INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

August 2023

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HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2023

MASTHEAD

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FEATURES

INA-RESPOND Newsletter

InVITE & PROACTIVE Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Restu Amalia, Riza Danu Dewantara

InVITE

As of August 7, 2023, from the 700 participants initially enrolled in the study, 287 (41%) have concluded their participation, leaving 413 (59%) actively engaged. The study spans three distinct sites, with all currently focusing on visits 4 and 5. The breakdown of these visits per site is detailed in Table 1.

There were some retention challenges faced during the study's course. Of the 287 participants who concluded their participation:

- 226 (32.28%) successfully completed the study.
- 44 (6.29%) chose to withdraw for various reasons, such as personal constraints or a diminishing interest in participation.
- Three (0.43%) were unable to receive the full vaccine regimen within the stipulated 12 months after enrollment and were thus excluded.
- Two (0.29%) were advised against continuing due to concerns over their best interests.
- One (0.14%) participant was found non-compliant with the study's set procedures.
- Regrettably, the study lost one (0.14%) participant due to their passing.
- Ten (1.43%) participants had other miscellaneous reasons leading to their discontinuation.

Another aspect the study has been keenly observing is the symptomatic visits recorded among the participants. Detailed data regarding these visits, as of August 7, 2023, can be found in Table 2. It's paramount to understand that the presence of COVID-19 symptoms in some participants doesn't equate to a definitive diagnosis of the disease.

On a related note, as of August 9, 2023, the revision of the Material Transfer Agreement is still under collaborative discussion between INA-RESPOND and NIAID, including both parties from NIAID and Tangerang General Hospital.

Finally, for specimen transportation, the Credo Box is primed and ready for shipments from Site 02 (TC Hillers Hospital) and Site 03 (dr. Ansari Saleh Hospital).

Site	Symptomatic Visit		
	# of visit	Positive	Negative
01	103	61	42
02	14	6	8
03	2	1	1
Total	119	68	51

Table 2. Symptomatic Visit Details per Aug 7, 2023

Site	Screening / Visit 1	Enrollment Failure	Enrolled	Ongoing	Add. Visit 1	Visit 2	Add. Visit 2	Add. Visit 3	Visit 3	Agree Ext.	Not Agree Ext.	Ext. Visit 4	Ext. Visit 5
01	345	2	343	221	88	326	314	306	315	286	29	271	66
02	228	1	227	97	97	214	191	188	195	151	44	151	53
03	130	0	130	95		130			129	95	35	95	0
Total	703	3	700	413	185	670	505	494	639	532	108	517	119

Table 1. Details of Visits per site per Aug 7, 2023

INA104

As we approach the end of our comprehensive research endeavors, it's worth noting the progress we have made. All subject visit activities have been meticulously carried out and completed across various sites. The majority of these sites have already wrapped up their contributions, leaving only three — sites 520, 540, and 680 — still in the process of final preparations for their study close-out visits. These sites have set their sights on a closure in September 2023.

The post-closure phase is critical. Each site, after its formal close-out visit, has the responsibility of finalizing any outstanding action items. This includes the crucial task of document archiving, ensuring that all data, findings, and insights are preserved for future reference and analysis. We anticipate that all these post-closure processes will be wrapped up by October 2023, marking a significant milestone in our project timeline.

Transitioning from the close-out visits, our next significant phase is the preparation of study manuscripts. This is where all our collective hard work, data, and insights come to fruition. The INA-RESPOND Secretariat, in collaboration with the Protocol Core Team and the sponsor, is gearing up for this task. Additionally, the invaluable contributions and involvement of Principal Investigators and Co-Investigators from each site cannot be understated. Together, we're focusing on creating seven in-depth manuscripts that encompass:

1. Baseline characteristics and predictors for 1-year all-cause mortality, providing insights into early trends and factors.
2. An in-depth analysis of Late Presenters.
3. Comprehensive data on 3-year all-cause mortality predictors.
4. Detailed findings on 3-year virological progression and the factors that influence these outcomes.
5. A close look at 3-year immunological progression and its associated variables.
6. A multifaceted assessment focusing on the initial opportunity infections or mortality after ART initiation, coupled with 3-year disease progression.
7. An important and specialized analysis dedicated to Pediatric subjects.

Beyond the primary manuscripts, we have received a plethora of concept plans developed and submitted by INA104 Sites. These plans touch upon diverse and critical topics, namely Viral Load, Immune Response (both CD4 and/or Viral Load), Comorbidities, Co-infections, and Opportunity Infections. Each plan has undergone rigorous reviews by experts from the Secretariat, the core team, and the NIAID Team. Through this review process, we've streamlined the content, ensuring there's no overlap with primary manuscripts and that the breadth and depth of each topic are maintained. Furthermore, collaboration is at the heart of our endeavors. We've ensured that sites with similar thematic contributions collaborate, amalgamating their data to provide richer insights. Once approved, these concept plans will form the foundation for deeper discussions and reviews, involving the Site Research Team, the Science Team from the INA-RESPOND Secretariat, and the Protocol Core Team.

In conclusion, as we advance in our research journey, collaboration, rigor, and a commitment to excellence remain our guiding principles. The forthcoming months promise intensive work, insightful discoveries, and the shared goal of advancing clinical research knowledge.

Check out the photos from our Site Close-Out Visits on page 5. From top to bottom, left to right: 510 RSHS, Bandung; 550 Wahidin Soedirohusodo, Makassar; 600 RSUP H. Adam Malik, Medan; 700 TC Hillers Maumere; 650 Budi Kemuliaan, Batam; 670 dr. Dzainoel Abidin, Aceh; 690 RSUD Abepura, Jayapura.

SITE CLOSE OUT

VISITS

INA-RESPOND Newsletter

EFFECTIVE UTILIZATION OF A NOTE TO FILE

By: Louis Grue, Mila Erastuti, Tiya Saraswati, Virtania Meirina Agusta

Anyone who has been involved in conducting INA-RESPOND's studies might be familiar with the term "Note to File (NTF)" and might have had experience in generating this document. The INA-RESPOND Good Documentation Practices SOP states that a NTF could be utilized and may be useful where additional information pertaining to a record is elsewhere required, while no such provision is available in prepared study documents or forms to accommodate it.

A NTF can be a helpful tool and can be typically generated when it is necessary o formally clarify a process, procedure, protocol defined activities, or regulatory requirements, in order to satisfy Good Documentation Practice (GDP), fulfil inappropriate International Council on Harmonization (ICH) Good Clinical Practices (GCP) and local regulatory guidelines, therefore, it is an eligible document to be reviewed during regular site monitoring visits, regulatory inspections, or sponsor audits. We all may have heard a jargon (saying) during clinical trial conduct "if it isn't documented, it didn't happen". The following are some instances in applying an NTF: defining regulatory document's location, describing a test article storage temperature excursion, providing clarification of missing, unavailable or inadequate documentation during clinical trial process, documenting the reason for missing, delayed, or erroneous documents in Site Regulatory Binder (SRB), or discrepancy between site regular practice and study protocol.

INA-RESPOND has a specific NTF form which contains several sections of required information, such as, date of issue, protocol number, protocol title, site number, site Principal Investigator name, subject, description, the detail of person who prepare the NTF and the countersign review, if needed. A completed NTF should be filed in SRB at a clinical study site and uploaded into INA-RESPOND Electronic Data Management System (EDMS). Each part of NTF should be completed in a comprehensive manner to describe an issue or to elaborate on a

specific situation. Root-cause analysis is strongly recommended to determine the underlying cause of an issue, to develop effective corrective and preventive actions.

It is important to understand the appropriate application of an NTF. Essentially a NTF does not replace the original source documents or forms. Any subject or topic should be primarily documented in appropriate study documents or forms. Recognizing all available original source documents or forms applied in the study is important, hence, easier to determine where a documentation or clarification related to the clinical trial process should be suitably written. Furthermore, if there is no specific suitable format clinical trial documents or forms are available, then clarification made in NTF could be considered and deemed applicable.

In practical settings, inappropriate utilization of NTFs were sometimes found, for instance, NTF is generated to clarify any missed study assessment, missed visits, or missed participant's procedures while no documentation made in primary source documents, such as in the participant's Medical Record or Source Document Worksheet. An NTF is used to explain errors in a document such as SOP number, version, effective date. Nevertheless, direct correction according to GDP might be applied in a certain situation as deemed appropriate. Another example of an inappropriate NTF is found when it is generated to document protocol deviations, while Protocol Deviation (PD) form itself was not completed. For example, Investigator did not obtain the Informed Consent prior to the screening process. Supposedly, this deviation should be documented in the Protocol Deviation (PD) form and to develop effective Corrective Action and Preventive Action (CAPA) to manage the deviation.

Moreover, inappropriate utilization of NTF causes scattered documentation which increases risk for incomprehensive documentation. Practically, an NTF should be filed alongside its referenced document within the same SRB section or aggregated in a separate SRB section. Difficulty in finding and connecting an NTF to its referenced document may arise when the entire NTF is stored in a separate SRB section away from its referenced document section, thus the NTF could not be directly accessed and the purpose of an NTF, for example to clarify an issue, itself could not be achieved. As a best practice, it is suggested to only file a 'general NTF' in a dedicated SRB section and leave a 'referenced NTF' pasted with its referenced document in respective SRB section. Developing an NTF listing would also be advantageous to identify all generated NTFs in the study.

A NTF quality control process is required to avoid any unnecessary NTF filed in SRB. On a regular basis, Research Assistants (RA) should conduct a file review process to assure the SRB is established according to EDMS structure and no redundancy of subject/topic results among the generated NTFs.

Effective NTF utilization will improve the quality of clinical research documents produced in the study and will support excellent data quality and integrity. Thus, it demonstrates clinical trial conduct has been implemented according to clinical research protocol, and GCP guidelines.

If you have any questions about the appropriate use of a NTF, you have resources within the INA-RESPOND Secretariat who are available to assist you with developing the most useful NTF for your specific issue.

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INA-RESPOND Newsletter

COLLABORATION - THE POWER OF TEAMWORK: CREATING SUCCESS TOGETHER

By: Dedy Hidayat

FREE WRITING

In the dynamics of an office environment, where a diverse group of individuals works towards common goals, the essence of collaboration becomes increasingly significant. It forms an intricate web that interconnects everyone, setting the foundation for an effective, efficient, and harmonious workplace.

The Importance of Collaboration

The process of working together to attain a common goal is known as collaboration. It entails open communication, mutual respect, and collaborative decision-making. Collaborative endeavors generate a plethora of ideas, talents, and views that add to the richness of the finished outcome. Collaboration fosters creativity, encourages learning, and increases productivity. When teams work together, they provide more complete and imaginative solutions.

The Building Blocks of Collaboration

Open Communication

One of the most important aspects of collaboration is open communication. A collaborative team fosters an environment in which everyone feels comfortable sharing their ideas and views. Active listening entails not just hearing your team members' words but also understanding their views.

For example, open communication allows every team member to share their concerns and ideas during a team meeting to discuss a project bottleneck. Active listening ensures that these concepts are comprehended, taken into account, and incorporated into problem-solving solutions.

Mutual Respect

Respect is another crucial element of collaboration. It involves valuing and acknowledging the ideas, skills, and contributions of each team member. Mutual respect cultivates an environment where diver-

sity is celebrated, and every individual's unique skills are harnessed.

Imagine a situation where a team is working on a creative project. The designer suggests an innovative layout that is quite different from traditional designs. While some may be hesitant about this unconventional approach, respecting the designer's expertise and perspective can lead to the creation of a unique and impactful design.

Shared Decision-Making

Collaboration also involves shared decision-making, which is based on the consensus of the team. Instead of a single person dictating the course of action, decisions are made collectively, considering the insights and opinions of all team members.

In health research on a new drug, for example, epidemiologists, physicians, and lab scientists may collaborate to decide on the drug's formulation, trial design, and distribution, ensuring that decisions correspond with research and public health goals.

The Outcomes of Collaboration

Collective Problem Solving

When teams work together, their expertise, skills, and perspectives are combined to handle issues and solve problems. Collective problem-solving frequently results in more effective and imaginative solutions because it relies on a varied pool of ideas and perspectives.

In the field of health research, for example, when confronted with a problem such as the sudden emergence of a novel virus, a collaborative team would gather input from various experts such as virologists, epidemiologists, public health officials, and medical practitioners. Each expert contributes a distinct point of view and set of data. This multimodal approach, when combined, provides a thorough understanding of the virus and leads to more effective tactics to stop its transmission.

Enhanced Learning and Growth

Collaboration promotes learning and development. Team members share their knowledge and experiences as they work together. They benefit from one other's accomplishments and failures, which helps their professional development.

A junior team member, for example, will learn new abilities and gain insights into handling challenging duties by working closely with a more experienced colleague on a project. One of the most major advantages of teamwork is on-the-job learning.

Improved Team Dynamics

Collaboration strengthens relationships and enhances team dynamics. Team members learn more about each other's skills, limitations, work styles, and personalities as they collaborate. This knowledge creates mutual respect and increases team performance.

To summarize, collaboration is not just a tool for accomplishing professional goals; it is also a pillar of office ethics. It promotes a culture of mutual respect and shared success, which is essential for fostering a good and effective workplace. We don't just develop better teams when we support collaboration; we also build better environments.

I dedicate this piece to our Scientific Lead, dr. Herman Kosasih, who is retiring in August 2023, to express how grateful many of us are for his years of unwavering mentoring. His extraordinary ability to sustain strong collaboration has been the backbone of our team, and his dedication to encouraging both learning and growth has left an unforgettable imprint on all of us, especially for me who come from a non-medical background. We wish him the joy and contentment he so richly deserves in the next chapter of his life.

INA-RESPOND Newsletter

EXERCISING OUTDOORS: NAVIGATING AIR QUALITY CONCERNS

By: Marco Ariono

SPORTS & LIFESTYLE

In an era where the benefits of physical activity are universally recognized, outdoor exercise has surged in popularity among those desiring a blend of fitness and fresh air. However, with the rise of urbanization and industrialization, the quality of the air we breathe has become an increasing concern. Despite its importance, air quality during exercise is often overlooked. Six pollutants are designated as criteria air pollutants: lead, ozone, sulfur dioxide, nitrogen dioxide, and particulates with aerodynamic diameters between 10 and 2.5 μm. One particular particulate matter (PM) has garnered attention for its implications in various conditions, including asthma, hypertension, diabetes, and depression. The intricate relationship between exercise and air quality directly impacts the effectiveness of our workouts and has long-term health implications^1-3.

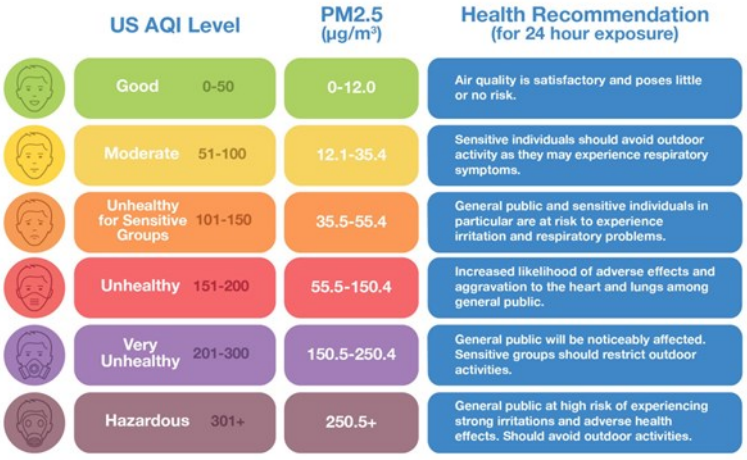

Figure 1. Air quality index chart with corresponding PM2.5 μg/m3
Source: https://www.iqair.com/

The Impact of Air Quality on Health

Human activities detrimentally affect the environment, polluting the water we drink, the air we inhale, and the soil nurturing our plants. Air pollution has myriad adverse health consequences. Vulnerable and sensitive individuals can experience health effects even on days with moderate air pollution. Acute exposure to pollutants is strongly linked to conditions like COPD (Chronic Obstructive Pulmonary Disease), cough, shortness of breath, asthma, respiratory diseases, and increased hospitalizations^4-6. Long-term consequences of exposure include chronic asthma, pulmonary insufficiency, cardiovascular diseases, and related mortalities.

Assessing Air Quality: The Air Quality Index (AQI)

Before embarking on outdoor activities, consulting the Air Quality Index (AQI) is paramount. The AQI offers a standardized measure of air cleanliness, considering multiple pollutants and categorizing air quality from "Good" to "Hazardous"^7.

When the AQI signals poor air quality, individuals are better equipped to make informed decisions regarding the intensity, location, and type of exercise. By consulting the AQI, one can prioritize health while still benefiting from outdoor activity.

Why Should We Consider the Quality of the Air We Exercise In?

Engaging in physical activity increases respiratory rates, drawing more air into our lungs than during rest. This heightened respiration in polluted areas poses risks. The polluted air contains harmful particles, and during exercise, the chances of inhaling these pollutants increase, potentially compromising our health^8.

Breathing patterns during exercise play a pivotal role. Intense workouts often induce mouth breathing, bypassing the natural filtration mechanisms of the nose.

The mouth, unlike the nose, permits contaminants unfiltered access to the lungs. The interplay of increased respiratory rates, mouth breathing, and fine particulates enhances the penetration of pollutants into the respiratory system. Recognizing this relationship emphasizes the importance of monitoring air quality and making informed choices about outdoor activities^8.

Mitigating the Impact: Strategies for Exercising in Polluted Areas

To minimize the risks of exercising outdoors in areas with compromised air quality, consider the following strategies^8:

1. Check the AQI: Numerous online platforms and mobile apps provide real-time air quality data, enabling individuals to assess the safety of outdoor exercise.
2. Choose Optimal Times: Air quality fluctuates throughout the day. Avoiding peak pollution times, like rush hours in urban areas, can reduce exposure.
3. Location Matters: Green spaces like parks and trails typically have cleaner air than congested streets. Opt for greener locations as vegetation can help mitigate pollution.
4. Modify Duration and Intensity: On days with poor air quality, consider reducing the intensity and duration of workouts to limit pollutant inhalation.
5. Monitor Your Body: Be attuned to bodily responses during workouts. If any discomfort, shortness of breath, or irritation arises, it's prudent to cease exercise and seek cleaner air.
6. Avoid Traffic-Intense Areas: Roads flanked by tall buildings often harbor poor air quality. Similarly, intersections with traffic lights see increased vehicle emissions. Opt for less congested routes.
7. Exercise Outside of Rush Hours: In densely populated areas, avoid outdoor exercise during peak traffic times.
8. Opt for Eco-Friendly Transportation: Using cars contributes to pollution. Consider walking or cycling, promoting both physical activity and environmental conservation.
9. Limit Indoor Air Pollutants: If exercising indoors, be mindful of potential pollutants. For instance, avoid workouts immediately after cleaning, as certain products can degrade air quality.
10. Stay Active!: Environmental and pulmonary health experts agree that the health risks of sedentary lifestyles outweigh the dangers of exercising in polluted air.

Conclusion

Balancing the rewards of outdoor exercise with concerns about air quality demands judicious decision-making. Recognizing the pivotal role of physical activity in overall health, individuals need to proactively protect their well-being during outdoor workouts. Familiarity with the AQI and understanding the interplay between exercise and air quality empower individuals to make informed choices about outdoor physical engagements. While the benefits of regular exercise are indisputable, it's essential to approach outdoor workouts with caution and flexibility when confronted with suboptimal air quality.

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INA-RESPOND Newsletter

COMIC CORNER

RESURRECTION OF THE THYLACINE: EXPLORING THE SCIENTIFIC PATH TO DE-EXTINCTION

By: Aly Diana

Source: Cartoon by Graeme Dazeley - 'Daz' - published in Mercury 7/3/1997 (https://www.utas.edu.au/library/exhibitions/Thylacine/

The Thylacine, scientifically known as *Thylacinus cynocephalus* or the Tasmanian Tiger, was an extraordinary carnivorous marsupial and the sole member of the Thylacinidae family to survive into modern times. Historically, the Thylacine was widespread across Australia, but its presence on the mainland ceased around 3,000 years ago. Roughly 14,000 years ago, changes in sea levels isolated a population in Tasmania, which persisted until the early 20th century. European settlers viewed the Thylacine as a menace to the sheep industry in Tasmania, leading the government to institute aggressive eradication measures, including a bounty of £1.00 for each Thylacine killed. As a result, the Thylacine population dwindled rapidly, culminating in the death of the last known individual at the Hobart Zoo in 1936. The species was officially declared extinct in 1982.

The potential resurrection of the Thylacine holds immense ecological value. As a top predator, the Thylacine helped regulate prey populations, curtailing overgrazing and influencing vegetation patterns. Its disappearance disrupted these vital ecological relationships, causing shifts in flora and possibly leading to the proliferation of mesopredators. Reintroducing the Thylacine could balance trophic cascades, maintain predator-prey dynamics, conserve biodiversity, bolster ecosystem services, and assist ecosystems in adapting to anthropogenic changes. The Thylacine's viability for de-extinction is highlighted by its recent extinction, the availability of high-quality DNA, and the persistence of its natural prey and habitat.

Launched more than a decade ago but paused due to lack of funds, the project has witnessed a revival. The Colossal TIGRR Collaboration, operating from 2022 to 2026, combines the expertise of renowned individuals like Harvard University geneticist George Church and tech entrepreneur Ben Lamm of Colossal Biosciences. Additionally, the University of Melbourne's Andrew Pask leads the Thylacine Integrated Genomic Restoration Research (TIGRR) Lab, which has benefitted from a generous donation from the Wilson Family Trust. While resurrecting the Thylacine is no longer just a dream, the endeavor may still require a decade or longer.

This ambitious project encompasses nine detailed steps across genetics, technology, and ethics, challenging the

limits of conservation science. Step 1: **The Blueprint of Return**. The first crucial step in de-extinction is crafting a comprehensive genetic blueprint, or genome. The Thylacine genome, unveiled in 2017, is among the best-quality extinct genomes ever produced. This guide holds the instructions for reviving the Thylacine, with ongoing technological advancements in genome sequencing paving the way for further refinement. Step 2: **Kinship Exploration**. The DNA sequences of the Thylacine's nearest relatives, such as the dunnart or marsupial mouse, have been identified. These species form the groundwork for piecing together the Thylacine genome. Step 3: **Bioinformatics Puzzle**. This step is a sophisticated computational challenge, comparing marsupial genomes to identify the necessary changes for producing a "Thylacine" cell. The TIGRR lab is at the forefront of this complex task. Step 4: **Stem Cells and Progress**. The development of methods to extract stem cells from marsupials, like the fat-tailed dunnart, is in progress in collaboration with the TIGRR lab and the Australian Research Council. These techniques are pivotal for Thylacine de-extinction and also have broader implications for conserving endangered marsupials. Steps 5 to 7: **Assisted Reproduction Advances**. These phases focus on creating assisted reproductive technologies (ART) for marsupials. The TIGRR lab spearheads this initiative, aiming to enable living stem cells to produce embryos suitable for implantation in surrogate species. Steps 8 and 9: **Highlighting the Marsupial Advantage**. Marsupials possess a unique edge in the de-extinction process due to their reproductive method. Given that marsupials birth underdeveloped young that mature in pouches, the prolonged gestation period typical of other mammals can be avoided. For de-extinction, this implies that offspring can be bottle-fed early on, negating the need for surrogate mothers or intricate gestation.

These nine steps lay the groundwork for the possible revival of the Thylacine. However, the endeavor extends beyond resurrecting one species—it offers potential advancements in marsupial conservation and technology. The ongoing research is already yielding insights into genetics, stem cell research, and reproductive methods, which can have a lasting impact on the conservation of at-risk species.

The Resurrecting the Thylacine Project ventures into the unexplored convergence of science and ethics. As we embark on this journey, the initiative ignites discussions about our responsibility to Earth's biodiversity. While debates about resource allocation and ecological consequences continue, the project stands as a testament to humanity's unique ability to amend past mistakes and thereby influence our planet's future. As the project evolves, we edge closer to potentially reuniting with a long-gone species, deepening our grasp of genetics and conservation science.

Disclaimer: I am not commenting on the ethical dimensions of this project. This article merely offers a brief overview of years of research, which is not my primary field. Nonetheless, I hope it sparks curiosity, interest, or a glimmer of hope among readers.

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