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27 OCT 2017

An Interview with Yuri Deigin of Youthereum Genetics: the Merging of an Initial Coin Offering and Pluripotency Factors

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Initial coin offerings (ICOs) are driving most of the light and heat in the blockchain world these days. People are raising enormous sums in cryptocurrencies for ventures with somewhere between little plausibility and ordinary levels of startup plausibility. In many ways it looks a lot like the last years of the internet bubble way back when; there are a lot of parallels. The flows of funding may be driven by some combination of people bypassing Chinese currency controls, early holders of Bitcoins and Ether diversifying their holdings within the blockchain ecosystem, and various large investment concerns whose owners have found they can make a quick buck by flipping blockchain tokens, all of which adds fuel to the fire. As I asked earlier this year, if fairly dubious ventures can pull in tens of millions of dollars doing this, why can't we use this to fund thoughtful, legitimate initiatives in rejuvenation research? The challenge here lies in finding a meaningful use for blockchains and network effects in our world of research and development.

Some groups are forging ahead with that effort. I've mentioned Open Longevity's ICO, in which they seek to fund collaborative human trials of various potential pharmaceutical means to slow aging, but for today the focus is on Youthereum Genetics, a newer venture that also seeks to use an ICO as a mechanism to fund research and development. The Youthereum principals are initially intending to work on a means to deliver pluripotency factors involved in the creation of induced pluripotent stem cells to spur regeneration. A demonstration of this was conducted by a research group and published earlier this year, resulting in health benefits for the progeroid mice often used in early stage aging research. This was somewhat surprising as an outcome: haphazardly inducing cells to become pluripotent in a living organism sounds like a rapid short-cut to cancer.

The next steps will be to try this in normal mice, quantify the most useful dose and delivery method, and continue to watch carefully for evidence of cancer as a side-effect. In the best case this may be a road to a regenerative therapy analogous to stem cell transplants, but that remains to be seen. As in so many areas of research where interesting results may or may not lie ahead, the first question is where the funding for that work will be found. The Youthereum team hope that tapping into the blockchain market is the way to go.

I recently had the chance to chat with Yuri Deigin of Youthereum Genetics, and to ask some questions about his aims. As you can tell he is proceeding from a programmed aging point of view - something that I tend to present as standing in diametric opposition to the more mainstream view of aging as accumulated damage. Possibly oversimplifying, this is the question of whether in aging epigenetic change (a program) causes damage, or whether damage causes epigenetic change (a reaction). A programmed aging point of view leads one to intervene in processes that

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The Root Causes of Aging

Aging is Caused by Damage
Accumulating Cross-Links
Buildup of Amyloid Between Cells
The Failing Adaptive Immune System
The Failing Innate Immune System
Declining Lysosomal Function
Mitochondrial DNA Damage
Nuclear DNA Damage
Buildup of Senescent Cells

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Using the Fight Aging! Content Feeds
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Required Reading

Calorie Restriction and Longevity
Cryonics, the Necessary Backup Plan
Envisaging a World Without the FDA
How to Argue for Longevity Science
The Odds of Human Longevity

are, to the accumulated damage point of view, secondary consequences only, and attacking secondary consequences just won't be very effective. We are close to the years in which one side or the other will be definitively proven correct, due to the implementation of specific approaches to the treatment of aging as a medical condition.

Nothing is completely black and white, however, and it is interesting to see the development of areas where theorists from either side of this divide will meet in the middle at approaches to therapies that both will consider potentially useful enough to try, but for different reasons. Some classes of stem cell therapies and efforts to achieve similar effects through changes in signaling or reprogramming cells in situ rather than through delivery of cells are a good example of the type. From a programmed aging point of view, these are levers with which to change epigenetic signaling to more youthful levels, while from an accumulated damage point of view, they could be essentially compensatory in nature, like stem cell therapies, but picking the slack to some degree for native regenerative processes that are hampered by damage.

Quote:

Why Youthereum Genetics, and why now? Who are you, and how did this organization come to be?

I am a Russian-Canadian transhumanist longevity activist, amateur theoretical biologist, and a biotech entrepreneur. Previously, those areas of my life did not intersect, but in the past few months the stars have aligned to prompt me to finally combine my passion and expertise, and channel them into an undertaking I consider the most important in my life: curing aging. Or - getting off the high horse - at least developing some significant life extension therapies for humans, because at the moment there are none. By "significant" I mean something that can prolong our lives by at least 30%. No therapy outside of caloric restriction has been able to achieve this milestone even in mice - not rapamycin (26%), not metformin (14%), not telomerase (24%), not senolytics (26%) or any other 'geroprotector'. And caloric restriction which holds the record for non-genetic lifespan extension (up to 50% in various rodents) failed to produce anywhere near as spectacular a result in primates. In the two macaque studies conducted on CR, at most a 10% median lifespan increase was observed in females and in some groups CR actually shortened lifespan.

Personally, I believe that the reason behind this inability to put a significant dent in aging in the past 50+ years lies in its programmed nature. Over the years, I have seen plenty of evidence in support of this hypothesis with the most convincing being results from parabiosis and young plasma experiments. I think that aging is ultimately controlled by the hypothalamus, just like all other aspects of ontogenesis. This concept dates back to the 1950s and is described in detail in the works of Dilman, Frolkis and Everitt's. Recent research by Dongsheng Cai and his colleagues provides further evidence for the hypothalamic hypothesis. On the cellular level, aging is most likely both tracked by and executed via epigenetic regulation of gene expression. Several years ago it was first observed that a person's age is highly correlated to his/her epigenetic profile. Later it was recognized that these 'epigenetic clocks' are effective life expectancy predictors, which confirmed that epigenetics is a key component of the aging process. Many organisms were found to have such 'epigenetic clocks' that are highly correlated with both their age and probability of death.

Moreover, Nature knows how to roll back or even completely reset the epigenetic clock. This is done for every new embryo and is most likely the reason why every new animal is born young despite having started as an oocyte cell of the same age as its mother (as mother's oocytes were formed while she herself was still in utero). Finally, experiments with epigenetic rejuvenation which demonstrated that rolling back epigenetics rejuvenates not just individual cells but entire organisms (and prolongs their lifespan) have confirmed that epigenetics is not just a consequence but an important driver or aging. This is where Youthereum Genetics comes in. Based on the recent work of Juan Carlos Izpisua Belmonte's group at Salk, who have shown that periodic induction of OSKM transcription factors can prolong lifespans of progeric mice by up to 50%, we hypothesize that aging can be rolled back by periodic epigenetic rollbacks. Our strategy is aimed at translating this hypothesis into a safe therapy that produces sizable, noticeable rejuvenation in

Mutations
The Need For Activism and Advocacy
Potential Gene Therapy Targets
Predicting the First Rejuvenation Therapies
SENS: Bringing an End to Aging
Stem Cells and Regenerative Medicine
Those Determined to Merely Slow Aging
The Three Types of Aging Research
Transhumanism and Human Longevity
What is Robust Mouse Rejuvenation?
Why Prioritize SENS Research?

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humans.

Why us and why now? In a nutshell, because I grew too tired of waiting for someone else to do it and not seeing anyone step up to the plate. So I put together a team that is capable of designing and overseeing experiments for all the steps involved in first verifying the science behind our hypothesis and then translating it into a therapy should science hold up. The only thing left to do now is a small matter of raising the necessary funding. I am being sarcastic, of course. It is a huge challenge, especially given the amounts required and the associated scientific risks involved. But I am willing to try, even in the face of high odds against.

What is your model for what is going on under the hood in animals transfected with pluripotency factors? Why does it produce benefits?

As I mentioned, I am of the Programmed Aging Witnesses cult. At least that's what some opponents of programmed aging call us. I believe that most if not all forms of various intra- and intercellular damage that we see the body accumulate with age do so because our cells gradually tone down the volume of various damage repair mechanisms. Our cells do so via epigenetic regulation of various genes upon receipt of endocrine signals that originate in the hypothalamus based on circadian rhythms and some sort of an internal clock. We know there is a clock because we can see how finely tuned the timings of various developmental and cyclical processes are - from embryogenesis to puberty to menstrual cycles.

So my belief is that the body has enough capacity for self-repair to function at the level of a 25-year-old for hundreds if not thousands of years, or maybe even longer. If the germ line can do so for billions of years, periodically generating a new organism from scratch, it seems logical to me that just a fraction of those remarkable bodybuilding abilities should be enough to sustain our bodies for much, much longer periods than we see today. So if we find a way to trick our cells into thinking that we are 25, they will function (and get replenished) at the level of a 25 year old regardless of our chronological age. To do so, they would need to have gene expression profiles (epigenetic profiles) typical of 25-year-old humans. And we know from the work of Hannum and Horvath that the epigenetic profiles of 25-year-olds are quite different from profiles of 45- and 65-year-olds.

So when we induce OSKM factors in cells, what I think happens is epigenetic rewinding that is associated with upregulation of various repair mechanisms. It is an empirical fact that induced pluripotent stem cells experience significant rejuvenation that ameliorates virtually all the famous Hallmarks of Aging: telomeres elongate, laminar defects get fixed, mitochondrial function gets restored and so on. There is a great article about this by Vittorio Sebastiano and Tapash Jay Sarkar of Stanford with plenty of details.

That said, one doesn't have to believe in programmed aging to see the potential of epigenetic rejuvenation for life extension purposes. In fact, Aubrey de Grey, who is one of our advisors, despite being a staunch opponent of the programmed hypothesis, also believes epigenetic rollback holds therapeutic promise. In his view, the ability to rejuvenate the aged body by reactivating early-life pathways does not in any way conflict with the idea that aging is unprogrammed and results from the gaps in our anti-aging machinery rather than the presence of actively pro-aging machinery. I would be more than happy to be proven wrong on the underlying mechanisms of epigenetic rejuvenation as long as it provides us with a lifespan extension comparable to that seen in Belmonte's work.

Conversely, why won't this treatment produce an unacceptable level of cancer risk? That is always a concern in this sort of thing.

Absolutely, teratomas are probably the biggest concern of this approach. In fact, before Belmonte showed that there is a Goldilocks zone of OSKM induction that extends lifespan without producing teratomas, cancer risk of this approach was thought to be prohibitive for its translation. Apparently, it isn't. The trick is to roll the cells back ever so slightly to prevent them from de-differentiation, but to do so often enough to prevent (or at least slow down) the accumulation of age-related damage that results from the relentless downregulation of damage repair

mechanisms with age.

How does this fit together into your view of aging? What do you expect from this and other efforts in the years ahead? Where would you expect the biggest wins to emerge?

This fits my view of aging like a glove. In fact, the reason I got so excited about Belmonte's results back in February was because before I learned about them, I hypothesized that if we ever learn to roll back epigenetic changes, doing so periodically can provide us with a good enough "hack" to significantly delay aging until we completely decipher its mechanisms and learn to stop them for good. So epigenetic rejuvenation is precisely where I think the biggest gains in life extension could emerge. One other important area that we also plan to explore at Youthereum, albeit in a separate research track, is trying to decode hypothalamic exosome secretions. We think that Dongsheng Cai's latest paper, which showed that 16-months old mice exhibit signs of rejuvenation after a one-time injection with hypothalamic exosomes isolated from cultured hypothalamic neuronal stem cells, is really onto something.

Tell us about your take on how to merge the flow of funds in the blockchain market with the goal of doing something useful in longevity science. So much of what is going on in the ICO space seems a very clumsy effort to bolt one thing, the blockchain, onto another completely unrelated thing that has no logical connection to the blockchain. How are you different?

We are not trying to pretend that we will contribute something to the blockchain infrastructure. We won't, we are a decentralized biotech crowdfunding project that is raising money first and foremost for scientific research. In other words, we are users of the blockchain technology, not its developers. We plan to use it to eliminate any middlemen between us and our funding contributors, and to ensure that all our backers' rights to the therapies we plan to develop are not affected by various governmental red tape - current or future. Those are the two main benefits of decentralization, in our opinion. So we view ICOs as just a more efficient crowdfunding mechanism, even if that makes some blockchain purists cringe. I am not sure why they would cringe, though - by embracing the blockchain paradigm and bringing real-world projects into their realm we are actually validating their technology and greatly expanding its potential user base.

How does Youthereum Genetics differ from Open Longevity, who are trying their own hand at an ICO?

While Mikhail Batin of Open Longevity and I agree that we need more people to do everything possible to develop radical life extension therapies ASAP, we differ on what kinds of interventions could actually produce such life extension. I believe that no therapy that exists today, including any clinically approved drugs, can prolong our lifespans by more than 10%, let alone 30%. So in my view, conducting clinical trials for the Fasting-Mimicking Diet (FMD) or use of statins to see if they have the potential to prolong lifespan is not very useful. Epigenetic rejuvenation, on the other hand, does, in my view, have the potential to prolong our lifespans by over 30% or even much, much greater. That is why I am betting so much of my time and money on it.

If this all goes swimmingly well, and you are buried in funds, with decent animal data on the use of pluripotency factors as a therapy, what next?

Let me try answering this by first describing our research plan. We intend to subdivide it into 3 parallel research tracks: (1) development of an optimal dosing regimen using OSKM factors; (2) search for safer factors of epigenetic rollback that do not lead to complete de-differentiation; (3) creation of the best means of gene delivery, preferably patentable. So our key hypothesis is as follows: in order to reliably rejuvenate the entire body, we need to periodically roll back the epigenetic clock of most cells in the body, if not all cells. Thanks to the work of Belmonte's group, we know that this is possible by delivering OSKM factors (or other transcription factors) into the cell. However, this is a tricky endeavor: roll back too little and you get no sizable effect; roll back too much and you might get cancer, as cells would lose their identity and become pluripotent again. After all, their ability to turn cells back into pluripotent state was the main selection criterion for picking the 4 OSKM factors from the original 24 candidates. So, while OSKM factors are

effective and represent a "bird in hand", they are far from ideal for our purposes.

We should strive to find better, safer epigenetic rollback factors; we plan to start by revisiting the remaining 20 factors of Yamanaka's original 24, and also try to use the Oct4 factor alone, since there is evidence that it alone is able to roll back epigenetics and is generally the main "guardian of the epigenetic gates." However, narrowing down the factors is only half of the challenge. Delivering them safely and, ideally, cheaply is the other half. The epigenetic aging program is quite robust even in the face of weekly rollbacks, as demonstrated by Belmonte et al., therefore, obtaining meaningful rejuvenation in humans would most likely require monthly or even weekly induction of epigenetic rollback factors (whether OSKM or otherwise). The most cost-effective way of achieving this would be to integrate a special, normally silent polycistronic cassette containing the genes for the rollback factors into virtually each cell of a patient. Such a cassette would be activated by a unique and normally inert custom agent that would need to be developed separately, and would enable this approach to be patentable. Today such cassettes are activated by, for example, tetracycline or doxycycline. With this approach, the marginal cost of a weekly induction of rejuvenating factors would only be the cost of the induction agent (presumably, a small molecule or a peptide)-comparatively cheap.

In summary, we see the most optimal research plan as a step-by-step, iterative improvement of the already proven approach, the induction of OSKM factors with doxycycline; such a cassette with OSKM factors can be delivered to the body using a lentiviral carrier available on the market today. This will proceed in parallel with the development of an ideal therapy: maximally safe and effective factors activated by a unique, inert, patentable agent. Patentability is crucial for being able to interest Big Pharma in in licensing this therapy upon reaching the IND stage. If the project successfully reaches the IND stage, we believe Big Pharma companies will then be sure to license this therapy to begin clinical studies, first for prevention of atherosclerosis, Alzheimer's disease, diabetes or other age-related indications that anti-aging drugs are using today for regulatory purposes, as aging itself is not yet classified as an indication by the WHO. In a nutshell, that is our plan - get the therapy to the IND stage and then let Big Pharma do what it does best: validate it clinically. We estimate that to get to the IND stage it would take 5-6 years if all goes well.

Comments

"creation of the best means of gene delivery, preferably patentable."

Stem cells have now (almost) been created using antibodies:

http://www.scripps.edu/news/press/2017/20170911Baldwin.html

"the TSRI team discovered two antibodies that can be substituted for both Sox2 and c-Myc, and in a similar set of tests they found two antibodies that can replace a third transcription factor, Oct4. The scientists showed that instead of inserting these transcription factor genes they could simply supply the antibodies to the fibroblast cells in culture.

In this initial study, the scientists were unable to find antibodies that replace the function of the fourth OSKM transcription factor, Klf4. However, Baldwin expects that with more extensive screening she and her colleagues eventually will find antibody substitutes for Klf4 as well. "That one I think is going to take us a few more years to figure out," she said."

Posted by: Jim at October 27th, 2017 5:20 PM

Also mini proteins may be much easier and cheaper to manufacture than antibodies:

https://www.genengnews.com/gen-news-highlights/novel-technique-designs-mini-proteins-that-may-lead-to-new-types-of-therapeutics/81254982?q=rosetta

""These mini-protein binders have the potential of becoming a new class of drugs that bridge the gap between small-molecule drugs and biologics. Like monoclonal antibodies, they can be designed to bind to targets with high selectivity, but they are more stable and easier to produce and to administer," said Dr. Baker who with colleagues published their study in Nature ("Massively Parallel De Novo Protein Design for Targeted Therapeutics").

The technique relies on the Rosetta computer platform, developed by Dr. Baker and colleagues at the University of Washington. They designed thousands of short proteins, about 40 amino acids in length, that the Rosetta program predicted would bind tightly to the molecular target. "

Posted by: Jim at October 27th, 2017 5:45 PM

If you mean this work https://www.nature.com/articles/nbt.3963 I already talked with researchers and they said that efficiency of thransformation now is too low for in vitro application. We will keep our eyes.

Posted by: Ariel at October 27th, 2017 6:00 PM

Sorry, I mean in vivo.

Posted by: Ariel at October 27th, 2017 6:01 PM

Hi,

Just a 2 cent,

I hope this turns out nice. Here is an article about that. From this study it seems these iPSCs factors sox nanog oct klf c-myc are capable of reversing progeria in progeric mice (as stated about repairing lamin and chromosome defects in HGPS) and reduce health diseases burden in old wild-type mice. I hope they can drive this more strongly without inducing tumors because the study could not revert thne aging in the old wild-type mice; but did slow it and helped health wise (healthy aging); the extension of lifespan was in the progeria mice not the healthy old ones. I guess it's the cancer probability vs weak result/effect (c-myc is often elevated in cancers and makes for proliferation/division). Epigenetics are really all over the place, programmed aging is just so hard to decode with meaningful results. I am thinking telomere elongation and epigenetic clock resetting by iPSCs factors (by telomerase activation/hTERT) is risky but still worth it. It would also thwarth replicative senescence since telomeres wiould be maintained by telomerase. Though you would think that this resetting would have more dramatic effect, as stated, to revert you to your 20-year old body. IT seems more complicated/nuanced. I think that is where the (already accumulated/irreversible) damage road block comes in and programmeg aging can'T revert that; and thus stumbles at. The fact that old wild type mice were not reverted to young vigorous 'epigenetically young' mice in the iPSCs factors exposure study, means that permanent/irreversible changes have happened in the old mice. That is where full replacement seems the only real solution (rather than reprogramming).

In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming
1.http://www.cell.com/cell/fulltext/S0092-8674(16)31664-6

Posted by: CANanonymity at October 27th, 2017 10:39 PM

Epigenetic changes are a form of damage and are clearly described in Hallmarks of aging. The work by Ocampo and Belmonte brings us a step closer to understanding that relationship. It isn't programmed aging its wear and tear and Epigenetics does not conflict with that model.

Posted by: Steve Hill at October 28th, 2017 3:19 AM

Great interview. I have a lot of respect for Yuri for having the balls to try this. I wish him well. I don't think it's programmed aging either, just a natural continuing drift from the developmental clock, but I think this has a lot of potential as a therapy.

Posted by: Mark at October 28th, 2017 4:16 AM

Thanks for the kind words, everyone.

CANanonymity, yes, that is precisely the paper by Belmonte's group that inspired this project. I tried to provide a summary of its most important aspects here:

https://medium.com/@yurideigin/reversing-aging-epigenetic-rejuvenation-8c498103c353

Normally aging mice actually did exhibit signs of rejuvenation after just 3 cycles of OSKM induction in that study. Just no lifespan data yet.

Steve, my comrade, I don't really want to get into this debate here (we could do so on Facebook, if you'd like), but I see evidence that for me contradicts the hypothesis that epigenetic changes are stochastic damage: some genes are methylated (repressed), while others are conversely demethylated (activated) with age. And it's not some random genes for each person, it is a highly conserved pattern for the same age group.

Moreover, revesring epigenetic changes reverses all other hallmarks of aging, as described in Vittorio's paper I linked to above. Which to me suggests causality, not randomness.

In any case, I would be happy to be wrong as long as the approach works.

Posted by: Yuri Deigin at October 28th, 2017 8:00 AM

@Steve, "Epigenetic changes can be classified into two main classes: shift and noise. Shift means changes that occur in a coordinated manner among all cells of a given type and tissue, whereas noise means changes that occur in some such cells but not others, increasing the variability of that type of cell. Shifts are caused by some sort of program (genetic changes to the cell's environment), so yes, they can potentially be reversed by restoring the environment and putting the program into reverse. Noise, on the other hand, is not reversible. And we have for several years worked on determining whether it happens enough to matter in a currently normal lifetime. We have not got to a definitive answer, but it's looking though no, epigenetic noise accumulates too slowly to matter, other than maybe for cancer (which, of course, we are addressing in other ways)."

from message from Dr Aubrey de Grey, as part of coming interview .

Posted by: Ariel at October 28th, 2017 11:16 AM

Some years ago I used to get into big arguments over this on Longecity. Good memories.

The Programmed Church never gave a valid explanation why cells age in culture the exact same way they do in vivo - there's no vagus nerve and no hypothalamus in the petridish, neither is there more than 1 niche of cells if the culture is properly prepared.

Furthermore mitotic somatic cells are replaced regularly so obviously any programmatic changes in them are easily disregarded in the grander scheme of things.

Even though we could definitely have a better regenerative capacity if it's fine tuned - and a

longer lifespan as a result of it - it isn't the whole of aging, I'm sorry to say. Everything that happens due to ROS and glycation is stochastic so lysosomal inclusions, mitophagy failure and so on, those are accumulative and not programed.

That being said I do think reprogramming is a valid therapy in the near term.

Posted by: Anonymoose at October 28th, 2017 11:51 AM

Do not confuse epigenetic programme, which *do* exist -- for example, as a reaction on enviromental changes, and can be reversed using OSKM or anoher factors, and genetic programme from programming theory of ageing (which may or may not exist). Epigenetic reprogramming works in any case, whether ageing is programme in general sense or no.

Posted by: Ariel at October 28th, 2017 12:15 PM

Well that's the thing, some people see epigenetic programs as "proof" that aging is programmed.
I remember Blagosklonny had a good quote on that "don't mistake the shadow of the development programs as an aging program".

Posted by: Anonymoose at October 28th, 2017 12:34 PM

"(...) my belief is that the body has enough capacity for self-repair (...) The germ line can do so for billions of years, periodically generating a new organism from scratch (...)"

So yes indeed that looks like very good point to me, a germ cell has to use the same both life-sustaining and damaging processes as the other cells in the body do (for example, damage during energy creation in mitochondria or collection of garbage in lysosomes that can not be discarded), then how does a germ cell repair itself so efficiently?! Just by reprogramming epigenetics (which in turn rev up the repair mechanisms to clean up the "un-cleanable" garbage or to repair the "un-repairable" cellular/mitochondrial damage?!

Anybody can shed some light on it? Does Aubrey address this issue in his book or in his research?

Posted by: veriti at October 28th, 2017 1:28 PM

A zygote doesn't have problems of glycation of the ECM, amyloids, depletion of stem cells, inflammaging, overspecialized immune system, cancer, ... and can expel all its lysosomes and create new ones from scratch. As for clonal expansion of defective mitochondria... I suppose that, if a zygote has that problem, it simply dies long before birth (the same for cancer).

Posted by: Antonio at October 28th, 2017 1:59 PM

Oh, I forgot senescent cells. Well... a senescent zygote would not develop, and would get finally destroyed or expelled.

Posted by: Antonio at October 28th, 2017 2:01 PM

And herein lies the problem why this area is so damn underfunded in 2017

Years on and we're still debating these core issues related to what aging is, and what it is not, trying to kill each other in the womb

What a shame - and this is not lost on the general public who the advocates are trying to persuade

This is the negative side of this "Facebook expert" era

Posted by: Quan Jin at October 28th, 2017 3:07 PM

"Years on and we're still debating these core issues related to what aging is, and what it is not, trying to kill each other in the womb"

Any idea with merit deserves to be explored and debated. As long as we follow the "onus probandi" principle.

"And herein lies the problem why this area is so damn underfunded in 2017"

No.

"This is the negative side of this "Facebook expert" era"

What exactly?

Posted by: Anonymoose at October 28th, 2017 3:47 PM

The incessant debate of damage versus programmed aging camps has been dragging on for years

It will only be solved in the clinic - not in the hallowed halls of cyber-space and by the acolytes of each camp

Outsiders to this see that we can not agree on such basic tenants and hence it stifles the entire space

Posted by: Quan Jin at October 28th, 2017 4:20 PM

I'd be surprised if any outsider knows what an aging theory is, and if he can name more than one best case scenario.

If you want to leave to the mainstream to decide - they've already decided on aging as a stochastic process - so we can move on.

The whole point of our community thought is not to agree with everything the mainstream has to say. So topics like these are open for discussion.

And I can assure you - not getting public support has nothing to do with us not acting like a religious cult with one opinion, one messiah and one goal. And much more to do with most people simply not believing it can be done, most people being bitten by snake oil salesmen in all sorts of forms and shapes, and most mainstream scientists to this day being very vocal that it cannot be done.

Posted by: Anonymoose at October 28th, 2017 4:46 PM

Thank you very much Antonio! Very interesting. I should probably find some "expert facebook" page so I can read more about the zygote cleanup preparation ;-) But here would be my follow-up question, how come a zygote can expel all its lysosomes but a somatic cell can not?

Would such expulsion be possible as a solution for a typical somatic cell cleanup instead of creating an enzyme that has to be delivered into the cell (and then into the lysosome)? Maybe

it would be less toxic for the body to have such an enzyme to work only on the expelled lysosomes in extracellular space?

Posted by: veriti at October 28th, 2017 5:10 PM

Your welcome :) I'm not sure about the lysosome expelling stuff, it was only a possible explanation. Maybe it occurs during meiosis or mitosis, when the interior of the cell is greatly modified, in some phase of the egg formation. I'm not a biologist.

Posted by: Antonio at October 29th, 2017 1:28 AM

Of course, if all cells in the body did that, you would have a lot of toxic waste outside cells, the macrophages would try to eat it, and you would have the same problem again.

Posted by: Antonio at October 29th, 2017 1:30 AM

Interesting what Aubrey says about epigenetic changes. His (detailed) take on this is long overdue. When you look at increased methylation, it is pretty consistent across tissue types, and it's often methylating inactive genes (through chromatin), so it's not going to be too detrimental i'm guessing. Demethylaton I think is probably a mix of stochastic changes through ROS and adaptations to stimuli. And hence it's more variable acrosss different tissue types. Like Aubrey I'm not yet sure how important all this is to aging, outside of the changes to gene expression regulated by telomere length, which clearly are important. And yet the Horvath clock correlates well with mortality, independent of telomere length...

Posted by: Mark at October 29th, 2017 2:08 AM

Yes - it is manifesting a cult-like dimension - and it evidenced all throughout this blog every few months - https://www.fightaging.org/archives/2017/02/sens-after-de-grey/

Posted by: Quan Jin at October 29th, 2017 8:40 AM

Quan Jin: What's exactly the problem there?

Posted by: Antonio at October 29th, 2017 9:25 AM

What about Brain and central nervous system cells? They don't divide (after adulthood) much so how would this treatment effect them? The heart cells in a 70 year old man are no older than when he was 20; they divide,however his brain cells for the most part don't and are 70 years old.

Posted by: TW at October 29th, 2017 5:12 PM

What set of research does SENS / Aubrey base his beleif on that "epigenetic noise accumulates too slowly to matter" to affect any other disease than cancer??

Posted by: DrugDev U.S. at October 29th, 2017 7:12 PM

@DrugDev US - Aubrey/SENS assume that our cells have to maintain such a high fidelity of DNA/DNA methlylation to avoid cancer, that genetic drift won't play a role in aging over a

normal lifespan. Obviously proving that either way at the moment is not possible.

Posted by: Jim at October 29th, 2017 10:14 PM

DrugDev:

http://www.sens.org/research/past-projects/epimutations-in-single-aging-cells

http://www.sens.org/research/publications?keys=bisulfite&research_themes_tid=All&field_publication_type_value%5B%5D=1&items_per_p

And probably some not yet published research.

Posted by: Antonio at October 30th, 2017 1:12 AM

@Quan Jin you are making mountains from molehills here. Academics and enthusiasts have always debated the nature of aging. This happens in science generally and science rarely stands still for long. There is absolutely no problem discussing and debating between theories because this is how we can learn new things and any good scientist should be open to talking and including new data in their views.

As someone who works with the general public in advocacy, and we are quite successful in doing so, I assure you, the majority of punters have 1: No idea this website exists and 2: Have no idea there are different aging theories or the debates that go on.

The majority of the public appears to believe that aging is wear and tear and damage based which makes it easier to discuss SENS and Hallmarks with them.

Whilst I agree to a point, there are some people who are dogmatic in their adherence to one theory or another and inflexible, such people are not generally researchers. We are close now to finding out some fundamental things about aging and they will likely be settled in the near future. If something in SENS or Hallmarks is proven wrong then what a good scientist will do is adapt to that new information, and it will be very clear then who is following science or dogma at that point.

I do, however, think you are making a big deal of some minor squabbles and some dogmatic thinking on what is a niche website unlikely to be of interest to the general public. I mean no offense to Reason by that but this isn't where Joe Public comes to read his science news.

So I think your concerns about dogma whilst certainly applying to some here are not a significant problem as you suggest. They are absolutely not why this field isn't as well funded as it should be and as someone who works professionally on the frontline advocating, lobbying and fundraising I would be more than happy to give you a very detailed explanation of what the bottlenecks are.

It certainly isn't a bit of dogma and the odd slap fight on a niche science website.

Posted by: Steve Hill at October 30th, 2017 4:53 AM

I am puzzled by the thought of SENS failing. If SENS managed to eliminate all evidences of aging, what would be left to observe as aging - either as cells or systems?

Of course, that's a very tall order but I don't see why SENS would ultimately fail regardless of which hypothesis of aging proves most correct. Nor do I see how any one hypothesis of aging would be completely correct anyway as there is inconsistency in all of them.

Posted by: Eighthman at October 30th, 2017 7:30 AM

Well, SENS is big. For example, even if you clear out beta amyloid, there is still TTR amyloid and many other amyloids. Also, there is the possibility that an 8th kind of damage becomes apparent for, say, 1000 year olds, that doesn't have any visible effect during current lifespans.

Posted by: Antonio at October 30th, 2017 8:37 AM

@Antonio - Actually, the early embryo has a lot more to contend with than realized - oxidation, inflammation, infectous insults, senescent cell dynamics in patterning, DNA repair, etc. to name a few

But more importantly, are the dynamics occuring at the reprogramming "tissue field" level, which this type of work, which while elegant at the cell de-differentiation level, unfortunately obscures and does not reveal the full potential picture.

This is critical historical information to incorporate into a model of rejuvenataion in this reductionist era

The seminal work on embryonic fields and teratocarcinoma normalization was done by Mintz et al at U-Penn back in the 1970s:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC433040/

The regenerative biology space is full of related papers on dynamics in blastema fields, and their ability to get rid of "junk tissue insults" of all types:

downloads.hindawi.com/journals/tswj/2010/742904.pdf

Similar dynamics also occur in the plant kingdom in such symplastic fields:

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC335936/

Here are also some links to nice reviews on the general theme of regenerative micro-environments and their ability to organize in / out, and well as modify the diseased phenotype, as well as a subset of the tissue re-organization theme, related to the topics of revertant mosaicism (primarily seen in tissues with an active regenerative niche) and cellular competition (seen in both development and the maintenance of tissue fitness)

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706275/

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1735296/pdf/v040p00721.pdf

http://jcb.rupress.org/content/200/6/689.full

http://precedings.nature.com/documents/6045/version/1

Posted by: Ira S. Pastor at October 30th, 2017 8:45 AM

I guess the big question is whether we need to remove every last piece of accumulating detritus inside and outside of cells, or whether we can rejuvenate cells (as per the interview) and have the rejuventated cells do a lot of it, just leaving SENS to mop up the really difficult stuff.

Posted by: Mark at October 30th, 2017 11:04 AM

@Mark

Yes - this is a core point that extends througout all forms of bio-rejuvenation research, whether it be "old school" pharma products, damage removal strategies, gene therapy / editing, etc.

At the end of the day, we are all "tissue mosaics"

When one of our organs become "pathologic", not all of the cells in that particular tissue represent the diseased phenotype

The cell competition dynamics written about by Moreno et al., and other groups, do a very good job of keeping tissue fitness in line in humans for many decades

But more extensive control is seen in the regenerative micro-environments spoken of above (embryonic, blastemic, symplastic, epimorphic, tissues with high physiologic trunover, etc.)

Pharma's strategy over the past 100 years has been that we are either well or sick and has cared little about this third dimension of biologic complexity

Hence we have just "dumped in" pharmaco-therapeutic interventions that care little about the "salt and pepper" outcomes that result

Posted by: Ira S. Pastor at October 30th, 2017 11:39 AM

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