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Commentary

Is rapamycin a rapalog?

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Abstract. David Glass and Dudley Lamming debate the question of "Is Rapamycin a Rapalog" while the world votes.

Keywords: Rapamycin, RAD0001, everolimus, mTORC1, mTORC2, aging

1. Introduction

Rapamycin, a molecule purified from bacteria discovered on Easter Island in 1975, has over the last decade attracted significant attention for its ability to extend the lifespan of model organisms including mice, even if given transiently or intermittently [1–4]. Importantly, rapamycin may also be able to protect tissues from the ravages of age and potentially functionally rejuvenate some aged tissues; tissues benefiting from short-term rapamycin treatment include (in rodents) the heart [5], hematopoietic stem cells [6], and the kidney [7], and (in humans) the immune system [8]. Despite the significant potential benefits that rapamycin may offer as a therapy to slow, treat, or reverse age-related disease in humans, work has proceeded cautiously due to the fear of the side effects of rapamycin, which include immunosuppression, dermatological events and metabolic disruption. Many of these side effects result, in whole or in part, from the "off-target" effects of rapamycin on a protein kinase, the mechanistic Target of Rapamycin Complex 2 mTORC2 [9, 10].

There has been significant interest in developing compounds that avoid or mitigate the effects of rapamycin by avoiding off-target inhibition of mTORC2 [9]. While the vast majority of work with rapamycin has utilized the original parent compound, short-term treatment with a rapamycin derivative – RAD0001 (Everolimus) – has shown potential benefits in humans [8], and Everolimus shows reduced, although still significant, metabolic side effects in mice [11]. Analogs of rapamycin have traditionally been called "rapalogs", which led one of us (DJG) to pose the question: is rapamycin a rapalog?

2. Debate

DJG: Debate question for the day: Does Rapamycin belong in a group of compounds labelled "Rapalogs"?

DWL: It is the founding member of the class.

DWL: I view it as asking if the USS Nimitz is a Nimitz-class carrier. The Navy thinks the founding vessel of each class of aircraft carrier, ship, submarine, etc. is a member of that class.

DJG: What is the definition of a rapalog? A rapalog is a "rapamycin analog," per the first use of the term in Pubmed [12]. Can a thing be an analog of itself? Put another way, is a chocolate chip cookie an analog of a chocolate chip cookie? No.

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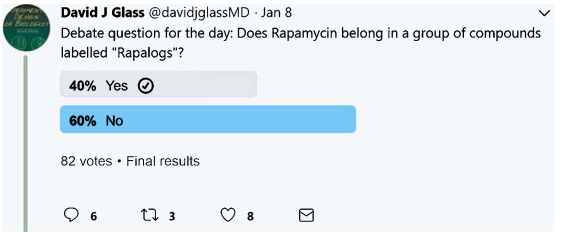

Fig. 1. Twitter poll on "Is Rapamycin a Rapalog?"

DWL: Hmm, Wikipedia says that rapalogs are "rapamycin and its inhibitors" [13].

DJG: I know, let's ask the internet! We will do a Twitter poll.

DJG: The people have spoken, and rapamycin is not a rapalog.

Noted mTOR expert Dr. David M. Sabatini [14]: (Arriving in a flash of light) DWL, you would been correct if it was a Nimitzlog-class carrier. (Vanishing in a puff of smoke)

DJG: Well, that is that folks. Although I always thought that the bit about saying rapamycin three times fast and having David Sabatini appear was a myth.

DWL: Nope, it's definitely true (at least on Twitter). I guess we will be stuck writing "Rapamcyin and the rapalogs" for the indefinite future.

In conclusion, rapamycin is not a rapalog. Unless, of course, one is referring a class of molecules that has rapamycin-like activity but is not confined to chemical derivatives of rapamycin (e.g. [15]); this debate is left for a separate occasion.

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