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PERSPECTIVES AND NOTES

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Exploring the limits of saving a subspecies: The ethics and social dynamics of restoring northern white rhinos (*Ceratotherium simum cottoni*)

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Abstract

The northern white rhino (*Ceratotherium simum cottoni*) is functionally extinct with only two females left alive. However, cryopreserved material from a number of individuals represents the potential to produce additional individuals using advanced reproductive and genetic rescue technologies and perhaps eventually a population to return to their native range. If this could and were done, how should it be done responsibly and thoughtfully. What issues and questions of a technical, bioethical, and societal nature will it raise that need to be anticipated and addressed? Such issues are explored in this article by an interdisciplinary team assembled to provide context to the northern white rhino project of the San Diego Zoo Global.

KEYWORDS

Ceratotherium, conservation, genetic technologies, genomes, hope, northern white rhino, reproductive technologies, saving species, zoos

1 | NOLA: THE END AND THE BEGINNING?

Nola, the last northern white rhinoceros (NWR) in North America died on November 22, 2015, at 41 years of age at the San Diego Zoo Safari Park (SDZSP). In October 1989, Nola was flown to San Diego to became part of a captive herd of four NWR and eventually part of the NWR Initiative at the SDZSP, established in the hope of developing a breeding population of NWR. Despite scores of successful births of white rhinos of the southern subspecies, Nola died without leaving progeny. In her decades at the SDZSP Nola was seen by millions of visitors, who learned that she was among the last of NWRs anywhere—the last known wild NWR in the wild was seen in 2006 (Emslie, 2012).

But this rhino who never had a calf left hope for the future of her subspecies. Her living cells, and those of a handful of other NWRs ($n = 12$), survive in a frozen state at −196°C in the San Diego Zoo's Frozen Zoo® where, to date, cells from nine NWR individuals have been transformed into induced pluripotent stem cells (iPSCs). Visitors to the lab can see cells from Nola's long-time companion, Angalifu, induced to beat out the rhythm of life in a tissue culture dish. In these living cells, there is also the beat of new possible approaches for conservation of species, possibilities fraught with technical, ethical, and moral challenges.

As genetic technologies are dramatically improving, so too are their possible applications. But just because they can be used does not mean they should. What path should humans follow with Nola's cells and those of her kind? The story of Nola has the potential to reanimate a conservation community beaten down by increasing stories of loss.

But it also raises some critical questions—essential ethical, moral, and practical questions to answer as species conservation enters the era of greatly improved genomic and reproductive tools. Should we accept the end of the evolutionary line for the NWR, or intervene in a manner never done before by deploying the emerging possibilities for species conservation posed by genetic rescue and advanced reproductive technologies? Would changing a species genetically mean you were no longer conserving the same species? Or as one reviewer notes, would this approach be considered successful only if conservation found hope in cryo-preserved tissues and petri dishes?

In October 2019, to build on the work undertaken in the NWR Initiative by San Diego Zoo Global (SDZGlobal) and the larger conservation community, SDZGlobal convened a multidisciplinary group with expertise in conservation genetics, reproductive physiology, sociology, ethics, law, cryobiology, and conservation biology. This article arose from the meeting's discussions. It is not an assessment of the work to date. It is not a comprehensive treatment of the ethics of or societal issues flagged up by this project—for these there is a growing literature (e.g., Minteer, 2019). Rather it is a mapping of some of the issues of a bioethical or societal nature facing the NWR project and those of its kind likely to emerge in the next decade.

2 | THE HISTORY OF THE NORTHERN WHITE RHINO CONSERVATION

White rhinos were found in two discontinuous populations, one from South Africa to Zambia, the southern white rhino (SWR) and the other, the NWR in South Sudan, the Democratic Republic of the Congo, Uganda, Chad, and the Central African Republic (Emslie & Brooks, 1999). The taxonomy of the white rhinos is contested, the focus of disagreement being whether the observed differences warrant species-level differentiation (Groves, Fernando, & Robovský, 2010) or continued differentiation at the subspecies level (Tunstall et al., 2018). No matter which of these is chosen there are clear and significant genetic differences between the two populations (George et al., 1993).

Both populations of white rhinos were numerous at the time European chroniclers traveled through Africa. This did not last long. Hunting and habitat destruction led to the almost complete extinction of the SWR during the 19th century. Thanks to extensive protection measures starting at the end of the 19th century (Emslie, Amin, & Kock, 2009) the SWR population rebounded to approximately 20,000 animals, although poaching continues to be severe (Mokonyane, 2019). The NWR, thought to be numerous until the mid 20th century, underwent drastic decline due to human activities such as armed conflict, commercial and bush meat hunting. The wild population shrank from 2,360 animals in the 1960s to 15 animals in the 1980s (Hillman Smith & Ndey, 2005).

The genetic information emerging in the 1980s documenting the difference between NWR and SWR galvanized increased conservation efforts for the NWR and the establishment of the Garamba National Park in the Democratic Republic of the Congo. Despite continued poaching and hunting, the small wild population reproduced well and increased to 30 in 2003 (Hilman Smith & Ndey, 2005) but then fell sharply with the last individual seen in 2006 and the last sign seen in 2007 (Emslie, 2012).

Record keeping for the captive NWR population started in 1948 (Christman, 2012). Despite their 70-year history in captivity, only one wild-born female ever gave birth. In support of reproduction prospects, four NWR were transferred to SDZSP in 1989 and, in 2009 four NWR were sent from the Dvůr Králové Zoo, Czech Republic to the Ol Pejeta Conservancy in Kenya (Holeckova, 2009). The hope for natural breeding died with the death of the last two male NWR, leaving behind in the Ol Pejeta Conservancy the last two individual NWR on Earth, both female. Traditional species conservation efforts both in the wild and in zoos failed to preserve the NWR.

In December 2015, a group of scientists gathered in Vienna, Austria to discuss how science could be applied to the prevention of extinction, leading to the publication of a roadmap for the NWR (Saragusty et al., 2016). Work based on this roadmap is progressing well. In addition to the fibroblast cell cultures, sperm and reproductive tissue samples are cryobanked. These samples are crucial for the ongoing research and will form the basis for in vitro fertilization of oocytes collected from the last two females (Fortin, 2019) and eventually possible in vitro gametogenesis and the re-establishment of the population ((Hildebrandt et al., 2018, Korody et al., 2017, Pennington & Durant, 2019, Pennington, Marshall, Capiro, Felton, & Durrant, 2019, Tunstall et al., 2018). This article is an extension of the initial roadmap.

3 | OPTIONS,RELATIONSHIPS AND REQUIREMENTS

In the last decade, the increasing biodiversity crisis has generated new proposed ways for humans to save species, including the integration of genetic rescue and assisted reproductive technology (ART). Genetic rescue has recently been defined as "a decrease in population extinction probability owing to gene flow, best measured as an increase in population growth rate" (Bell et al., 2019). It has traditionally been pursued by moving live animals from one population to another, most famously with the Florida panther (Van de Kerk, Onorato, Hostetler, Bolker, & Oli, 2019), though gametes have also been moved (Hildebrandt et al., 2012), both across populations and over generations, as with the black-footed ferret (Wisely, Ryder, Santymire, Engelhardt, & Novak, 2015). Emerging work based on the new tools of synthetic biology has raised possibilities of moving genes or even rewriting genomes (Redford, Brooks, Macfarlane, & Adams, 2019).

ARTs are medical approaches designed to correct infertility. They include fertility medication, cryopreservation of gametes, and in vitro fertilization (Roth & Swanson, 2018). ARTs have been applied in captive rhinos, including SWRs for which ovulation induction, and artificial insemination has been implemented successfully (Hildebrandt et al., 2007; Pennington & Durant, 2019).

The larger plan for preventing NWR extinction consists of a nested set of objectives that build on one another but each of which could serve as a coherent final initiative with its own measures of success. All would include a set of stakeholder engagement objectives designed to contribute to ending human-caused extinction across all taxa, with particular attention to NWR and other rhino species. Clearly creating a NWR in the lab would not achieve rhino conservation if conditions are not in place for it and its progeny to survive in the wild.

The first, and most limited, objective would be the implementation of the full set of competencies in cellular, molecular, and reproductive biology needed to produce reproductively capable males and females for use in genetic rescue. Developing the technology to accomplish this includes steps outlined in Saragusty et al. (2016): producing in vitro gametes from iPSC of unrelated NWR individuals, using them to create embryos for embryo transfer and successful gestational surrogacy—ideally in SWR, neonatal and adult husbandry, and species-appropriate breeding behavior. This initiative builds on and extends the role of zoos in contributing to basic biological knowledge to conservation science (Minteer, Maienschein, & Collins, 2018).

The first objective will require a stable supply of research materials including cells from NWRs, horse oocytes as research models as outlined by Saragusty et al. (2016), and surrogate SWRs to sustain pregnancies to term. The SDZSP has NWR cell lines through its Frozen Zoo®, as well as a herd of SWRs for both research and display. Horse oocytes can be purchased but accessing NWR oocytes to create embryos is a challenge.

The first objective benefits from collaborative relationships and exchanges between and across institutions. These include the Dvůr Králové Zoo in the Czech Republic owner of the last two NWRs, SDZG with 12 NWR cell lines and 9 cultures of induced pluripotent NWR stem cells, as well as herds of both research and display SWR, the Leibniz Institute for Zoo and Wildlife Research in Berlin, leaders of the Biorescue project, with the aim of saving the NWR from extinction. Also involved is Avantea Srl in Italy, so far, the only entity to succeed in producing NWR embryos by in vitro fertilization. This was accomplished with the cooperation of the Kenya Wildlife Service and the Ol Pejeta Conservancy using NWR-oocytes and in vitro fertilization via intracytoplasmatic sperm injection (www.izw-berlin.de).

As a subspecies of the white rhino, the SWR is possibly the most appropriate recipient for NWR embryos. The few embryo transfers attempted in rhinos have not resulted in pregnancies. Thus, successful gestational surrogacy has not yet been established. However, the birth of a healthy NWR-SWR hybrid calf following natural breeding confirms a close physiological similarity between the two subspecies (Christman, 2012). When pregnancy initiation and maintenance have been successful, neonatal and maternal husbandry must be enhanced to ensure survival of embryo transfer calves.

The second objective would be production of 25–40 live NWRs in a managed population within the SDZSP and elsewhere. Between the needs for technology development and the demographic realities of rhino reproduction (sexual maturity at eight, 4 years, or so between births) this is likely to take at least 40 years. These animals would need to represent a significant portion of the known genetic variation. Individuals would be produced using the technologies spelled out in Saragusty et al. (2016). Using accumulated knowledge in rhino captive breeding, husbandry would be applied to help this small population breed naturally. The herd would be distributed into two or more groups to avoid catastrophic loss. This work would build on the role of breeding in zoos' early wildlife preservation practices and the ability of zoos to support habitat management and educate visitors to foster a connection with animals (Minteer et al., 2018).

Displaying the NWR in zoos would be inextricably linked to conservation of animals in the wild. To be successful, the second objective requires strengthening the values promoted by the third objective: the re-establishment of animals in their original range. This would entail creating direct benefits within and across range countries relegating the illegal market in rhino horns to an undesirable activity. Such an effort would need to be integrated with others to ensure the availability of suitable habitat, proper security, stakeholder involvement, and regulation at all levels.

The third objective would have two goals: (a) the reestablishment of one or more breeding populations of NWRs within suitable habitat within their former range and (b) ensuring their safety while striving to progress to the point that commercial utilization of rhino products is no longer a threat to the species' survival. This objective builds upon the longstanding role of zoos in reintroducing species to their former habitat, which requires integrating in situ and ex situ preservation as well as collaborating with community-based conservation projects (Minteer, 2019; Redford, Jensen, & Breheny, 2012). As well as ethically necessary such work with communities is also required because historical, social and political chronicles of land dispossession have combined with displacement, relocation and food insecurity to turn some communities against conservation and wild animals and enable the expansion of rhino hunting (Hübschle, 2017).

Several existing protected areas within the range of NWR could be considered for reintroduction efforts if conditions were appropriate, provided the safety of the introduced animals can be guaranteed. The driver of rhino killing is to use the horn as an ingredient in Traditional Asian Medicine, though they are also a status symbol (Hübschle, 2017). Key drivers on the supply side include the entry of transnational organized crime and attitudes of local peoples toward rhino conservation. In addition to suppression of demand for rhino horn, regulation and enforcement creating enabling social conditions for success would include generation of income from sources such as tourism and conservation-related jobs.

Restoring rhinos to their historical range is intrinsic to the NWR Initiative. It makes the other aspects of the project coherent, explains why it should be supported as well as providing its educational context. It is the audacity and ambition of the project as conceived in its fullest sense that provides its meaning, narrative, and symbolic value. The science and community components alone are not enough. Of course, any reintroduction cannot and must not be done outside of the context of the priorities of range states and with their support. However, it is hoped that reintroduction of NWRs would bring renewed support and resources to protected areas where they might be returned. Without such political, social, technical, and financial help, rhino reintroduction would not succeed.

When the NWR project is considered as a set of nested objectives—scientific, zoological, educational, and conservation—it is clear that the conservation component empowers the other project components and gives them meaning. The project will generate new scientific knowledge and tools, and will provide new educational and experiential opportunities, but that is not what the project is *about*. Its *meaning*—its symbolic value and why it captures people's imaginations—is its potential to be an educational, social, and scientific game-changing species conservation success story, encouraging a new paradigm and expansion of the One Plan Approach of the IUCN (Byers, Lees, Wilcken, & Schwitzer, 2013).

This is further evident when analyzing who benefits from the project. It is only when the NWR project is considered as a conservation program with benefits beyond the researchers, zoological parks, and their visitors that it come into focus. These broader benefits are crucial not only for the project's justification, but also for its value. If this is a project that primarily benefits affluent researchers, affluent organizations, and affluent tourists, it has a different meaning, and it intersects with different and problematic narratives. An objective would be to create a comprehensive, collaborative project to use the promise of rhino return to foster ecological protection as well as social improvement and empowerment.

4 | SOME OF THE CHALLENGES FOR A NORTHERN WHITE RHINO PROJECT

Our multidisciplinary group identified a number of issues that pose challenges and opportunities to the NWR project and to others like it. This is an illustrative list rather than a comprehensive one. Addressing each of these challenges must be done by a combination of stakeholders with a skill set such as that represented by the authors in addition to the vital involvement of national authorities and local communities.

1. Animal welfare: The goal of all the possible initiatives is to help the NWR. Unreasonable risk of harm from animal management, husbandry, or research to existing rhinoceros or to potential future rhino calves is not acceptable. Success of the project must not come from harm to individual rhinoceros. Risks of harm—both from intervening and from *not* intervening, can never be eliminated but planning, careful experimentation, and constant vigilance will be needed.
2. Time: Creating numbers of live NWRs will take time. Long term projects demand long term commitment from financing entities but, perhaps more importantly, from people—trainers, veterinarians, researchers, and others willing to work for decades toward an end they will quite often not live to see achieved. Yet, all conservation efforts that address persistence and sustainability are long-time efforts. The NWR Initiative may help focus attention on this essential feature.
3. Getting it right: Any NWR initiative may carry the huge pressure to "get it right"—that is to succeed in producing viable, healthy rhino calves. It would be one of the earliest efforts to use the tools of molecular biology in the cause of conservation. An early success, akin to the birth, more than 41 years ago, of a healthy Louise Joy Brown, the first in vitro fertilization human baby, would bolster the effort. A failure, such as the death, more than 20 years ago, of volunteer Jesse Gelsinger in a gene therapy trial, could set the field back for many years. In some ways, though, the situation is even harder. The NWR Initiative will have pressure not only to succeed (or, at least, not to "fail") but to do so in an open and public way. Transparency will be crucial as will keeping the public informed not just of the successes along the way but also of the failures.
4. Species boundaries and genetic conservation: The NWR project raises questions related to species categorizations, as well as about the importance of genomic distinctiveness. The SDZG plan is to reconstruct a NWR population without incorporating any non-NWR genetic material. The conservative nature of the NWR Initiative preserves future options for admixture or sustainability of evolutionary lineages. We ask, though, would the NWR project be any less successful, in a conservation sense or with respect to conservation value, if some amount of SWR genetic material were part of the reconstituted population? For example, somatic cell nuclear transfer (cloning) of NWR nuclei into SWR ova, would result in offspring with under 0.0001% of its DNA from SWR mitochondria. If the NWR project succeeds in producing NWR calves, it will, at a bare minimum, have to rely on SWR females to gestate, and presumably nurse and foster any new NWR calves. Would this bring into question the "purity" of the resulting rhino calf genetically, epigenetically and/or behaviorally? Note that the current plan does not preclude these options and offers future conservationists the opportunity to decide.
   The NWR project poses larger questions about what counts as species conservation when biotechnologies are involved; what is valuable about species conservation and how those values intersect with the use of different biotechnological tools (Piaggio et al., 2017); and how much deference there should be to maintaining historically distinct lineages and how that distinctness is defined. Forcing discussions about these questions is, we believe, a benefit of this effort.
5. Moral hazard: The NWR project also intersects with moral hazard and technofix concerns that have been raised regarding some uses of biotechnology in conservation. "Technofix" refers to the use of technology to address problematic outcomes of human activities, rather than addressing their underlying causes. In its most narrow conception (first objective), the NWR project would not address the reasons for the decline in the population of NWRs and it would not return NWRs into their historical range. It would only create and maintain a population of organisms that are genetically related to past NWRs. This would be technologically and scientifically impressive, and of arguable conservation value. However, by itself, it would not address the underlying problem—that is, the human activities and systems that caused the NWR to be at the brink of extinction.

Moreover, if the ability to reconstruct genetically similar populations from cryopreserved tissue of endangered species were used to try to justify less robust efforts to address the underlying causes of extinction both generally and in particular cases, then it would function as a moral hazard. The promise of the technofix for the undesirable outcomes make it more likely that the outcomes would occur and less likely the underlying problems would be addressed. The point here is not that the NWR is a technofix or a moral hazard. But rather, whether it would become one depends not only on the scientific and technological aspects of the project, but on how those aspects are situated within broader program goals and efforts.

5 | BIOTECHNOLOGICAL CONSERVATION AND THE LIMITS TO SAVING A SPECIES

Some proponents of the use of biotechnology in conservation argue that embracing it is part of a necessary reconceptualizing of the practice of conservation (Brand, 2013; Phelps, Seeb, & Seeb, 2019). With this logic, climate change, and broader anthropogenic factors have resulted in environments that are so altered that it is no longer appropriate to conceive and operationalize conservation in terms of maintaining or reestablishing systems as they were or would have been without human impacts (Hobbs, Higgs, & Harris, 2009). Instead, in this view, a more activist, creative, and forward-looking approach is needed, one that includes moving species to where they need to be (managed relocation), helping species adapt to novel environmental conditions (facilitated adaptation, gene drives), and designing ecological systems to maintain services and biodiversity (rewilding).

Although the NWR project makes uses of biotechnology for conservation purposes, it does not embrace or exemplify this more creative and interventionist conception of conservation. To be sure it is interventionist on the scale of individual animals but not in the system-wide sense of ecological restoration. The NWR project is frankly nostalgic, in the sense of Jørgensen (2019) who argues that recovery of nature such as that of the NWR depends on "emotional responses to the lost, particularly a *longing* for recovery that manifests itself in emotions such as guilt, hope, and grief." The project is an effort to prevent an iconic and charismatic subspecies from going extinct. It aims to create an ex situ population of NWRs that are neither genetically edited nor mixed with other species. It aims to develop a captive breeding and reintroduction program with the goal of returning NWRs to their historical range where human activities have caused them to be extirpated. In its expansive conception, it aims to address the underlying and systemic causes of the NWR's functional extinction. In all these respects, it fits neatly within familiar conservation paradigms.

However, the NWR initiative contains the element of a more hopeful hypothesis. Successes along the way would reinforce the value of cryopreserved biological material for conservation of at-risk species, including those that are functionally extinct, and result in the development of knowledge, technologies, and techniques that will substantively advance biotechnological conservation. In fact, if the constructed gamete approach being pursued by the participants in the NWR Initiative accomplishes its purposes, the successful use of any biological materials beyond the established cell cultures from the currently preserved NWRs might not be required. It would therefore be a proof of concept for sub-species de-extinction as well, since it would reconstitute a NWR population in a way that does not depend on there being any living members of the subspecies.

Moreover, a successful NWR project would contribute to an emerging genomic focus in conservation, which could have implications for the conservation profession. Technological innovations often restructure scientific practices in deep and extensive ways (Jasanoff, 2016). For example, the ongoing genetic turn in medicine has led to new ways of addressing medical problems, new conceptions of disease and illness, new forms of treatment, new institutional structures, new expertise, and new experiences for both patients and practitioners (e.g., Scully, 2008). The NWR project sits with a set of similar species restoration or de-extinction projects, including ones focusing on the quagga (a subspecies of the plains zebra), the passenger pigeon and the woolly mammoth (Novak, 2018). As such there is a growing literature on risks, legal concerns and governance of de-extinction projects (e.g., Valdez, Kuzma, Cummings, & Peterson, 2019).

It is likely that the introduction of biotechnology to conservation will restructure the field of conservation biology in significant respects (Sandler, 2020). It could change how problems are conceived, who is drawn to the profession, as well as who is empowered and disempowered in it. This in turn could influence the way research is done, where funding is allocated, what programs are created, and what skills and knowledge are valued (Braverman, 2018). But not all are excited about such prospects. Minteer (2019, p. 117) believes that attempts to revive extinct species (though not exactly what the NWR is) is not a "… proper act of ecological contrition. It is yet another example of the refusal to recognize moral and technological boundaries in nature …".

The NWR project is at once both highly conservative in its goals—that is, it aims to prevent loss, maintain species distinctness, and reestablish past ecological relationships - and highly innovative in its tools. Its methods fit squarely within the growing movement that advocates embracing novel technologies and strategies, including biotechnologies, to address hard conservation problems—and thus potentially radical in its implications.

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All authors declare that there are no potential sources of conflict of interest.

AUTHOR CONTRIBUTIONS

Ryder assembled team; Redford led in writing; equal contribution by all other authors.

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