April 30, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: World J Trans Med editorial.docx).

Title: Translating laboratory anti-aging biotechnology into applied clinical practice: problems and obstacles

Author: Marios Kyriazis
Name of Journal: *World Journal of Translational Medicine*

ESPS Manuscript NO: 17795

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated. Minor typographical corrections are added.

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 02446005.
I have expanded on the suggestion thus:
However, it is surprising how few people (both the public and academics) actually consider the translational and clinical issues relating to such treatments [5]. For instance, a PubMed online search of 'rejuvenation biotechnologies in aging' reveals 53 papers discussing theoretical or laboratory aspects of rejuvenation biotechnologies, but a search of 'clinical applications rejuvenation biotechnologies in aging', reveals just one relevant paper, analysing the clinical application of these technologies.

(2) Reviewer 00004093
I took the reviewer's comments into account and expanded the text (with added references as suggested) as follows:

At this point, it is worth mentioning that many biotechnology approaches do not take into account newer concepts such as the heterogeneous process of disease evolution, described by Molecular Pathological Epidemiology (MPE) (REF Ogino S, King EE, Beck AH, Sherman ME, Milner DA, Giovannucci E. Interdisciplinary education to integrate pathology and epidemiology: towards molecular and population-level health science. Am J Epidemiol. 2012 Oct 15;176(8):659-67).

Nor do they consider the role of epigenetic regulation in disease (REF Barrow TM, Michels KB. Epigenetic epidemiology of cancer. Biochem Biophys Res Commun. 2014 Dec 5;455(1-2):70-83).

Ogine et al. (Ogino S, Lochhead P, Chan AT, Nishihara R, Cho E, Wolpin BM, Meyerhardt JA, Meissner A, Schernhammer ES, Fuchs CS, Giovannucci E. Molecular pathological epidemiology of epigenetics: emerging integrative science to analyze environment, host, and disease. Mod Pathol. 2013 Apr;26(4):465-84) quote:

MPE is founded on the unique disease principle, that is, each disease process results from unique

profiles of exposomes, epigenomes, transcriptomes, proteomes, metabolomes, microbiomes, and interactomes in relation to the macroenvironment and tissue microenvironment… Although epigenome-wide association study attracts increasing attention, currently, it has a fundamental problem in that each cell within one individual has a unique, time-varying epigenome. (emphasis mine)

In other words, unique individual patterns of disease evolution may lead to unpredictable outcomes, and any future treatments designed against age-related disease must address this, by using tools of personalised medicine developed through MPE concepts. Otherwise, these putative treatments may prove ineffective in some individuals, depending on epigenetic factors, i.e. environmentally-dependent changes of their disease phenotype.

3 References and typesetting were corrected

Thank you again for publishing my manuscript in the *World Journal of Translational Medicine*

Sincerely yours,

Marios Kyriazis

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