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Letter to the Editor

LETTER TO THE EDITOR

A treasure from a barren island: the discovery of rapamycin

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Rapamycin (also known by its generic name, sirolimus) is a mammalian target of rapamycin (mTOR) inhibitor and is used as an immunosuppressant mainly in special circumstances such as skin cancer or in other situations where calcineurin inhibitor avoidance is desirable. Rapamycin is currently not part of standard regimes for immunosuppression in renal transplantation, mainly due to its side effects, which include hyperlipidemia, pneumonitis and impaired wound healing. The history of its discovery is little known among nephrologists.

In 1964, a Canadian expedition left Halifax on the HMCS *Cape Scott* (Fig. 1) to the Chilean territory of Easter Island (Rapa Nui) to study its population. This island has captured the minds of explorers for more than a century, but plans for an airport in 1966 threatened to disrupt the biosphere of this unique ecological niche. Because of this, a medical expedition was planned by Dr Stanley Skoryna and Georges Nogrady to document the population and biosphere. Stanley Skoryna (1920–2003) was a McGill University surgeon and gastroenterologist and Georges Nogrady (1919–2013) was a microbiologist [1]. During efforts to find new antibiotics from natural sources, soil samples were obtained by Nogrady and taken back to Canada, where they were handed over to Suren Neth Segal (1932–2003) at the Ayerst Laboratory in Montreal.

One bacterial species, *Streptomyces hydroscopicus*, was isolated and found to produce a molecule with antifungal activity [2]. The original hypothesis had been that antibacterial compounds in the soil might explain why the natives of Easter Island had a low incidence of tetanus despite walking barefoot [3]. The new molecule was named rapamycin after Rapa Nui [3]. Sehgal also discovered that it had antiproliferative activity and sent samples to the National Cancer Institute, where activity against solid tumors quickly gained priority status [4, 5]. However, around this time, Ayerst consolidated its workforce and the Montreal research facility was closed [4]. Sehgal took samples of *S. hydroscopicus* home and placed them in his freezer, where they stayed for some time [1].

Ayerst and Wyeth later merged in 1988 and Sehgal was able to push rapamycin back onto the research agenda [4]. In 1999, the US Food and Drug Administration approved rapamycin as an immunosuppressant. Rapamycin (Fig. 2) is a macrolide that has a mechanism of action distinct from its counterparts, tacrolimus and cyclosporine. Interestingly, rapamycin forms a pharmacologically active complex with the same intracellular target as tacrolimus, i.e. FK binding protein-12 (FKBP-12) [6]. However, the rapamycin–FKBP-12 complex binds and inhibits mTOR, as opposed to calcineurin. The mTOR signaling pathway has a number of important functions, including responding to multiple signals to control processes required for cell growth and proliferation [7]. By interrupting the signal from the interleukin-2 receptor as well as other cytokine and growth factor receptors, rapamycin blocks the signal transduction pathway necessary for T-cells to progress from G1 into the S phase of the cell cycle and thus proliferate [8].

The discovery of rapamycin is notable becuase of the pioneering spirit of Stanley Skoryna and Georges Nogrady, which led them to find what Barry Kahan called ‘a treasure on a barren island’ [3], although they were unaware of its importance. Suren Sehgal and his persistence and belief in the utility of the novel compound are also worth remembering, as is the thought that the original sample spent time in Sehgal’s own freezer. More widely, soil samples have been quite beneficial for transplant nephrology, given that not only rapamycin, but also cyclosporine [9] and tacrolimus [10] were discovered in this way. Current and future nephrologists, especially those working with transplant

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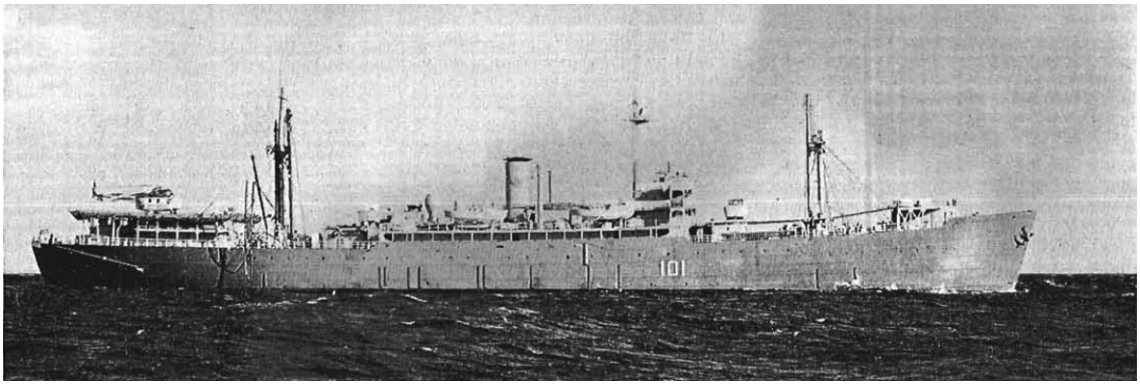

FIGURE 1: The HMCS *Cape Scott*, a vessel of the Royal Canadian Navy that carried the expedition to Easter Island (image in the public domain).

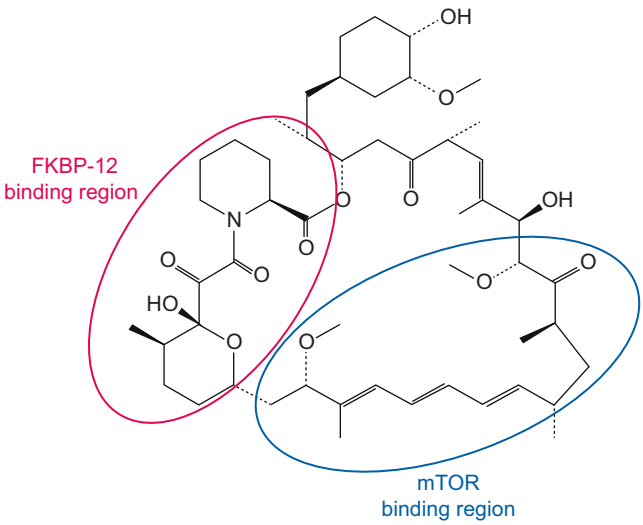

FIGURE 2: Structure of rapamycin showing the binding domains for FKBP-12 and mTOR.

patients, should remember the events and personalities leading to this discovery.

CONFLICT OF INTEREST STATEMENT

A.W. is a member of the *CKJ* editorial board. The results presented in this article have not been published previously in whole or in part.

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