

The origin story of rapamycin: systemic bias in biomedical research and cold war politics

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ABSTRACT METEI (Medical Expedition to Easter Island) was a Canadian-led expedition to Easter Island in 1964 that led to the discovery of rapamycin, launching a billion-dollar drug industry and major field of biomedical research. *Stanley's Dream*, by medical historian Jacalyn Duffin, provides remarkable details about METEI and raises important and timely questions about systemic bias in biomedical studies, the relationship between science and geopolitics, as well as obligations of pharmaceutical companies to indigenous communities. As such, this book is a must-read for those interested in the intersection of science and society as well as anyone who has used rapamycin, or one of many derivatives, in their laboratory or clinic.

Monitoring Editor

Doug Kellogg
University of California,
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Received: Aug 31, 2022

Accepted: Sep 9, 2022

MEDICAL EXPEDITION TO EASTER ISLAND (METEI) AND TARGET OF RAPAMYCIN (TOR): SUMMARY AND BACKSTORY

It is well known by many that rapamycin was discovered on Easter Island as an antibiotic produced by an aerobic Gram-positive soil bacterium, specifically *Streptomyces hydropiscus* AY B-994 [NRRL 5491], and named in reference to the island's indigenous name Rapa Nui (Wullschlegel *et al.*, 2006). Studies in the 1970s and 1980s showed that this molecule acts both as a potent inhibitor of fungal cell growth and as an immunosuppressant and anticancer drug in humans (Loewith and Hall, 2011; Zoncu *et al.*, 2011; Livi, 2019). The observation that rapamycin targets both yeast and human cells suggested immediately there was a common mechanism of action and paved the way for pioneering studies in the 1990s that identified the highly conserved TOR kinase (also named mTOR or MTOR) (Loewith and Hall, 2011; Zoncu *et al.*, 2011; Livi, 2019). Following the discovery of TOR, the field exploded with studies describing how this kinase and its interacting partners form the center of an intricate signaling network that controls virtually every aspect of growth and metabolism. Indeed, dysregulation of TOR is involved in many human diseases, including cancer, and plays roles in aging as well

as responses to environmental and nutritional stress (Saxton and Sabatini, 2017; Mossmann *et al.*, 2018; Magaway *et al.*, 2019).

Less well known is how an isolate of *S. hydropiscus* found its way from Easter Island into the hands of pharmaceutical researchers at Ayerst Research Laboratories (later Wyeth-Ayerst and then Wyeth), where rapamycin was ultimately isolated and characterized. Moreover, few people are likely to understand precisely why an international team of scientists and physicians went to Easter Island in the first place. Fragments of this story have been pieced together that provide a limited sketch of METEI (Halford, 2016; Hall, 2017). By contrast, *Stanley's Dream* (Duffin, 2019), published just prior to the COVID-19 pandemic, is expansive and stems from Duffin's serendipitous access to a treasure trove of documents directly from the expedition, including primary data from human studies of the island's inhabitants (Rapanui) and personal diaries of METEI members. Duffin also tracked down and interviewed surviving members of the expedition or, in many cases, their relatives. Finally, she made a visit to the island herself to meet surviving Rapanui who interacted with expedition members and who were subjects of the METEI study.

What emerges is how METEI was the inspiration of two physician-scientists from Montreal: Stanley Skoryna ("Stanley" from the book's title), a surgeon and cancer researcher at McGill University, and Georges Nogrady, a physician and bacteriologist from the University of Montreal. Both men were motivated by questions concerning human adaptation to environmental stress and change, particularly as it related to global concerns in the early 1960s of overpopulation, emerging diseases, constraints on availability of natural resources, as well as the proliferation of nuclear weapons.

DOI:10.1091/mbc.E22-08-0377

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Abbreviations used: CBD, convention on biological diversity; METEI, medical expedition to Easter Island; TOR, target of rapamycin; WHO, World Health Organisation.

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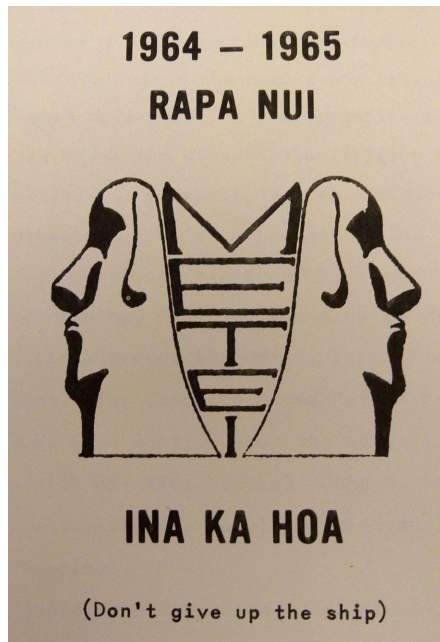


FIGURE 1: METEI logo and inscription by Georges Nogrady (Nogrady, 1974).

These concerns were embodied in what became known as the International Biology Program, where goals included identifying global health and environmental challenges and proposing solutions on an international scale (Stebbins, 1962).

Skoryna was the driving force behind METEI, learning that the government of Chile, to whom Easter Island belongs, planned to build an international airport on the island. Skoryna and Nogrady viewed this as the perfect opportunity, naively as it turned out, to study the island and its people before and after construction of the airport. Their goal was to observe and quantify the impact of increased exposure of an isolated population and their environment to the outside world. Through a combination of personal and professional connections, dogged determination, and some creative financing, Skoryna essentially single-handedly brought METEI into existence. His efforts included securing funding from the World Health Organization (WHO), recruiting an international group of physicians and scientists to participate, as well as convincing the governments of Canada and Chile to sponsor and permit, respectively, a large-scale study of the island. Of central importance was securing the help of the Royal Canadian Navy, who ultimately supplied the maintenance vessel HMCS Cape Scott and its crew for the expedition.

Skoryna's efforts culminated in the visit of approximately 40 medical and scientific personnel to Rapa Nui, where they set up laboratories and living quarters and worked from December 1964 to February 1965. In addition to conducting extensive physical exams and collecting biological samples from most of the island's population of approximately 1000 individuals, METEI researchers also surveyed the entire island, including documenting and collecting samples of local flora and fauna. As part of this effort, Nogrady divided the 63 square mile island into 64 quadrants and collected soil samples from each, over 200 in total, including in open areas adjacent to the famous giant Moai stone statues, among crops, within underground caves, and in tidal areas. One goal was to characterize the diversity of microorganisms on the island, including the identification of possible pathogens, for example, an unknown causative agent of a

recurring febrile respiratory condition among the Rapanui called "kokongo." However, Nogrady also recognized that the island could be home to microorganisms that produced novel and beneficial natural products, an insight that proved to be correct.

BIOETHICS OF METEI

While the discovery of rapamycin is most often the reason cited for METEI, the primary focus of the expedition was the island's human population. Indeed, Skoryna's funding application to the WHO was titled "Immuno-Epidemiological and Genetic Studies on the Population of Easter Island." While it was logical to Skoryna and Nogrady to choose an isolated population for the study of effects of environmental change, in retrospect this is a clear example of biased and colonialist behavior, where a white (and predominantly male) group decides to study an indigenous non-white people (Washington, 2006). To be fair, METEI was not nefarious like the Tuskegee syphilis study (Brawley, 1998) or as culturally intrusive as the Havasupai tribe genetic studies (Garrison, 2013). However, METEI was designed primarily to investigate the health of the Rapanui for scientific purposes, not to address their health or well-being. In addition, while the physicians and scientists involved in examinations may have been well regarded by most Rapanui, participation in the study was encouraged by bribery with gifts, food, and supplies, as well as apparently subtle coercion by a long-serving Franciscan Priest on the island. Duffin also describes passages from diaries and letters revealing the existence of sexism and gender bias in terms of how male members of METEI interacted with both METEI and Rapanui women.

It also turned out that a key assumption by Skoryna was false, namely, that the Rapanui represented a genetically homogenous population. This was viewed as important for in-depth genetic studies of relatedness and disease susceptibility, among other questions related to human adaptability. This mistake highlights a lack of understanding of the complex and tragic history of Rapa Nui, which includes disease, slavery, and significant migrations, and where the modern population includes individuals of mixed Polynesian and South American ancestry. It also turned out that the islanders were not as isolated as Skoryna had initially believed, which complicated another goal of the study, which was to compare the population before and after construction of the airport. Much of this information should have been known to Skoryna, including descriptions of the Rapanui as of mixed ancestry by Norwegian explorer Thor Heyerdahl of "Kon-Tiki" fame, as well as others. In many ways, both the concept and the execution of METEI was rushed and ill conceived. As Duffin speculates, some of these factors likely contributed to the fact that the planned follow up expedition never happened.

METEI AND GEOPOLITICS

METEI was conceived during the Cold War, providing additional context to Skoryna's efforts to build an international team and was influenced by political conditions between Rapa Nui and Chile. Political struggles between United States-aligned and Marxist forces in Chile were also at play, foreshadowing both the election of Salvador Allende and the subsequent military takeover by Augusto Pinochet in the 1970s. In this regard, one explanation offered by Duffin for construction of the airport on Rapa Nui was not for tourism or to benefit the island's population but rather for construction of a satellite tracking station as a joint venture between the United States and Chile.

Immediately upon their arrival, METEI researchers encountered first hand the troubled relationship between Chile and the Rapanui, discovering a population that was economically impoverished, politically dominated, and geographically restricted to a specific

region of the island. The island was essentially under military rule, controlled by a Chilean military governor and supplied from the mainland by a single annual visit by a military ship that did not always arrive when scheduled. Tensions existed too as Chile was concerned that the population of the island would demand independence and/or align with Tahiti, controlled by France and a reflection of Polynesian origin of many Rapanui.

These tensions spilled over just prior to the arrival of the expedition, where an impromptu election was held for mayor that resulted in the selection of a candidate, aligned with the politics of Allende, who wanted greater autonomy and democratic reforms on the island. The election was deemed illegitimate by the local governor and Chilean marines arrived soon after the METEI camp was constructed. Skoryna appeared to take a neutral position, concluding the tensions were a “domestic matter” unrelated to the goals of the study. However, at the same time he played an active role in defusing tensions, negotiating with both sides to resolve the conflict and restore order on the island. Interestingly, Duffin’s research suggests the election for mayor was inspired in the first place, in part, by the expected arrival of METEI and the international attention it would bring to the island.

Together these events raise the question of the role of METEI in local politics and, more broadly, of the ethics of political manipulation to keep a scientific study intact. Despite these criticisms, the arrival of METEI is also credited for ultimately bringing greater democratic reforms to the island, including granting of citizenship for the Rapanui by Chile in 1966. METEI personnel also took over health care for the Rapanui after Chilean authorities arrested, for political reasons, the only doctor on the island. Duffin discovered during her visit to the island in 2017 that for many with a memory of METEI, they spoke fondly of the Canadian-led team, compared with American servicemen subsequently stationed on the island in the late 1960s and early 1970s.

RAPAMYCIN, BIOPROSPECTING, AND INDIGENOUS RIGHTS

METEI occurred prior to increased awareness of the rights of indigenous people regarding autonomy of their persons, land, and resources. Such recognition is embodied in several initiatives by the United Nations, including the 1992 Convention on Biological Diversity (CBD) and the 2007 Declaration on the Rights of Indigenous Peoples. Some of these rights pertain to the treatment of individuals themselves, where participation of the Rapanui in physiological examinations and biological sample collection clearly violated current standards of free, prior, and informed consent (FPIC). Other rights recognized by the UN pertain to the use of natural resources, including Article 32, which states that “Indigenous peoples have the right to determine and develop priorities and strategies for the development or use of their lands or territories and other resources.”

In this context, the discovery of rapamycin-producing bacteria on Rapa Nui is complicated. On the one hand, the path of the soil sample from a medical mission to the pharmaceutical industry was indirect and lengthy. Furthermore, METEI was established as an international government expedition with no corporate sponsors. Moreover, the concept of bioprospecting (or biopiracy as it has sometimes been dubbed) typically concerns commercialization of resources already recognized by an indigenous people, for example, the use of medicinal plants (Rose *et al.*, 2012; Girard *et al.*, 2022). In this context, the Rapanui had no knowledge of the drug-producing bacteria living in their soil. Furthermore, it is now known that Rapa Nui is not the exclusive source of *S. hydroscopicus*, as closely related isolates have been found in China, Japan, and Iran

(Yoo *et al.*, 2017). In this regard, it has been proposed that the strain found on Easter Island be renamed *Streptomyces rapamycinicus*, to designate its location of origin among several other strains now identified (Yoo *et al.*, 2017). Finally, as a fine point, for patent issues the original compound has been modified over the years, so that pharmaceutical companies do not produce the molecule identical to the original isolate.

On the other hand, rapamycin and its derivatives have been such an outstanding scientific, medical, and financial success that it is difficult to rationalize, especially with a more complete understanding of METEI, that no debt is owed to the Rapanui. For example, Pfizer, which purchased Wyeth in 2009, has made hundreds of millions of dollars annually for the sale of Rapamune. It continues to be profitable, although competition with generic substitutes and significant legal fines for off-label marketing have impacted their profits in recent years. In addition, additional derivatives of rapamycin are in clinical use, including Temsirolimus, prescribed for renal cell carcinoma by Pfizer, and Everolimus (AFINITOR), produced by Novartis, for treatment of a variety of tumors. Moreover, while rapamycin and its derivatives inhibit only half of the TOR kinase in cells, as the other half assembles into a protein complex that is insensitive to the drug, next-generation inhibitors called “Torins” inhibit all of TOR and are in clinical trials for a variety of uses (Liko and Hall, 2015). Thus targeting TOR will no doubt continue to be a profitable enterprise for the foreseeable future.

During her trip to Rapa Nui, Duffin encountered both individuals who had never heard of rapamycin and others who believed the island should have received a share in the profits of the rapamycin industry. It is important to point out that Rapa Nui is still controlled by Chile (Aguilera, 2022). Thus it is unclear whether financial resources targeted for the Rapanui would even make it to the island. Importantly, a shift in behavior of pharmaceutical companies is taking place as some have pledged to contribute more to improving conditions in underserved regions in the world and to adhere to UN treaties regarding bioprospecting (Rose *et al.*, 2012; Girard *et al.*, 2022). It appears, however, that the Rapanui have missed out on this opportunity of a potential change in corporate behavior.

RAPAMYCIN: RECOGNIZING THE ROLE OF NOGRADY

A final cautionary tale in the story of METEI is the role of recognition for scientific discovery. For example, it is well documented that an isolate of *S. hydroscopicus* from Easter Island was examined by researcher Surendra (Suren) Sehgal and colleagues at Ayerst Research Laboratories, where rapamycin was isolated and characterized. Sehgal went on to play a crucial role in keeping research on rapamycin alive during the transition of Ayerst into Wyeth-Ayerst and then finally Wyeth Labs, including stashing an isolate of *S. hydroscopicus* at home against company directives (Garber, 2001; Kahan, 2003; Halford, 2016). Ultimately these efforts culminated in the award of the license to Wyeth for Rapamune in 1999.

What has remained unclear is how one of Nogrady’s soil samples made its way to Sehgal. Here Duffin has pieced together the story that the likely link was bacteriologist Claude Vézina, who was both a colleague of Nogrady at the University of Montreal and employed at Ayerst and a colleague and friend of Sehgal. Vézina, it turns out, presented preliminary data at a symposium in Toronto in 1969 on the antifungal properties of specimens isolated from Nogrady’s soil samples. Vézina went on to co-author widely cited publications with Sehgal on the isolation and naming of rapamycin (Sehgal *et al.*, 1975; Vézina *et al.*, 1975). Nogrady himself was never acknowledged in any of these publications (neither was METEI), making him an unsung hero of the TOR field.

Besides the soil samples shared with Ayerst, Nogrady is known to have sent out many samples to colleagues both from his soil collection and from microorganisms isolated during METEI. Duffin catalogs research that resulted from Nogrady's efforts, all published by others and much of it focused on staphylococci isolated from individual Rapanui during medical examinations. Many mysteries remain, however, including Nogrady's map of the island, now lost, showing the precise location where each soil sample was taken, meaning that the exact spot on Rapa Nui where *S. hydroscopicus* was isolated is not known. Moreover, the fate of the soil sample collection itself is unknown. Duffin uncovered correspondence from 1966 indicating Nogrady sent a set of his samples to an international culture collection in Lausanne, Switzerland; however, no permanent record of his gift, let alone the collection itself, exists. At this point in time, it appears this contribution of Nogrady's legacy is lost to history.

CONCLUSIONS

Duffin's account reveals a mixed legacy for METEI. While Skoryna and Nogrady may have had their hearts in the right place, their decision to study Rapa Nui in the manner they chose inevitably contained racially biased and colonialist elements. Once on the island, the expedition also had a mixed record based on interactions with the Rapanui and political tensions on the island. Nogrady's soil sample collection is arguably the most important outcome of the trip from a biomedical perspective, although this too is problematic in terms of the lack of any obvious benefit to the island and its people. The Rapanui to this day struggle with their autonomy and remain in conflict with Chile regarding tourism and the negative ecological impact this industry has had on the island (Aguilera, 2022). Chile also controls immigration to the island that threatens the cultural identity of the Rapanui. It is impossible to learn of this history and not be moved, particularly knowing the importance of the Rapanui to the TOR field. Many individuals have used rapamycin to gain fame, financial success, clinical triumph, as well as tenure, all of whom owe gratitude to the Rapanui.

In his only published work from METEI, Nogrady published the proceedings of a conference in 1971 on the microbiology of the Easter Island (Nogrady, 1974). He closed his acknowledgments with the statement: "Hopefully, all efforts embodied in these results will alleviate the tragic mistakes committed by the white man against Oceanians, who are among the noblest members of the great human family." One can only feel that the TOR field should do more for the Rapanui, who have not shared in the wealth that has come from the discovery of a wonder drug. Unless and until this situation changes, it is appropriate to honor the Rapanui for their contributions and place in history.

ACKNOWLEDGMENTS

I thank Vicky Watson-Zink for discussions and for creating and teaching as Graduate Advisor to the Dean for Diversity, Equity, and Inclusion in CBS, both a graduate and undergraduate course on the history of racism and systemic bias in biomedical studies in the United States. The many shocking case studies presented ultimately led me to reflect on my own field, where I realized I knew virtually nothing about METEI and events that led to the discovery of rapamycin despite being a researcher in the TOR field for over 20 years. This

curiosity brought me to Jackie Duffin and her book, and I thank the author for several interesting and informative conversations. I also thank Bethany Halford for filling me in about her uncited sources for her 2016 article in *Chemical & Engineering News*. I thank D. Kellogg, J. Nunnari, K. Shiozaki, D. Starr, J. Thorner, J. Tsvetov, and C. Turner for conversations and for comments on the paper. Like Georges Nogrady, I express gratitude to the Rapanui and acknowledge the debt owed to them.

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