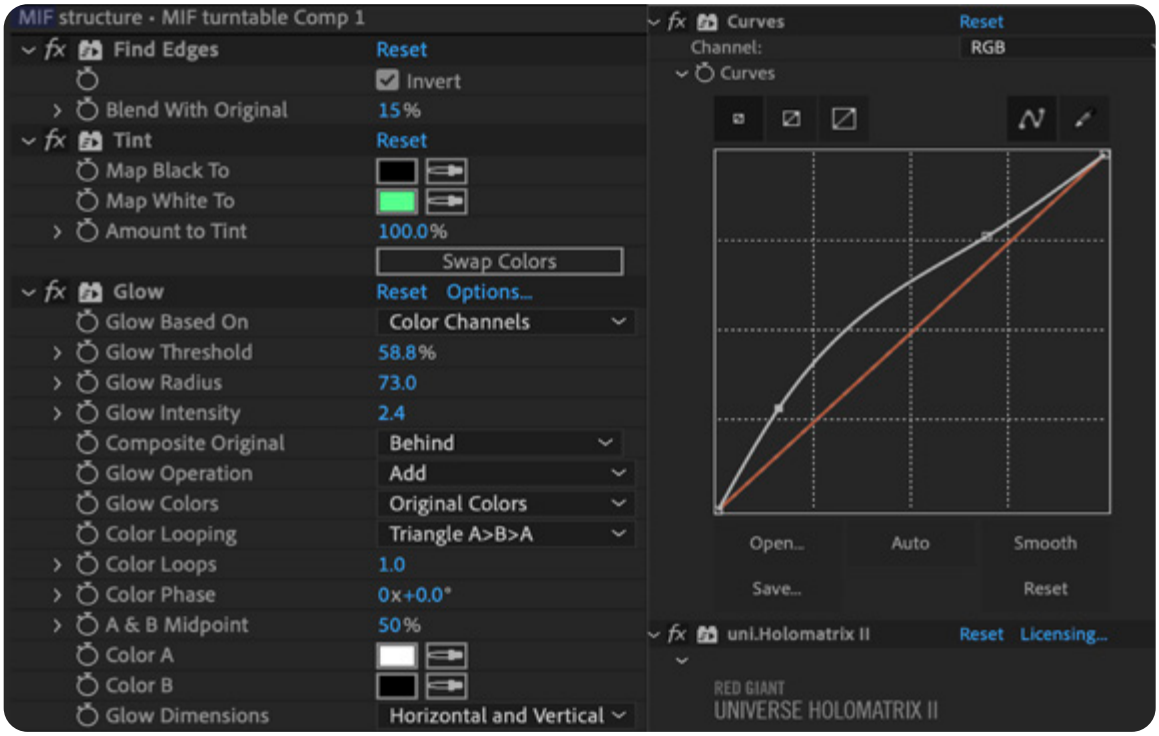


Figure 12. MIF Holographic effect parameters in AfterEffects.

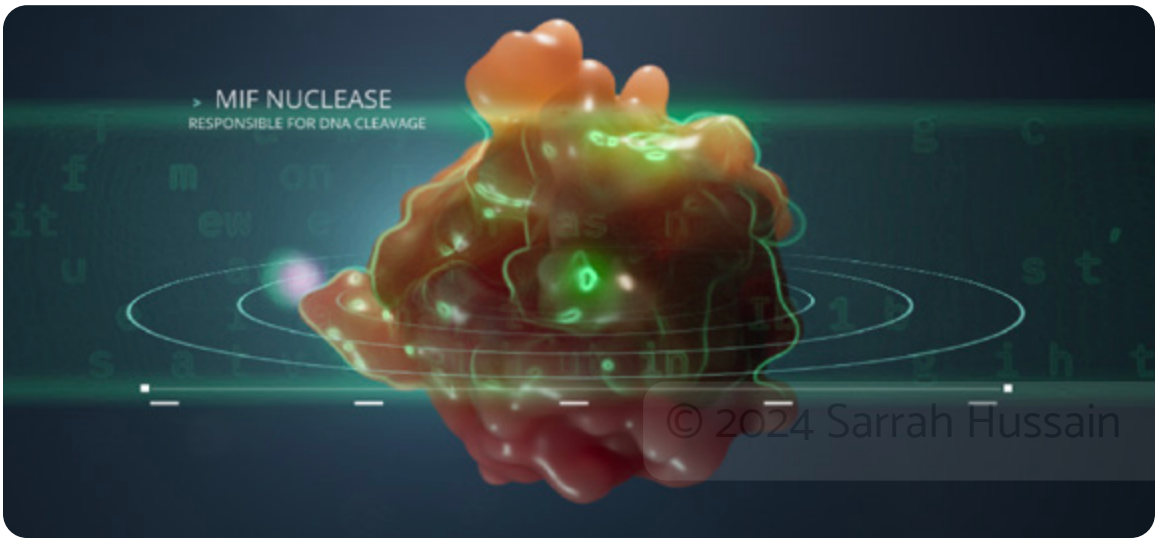


Figure 13. Final AfterEffects render output for MIF Holographic effect.

ii. *Creating realistic depth in PAANIB-1 particle simulation*

By creating a 3D layer Particle System in After Effects **(Figure 14A)**, I achieved a more realistic particle path during the PAANIB-1 introduction scene. I manipulated the AE camera and the producer physics to trace along a three-dimensional path **(Figure 14B)** to give the illusion that PAANIB-1 particles were flowing towards the viewer from a distance and entering into a neuron.

Figure 14. (A) Particle System generator parameters in AfterEffects. (B) Render view of 3D layer Particle System producer's keyframed path in AfterEffects.

Integration of interactive website and 3D animation

Upon the animation's completion, I was able to manipulate and export various scenes as standalone material for the site. I converted these scenes into **.GIF** files using an Adobe Express Converter for a faster and more optimized web output. Following the architecture of the flowchart and wireframes previously drafted, I organized all the visual information by aligning each scene with the predetermined structure and hierarchy of the module. Lastly, the full animation was embedded at the bottom of the webpage to serve as a comprehensive summary, allowing users to first engage with foundational text and visuals before being able to view the entire animation. This strategic placement was meant to ensure that the animation complemented the preceding information without overshadowing it, thus maintaining user engagement and encouraging self-guided exploration of more detailed content.

Results

3D Animation stills

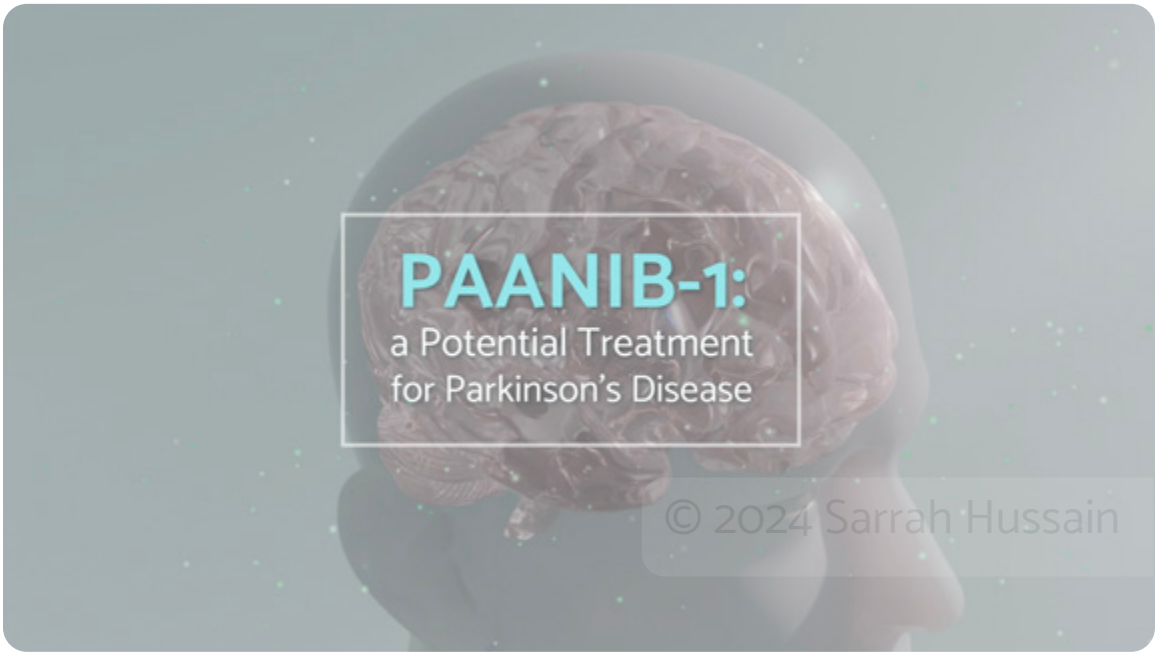


Figure 15. 3D Animation, title scene.

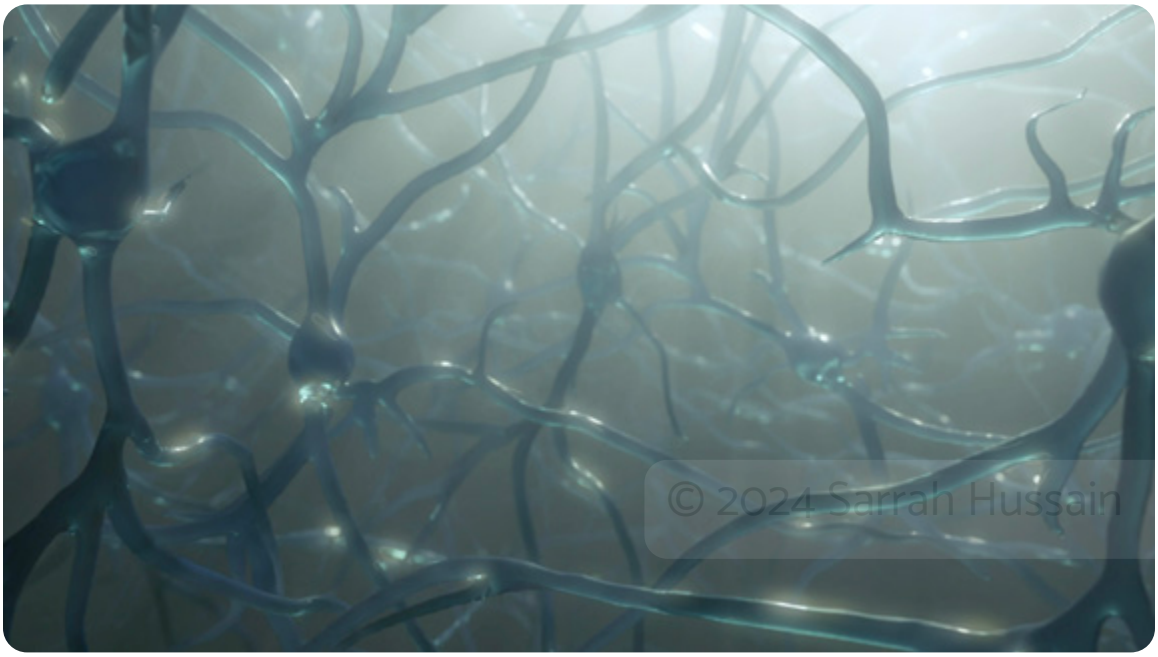


Figure 16. 3D Animation, pan and zoom through introductory neuronal landscape.

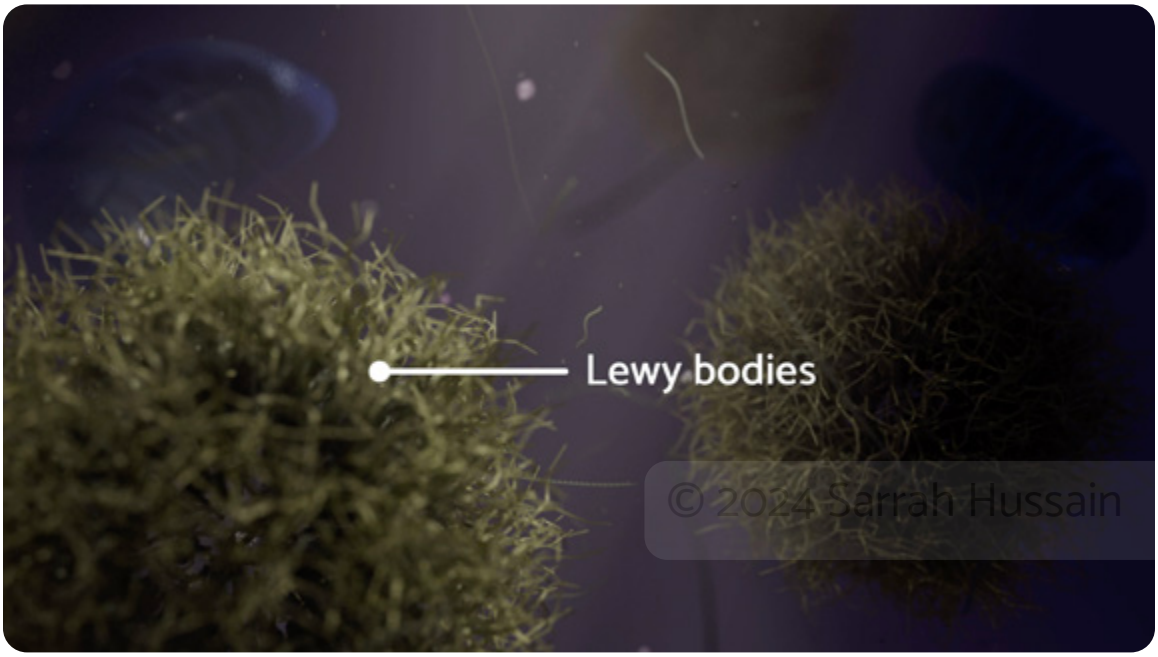


Figure 17. 3D Animation, Lewy body formation is brought into focus.

Figure 18. 3D Animation, cGAS-STING pathway symbolically shown as targets recognizing the presence of cytoplasmic DNA fragments.

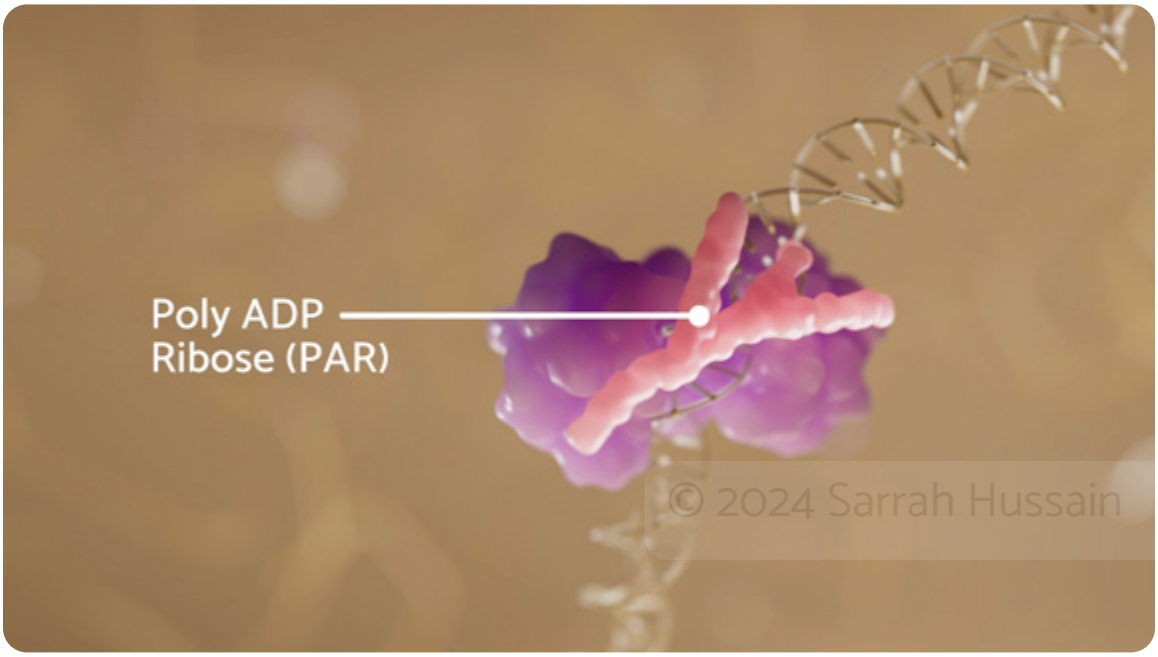


Figure 19. 3D Animation, introduction of the DNA-scaffold polymer Poly ADP-Ribose (PAR).

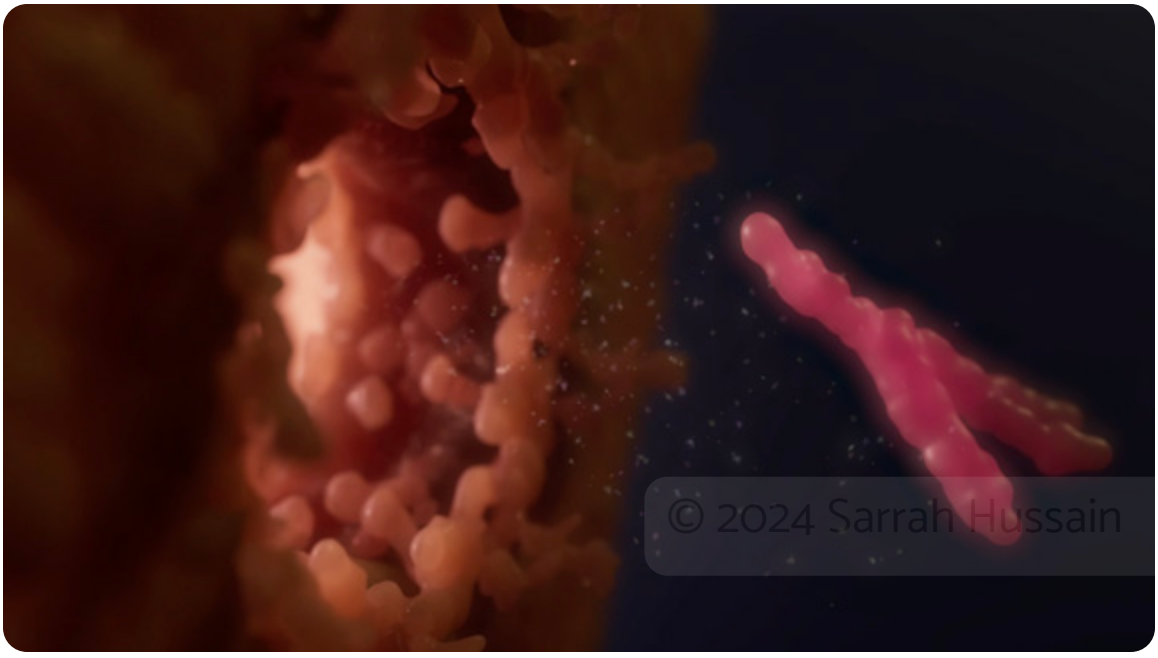


Figure 20. 3D Animation, PAR seen exiting the nucleus via nuclear pore complex.

Figure 21. 3D Animation, Mitochondria brought into focus as PAR molecule travels towards it.

Figure 22. 3D Animation, PAR shown approaching the mitochondrial membrane protein Apoptosis Inducing Factor (AIF).

Figure 23. 3D Animation, steps of Parthanatos summarized in motion graphics pathway.

Figure 24. 3D Animation, stylistic depiction of DNA fragmentation upon binding of MIF nuclease to DNA strand.

Figure 25. 3D Animation, introduction scene of PAANIB-1 molecule.

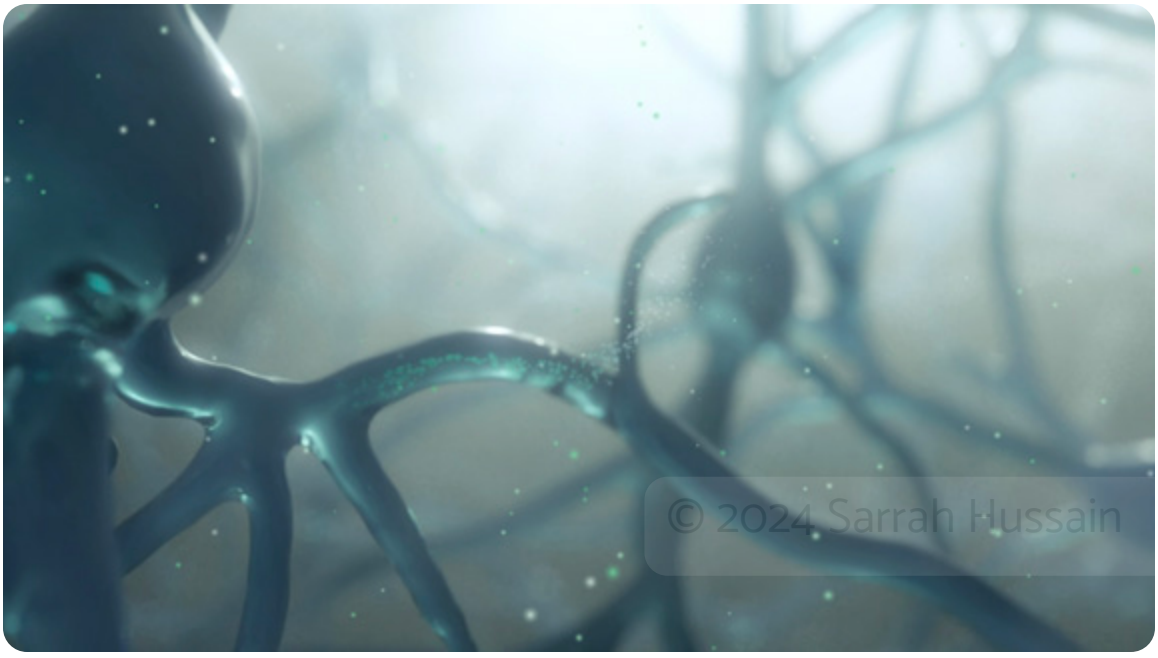


Figure 26. 3D Animation, PAANIB-1 particles brought into focus as seen entering neuron.

Interactive Website stills

Figure 27. Interactive Web Module, landing timeline introducing the progression of PD. Text not intended to be read. Full web text available in Appendix D.

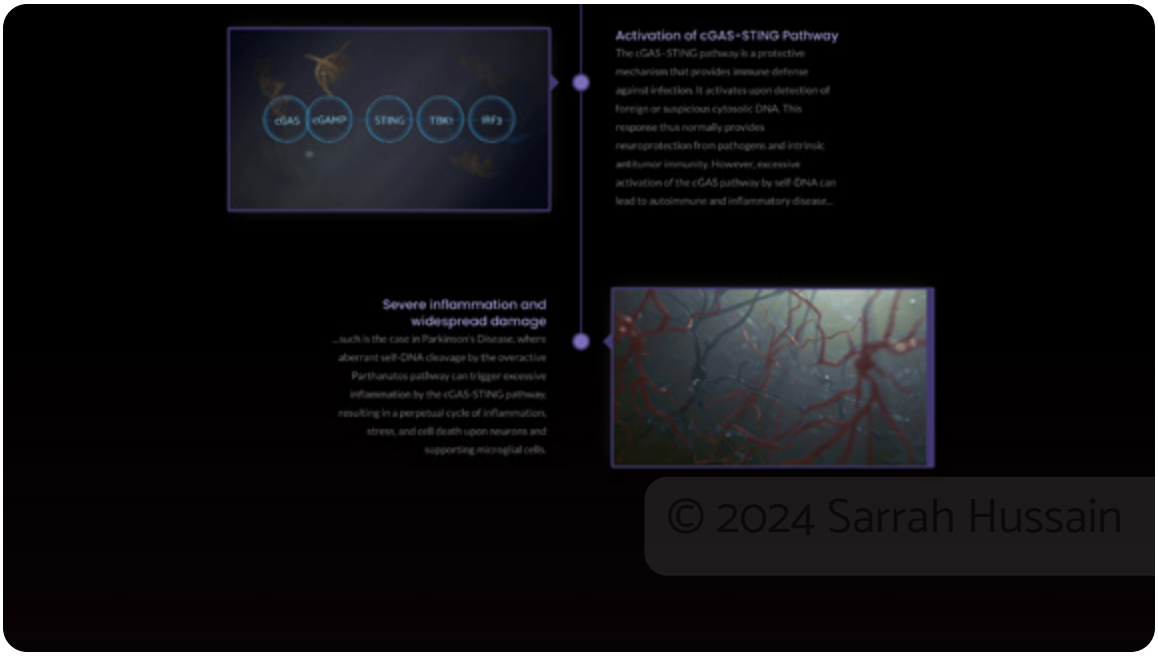


Figure 28. Interactive Web Module, continuation of landing timeline. Text not intended to be read. Full web text available in Appendix D.

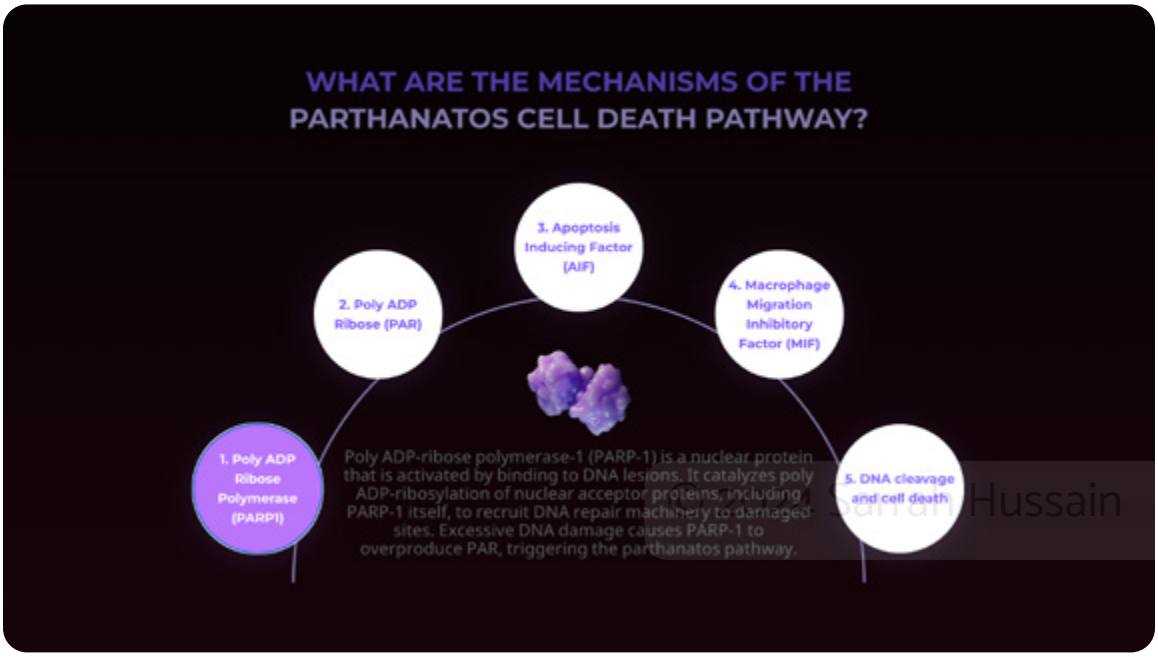


Figure 29. Interactive Web Module, semi-circle timeline of molecules involved in Parthanatos. Text not intended to be read. Full web text available in Appendix D.

Figure 30. Interactive Web Module, introduction of PAANIB-1, a potential therapeutic treatment for PD. Text not intended to be read. Full web text available in Appendix D.

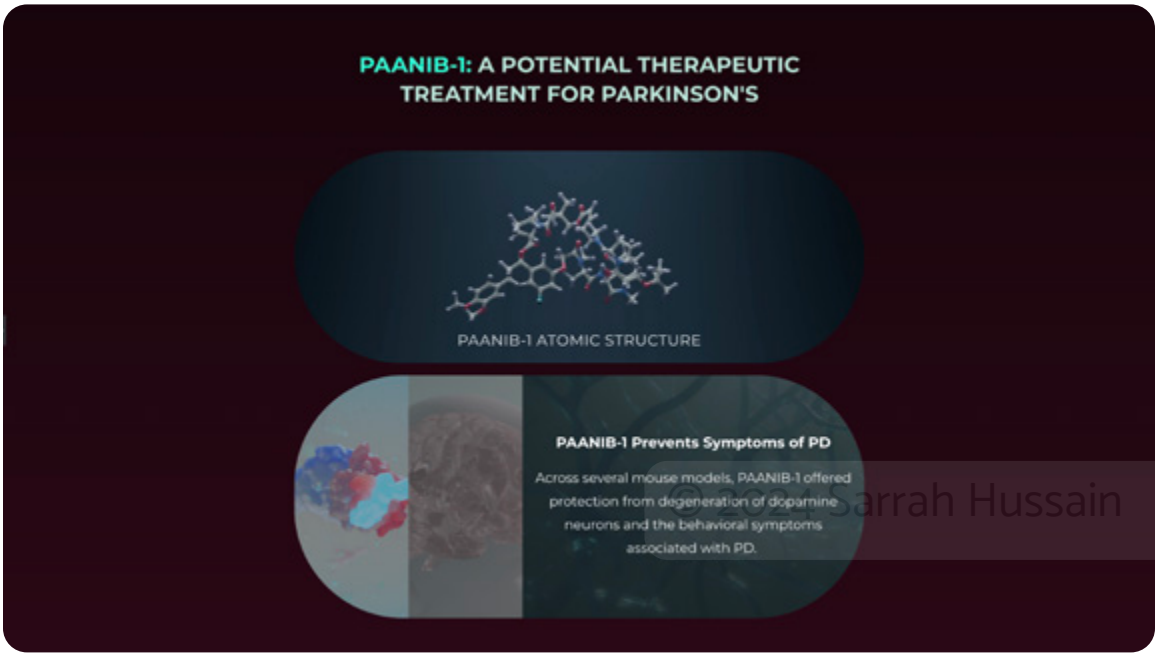


Figure 31. Interactive Web Module, hover state over image accordion revealing information about PAANIB-1. Text not intended to be read. Full web text available in Appendix D.

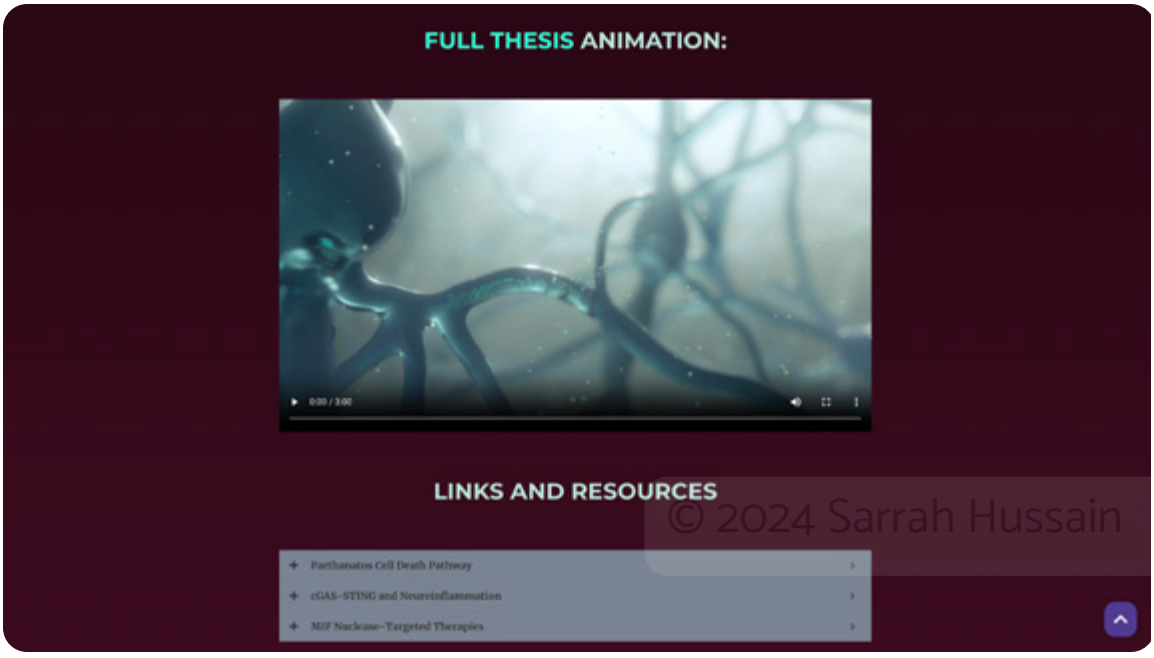


Figure 32. Interactive Web Module, bottom of webpage where full thesis animation is embedded and links to references are available. Text not intended to be read.

Access to Assets from this Thesis

The final 3D animation and interactive webpage can be viewed at **https://thedawsonlab.org** and **https://sarrahhussain.com/**. For more information, the author of this website can be contacted through the Department of Art as Applied to Medicine via **https://medicalart.johnshopkins.edu/.**

Discussion

Project Objectives and Efficacy

This project aimed to effectively communicate the mechanism of parthanatos, the primary pathway of interest, while also explaining the role of the cGAS-STING pathway—a secondary mechanism that exacerbates inflammation by responding to DNA fragments released during parthanatos. Additionally, the project aimed to introduce a novel potential therapeutic treatment for PD called PAANIB-1, which prevents the last step of parthanatos.

The animation touched upon all the above topics while prioritizing brevity and viewer engagement. In supplement, the interactive web page provided a more in-depth, self-guided experience to learn about the various pathways involved in PD and the exact mechanism of PAANIB-1 intervention.

Informal feedback was received from members of the Dawson Lab and colleagues within the Cell Engineering Institute, each with varying degrees of background knowledge and experience. This feedback allowed me to revise and improve the storyline and timing of the animation and verify scientific accuracy of molecular interactions.

Challenges During the Project

Crafting a successful and educational 3D animation about a non-linear topic presented multiple challenges. To ensure clarity, especially for audiences with limited

scientific background, the animation needed to provide a straightforward, linear explanation of parthanatos while still acknowledging its non-linear, positive feedback loop with the cGAS-STING pathway.

To accomplish this, a comprehensive script was drafted during the planning stage, which served as the “backbone” of the storyboard and animation. Delaying the procurement of a professional voiceover artist until the animation was fully completed allowed for greater flexibility in refining and revising the script.

Additionally, navigating the learning curves associated with the various programs utilized in the production of this thesis proved to be a substantial aspect of the project. It was my first time working with Cinema4D 2024, Redshift renderer, Maxon Red Giant Universe, and Maxon Trapcode, which necessitated effective time management throughout the production process. Prior to beginning work on the thesis deliverables, several weeks were dedicated to acquainting myself with these applications through experimentation with smaller-scale sample projects. While this initial investment of time was demanding, it notably enhanced my modeling and editing proficiency, and provided foresight into what effects were achievable and the optimal tools for their execution.

Lastly, given that research on the mechanisms of Parthanatos and PAANIB-1 is currently ongoing, certain knowledge gaps required that the animation be presented in a more generalized way. Specific details such as precise binding behavior between molecules or conformational changes were unavailable, thus requiring artistic interpretation. Given that the animation’s objective was a broad coverage of the relationships between pathways and how they relate to PD pathogenesis, many highly specific details were deemed nonessential for the purpose of this project.

Future Developments and Improvements

Moving forward, there would be a significant benefit in conducting formal assessments to gauge the effectiveness of both the animation and the web module. For example, collecting data from graduate students with pre- and post-surveys would provide valuable insights into the learning outcomes and overall impact of the educational materials. Additionally, as testing for PAANIB-1 viability becomes more definitive, there will be an opportunity to leverage the animation as a tool for educating donors and potential PD clinical trial patients.

While the web module is currently iOS compatible, there is room for improvement by increasing optimization for a more seamless user experience across multiple iOS devices. This would enhance accessibility and usability for a wider audience. Lastly, it would be worthwhile to continue iterating the webpage to reflect the latest developments in the field, to ensure that the educational content remains relevant, up-to-date, and informative.

Appendix A: 3D animation script

A groundbreaking discovery in molecular biology sheds light on a potential therapeutic treatment for Parkinson's disease -- a neurological disorder marked by the gradual loss of dopamine neurons in the brain. It involves the cGAS-STING pathway, a vital mechanism that detects damaged or suspicious DNA in the cell's cytoplasm and orchestrates a rapid microglial immune response as a result. This process is linked to parthanatos, a cell death mechanism to isolate damaged or infected cells and prevent the spread of disease.

But when excessively engaged, these pathways can lead to severe inflammation and unintended widespread damage, as the cGAS-STING pathway recognizes and responds to cytosolic DNA fragments created through parthanatos. But why and how exactly does parthanatos occur? In Parkinson's, a protein called alpha-synuclein misfolds, accumulates, and aggregates over time to form damaging fibrils, which disrupt normal cell function and cause severe oxidative stress on neurons.

In response, a protein in the cell nucleus called Poly ADP Ribose Polymerase, or PARP1, typically orchestrates the repair of such stress-induced damage by creating poly ADP ribose, or PAR, a scaffold to aid in DNA repair. But excess stress can cause an overproduction of PAR. As this surplus of PAR ventures beyond the nucleus, it finds its way to the mitochondria, where it interacts with a key mitochondrial membrane protein, known as Apoptosis Inducing Factor, or AIF. This interaction releases AIF into the cell's cytoplasm, setting it on a course back towards the nucleus.

During its journey, AIF binds to and escorts another protein called Macrophage Migration Inhibitory Factor, or MIF. Once this complex reaches the nucleus, MIF's

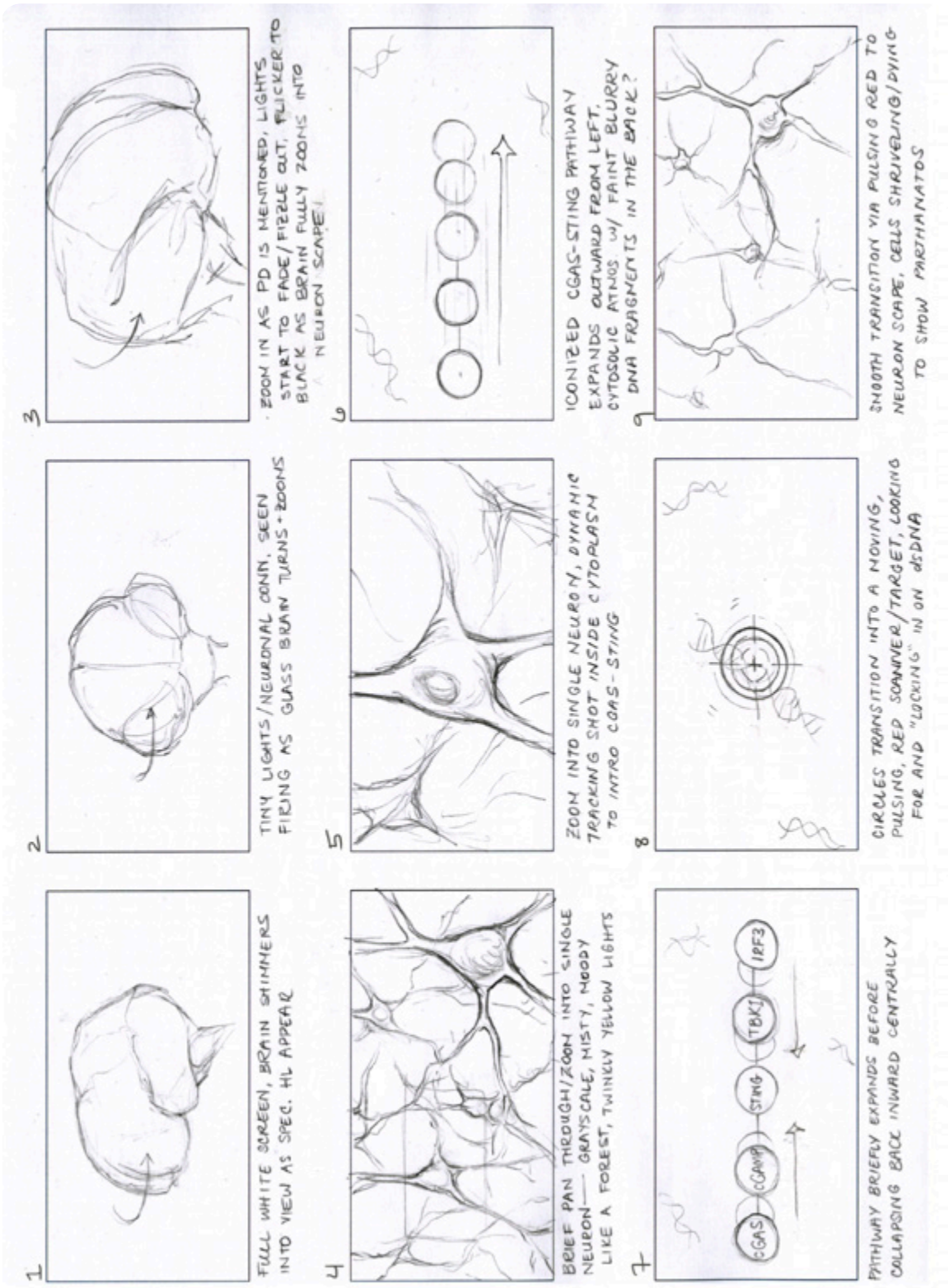
nuclease activity initiates DNA cleavage and fragmentation, triggering the decisive step of parthanatos, or cell death. The resulting DNA fragments can trigger new cGAS-STING pathway activity, thus perpetuating a cycle of inflammation and stress to neurons and supporting microglial cells.

So how should intervention be approached? Traditionally, it has been believed that blocking the initial stages of parthanatos would be the most effective in preventing DNA damage and cell death. For example, current cancer therapies that target early steps of parthanatos have drawbacks, as they hinder essential DNA repair in the process. Therefore, let us shift focus downstream to try and directly prevent MIF nuclease from triggering parthanatos without interfering with important upstream processes.

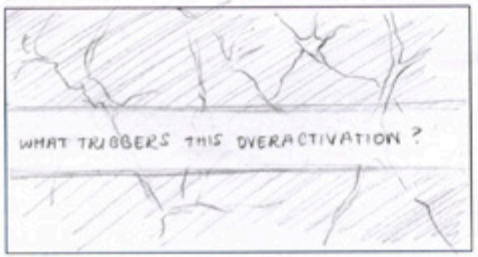
Exciting new research has unveiled PAANIB-1, a groundbreaking MIF inhibitor that stops the last step of parthanatos. PAANIB-1 blocks MIF's nuclease activity without interfering with its other functions and prevents the generation of harmful DNA fragments.

MIF's unique structure differentiates it from other nucleases in the body, thus ensuring selective inhibition and minimizing adverse effects. Targeting MIF using PAANIB-1 shows promising clinical potential, and there is hope for a future where the progression of neuronal damage and symptoms of Parkinson's Disease could be halted or even reversed.

Appendix B: 3D Animation Storyboard



10

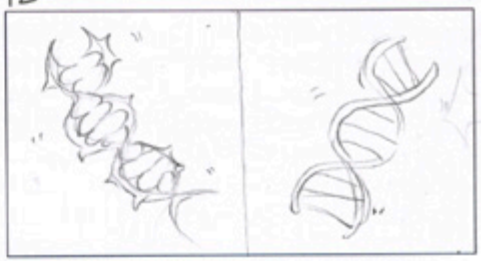


SCENE FADES TO A DULL RED OVERLAY/BLUR, TEXT APPEARS ON SCREEN W/ V.O.

11

"FOREIGN" DNA FRAGMENT, SHARP POINTY + METALIC/IRON TEXTURE, LIKE THORNY STEM OR BARBED WIRE. SCENE THEN SLIDES LEFT INTO SPLIT-SCREEN

12

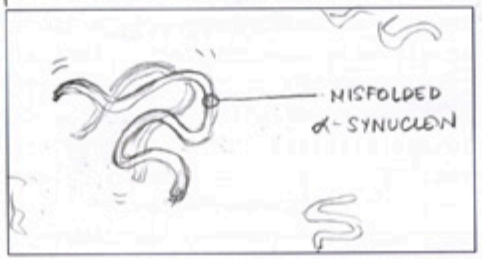


EXAMPLE OF SELF-DNA ON R SIDE, SHOWING THAT cGAS-STING CAN DETECT + RESPOND TO BOTH.

13

SCENE FADES TO DULL/BLURRED OVERLAY, TEXT APPEARS ON SCREEN W/ V.O.

14

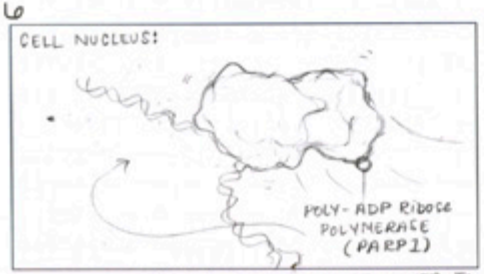


α-SYNUCLEIN MORPHS/MISFOLDS, MULTIPLE PROTEINS THEN START TO AGGREGATE INTO FIBRILS

15

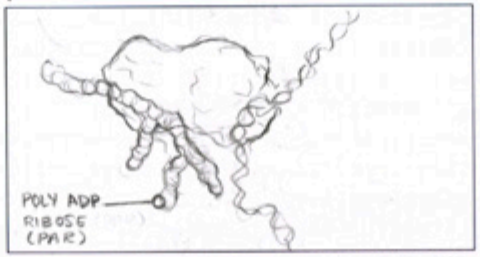
SMOOTH FADE INTO TANGLED FIBRILS/ LEWY BODIES, GLOBAL PULSING RED LIGHT TO SIGNAL OXIDATIVE STRESS.

16



CELL NUCLEUS LABEL AT TOP TO ORIENT VIEWER TO LOCATION. PARP1 ARRIVES AT DAMAGED DNA + LABEL APPEARS. QUICK ZOOM INTO PROTEIN WHERE PAR IS GENERATED

17



CAMERA PANS DOWN + AROUND TO SHOW THE OTHER FACE OF PARP1, WHERE PAR IS BEING FORMED TO ASSIST IN REPAIR

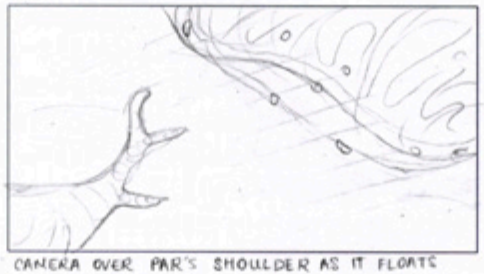
18

TRANSITION TO OXIDATIVE STRESS, LOTS OF PARP1 OVERPRODUCING PAR, PAR FLOATING AROUND IN EXCESS. FOLLOW ONE PAR OFF THE SCREEN TO A CUT TRANSITION

19

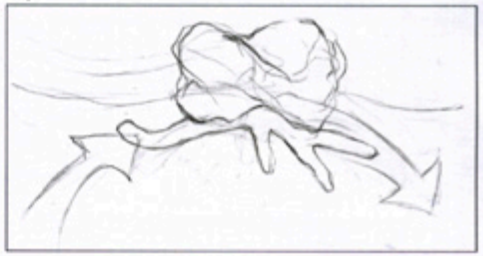
PAR SEEN EXITING THE NUCLEUS INTO THE CYTOPLASM— EITHER VIA A NUCLEAR PORE OR COULD BE MORE LITERAL LIKE A DOOR OR WINDOW FOR FUN

20



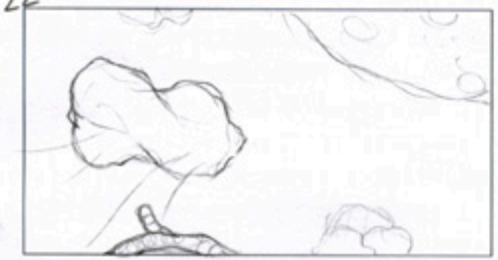
CAMERA OVER PAR'S SHOULDER AS IT FLOATS AHEAD TOWARDS MITOCHONDRIA LOOMING IN THE DISTANCE. MIT. IS CLEAR, JELLY-LIKE, STUDDED WITH AIF (COLORED) PROTEINS

21



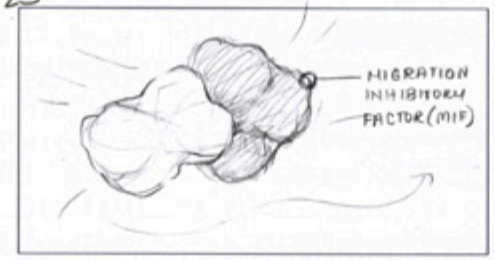
PAR INTERACTS W/ AIF, PULSE OF LIGHT AS AIF GETS PULLED AWAY OFF MIT. MEMBRANE AND INTO CYTOPLASM

22



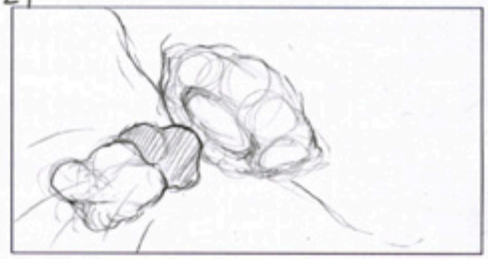
PAR FALLS AWAY GENTLY FROM AIF, AS IT VENTURES TOWARDS NUCLEUS IN DISTANCE. FAINT BLURRY MIF MOLEC. SEEN FLOATING IN THE PERIPHERY

23



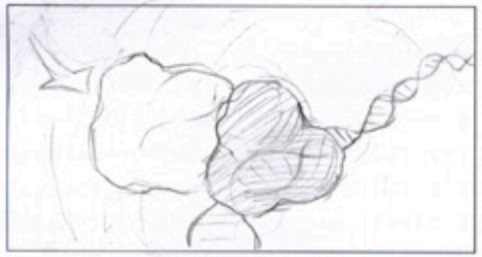
A SINGLE MIF PROTEIN COMES INTO FOCUS + BINDS TO AIF, BRIGHT GLOW. CONTINUES FLOATING OFF SCREEN R

24



AIF + MIF COMPLEX SEEN ENTERING INTO NUCLEUS VIA NUCLEAR PORE / WINDOW

25

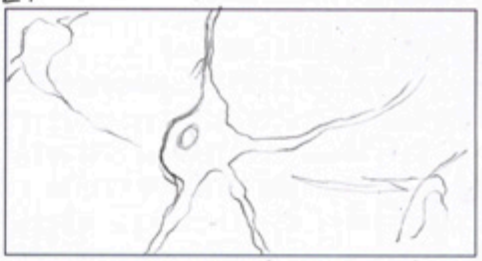


AIF-MIF TRAVELS FORWARD / IN TO CENTER OF NUCLEUS, WHERE IT MAKES CONTACT WITH A STRAND OF DNA. INITIATING FRAGMENTATION

26

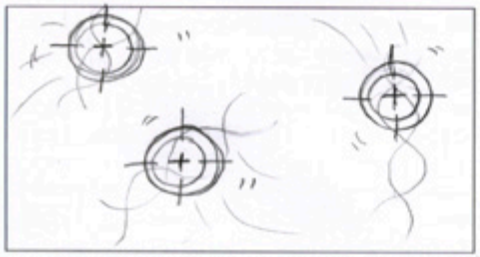
AIF-MIF RECEDES BACK AS DNA BREAKAGE IS HIGHLIGHTED, PULSING GLOBAL RED LIGHT HINTS AT PARTHANATOS FINAL STEP

27



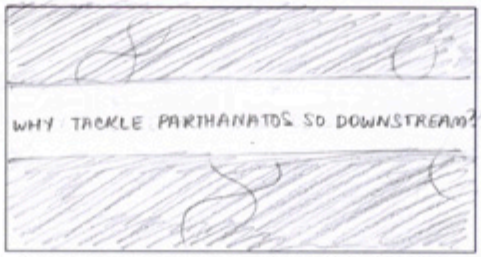
SHOWING PARTHANATOS : SHRIVELING AS CELL UNDERGOES PROG. CELL DEATH (SIMILAR TO PREVIOUS INTRO SCENE)

28



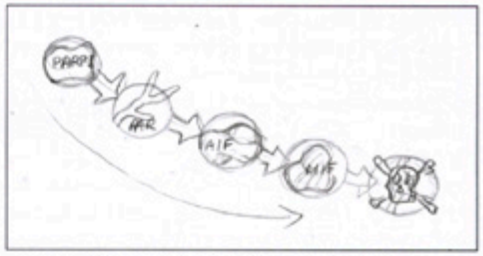
SMOOTH TRANSITION BACK TO NIF-CUT DNA, SETTING OFF cGAS-STING PATHWAY. PULSING RED LIGHT FOR INFLAMMATION

29



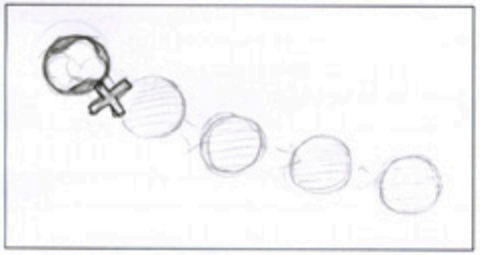
SCREEN DARKENS AND QUESTION/PROMPT APPEARS ON-SCREEN W/ V.O. THEN LABEL EXPANDS OUT TO TRANSITION TO SIMPLE CYTOPLASM

30



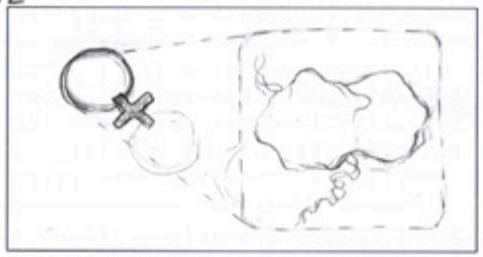
CYTOPLASMIC BACKGROUND, ICONIZED PARTHANATOS PATHWAY UNFOLDS ACROSS THE SCREEN IN A CASCADE, W/ LABELS + FAMILIAR MOLECULES

31



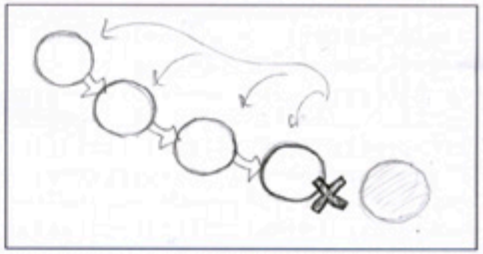
ARROW B/T PARP1 & PAR IS INTERRUPTED, CAUSING ALL DOWNSTREAM ICONS TO GREY-OUT AND ARROWS TO DISAPEAR

32



PARP1 ICON EXTENDS A HOLOGRAPHIC-TYPE CALLOUT, SHOWING CURRENTLY APPROVED TREATMENTS THAT BLOCK PARP1, BUT ALSO CRITICAL DNA REPAIR. RED X OR BAR OVER TOP TO SHOW THIS

33

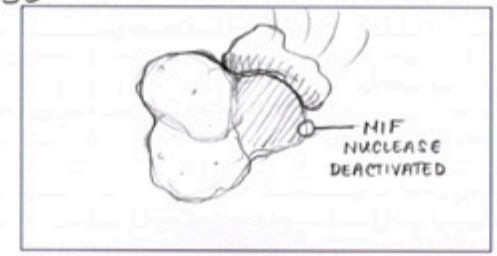


SHOW DISRUPTION OF PATHWAY AT NIF STAGE PREVENTING PARTHANATOS WHILE PRESERVING UPSTREAM PROCESSES. THEN SMOOTHLY FADE TO WHITE FOR NEXT SCENE

34

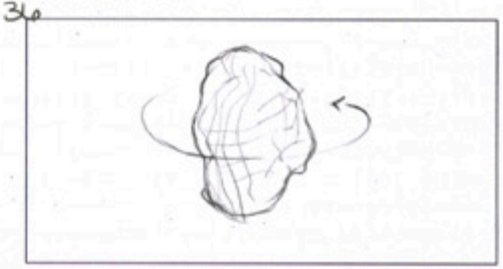
GREYISH-WHITE STAGE-LIKE SET ILLUMINATES FURTHER VIA CENTRAL SPOTLIGHT, AS NOVEL TREATMENT IS INTRODUCED

35



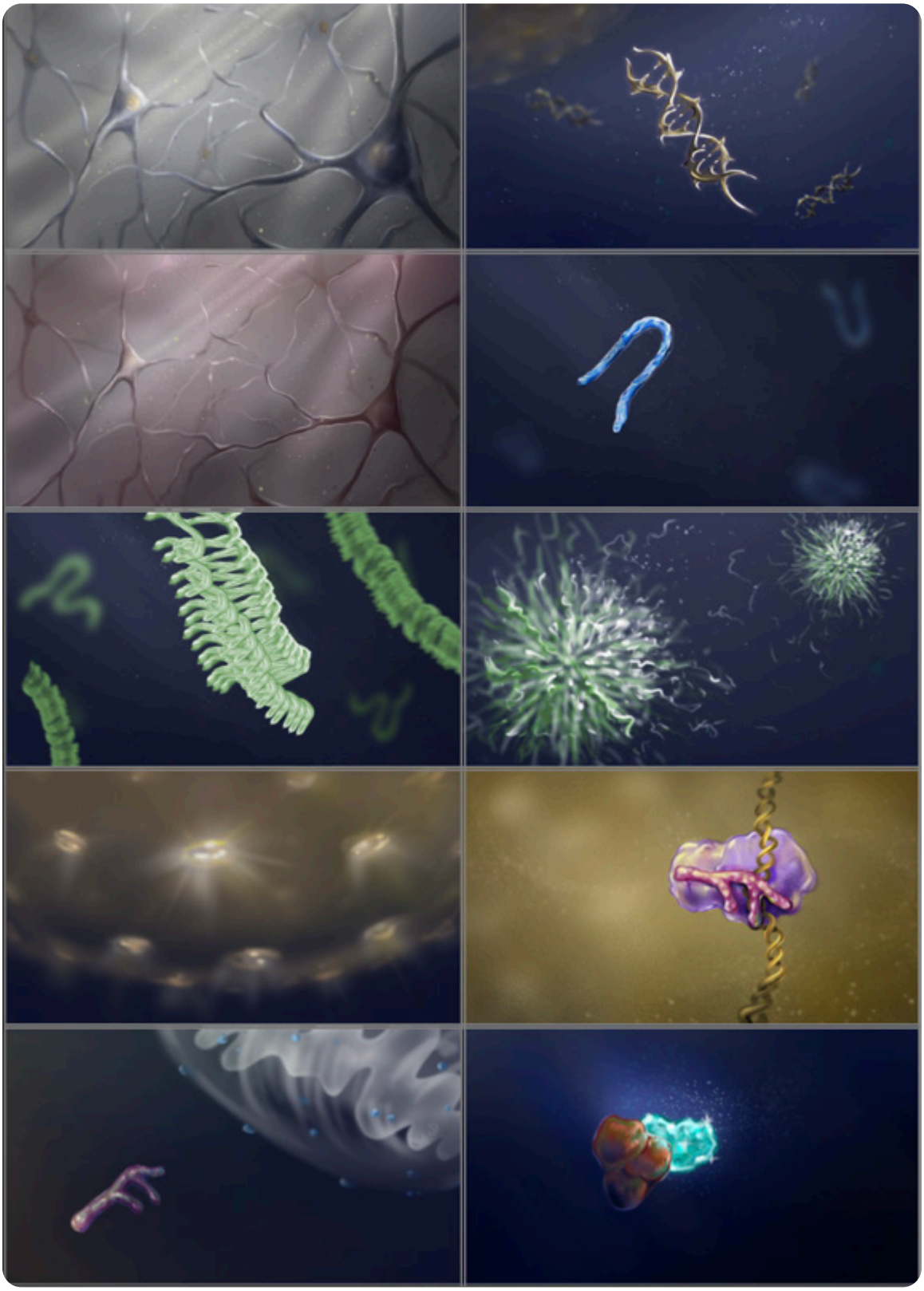
PAANIB-1 SEEN COMING INTO VIEW + BINDING TO NIF NUCLEASE. AND IT GREYS OUT. OTHER PARTS OF NIF LIGHT UP WITH ACTIVITY TO SHOW ITS OTHER FUNCTIONS REMAIN

36



CUT TO PAANIB1 SPOTLIGHT, 360-STYLE CAMERA ROTATES AROUND AS GREEN-SCANNER-LIKE LASER PASSES OVER SURFACE, AS ITS NOVELTY IS EXPLAINED

Appendix C: 3D Animation Concept Art



Appendix D: Interactive Webpage Text

How Does the Brain Deteriorate in Parkinson's Disease?

Toxic Protein Misfolding

PD is associated with the formation of neuronal cytoplasmic inclusions called Lewy bodies, caused by the misfolding and toxic aggregation of the presynaptic neural protein Alpha-Synuclein.[11] As these toxic fibrils accumulate, they disrupt synaptic communication and cellular homeostasis, producing immense oxidative stress.[11]

Activation of Parthanatos Pathway

As damage and stress overwhelm the cell, this triggers overactivation of PARP-1, a nuclear enzyme that facilitates DNA repair.[7] This causes an overproduction of the DNA-scaffold polymer PAR, which exits the nucleus and prompts nuclear translocation of the mitochondrial protein AIF, alongside MIF.[8] Once this AIF-MIF complex reaches the nucleus, MIF nuclease initiates DNA fragmentation, inducing cell death.[8,9]

Activation of cGAS-STING Pathway

The cGAS–STING pathway is a protective mechanism that provides immune defense against infection.[5,14] It activates upon detection of foreign or suspicious cytosolic DNA.[14] This response thus normally provides neuroprotection from pathogens and intrinsic antitumor immunity.[15] However, excessive activation of the cGAS pathway by self-DNA can lead to autoimmune and inflammatory disease[16]...

Severe inflammation and widespread damage

...such is the case in Parkinson's Disease, where aberrant self-DNA cleavage by the overactive Parthanatos pathway can trigger excessive inflammation by the cGAS-STING pathway, resulting in a perpetual cycle of inflammation, stress, and cell death upon neurons and supporting microglial cells.[4,16]

What are the Mechanisms of the Parthanatos Cell Death Pathway?

Poly ADP-ribose polymerase-1 (PARP-1)

Poly ADP-ribose polymerase-1 (PARP-1) is a nuclear protein that is activated by binding to DNA lesions.[8] It catalyzes poly ADP-ribosylation of nuclear acceptor proteins, including PARP-1 itself, to recruit DNA repair machinery to damaged sites.[9] Excessive DNA damage causes PARP-1 to overproduce PAR, triggering the parthanatos pathway.[3]

Poly ADP-ribose (PAR)

Poly ADP-ribose (PAR) is a polymer generated by PARP1 enzyme in response to DNA damage.[3,9] Composed of negatively charged ADP-ribose units, it forms chains on target proteins, aiding in DNA repair by recruiting repair factors.[9,13] PAR acts as a signaling platform, orchestrating the repair process at damaged sites.[13]

Apoptosis-Inducing Factor (AIF)

Apoptosis-Inducing Factor (AIF), primarily localized within the outer membrane of the mitochondria, normally regulates cellular metabolism and chromatin

condensation for apoptosis.[8,9] AIF can interact with PAR and influence AIF's translocation to the nucleus upon heightened cellular stress.[8,9]

Macrophage Migration Inhibitory Factor (MIF)

Macrophage Migration Inhibitory Factor (MIF) normally regulates cytokine production and inhibits macrophage migration.[13] MIF is the major nuclease involved in large-scale DNA fragmentation during parthanatos, and can also exacerbate PAR formation.[3,8,9] AIF may enhance MIF nuclease activity by increasing its binding to ssDNAs.[7,13]

DNA cleavage and cell death

During parthanatos, MIF is carried into the nucleus by AIF, where MIF nuclease preferentially binds to stem-loop single-stranded DNA and cleaves 3' unpaired bases of stem-loop ssDNA into 20- to 50-kb fragments.[3] The cGAS-STING pathway can respond to this self-DNA that mislocalizes to the cytoplasm and drives autoinflammation.[12]

PAANIB-1: a Potential Therapeutic Treatment for Parkinson's

PAANIB-1 is Highly Selective

PAANIB-1 specifically targets the nuclease domain of MIF.[17] This reduces potential side effects arising from altering MIF's other neuroprotective functions, such as tautomerase, oxidoreductase, and glucocorticoid suppressing activities.[17]

PAANIB-1 is Brain Penetrant

PAANIB-1 efficiently crosses the blood-brain barrier (BBB), achieving potent therapeutic concentrations in the brain following administration.[3]

PAANIB-1 Prevents Symptoms of PD

Across several mouse models, PAANIB-1 offered protection from degeneration of dopamine neurons and the behavioral symptoms associated with PD.[17]

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Vita

Sarrah Hussain was born in Karachi, Pakistan and moved to Pennsylvania at the age of 3. She attended Lehigh University with a major in Behavioral Neuroscience, and was further enlivened by pursuing a second major in Fine Art.

During her time at Lehigh, Sarrah's academic endeavors took her on a few fascinating adventures. Made possible by a research grant from the Andrew W. Mellon Foundation, she worked with other neuroscience researchers and artists to illustrate an open-source neuroscience textbook in 2020. Additionally, in 2021 she was honored with the Iacocca International Internship Award, through which she contracted medical illustration work with publishers in Padua, Italy. However, her years working in a neurogenetics lab were some of the fondest of her undergraduate career, where she helped author two research publications and illustrate several projects. By this point, Sarrah felt lucky to know that medical art was undeniably where her passion and purpose lay.

Graduating *summa cum laude*, she received the Lehigh President's Scholar Award Fund, allowing her to further her additional longtime interests in business and entrepreneurship, earning a Master of Science in Business Management in 2022. During this time, she also worked tirelessly to refine her artistic skills and build her portfolio, knowing that a formal education medical illustration was her next step.

Sarrah matriculated at the Johns Hopkins University School of Medicine graduate program for Medical and Biological Illustration in 2022. She is a candidate to receive her Master of Arts degree in May of 2024.