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REVIEW ARTICLE

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Three Tiers to biological escape velocity: The quest to outwit aging

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Abstract

As longevity companies emerge with new products and the fields of anti-aging research develop new cutting-edge therapies, three distinct classes of longevity methodologies emerge. This discussion finds that there are three clear classes (Tiers) of longevity systems that are currently under development, and all three will be paramount to achieve biological escape velocity (where tissues can be repaired faster than aging can damage them). These classes are referred to as Tier 1, Tier 2, and Tier 3 treatments and are described in detail below. These three Tiers are required for easy identification for pharmaceutical companies and research companies to determine the type of therapy they may choose to deliver being noninvasive, invasive, time consuming, or simple end user products. Specific targets and goals need to be defined clearly from an early perspective in the development of these technologies for future precision medicines. This allows consumers of future anti-aging technologies to consider which Tier a particular therapy may be, delivering a more informed choice.

KEYWORDS
age reversal, biological escape velocity, longevity

1 | INTRODUCTION

Evidence is growing that a range of techniques and therapies may alter the path of biological aging. Many drivers of the aging process are becoming understood, and therapies in the form of drugs, lifestyle changes, or other interventions are rapidly arriving.

Tier 1 interventions such as staying fit,[1,2] taking pills such as fasting mimetics like metformin or rapamycin,[3–5] fasting,[3,6,7] and an epigenetic diet[8] remain insufficient to slow down the damaging effects of aging. Homo sapiens evolved from a diverse range of random gene mutations over a period of hundreds of millions of years,[9] and as complex as those genes are, some genes deliver disease or aging.[10] This paper will show that Tier 1 interventions are relatively easy to implement as they remain cost effective and noninvasive, with the most challenging part simply being able to change behaviors that relate to diet or refraining from eating during fasting periods.

The most common and well-known practices for Tier 1 are diet and exercise. Building muscle to ward off sarcopenia and osteopenia remains paramount to resist biological decay. Testosterone replacement therapy has become very popular to fend off age-related physical decline, and 17α-estradiol (17α-E2), a weak endogenous steroidal estrogen that is also a nonfeminizing version of estradiol, has been shown to extend life in male mice by 19% but did not show any effect in female mice.[11] 17α-E2 also shows improved glucose tolerance in male mice and reduces age-related metabolic dysfunction and inflammatory symptoms.[12,13]

Other technologies are also showing big promise against age-related decline. Small molecule suppressors for an enzyme called

nicotinamide N-methyltransferase (NNMT) are now being considered to regulate metabolism and prevent the loss of muscle, improve insulin sensitivity, modulate glucose, and reduce body weight in animal models.[14] Inhibition of NNMT has also been shown to activate senescent muscle stem cells and the rejuvenation capacity of aged skeletal muscle.[15]

An interesting metabolite that is easily accessible to consumers is Urolithin A, which is converted from ellagitannins by gut bacteria and improves muscle strength and mass and was found to work in people between the ages of 65 and 90 years of age. Mitochondrial dysfunction has been associated with many forms of age-related decline including muscle loss, and Urolithin A has shown a capacity for mitophagy and mitogenesis, which may also hold benefit for many other age-related conditions.[16,17] Alpha-Ketoglutarate is also implicated in resisting muscle loss by improving hypertrophy via preventing protien degradation in muscles.[18]

The nuclear factor erythroid 2-related factor 2 (NRF2) pathway has also become a target to resist aging, with its activity functioning as the first responder against an array of endogenous divergent facets such as redox metabolism, inflammation, and proteostasis.[19] Activation of NRF2 is now a target for longevity researchers as its function offers therapeutic potential for numerous diseases that involve oxidative stress or inflammation including neurodegenerative, metabolic, and cardiovascular diseases. NRF2 can be easily activated through dietary choices, including sulforaphane withaferin A, epigallocatechin-3-gallate, bacosides, silymarin, and curcumin.[11,20]

Many other interventions emerging through the longevity community exist with early enthusiasts reaching for products that slow down the onset of age-related decline, such as fasting mimetics,[21] senolytic technologies to purge senescent cells,[22] products to prevent glycosylation,[23,24] regulation of mitochondrial biogenesis,[25] maintenance of youthful levels of nicotinamide adenine dinucleotide (NAD),[26] and many more. Many drivers of the aging process can now be modified with simple Tier 1 interventions. The aforementioned technologies remain only a small number of the emerging technologies now at humanity's fingertips, though the trend is clear that dietary supplements or pharmaceutical interventions are appearing to attenuate negative aspects of biological aging.

Many of these dietary products are also being used with liposomes or cationic lipid nanoparticles as nanoparticles have the ability to deliver hydrophilic and hydrophobic therapeutic agents, enhance absorption, protect various molecules from stomach acids, and reduce toxic side effects.[27,28]

Dihomo-γ-linolenic acid (DGLA) is also showing great promise in healthy aging as an antiinflammatory, antithrombotic, and an antiproliferation approach for disease, notably cancer.[29,30] DGLA is able to disrupt cellular lipid metabolism, including eicosanoid biosynthesis that (through its antiproliferation effects) may be able to slow down cell division and increase lifespan. Low levels of serum DGLA are associated with mediocre health outcomes in myocardial infarction (MI) and an increased risk of total death in elderly patients with MI.[31]

These Tier 1 interventions remain noninvasive, relatively simple for end users, and mostly cost effective. However, Tier 1 interventions are unable to predict disease, prevent genomic mutations, or regulate profound gene activity to prevent the onset of age. Disease prediction and penetrance is paramount in longevity as ticking genetic time bombs may lurk deep down making efforts of Tier 1 interventions futile should those ticking biological time bombs initiate disease. This is where Tier 2 interventions take their place.

Tier 2 captures full spectrum biological surveillance looking at the entire human biological condition, from genomic data (including methylation[32]), nuclear dynamics such as acetylation[33] and telomere length,[34] exosomal viability,[35] glycomic signatures,[24] metagenomics (microbiomic, mycobiomic, virome[36–38]), metabolomic,[39] proteomic, transcriptomic,[40] NAD levels,[41] sirtuin activity, FOXO activity,[42] relevant blood markers, family history, diet, and many other diagnostic targets.

Sophisticated interventions such as telomerase induction therapies,[43] restorative proteomic therapies to rejuvenate tissues,[44] and prevention of genomic instability[45] are among emerging technologies that can assist in maintaining youthful tissue function.

Understanding Tier 2 diagnostics and the overlap from one biological system that may interact with another biological systems is key in understanding human longevity. An example could be that a microbe inside the human gut may break down a particular food and leave a particular type of metabolite that interacts with a single nucleotide polymorphism (SNP) that may lead to disease. Chen et al. recently demonstrated that particular gut microbiota are associated with neuroinflammation resulting in the pathogenesis of Alzheimer's disease.[46] This type of research where diverse systems overlap with downstream effects remains in its infancy, though the benefits for human health may be profound.

The resulting research will contribute to full spectrum biological surveillance, which is yet to be seen in even the world's most sophisticated medical community. However, the challenges to collate this type of deep data remains elusive to commercialization and that it most likely requires powerful artificial intelligence (AI) to process such an overwhelming amount of data, from gene testing and methylation results to lifestyle, diet, and other hallmarks of human existence; understanding of how multiple biological pathways interact with one another remains undeveloped. AI and in silico modeling will no doubt play a large part in future years in organizing the data across multiple biological systems and designing tailor-made recommendations to individual subjects.

Being able to predict what disease and when a person may get that disease is the holy grail in medical science. Disease prediction and prevention has in part now arrived with many emerging technologies. Death prediction is even possible via technologies known as aging clocks and mortality timers.[47] Knowing this type of confronting data (mortality prediction) allows a subject to take evasive action. Most if not all humans will have a predisposition to some disease or another at some stage, and these so called “ticking time bombs” laying dormant in humanity's genes can not only be found years before they happen, many of them can be defused with various interventions. Full spectrum surveillance is clearly an extremely powerful approach in human health and longevity, as

preventative medicine now makes it possible to prevent disease before it starts.

Tier 2 therapies are focused on investigative and preventative diagnostics. Full body MRIs, electrocardiograms, pathology, and glycomic, genetic, and methylation screening are all part of Tier 2 treatments. Much of Tier 2 is already available across the world for those willing to take preemptive action and investigate not only their biology but determine whether they possess biological time bombs laying dormant in their cells. Tier 2 functions as the disease prediction and prevention phase.

Due to Tier 2 diagnostics being time intensive, until AI can process the vast wealth of data that full spectrum biological surveillance needs to generate, it is likely to remain costly and only available from specialized clinics.

Without Tier 2 insight, subjects wishing to maintain healthy physiology are simply blinded to any dangers hidden inside their biology. However, biology can also be changed and reprogrammed, and this is where the requirement for Tier 3 exists.

Tier 3 treatments remain expensive and elusive but are already emerging onto the world stage. Numerous companies are now pursuing genetic engineering to achieve longevity by maintaining tissue vibrancy, disease resistance, and organismal vitality.[48] Many genes are already identified as aging genes or youth genes,[10,49] and modifying the expression or existence of these genes will hold profound downstream impacts for lifespan.

CRISPR Cas9, Base and Prime editing, Programmable Addition via Site-specific Targeting Elements (PASTE), and other versions of gene editing are becoming cost effective and may cause the trajectory of these technologies to become mainstream services that the general public can access easily.[48,50,51] Gene and epigenetic silencing such as CRISPR DCas9 are also options that may be considered for those consumers apprehensive about full gene editing.[52]

Tissue reprogramming with Yamanaka Factors is also well underway and may allow aged organisms to rejuvenate their organs and tissues in vivo.[53] Whilst no other therapy currently discussed in this paper can rewind aged tissues, Yamanaka Factors appear promising in what could be a first step in rewinding biological time; however, differences in an individual's methylation status and biological age sees that cellular reprogramming will never be a one size fits all, as rewinding cells too far back could have dire consequence for specific tissues.[53–55]

Tier 3 technologies that are able to reprogram genes, the epigenome, including cells and tissues back into a youthful state also lead to a startling paradigm, and that is the era of human natural selection may be disappearing. Evolutionary escape velocity has already been reached with Tier 3 technologies, with the human species no longer requiring gene mutations over the course of thousands of years to become stronger or healthier as technologies to edit genes are already here.[56] Humans have the power over their default gene configuration to ensure that genes can be edited at will and if tissues can be rejuvenated faster than aging can destroy them, then we have reached another goal known as biological escape velocity. Human evolution on Earth functions by random gene mutations to ensure life forms evolve and are adaptable to survive in their environment, though this process of natural selection takes thousands of years.[57,58] Through genetic mutations genes may give lifeforms stronger or weaker survival traits. Those with the mutations that see them become weaker may not survive long enough to pass on their inferior genome, whereas the stronger mutations increase the chances of passing down the superior genome. The human race has now devised ways to ensure that inferior genomes no longer cause early mortality or are passed down to their offspring. Inferior genomes look set to be edited out with technologies such as CRISPR-Cas9, PASTE, or base and prime editing, and this control over natural selection is evolutionary escape velocity, whereas repairing tissues faster than aging can destroy them is biological escape velocity. Ultimately the human body is genetic code, and simply reprogramming that code, or adjusting the proteins from that code, infers that power over human evolution and aging can be exerted.

Messenger ribonucleic acid (mRNA) is another prime contender for Tier 3 therapies, as the manipulation of proteins and the ability to restore them back to youthful levels also holds great promise for rejuvenation treatments.[59] mRNA may also be more palatable to commercial services as it does not require gene editing and can induce healthy protein function in subjects that may even have single nucleotide polymorphisms for a particular protein, thus bypassing the body's need for transcription of that faulty gene.

Restoring various serum proteins back into the blood will become a major target to restore youthful function back into aged tissues, and there are many beneficial proteins that hold rejuvenation properties such as insulin growth factor two (IGF2),[60,61] growth hormone releasing hormone ((GHRH),[62] gonadotropin releasing hormone GnRH),[63] and growth differentiation factor 11 (GDF11).[64,65] Moreover, reducing other serum proteins that appear to induce age-related disease would also be paramount in seeing tissue engineering therapies successful. CCL11 (eotaxin) has been associated with lower neurogenesis and improper learning and memory in mice.[66] Because eotaxin is correlated with so many neurological conditions (neurodegenerative, neuroinflammatory, and neuropsychiatric disorders), it has earned the name “Endogenous Cognition Deteriorating Chemokine” (ECDC) or “Accelerated Brain-Aging Chemokine” (ABAC).[67] Eotaxin is known to increase with age and negative regulation should be a key target for healthy aging.[68] Furthermore, other serum proteins also deliver deleterious effects in human tissues such as β2-microglobulin, which is considered a pro-aging factor that also contributes to impaired cognition and improper neurogenesis.[69] These types of proteins (eotaxin and β2-microglobulin) that are implicated in age-related decline must be managed, otherwise healthy aging cannot be achieved effectively. This list is not exhaustive and is only offered as a guide for future Tier 3 technologies.

No matter what a subject's genome, superior or inferior, the natural evolutionary pathway is soon to be redundant. Humans now control how their species will age and evolve. Unborn babies that

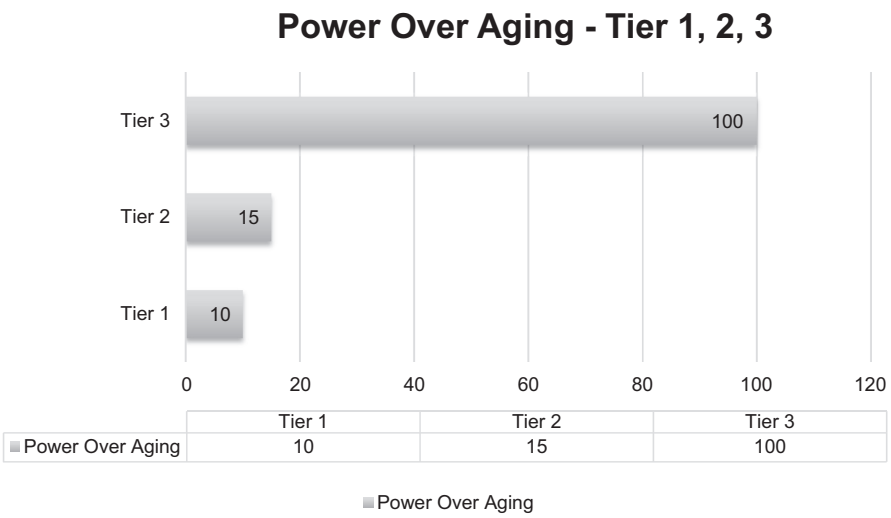

FIGURE 1 Chart illustrates the effect of each Tier on biological aging

exhibit a disease phenotype may now be genetically edited and no longer will they be born weak with little chance of survival; natural selection has changed forever with Tier 3 technologies.

The Tier 3 technologies used to achieve biological escape velocity clearly indicate that the death of human natural selection is here, as interest in making humans or their offspring smarter, healthier, and stronger gathers momentum. For the first time Homo sapiens are taking control of evolution and aging, as the techniques that will overcome aging are now within grasp.

Even though Tier 1 has its place in longevity, and with Tier 2 providing extreme insight into a subject's biology, Tier 3 technologies remain the only observable therapies that may be able to prevent aspects of aging and deliver rejuvenation of tissues faster than aging can damage those tissues (Figure 1).

2 | CONCLUSION

This discussion evidently finds that there are three distinct classes of longevity and anti-aging technologies that are emerging globally, and the ability of each class is clearly apparent in fending off aspects of biological decay. Tier 3, however, reigns supreme in rejuvenation therapies that may make up future pathways to reach biological escape velocity. Only a few years ago, much of this paper's discussion remained science fiction, as the technologies remained theoretical or highly fringe. As those technologies have now entered mainstream medicine, coupled with the knowledge of the genetic and epigenetic targets that can attenuate aging, including genes that make bones weak, loss of immune function, and the simple causes of wrinkles and why humans lose muscle during age (among many others), the pieces to the aging puzzle are slowly coming together. Altering genes, epigenetic expression, cellular reprogramming, and systemic tissue rejuvenation is certainly coming to mainstream health and medicine soon. Preventing the number one cause of suffering and disease, which is aging, is clearly a common-sense approach to long-term human health.

3 | LIMITATIONS OF STUDY

None.

AUTHOR CONTRIBUTIONS

Raymond D Palmer.

CONFLICT OF INTEREST

Raymond D. Palmer is Chief Science Officer of Full Spectrum Biologics, author of *The Anti-Aging Toolkit*, and holds multiple patents in biotech.

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