Commentary: rapamycin for the aging skin

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Abstract A response is provided to a commentary on a recent study examining the impact of low-dose topical application of rapamycin on markers of aging in the skin. The barriers to clinical implementation of therapies targeting the fundamental aging process are discussed, and the topical study is placed in context with the broader effort to develop new therapeutics for age-related disorders.

Dr. Blagosklonny has commented on our study examining the impact of low-dose rapamycin on markers of senescence and aging in human skin (Blagosklonny 2019; Chung et al. 2019). Dr. Blagosklonny commented that there is a lack of novelty in the study. This comment is based upon a patent application claiming ownership of the potential impact of rapamycin on a wide variety of age-related disorders; “wherein the age-related disease, condition, or disorder is insulin resistance, benign prostatic hyperplasia, hearing loss, osteoporosis, age-related macular degeneration, Alzheimer’s disease, Parkinson’s disease, a skin disease, or aging skin.” The patent was never issued and is now officially abandoned. A patent which has such broad claims may fail for several reasons, in part, because it fails to meet the requirement that the invention be enabling; it must disclose the invention in sufficient detail to enable a person having ordinary

skill in the art to make it without undue experimentation (Seymore 2019). It is worth noting that the fundamental purpose of a patent application is to bring new inventions into the public domain. The rights and protection afforded by the patent process are designed to provide protection while specific claims are rendered into practice. Thus, patents in which novel uses, dosing, and route of delivery for existing drugs are critically important to allow the repositioning of FDA-approved therapeutics for novel clinical applications (Seymore 2019). This situation applies to the mTOR inhibitors such as rapamycin which are largely in the public domain. These compounds have great potential for therapeutic use in age-related disorders, but there are barriers to the development of these compounds including side effects, regulatory hurdles, and a lack of incentive for investment in these novel applications. This underscores a dilemma faced by the community of scientists examining the basic biology of aging. The foremost drug candidates for transition into clinical use, most synolytics, metformin, and mTOR inhibitors such as rapamycin, are no longer under patent protection, limiting the effort to truly define the clinical usefulness of the compounds. Additional hurdles include defining the endpoints for FDA approval in the broad context of aging (Justice et al. 2018). The ultimate goal of Geroscience is to change clinical practice and bring therapies targeting the fundamental process of aging into the public domain (Campisi et al. 2019). This is an enormous and complex challenge due to the issues outlined above and the documented variation in longevity-enhancing interventions due to genetic variability (Liao et al. 2010). Studies

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examining the impact of rapamycin on longevity and late-life function in companion dogs (Urfer et al. 2017; Wilfond et al. 2018) will provide information regarding the genetic basis for differential responses to mTOR inhibitors as well as additional clinical applications.

The development of therapies targeting senescence, synolytic therapy, has parallels with the development of mTOR inhibitors for age-related disorders. It has been demonstrated that targeting senescence can alleviate multiple late-life disorders, and a number of drugs have been identified which have the potential to trigger cell death in senescent cells (Kirkland and Tchkonja 2017). New chemical entities which will selectively target senescent cells are in development, and synolytic trials with existing drugs focusing on specific age-related disorders such as osteoarthritis have been proposed according to a specific set of guidelines (Kirkland and Tchkonja 2017). The identification of specific age-related diseases which may be amenable to therapy targeting basic aging processes may be a more tractable route than trials seeking to decrease the overall rate of aging, and the two approaches can be employed in parallel. Based on preclinical data, cognitive decline, fibrotic disorders such as pulmonary fibrosis, and idiopathic cardiomyopathies may prove to be amenable to either synolytics or mTOR inhibitors (Chiao and Rabinovitch 2015; Lawrence and Nho 2018; Kaeberlein and Galvan 2019). One can envision a scenario in which specific dosing regimens and/or routes of administration using synolytics or mTOR inhibitors are employed to alleviate age-related disease. This would have the advantage of specific endpoints and potential patent protection based upon novel therapeutic approaches. The development of long-term systemic therapies to delay global age-related dysfunction is the goal for the field, but more targeted approaches could be examined in parallel, providing some benefits of anti-aging therapies as well as important information regarding outcomes, tissue-specific markers, and fundamental biological responses. This was the rationale behind our study. The novelty lies in the use of a very low dose of rapamycin, based on our preclinical work, to impact senescence and age-related cellular dysfunction (Bitto et al. 2010; Lerner et al. 2013). Whether such low levels are sufficient to impact biology in human tissue was unclear. Extensive data existed documenting both safety and efficacy of topical formulations using high concentrations of rapamycin to alleviate facial angiofibromas in pediatric patients suffering from tuberous sclerosis

(Koenig et al. 2018; Wataya-Kaneda et al. 2018), suggesting that a topical study using 1000-fold lower concentrations would pose minimal risk.

Dr. Blagosklonny comments on the exclusion of diabetic patients. Due to the fact that new onset diabetes is one known complication of systemic therapy (Verges and Cariou 2015), the inclusion of subjects with elevated blood glucose would be contraindicated. Dr. Blagosklonny also suggests that topical application should not be construed as an approach to provide systemic delivery of rapamycin for anti-aging therapy. We agree and part of the conceptual basis of our study was that the local application of low-dose rapamycin would not result in systemic delivery. This was confirmed in our study.

Dr. Blagosklonny identifies the cosmetic uses for topical rapamycin but we also envision a more important unmet clinical need in the treatment of fragile skin in the elderly. Fragile skin is a major concern for the elderly, causing substantial morbidity in this underserved population (Lichterfeld-Kottner et al. 2019). A reduction in dermal complications in the elderly could have substantial clinical benefit and financial benefits in terms of health care dollars saved treating these complications.

In summary, the study, while not conceptually novel, represents a novel approach and is a small but important step in the evaluation of mTOR inhibitors as therapies for age-related disorders.

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