

Seven Ways Not To Think Carefully About Aging

Richard Miller

Corresponding author: Richard Miller (millerr@umich.edu)

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Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. Depending on transfer agreements, referee reports obtained elsewhere may or may not be included in this compilation. Referee reports are anonymous unless the Referee chooses to sign their reports.)

Dear Richard,

Thank you again for sending us your commentary article, as well as for your patience with our feedback. As mentioned, we have asked two dedicated experts to assess your manuscript, and in the meantime got feedback from both, which I enclose below.

As you will see, the colleagues much appreciate the perspective and initiative taken and find the piece highly insightful and worth publishing. They also provide constructive feedback on how to further improve it by enhancing discussion of various of the aspects covered, adding complementary references, and suggesting concrete examples of how to support integration of your considerations in onwards research projects.

With respect to the figure, I have discussed this with other editors here in the team, and given it largely covers the structure and headlines of the text, hence is rather redundant, we suggest it might be fine to be omitted for ease. Please let me know.

Please also consider below instructions for the final formatting of the piece.

I hope you will find the colleagues' comments helpful. I am sure that a next version incorporating the suggestions made by the referees will be well-noted and appreciated. I would thus like to invite you to submit such a revised version using the link enclosed below.

Please let me know any time in case I can be of any help with this.

with
Best wishes,

Daniel

Daniel Klimmeck, PhD
Senior Editor
The EMBO Journal

Instructions for preparing your revised manuscript:

>> Manuscript format: please provide the manuscript as a .doc file; the figure and respective legend and callouts should be removed.

>> COI/DCIS statement: the title 'Conflict of interest' needs to be renamed to "DISCLOSURE AND COMPETING INTERESTS STATEMENT".

>> Reference format: please adjust to EMBO Journal format, alphabetical with 10 authors + et al.; "References Cited:" should be renamed to "References"

>> Section order should be as follows: Title page - Abstract - Introduction - Acknowledgements (if any) - Disclosure and Competing Interests Statement - References - Figure Legends - Table(s) (if any)

Referee #1:

In this article, the author criticises a number of assumptions and paradigms in the field of ageing. I think this sort of criticism is important and valuable, and I agree with the majority of arguments. That said, I have some comments and suggestions, as follows.

Problem 1. I agree there is no single cause of aging, and most scientists agree too, I think, so I am not sure this is a big misconception in the field. Is it okay to ask what are the "causes" of aging? I prefer the term "drivers" myself, but would not use the word "driver". I'd also point out that there is not an infinite number of mechanisms of aging.

P2. I partly agree, and others (e.g. Alan Cohen) have made a similar point that aging or age cannot be captured by a single number. That said, we can probably get a number for the chance of dying.

P2a. I agree and others have made similar criticisms. For instance, please see:
<https://pubmed.ncbi.nlm.nih.gov/39392224/>

And is ref 5 using transcriptome or epigenetic clocks?

P3. The author briefly mentions the normal functions of senescent cells, but possibly this could be emphasized, as it argues against senescent cells being merely dysfunctional. Please see:
<https://pubmed.ncbi.nlm.nih.gov/38900869/>

P4. As far as I understand, the epigenetic age of cells is not just related to cell division or cell senescence per se, for instance:
<https://pubmed.ncbi.nlm.nih.gov/37034474/>

Ultimately, we are made of cells and aging should entail intrinsic cellular changes, though whether current cellular rejuvenation methods address these is unknown. I agree with the technical challenges of intervening using these technologies, but the same could be said for many other anti-aging interventions.

P5. Aging rate indicators are interesting, but in humans we have no established longevity interventions, and few in mice, so I suspect these will be hard to calibrate. I would also point out that not all interventions extending lifespan are modulating aging. For instance, they could just be protecting against cancer. Many life-extending interventions could also be acting as CR mimetics. Please see:
<https://pubmed.ncbi.nlm.nih.gov/29444805/>
<https://pubmed.ncbi.nlm.nih.gov/40389451/>

P6. I agree, and please see for a preprint on this topic:
<https://www.preprints.org/manuscript/202510.2389>

P7. I agree, but we and others have made similar criticisms and should be cited, for instance:
<https://pubmed.ncbi.nlm.nih.gov/34271186/>

Conceptual framework section. Again, I have issues with proposed aging rates and whether longevity interventions are indeed manipulating aging (see P5 above).

I cannot find ref 19, has this work been published?

Overall, I think this is an interesting and timely piece that will make an important contribution, although some arguments could be more balanced and nuanced, and ultimately stronger, and the paper better placed in the context of previous works.

It is possible that some of my comments reflect misunderstandings of mine. If so then I would suggest that the authors use my misunderstandings as an indication that such points might be made clearer in the manuscript.

It is my usual policy to reveal my identity to the authors: Joao Pedro de Magalhaes.

Referee #2:

I read this essay with pleasure. Miller has done the field a service by naming, out loud, a set of assumptions most of us absorbed early in our careers and rarely think to revisit. The writing is clear, the examples well chosen, and I fully share the central message - that conceptual sloppiness has practical costs for what gets funded and studied.

The critique of the Hallmarks framework (Problem 7) struck me as particularly sharp. I've watched grant applications and talks lean on the Hallmarks wheel as a substitute for argument rather than a starting point for one, exactly as described - this section

alone justifies the piece. The discussion of biological age and clocks (Problems 2, 2a) is equally good, and the Rolex-watch analogy will stick with me.

A few thoughts the author may want to weigh to strengthen the piece:

1. On clocks and biomarkers: the case against "biological age" as a reified construct is convincing, but methylation and transcriptional clocks still have real practical value as relative, population-level readouts - screening large mouse cohorts of drugs or genetic models, say, where no one needs to believe the number is a literal age for the comparison to be useful. A sentence acknowledging this narrower, comparative use, distinct from the discredited claim of measuring a true biological age, might head off some defensive pushback from that community without softening the argument.
2. The forward-looking framework: the new conceptual framework at the end is compelling but still a bit programmatic. A short, concrete example of how an Aging Rate Indicator panel would actually be qualified and used in a human trial - TAME or something comparable - would give readers a clearer sense of the path forward and end the essay on a more constructive note.
3. What could replace the weak constructs: the essay is largely a critique of existing conceptual scaffolding. I would encourage the author to devote real space - not just a paragraph - to what could take its place, and Miller is well positioned to make this case. I would suggest organizing this constructive section around three distinct, and complementary, developments:
 - a) AI and machine learning as tools for building genuinely data-driven readouts of aging, rather than readouts built on legacy assumptions. Multi-omic phenotyping integrated across modalities can, in principle, generate composite indicators that do not inherit the conceptual baggage of a single clock or a single hallmark, and that are validated empirically against outcomes rather than against a preconceived notion of what aging is.
 - b) In vivo versus cell-based work: much of the conceptual apparatus this brief criticizes was built on, or is most comfortably applied to, reductionist cell-based systems. A frank discussion of the limits of cell-based models for capturing organismal aging - and of why findings anchored in whole-animal, in vivo work are more likely to generalize and to support the kind of empirically grounded indicators the essay is calling for - would strengthen the case considerably.
 - c) Genetic diversity in study design: many of the constructs under critique were built on genetically homogeneous cohorts (a handful of inbred strains, or convenience human samples), which is part of why they generalize poorly and invite reification. Studies designed around genetically diverse populations would test whether a proposed indicator is a robust, general feature of aging biology or an artifact of the particular genetic background in which it was first described.Taken together, these three threads - computational, experimental, and genetic - would give the essay's constructive section real substance, and would turn it from a promissory note into a concrete research agenda.
4. Tone: in places the prose is deliberately, and effectively, polemical ("there is no such thing as biological age"; "this conceptual scheme has very little to recommend it"). That tone fits the essay, but a reader closely identified with clocks, senescence, or the Hallmarks program may check out before reaching the constructive final section. Softening two or three of the most absolute formulations, without changing the substance, might keep more of that audience reading to the end.
5. Minor point: whatever its current limitations, the Hallmarks framework did help mobilize funding and cross-talk across a fragmented field when it first appeared. One acknowledging sentence wouldn't weaken the critique and would make the piece feel more balanced.

None of this dims my enthusiasm. I recognize some of this essay's positions will be seen as controversial by parts of the field, but I think that is precisely why it needs to be published - I am far from alone in feeling that entrenched conceptual habits are holding the field back, and a piece willing to say so plainly performs a real service. I recommend publication and thank the author for a stimulating and necessary contribution.

Comments from Rich Miller to suggestions of the reviewers. All comments are in this Arial font, indented, and preceded by the initials "RAM".

Referee #1:

In this article, the author criticises a number of assumptions and paradigms in the field of ageing. I think this sort of criticism is important and valuable, and I agree with the majority of arguments. That said, I have some comments and suggestions, as follows.

Problem 1. I agree there is no single cause of aging, and most scientists agree too, I think, so I am not sure this is a big misconception in the field. Is it okay to ask what are the "causes" of aging? I prefer the term "drivers" myself, but would not use the word "driver". I'd also point out that there is not an infinite number of mechanisms of aging.

RAM: I am glad that Pedro agrees that there is no single cause of aging. But I would argue that there are no "causes" of aging either, unless one includes the very large number of factors (thousands of variant genes, thousands of varieties of environmental injuries, hundreds of adverse pleiotropic effects) that lead to bad things in older people. The point of this section is to show that aging does not have a cause or a usefully small set of causes, and research aimed to proving that something (inflammation, somatic mutation, stem cell loss, senescent cell accumulation, dedifferentiation, protein aggregation, etc., etc.) leads to aging is off on the wrong track.

P2. I partly agree, and others (e.g. Alan Cohen) have made a similar point that aging or age cannot be captured by a single number. That said, we can probably get a number for the chance of dying.

RAM: I am glad that Pedro (and Alan Cohen) also take the position that the idea of "biological age" is fundamentally flawed. But I do not agree that "we can probably get a number for the chance of dying." There are indeed methods for estimating the likelihood that I will be alive in 2, 4, 8, or 16 years, and insurance companies use these all the time. None of these is "a number for the chance of dying." Even if one calculates the best obtainable estimate for the chance that I will be alive in 4 years (let's say 94.2%), this estimate is the central point in a confidence range, rather than a single real number, the kind of number people write down as a "biological age." In any case, the chance of dying is not a single number, but a distribution (an expected survival curve) over a range of future years: my chance of dying in 2027 is different from my chance of dying in 2028, and so forth.

P2a. I agree and others have made similar criticisms. For instance, please see:

<https://pubmed.ncbi.nlm.nih.gov/39392224/>

And is ref 5 using transcriptome or epigenetic clocks?

RAM: Ref 5 (now formatted as Poganik et al.) used a clock based on transcriptome patterns. The original text points this out: "One representative example (5) used a transcription-pattern-based "aging clock" to evaluate biological age."

P3. The author briefly mentions the normal functions of senescent cells, but possibly this could be emphasized, as it argues against senescent cells being merely dysfunctional. Please see:

<https://pubmed.ncbi.nlm.nih.gov/38900869/>

RAM: I think it would be very useful to have a review on the ways in which so-called "senescent" cells may have important homeostatic functions. But in this article I am trying to avoid going off on too many tangents, even important and interesting ones, in order to present the main conceptual problem areas as concisely and clearly as I can. As the reviewer notes, the article does mention this idea and cites a comprehensive review article for those who want to explore this area further.

P4. As far as I understand, the epigenetic age of cells is not just related to cell division or cell senescence per se, for instance:

<https://pubmed.ncbi.nlm.nih.gov/37034474/>

Ultimately, we are made of cells and aging should entail intrinsic cellular changes, though whether current cellular rejuvenation methods address these is unknown. I agree with the technical challenges of intervening using these technologies, but the same could be said for many other anti-aging interventions.

RAM: I agree entirely that we are made of cells and that aging does “entail intrinsic cellular changes,” and I say so in the article. I strongly support experiments to figure out which cells show which specific intrinsic age-related changes, how these are produced, and what consequences they may have. The point made in the article, however, is that pursuing these ideas does not require that one claim to estimate the “age” of a cell. Nor does investigation of whether age-dependent changes can be reversed require a demonstration that the “age” of that cell has somehow been made lower. Nor, in particular, is a claim that the “age” of a cell has become lower serve as a useful substitute for testing which age-dependent properties of that cell have been changed in some way.

P5. Aging rate indicators are interesting, but in humans we have no established longevity interventions, and few in mice, so I suspect these will be hard to calibrate. I would also point out that not all interventions extending lifespan are modulating aging. For instance, they could just be protecting against cancer. Many life-extending interventions could also be acting as CR mimetics. Please see:

<https://pubmed.ncbi.nlm.nih.gov/29444805/>

<https://pubmed.ncbi.nlm.nih.gov/40389451/>

RAM: Pedro is right to note that we don’t have any established anti-aging interventions that are proven to work in people, and to argue that “calibration” of aging rate indicators in people will need to be done without such a design. The transition to humans (as pointed out in the paper) will depend, at least initially, on a different line of argument, i.e. does a specific drug or diet or exercise routine or polymorphism create, in humans, a profile of plasma (or perhaps even tissue) metabolites or proteins that resembles that seen in slow-aging mice. A second good approach is related to that used by Belsky and his colleagues in the (human) Dunedin PACE study: what set of metabolic or proteomic patterns, in human plasma, identifies people who show the lowest rate of change in age-dependent functional or biochemical change in the 5 – 15 years after sampling?

The reviewer also expresses his opinion that “not all interventions extending lifespan are modulating aging.” This is surely correct as a general matter: for humans, for example, giving clotting factors to a hemophiliac or statins to someone prone to atherosclerosis will extend lifespan without necessarily altering the rate of aging. But in the best studied cases of life extension in mice (Snell and Ames dwarf, GHR knockout, Rapamycin, canagliflozin, methionine restriction, and caloric restriction) the anti-aging effects are indeed manifested by delay in many varieties of age-dependent pathology and functional capacity, not just in cancer risk or age at death. This is also true for slow-aging breeds of dogs and horses.

The reviewer also proposes that “many life-extending interventions could be acting as CR mimetics.” Our studies of aging rate indicators indeed do show many effects of caloric restriction that are also seen in other kinds of slow-aging mice; this is one of the criteria for deciding that a test is potentially useful as an ARI. But there is now also ample documentation of CR effects that are not seen in other varieties of slow-aging mice including mutants and drug-treated mice. For a proteomics example, see PMID 37653270. For a transcriptomic example, see PMID 31353263.

Pedro also comments in passing that we have “few” “established longevity interventions” in mice. I am not sure what he means by “a few”, but there are at least 13 replicated interventions: CR, methionine restriction, isoleucine restriction, Snell dwarf, Ames dwarf, PTEN overexpression, PAPP A KO, GHR KO, rapamycin, canagliflozin, 17 α -estradiol, NDGA, and 16-OH-estradiol, and this tally omits 9 other ITP drugs that had significant effects on lifespan of male or female mice.

P6. I agree, and please see for a preprint on this topic:

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P7. I agree, but we and others have made similar criticisms and should be cited, for instance:

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Conceptual framework section. Again, I have issues with proposed aging rates and whether longevity interventions are indeed manipulating aging (see P5 above).

RAM: Please see response to Reviewer's point [5] above. There is lots of good evidence that drugs (or diets or mutant genes) that extend lifespan also slow age-related change in multiple tissues unrelated to eventual cause of death. This collection of multi-factorial evidence is how we conclude that the drugs not only extend lifespan, but slow aging per se.

I cannot find ref 19, has this work been published?

RAM: Ref 19 has now been published. (This is now Austad et al., in EMBO J citation format.) It is <https://doi.org/10.3389/fsci.2026.1821393>. The citation in the article has now been updated.

Overall, I think this is an interesting and timely piece that will make an important contribution, although some arguments could be more balanced and nuanced, and ultimately stronger, and the paper better placed in the context of previous works.

RAM: I thank the reviewer for his sympathetic comments on the paper. I agree that many of the issues mentioned briefly in the article could usefully be expanded, with more details and citations to provide "balance and nuance." But the goal of the article is to present a set of opinions as clearly and as concisely as I could, without mis-stating any of the data and without mischaracterization of the opinions with which I am disagreeing. I hope it has achieved that goal, or at least come close enough to help readers think about the issues raised.

It is possible that some of my comments reflect misunderstandings of mine. If so then I would suggest that the authors use my misunderstandings as an indication that such points might be made clearer in the manuscript.

It is my usual policy to reveal my identity to the authors: Joao Pedro de Magalhaes.

Referee #2:

I read this essay with pleasure. Miller has done the field a service by naming, out loud, a set of assumptions most of us absorbed early in our careers and rarely think to revisit. The writing is clear, the examples well chosen, and I fully share the central message - that conceptual sloppiness has practical costs for what gets funded and studied.

RAM: Thank you.

The critique of the Hallmarks framework (Problem 7) struck me as particularly sharp. I've watched grant applications and talks lean on the Hallmarks wheel as a substitute for argument rather than a starting point for one, exactly as described - this section alone justifies the piece. The discussion of biological age and clocks (Problems 2, 2a) is equally good, and the Rolex-watch analogy will stick with me.

A few thoughts the author may want to weigh to strengthen the piece:

1. On clocks and biomarkers: the case against "biological age" as a reified construct is convincing, but methylation and transcriptional clocks still have real practical value as relative, population-level readouts - screening large mouse cohorts of drugs or genetic models, say, where no one needs to believe the number is a literal age for the comparison to be useful. A sentence acknowledging this narrower, comparative use, distinct from the discredited claim of measuring a true biological age, might head off some defensive pushback from that community without softening the argument.

RAM: I am not confident that "clocks" based on methylation or transcriptional patterns are useful, even at the population level, unless they have been carefully evaluated for resistance to interventions that do not slow aging. I give one such example in the paper (citing Ref 5; this is now Poganik et al., in EMBO J format) of a clock estimate that responded not just to aging, but also to pregnancy, to surgical stress, and to acute infection. It is possible that a methylation-based, or transcription-based, summary statistic (a "clock") could be of use as one of a set of age-sensitive measures in the context of a clinical trial (in mice or people), but the current fashionable use case is to consider such "clocks" as substitutes for such a comprehensive test set. I am hoping to discourage that.

2. The forward-looking framework: the new conceptual framework at the end is compelling but still a bit programmatic. A short, concrete example of how an Aging Rate Indicator panel would actually be qualified and used in a human trial

- TAME or something comparable - would give readers a clearer sense of the path forward and end the essay on a more constructive note.

RAM: Together with Austad and Kaeberlein I have just published a separate article that spends several pages on this question; it was formerly Re 19, now Austad et al. The article has just appeared in *Frontiers in Science* as <https://doi.org/10.3389/fsci.2026.1821393>. I cited that paper, but did not want to recapitulate the material in the EMBO Journal piece.

3. What could replace the weak constructs: the essay is largely a critique of existing conceptual scaffolding. I would encourage the author to devote real space - not just a paragraph - to what could take its place, and Miller is well positioned to make this case. I would suggest organizing this constructive section around three distinct, and complementary, developments:

a) AI and machine learning as tools for building genuinely data-driven readouts of aging, rather than readouts built on legacy assumptions. Multi-omic phenotyping integrated across modalities can, in principle, generate composite indicators that do not inherit the conceptual baggage of a single clock or a single hallmark, and that are validated empirically against outcomes rather than against a preconceived notion of what aging is.

RAM: A central theme of the essay is that we should **not** focus on “readouts of aging,” or substitutes for various age-sensitive clocks or arbitrary hallmarks. Instead, we can now work on a different and more important question: how to discriminate normal animals (mice, humans, etc.) from those that are in a slow-aging state, in which the changes due to aging occur more slowly. Machine learning approaches to solving this problem – the problem of distinguishing slow-aging from ordinary mice and humans – are indeed just now starting to emerge from multi-omic phenotyping (as the reviewer suggests). Ref 18 provides an early example, using metabolomic data from plasma of 7 kinds of slow aging mice compared to three varieties of control mice. We do not need composite indicators of age, or health, or short-term mortality risk – we need composite indicators of aging rate, a different thing from age.

b) In vivo versus cell-based work: much of the conceptual apparatus this brief criticizes was built on, or is most comfortably applied to, reductionist cell-based systems. A frank discussion of the limits of cell-based models for capturing organismal aging - and of why findings anchored in whole-animal, in vivo work are more likely to generalize and to support the kind of empirically grounded indicators the essay is calling for - would strengthen the case considerably.

RAM: I agree that it would be useful to provide a more detailed critique on “the limits of cell-based models for capturing organismal aging” and why findings based on whole animals, in vivo, are far more likely to be productive than studies of cultured cells. But my goal in writing this essay was to be as concise as possible, so that readers won’t get distracted by too many digressions. A comprehensive and well-referenced review article on the topic suggested by the reviewer would be very valuable. (It would also require an author, or authorship team, that knows a good deal more than I do about in vitro aging models.)

c) Genetic diversity in study design: many of the constructs under critique were built on genetically homogeneous cohorts (a handful of inbred strains, or convenience human samples), which is part of why they generalize poorly and invite reification. Studies designed around genetically diverse populations would test whether a proposed indicator is a robust, general feature of aging biology or an artifact of the particular genetic background in which it was first described.

Taken together, these three threads - computational, experimental, and genetic - would give the essay's constructive section real substance, and would turn it from a promissory note into a concrete research agenda.

RAM: the work on aging rate indicators was, for the reasons noted by the reviewer, done entirely using a genetically heterogeneous mouse stock, UM-HET3, except for data from mutant mice whose background stocks are heterogeneous but different from UM-HET3. I have added a sentence to the essay to emphasize this point. Of course additional work on other heterogeneous mouse stocks, as well as genetically non-uniform human and animal (e.g. dog) populations will provide important insights into whether the ARIs discovered in mice are robust in other genotypes and species.

The inserted text says:

“Most of the ARIs emerging from these recent studies have used genetically heterogeneous mice (UM-HET3, and mutants on segregating backgrounds), which may confer at least some resistance to strain-specific idiosyncrasies (citations are Sittig et al., 2016, and Miller, 2016), but clearly much additional work will be needed to see which of the candidate ARIs are reliable indices of aging rate in other mouse stocks, and in other species including dogs, marmosets, and humans.”

4. Tone: in places the prose is deliberately, and effectively, polemical ("there is no such thing as biological age"; "this conceptual scheme has very little to recommend it"). That tone fits the essay, but a reader closely identified with clocks, senescence, or the Hallmarks program may check out before reaching the constructive final section. Softening two or three of the most absolute formulations, without changing the substance, might keep more of that audience reading to the end.

RAM: I respect the reviewer's stylistic preference, and most of the articles I write do try to avoid direct confrontation, to avoid giving offense. In this instance, though, I have tried to be blunt and direct, and to make the case as strongly as I can without mis-stating any facts or misrepresenting anyone else's viewpoint. Although I think it is likely that some readers may find themselves disagreeing, sometimes strongly, with an opinion expressed in this paper, I hope they will read on to look for problems in my argument, and perhaps eventually start to reconsider assumptions they may have held onto but which deserve reconsideration. And readers who find themselves in agreement with some of the points made may find themselves cheered to learn they are not alone in their iconoclastic views, and find the courage to say so out loud.

5. Minor point: whatever its current limitations, the Hallmarks framework did help mobilize funding and cross-talk across a fragmented field when it first appeared. One acknowledging sentence wouldn't weaken the critique and would make the piece feel more balanced.

RAM: I think the Hallmarks framework has done more harm than good, for reasons spelled out in the essay. I am not sure we should “mobilize funding” by spreading misconceptions, even popular misconceptions endorsed by the leading authorities in the field. I certainly support cross-talk across disciplines, but anyone who reads an aging journal or goes to a major conference on the biology of aging will, fortunately, hear a good deal about topics and approaches that come from specialties other than their own, and this was the case well before the current Hallmarks fad.

None of this dims my enthusiasm. I recognize some of this essay's positions will be seen as controversial by parts of the field, but I think that is precisely why it needs to be published - I am far from alone in feeling that entrenched conceptual habits are holding the field back, and a piece willing to say so plainly performs a real service. I recommend publication and thank the author for a stimulating and necessary contribution

Dear Richard,

Thank you for sending us the updated final version of the commentary article.

I am pleased to inform you that your manuscript has now been accepted for publication in the EMBO Journal.

Your manuscript will be processed for publication by EMBO Press. It will be copy edited and you will receive page proofs prior to publication. Please note that you will be contacted by Springer Nature Author Services to complete licensing and payment information. Please note that as this is invited front-half content, OA charges applicable to this article will be covered.

We will proceed with transfer of the manuscript files to production shortly.

If you have any questions, please do not hesitate to contact me.

Thank you again for your kind contribution to The EMBO Journal Aging series, which is much appreciated.

with
Best regards,

Daniel

Daniel Klimmeck, PhD
Senior Editor
The EMBO Journal

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