Crypto Coin Denominated

Biotechnological Health Services Platform

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Executive Summary

A once in a lifetime scheme to benefit from the delivery of revolutionary new medical solutions. This process will result in a paradigm shift within the medical industry and will have a significant impact on the longevity and quality of life for existing and future generations. This is being achieved by finding early markers in the human DNA and treating major diseases with simplistic influenza like treatments with more predictable results and without side effects. A ground-breaking method has been invented by which the structural information of any molecule (e.g. drug) can be transferred into a living tissue by means of non-invasive procedures. In addition, the team devised subscription based monthly recurring services to collect biogenetically important data, with the benefit of detecting and investigating significant disparities in chronological vs biological age.

Targeting extending healthy lifespan and protecting against neurodegenerative pathologies by a non-invasive autophagy-enhancing intervention.

Ageing is driven by the progressive, lifelong accumulation of cellular damage (including damaged macromolecules and organelles) that causes disease and ultimately death. Autophagy (cellular self-eating) serves as a major cellular process for degrading (eliminating) cellular damages. Indeed, defects in the autophagic process accelerate the rate at which cells age and can increase the chance of an individual to acquire an age-associated degenerative disease, such as cancer, various neurodegenerative disorders (in particular, Alzheimer's, Parkinson's and Huntington's diseases), tissue atrophy and fibrosis, immune deficiency, infection by intracellular pathogens, and diabetes. Thus, autophagy acts as a major cellular mechanism for rejuvenating cellular constituents and decreasing the rate of the ageing process. The capacity of autophagy progressively declines during adult lifespan.

Developing autophagy-enhancing drug candidates hence represents a major focus in current pharmacological industry. The majority of autophagy-stimulating agents identified so far cannot penetrate through the blood-brain barrier, preventing their application in treating various neurodegenerative symptoms. Here we demonstrate a novel method called molecule information transfer by which the structure of any potential autophagy-inducing molecule can be transferred into the brain (a living organ) by a non-invasive way. This method is capable of transferring the effects of autophagy-inducing drugs into neurons, protecting them from undergoing cell death. We conclude that this method has potent neuroprotective and antiaging effects.

1 Introduction and What We Know About Aging

Understanding the molecular mechanisms (i.e. biological basis) of the ageing process remains a fundamental and fascinating problem in biology, with significant medical, social and economic implications. An outstanding researcher of the field, Cynthia Kenyon, wrote the following on this issue: "Some aspects of ageing remain particularly enigmatic. One of these is the all-important question of what actually causes ageing." (Kenyon, 2010). It is generally accepted that protein homeostasis - the balance between protein synthesis and degradation - declines with age and molecular damage accumulates during adult lifespan. But what are the genetic factors that primarily cause these age-associated cellular changes? This issue undoubtedly remains largely unresolved (as a consequence, no one could have stopped the ageing process, and generated an immortal biological system). Significantly, various age-associated diseases, such as cancer, diverse neurodegenerative pathologies (e.g. Alzheimer's, Parkinson's and Huntington's diseases), tissue atrophy and fibrosis, immune deficiency and diabetes, are also caused by the intracellular accumulation of cellular damage. This shared molecular root (accumulation of unrepaired cellular damage) of ageing and age-associated diseases explains why we get such a disease preferably at advanced ages rather than during young adulthood. Ageing thus can be considered a collection of seemingly independent age-related degenerative (i.e. associated with excessive cell death) processes, leading to disease, and ultimately, death. Individuals randomly acquire a disease from this collection in a late phase of the lifespan. This implies that „if a cancer cure were to be found that, for example, efficiently killed abnormally proliferating cells, it would only increase the risk of an individual to acquire another type of pathology" (Hekimi and Guarente, 2003). The only solution would be to effectively slow down the rate at which somatic cells age, thereby simultaneously delaying the incidence of potentially all age-associated diseases. "*Across the developed world, birth rates are falling and people are living longer. This requires a new focus on research to promote healthy ageing, rather than simply treating the diseases of old age*." (Abbot, 2004).

Aging is driven by the progressive, lifelong accumulation of cellular damage (Kirkwood, 2008; Vellai et al., 2003; 2009; Vellai, 2008). Such damages mainly include oxidized, aggregated and misfolded proteins as well as unfunctional organelles, in particular damaged mitochondria, which cannot exert their normal biological function and interfere with cellular processes, thereby acting as cellular toxins. The effective removal (degradation) of damaged intracellular components is essential for maintaining cellular homeostasis and functioning. When damage accumulates in the cytoplasm, cellular processes tend to become compromised, eventually leading to the senescence and subsequent death of the affected cells. A significant amount of cell loss then causes tissue/organ malfunctioning, which manifests as an age-associated disease.

During the past decade, we have discovered two important things in relation to ageing. First, we have shown that autophagy (cellular self-eating; a major self-degradation process of eukaryotic cells) plays a central role in ageing control (Tóth et al., 2008; Vellai, 2009; Vellai et al., 2009; Takács-Vellai and Vellai, 2010). Accordingly, distinct longevity pathways and cellular mechanisms (e.g. insulin/IGF1 and TOR signalling, pathways mediating calorie restriction, and mitochondrial respiration) influencing the rate of the ageing process converge on the autophagy gene cascade to determine lifespan. In other words, autophagy is required for lifespan extension in long-lived mutant and calorically restricted animals (as several mutations and lowered food intake can significantly extend lifespan in diverse eukaryotic organisms ranging from yeast to humans). We have also demonstrated (unpublished results) that the capacity of autophagy declines as the organism ages (**Figure 1**). This negative change in autophagic activity significantly contributes to the age-associated accumulation of cellular damage, thereby accelerating the ageing process and increasing the chance of an individual to develop an age-associated degenerative disease (**Figure 2**). We conclude that promoting autophagy at advanced ages by pharmacological interventions can significantly promote longevity and lengthen the period of healthy lifespan. We have identified autophagy-enhancing small molecules with potent antiaging and neuroprotective effects. These drug candidates are collectively called AUTENs (autophagy enhancers) (Papp et al., 2016; Billes et al., 2016; Kovács et al., 2017).

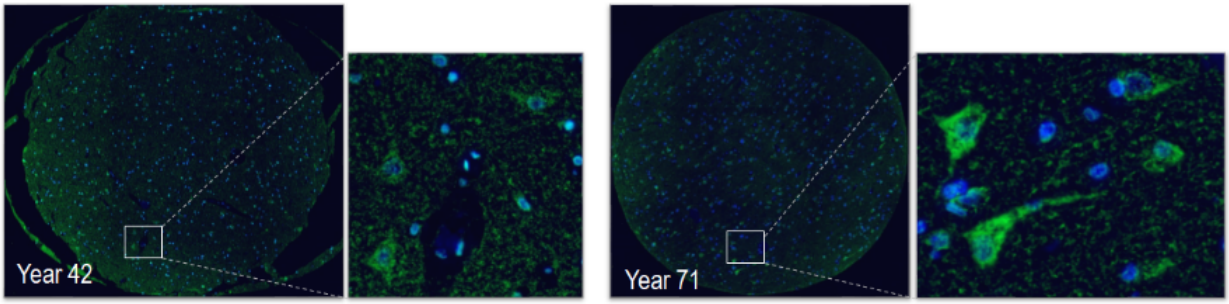


Figure 1. The capacity of autophagy displays an age-associated decline in the human central nervous system. Figures showing p62 antibody staining (green) on post-mortem human brain samples. p62 is a substrate of autophagy, thus its levels inversely correlate with the activity of the autophagic process. *Left panel*: relative p62 levels in neurons from an individual at age of 42 years. Right panel: relative p62 levels in neurons from an individual at age of 71 years. Fluorescence pictures were taken with the same exposure time. p62 levels are significantly higher in the old sample, showing a highly lowered autophagic activity in these neurons as compared with the young sample. This negative age-associated change in autophagic activity may significantly contribute to the development of various neurodegenerative pathologies at advanced ages (Kovács et al., unpublished results).

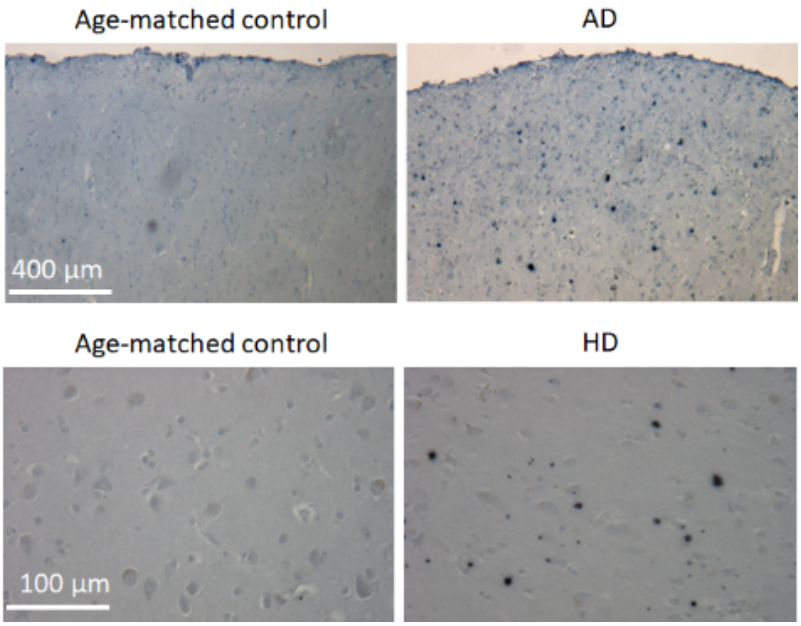


Figure 2. Decreased autophagic activity in human brain samples affected with Alzheimer's or Huntington's disease. Figures displaying p62 antibody staining on post-mortem human brain samples. p62 serves a substrate for autophagy, thus its levels inversely correlate with the activity of the process. Upper panels: an age-matched control (non-affected) sample (left) and a sample from an individual diagnosed for Alzheimer's disease (AD). Bottom panels: an age-matched control (non-affected) (left) and a Huntington's disease-affected sample (right). Black dots indicate p62-positive neurons. There are much more stained neurons in the disease affected samples than in control samples.

Second, we have recently provided a novel theoretical model for the mechanism of ageing (Sturm et al., 2015; 2017). Accordingly, ageing is primarily caused by the mutagenic activity of mobile genetic elements (MGEs) called "jumping genes", which constitute nearly half of the human genome. When mobilized, MGEs change their original genomic position and can frequently inserted into functional (coding or regulatory) DNA sequences, causing insertional mutations in the new genomic loci. In ageing somatic cells, MGEs become increasingly active during adult lifespan. This can lead to genomic instability and the incidence of various age-associated diseases at advanced ages. MGEs are often transposed into genes that participate in a maintenance process like autophagy, further contributing to accelerating ageing. However, in non-ageing cells, such as germline and cancer cells retaining their indefinite proliferation capacity, MGEs are effectively repressed by the Piwi-piRNA (P element induced wimpy testis in Drosophila - Piwi-interacting non-coding RNAs) pathway. Piwi proteins are indeed exclusively expressed in germline and cancer cells, as well as in somatic cells of certain cnidaria (e.g. freshwater hydra) and flatworms (e.g. planaria), which represent biological system considered to be potentially immortal. The first experimental evidences to prove the transposon-driven model of ageing are currently under consideration by a high standard journal. Theoretically, this knowledge can provide the basis to develop:

-potent anticancer agents that act as inhibitors of Piwi proteins (each type of cancerous cell lines examined so far accumulates Piwi proteins (Ross et al., 2014)

-potent antiageing agents that block the activity of MGEs

-a novel method that is capable of determining age from DNA sample (potential forensic application)

-novel early markers for detecting neurodegenerative processes (neurodegenerative diseases are currently untreatable, fatal disorders, and a major reason of that stems from the lack of a potent early marker that could detect the early – treatable – phase of such a disease)

2 Basic Scientific Facts About Autophagy and Degeneration of Cells

Autophagy (cellular self-eating) acts as a major cellular process for removing damaged intracellular constituents (Levine and Kroemer, 2008; Klionsky et al., 2008). (Note that the initial discovery of autophagy genes was awarded by Nobel Prize in Physiology and Medicine, 2016.) Autophagy hence is required for the rejuvenation of cellular components. Defects in autophagy can indeed lead to the development of various age-associated diseases and accelerated ageing called progeria (Takács-Vellai et al., 2005; Vellai, 2008; Vellai et al., 2009).

Three major mechanisms of autophagy can be distinguished, macroautophagy, microautophagy and chaperone-mediated autophagy. Among them, quantitatively the most significant one is macroautophagy (hereafter referred as to autophagy). During autophagy, parts of the cytoplasm are sequestered into a double membrane-bound vesicle called autophagosome. Then, the autophagosome is fused with a lysosome to form an autolysosome, in which the enzymatic breakdown of the sequestered material occurs into building blocks, which can be used in synthetic processes. Because autophagy plays a crucial role in the degradation of damaged macromolecules and organelles (e.g. the autophagic degradation of mitochondria is called mitophagy) and its capacity displays a marked decline during adult lifespan, the process becomes a promising drug target in current pharmacological research. Given to this huge effort, several autophagy-inducing drug candidates have been developed in the last years. Many of them however act upstream of the core autophagic process and thus exert undesired side effects. A relevant example is served by the immunosuppressant rapamycin, which promotes autophagy through blocking the cellular energy sensor TOR (target of rapamycin) kinase, a negative regulator of autophagy (inhibiting the inhibitor provides a stimulatory effect). Besides blocking autophagy, TOR influence translation (protein synthesis) and ribosome biogenesis. Thus, inhibiting the multifunctional TOR kinase certainly interferes with various biological processes. In other words, it may be not a good strategy to stimulate autophagy by simultaneously blocking general protein synthesis.

To overcome these difficulties, we have recently developed a novel generation of autophagy-inducing drug candidates called AUTENs (autophagy enhancers). These small molecules target a myotubularin-type phosphatase, MTMR14/hJumpy (**Figure 3**) (Papp et al., 2016; Billes et al., 2016; Kovács et al., 2017). MTMR14 antagonizes PtdIns3K (phosphatidylinositol 3-kinase), which is required for the synthesis of the autophagy isolation membrane (autophagosome membrane). Thus, under physiological and stress-induced conditions, MTMR14 represses autophagy to prevent the process from injurious hyperactivation, which can often lead to cell death (cellular overeating or type II programmed cell death). AUTENs therefore induce autophagy by inhibiting a negative regulator of the process, MTMR14.

An effective AUTEN-type molecule is AUTEN-67, which prevents the accumulation of toxic proteins, protects neurons from undergoing cell loss, and extends lifespan in various *in vivo* models of Alzheimer's, Parkinson's and Huntington's disease (**Figure 4**). Although found to have no undesired side effect and to possess good metabolic characteristics (absorption and metabolism), AUTEN-67 is a relatively large molecule that appears to be unable to penetrate the blood-brain barrier (BBB), a natural barrier that have evolved to protect the central nervous from injurious agents (toxins, microbes, etc.). The primary function of the BBB is to separate the extracellular fluid circulating in the central nervous system from the peripheral blood circulation. It essentially constitutes from the tight junctions of endothelial cells in the brain capillaries.

Note that many other drug candidates with potent neuroprotective effects also fail to develop further because they cannot penetrate this barrier. Therefore, an effective method that enable these agents to enter into the brain in a non-invasive way would greatly enhance the chance to develop novel neuroprotective drugs.

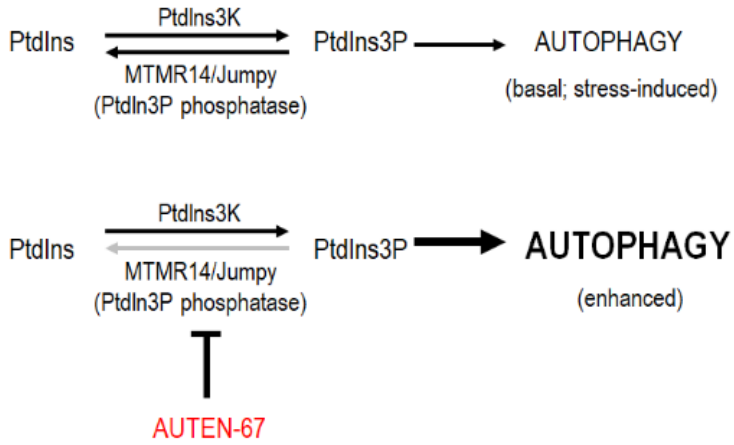


Figure 3. The mechanistic action of AUTEN-67. It induces autophagy by inhibiting the myotubularin-type phosphatase MTMR14, a negative regulator of the autophagic process. MTMR14 actually antagonizes PtdIns-3K that generates PtdIns3P from PtdIns. PtdIns-3K: phosphatidylinositol 3-kinase; PtdIns: phosphatidylinositol; PtdIns3P: phosphatidylinositol 3-phosphate; MTMR: myotubularin-related phosphatase. Arrows indicate positive regulatory interactions.

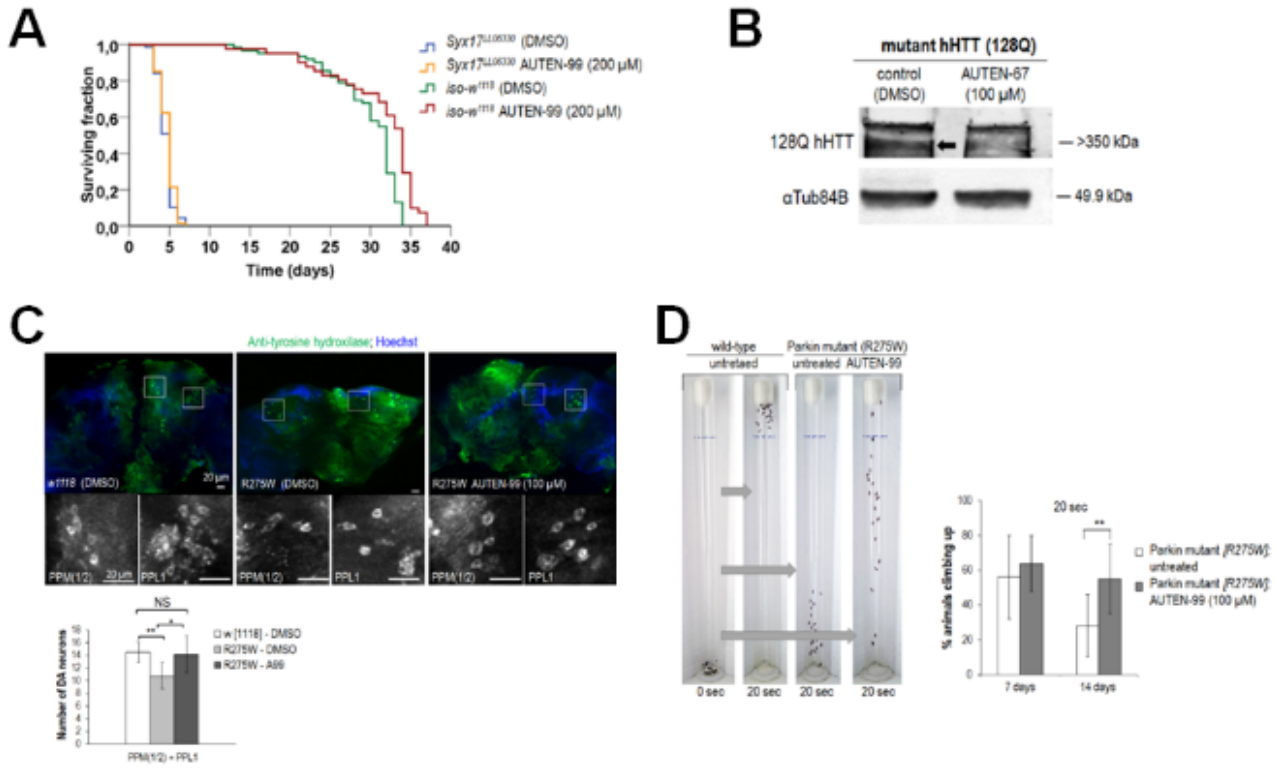


Figure 4. AUTEN molecules exert potent antiaging and neuroprotective effects.

A, AUTEN-67 extends lifespan in Drosophila in an autophagy-dependent manner. Green line indicates the growth curve of untreated control animals, while the red line shows the growth curve of animals treated with AUTEN-67. In an autophagy defective background (yellow and blue lines), AUTEN-67 is unable to promote longevity.

B, AUTEN-67 treatment highly reduces the level of toxic proteins. Western blot analysis displaying that animals expressing human mutant Huntingtin protein (128QhHTT) show reduced levels of the disease-associated protein in response to treatment with AUTEN-67. The arrow indicates the band of the toxic protein. AlphaTub84B was used an internal control.

C, AUTEN-99 treatment protects dopaminergic neurons from undergoing cell death. Anti-tyrosine hydoxilase (green) stains dopaminergic neurons in specific parts of the brain. Animals expressing mutant human Parkin protein (R275W) show reduced amounts of dopaminergic neurons. AUTEN-99 treatment nearly restores the number of neurons to levels found in control animals expressing the empty vector (w1118). Hoechst (blue) stains the nuclei.

D, Climbing assay showing that AUTEN-99 treatment restores movement ability in animals expressing a human mutant Parkin (R275W) protein. Normal animals can climb up on the wall of a glass vial within 20 sec (normal negative geotaxis). Animals expressing R275W cannot perform this behaviour, instead they remain in the bottom of the vial. Animals expressing R275W can climb up on the wall in response to AUTEN-99 treatment.

3 Treatment by Transferring the Molecular Information of AUTEN-67 into the Brain in a Non-Invasive Way

Many drug candidates with neuroprotective effects (they work fine in cell-based assays) fail in further tests because they cannot penetrate through the BBB. Therefore, we have turned to a novel technology that is capable of transporting the molecular information of any compound into a living organ, e.g. the brain.

We have recognized that certain types of millimetre wavelength (MW) therapeutic devices could be suitable for solving the above mentioned problem caused by the BBB. Their medical effects were recognized in the 1960's in the former Soviet Union, and widely used in the therapy from the 1970's. Based on the work of Gyevjatkov and colleagues (1991), novel devices were developed which work at the range of 30-60 GHz, i.e. between 5-10 mm wavelength. The energy of the used radiation is low (10-30 W/cm^2) and the area size of the treated surface is typically 10 cm^2. These apparatuses are freely available in the market (e.g. LENYO and TRIOMED MMW devices, the latter is available from www.cemmed.ru, www.cemmed.hu or www.cemmedeurope.com). These devices are capable of copying and storing the molecular information coming from the oscillation of a given molecule, and transferring (reflecting) this information into a living tissue. This way, the device can be used to treat a certain neurodegenerative symptom by a non-invasive way (without directly transferring the molecule into the organ).

By using a TRIOMED MMW device (it is suitable for taking up, storing and reflecting the wavelength of any compound into a tissue in respect of therapeutic aims), we decided to introduce the molecular information of a given drug with potent

neuroprotective effects directly into the brain by circumventing the BBB. The molecular information of AUTEN-67 was effectively transferred into the brain by using this method. The method can be widely used to transfer the neuroprotective (pharmacological) effect of any drug compound unable to penetrate through the BBB.

4 Case Studies and Results

There is a device that is able to fix the structure of any molecule and transfer this information into a living tissue. Thus, the item is capable of transferring molecule information (structure) from one place (e.g. from a glass vial) into another one (e.g. living tissue). This can be used to introduce molecules into the central nervous system in a noninvasive manner which normally do not penetrate through the BBB. Using this technology, we transferred the molecular information of the autophagy inducer AUTEN-67 into the fat body of the fruit fly *Drosophila melanogaster*, a tractable genetic model organism. The fat body is a widely used organ model for studying the activity of autophagy in this organism because under physiological conditions fat body cells do not exhibit detectable levels of the autophagic process. First, we treated animals with AUTEN-67 by adding the compound into the media on which the animals were fed (yeast extract), and found a significant increase in the number of autophagic structures, as compared with untreated control (**Figure 5A-A''**). Then, by using TRIOMED MMW device, animals were treated with the molecular information of air and yeast extract (negative controls). These treatments did not modulate autophagic activity in fat body cells (**Figure 5B, B'**). Animals were also treated with the molecular information of rapamycin, a well-known activator of the autophagic process (positive control). TRIOMED MMW-based rapamycin treatment effectively elevated the amount of autophagic structures in treated animals as compared with untreated control ones (**Figure 5C**). Finally, animals were treated with the molecular information of AUTEN-67. A huge increase in the amount of autophagic structures were detectable in treated animals (**Figure 5D, E**). Autophagy levels in animals treated with AUTEN-67 information were comparable with those found in animals treated with rapamycin. These results suggest that the molecular information of a drug candidate that otherwise cannot penetrate through the BBB can be transferred into a living tissue by a non-invasive way. Thus, AUTEN-67 can be potentially used for decreasing the rate of the ageing process, for delaying the incidence of neurodegenerative pathologies, and for effectively treating various neurodegenerative conditions.

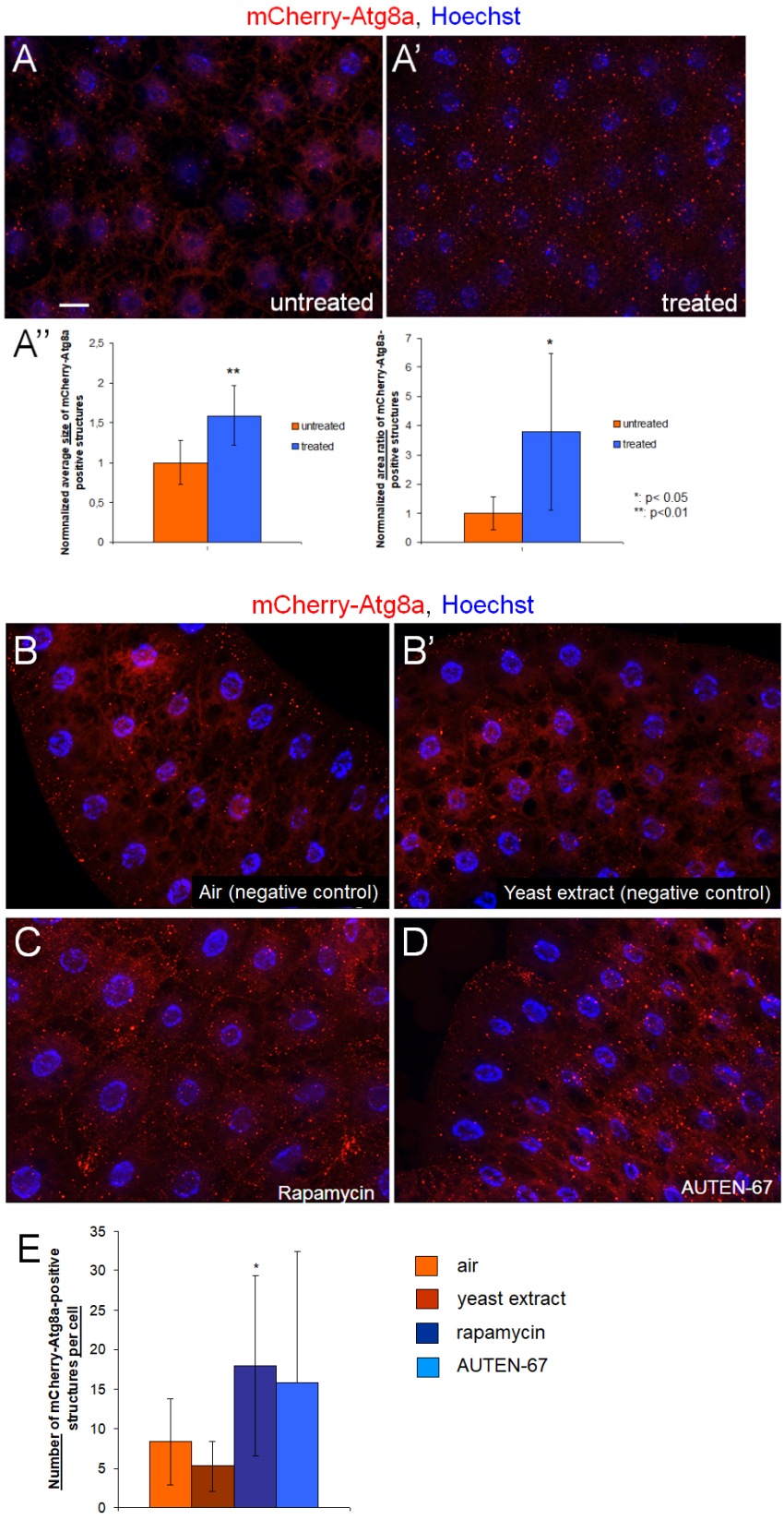


Figure 5. The molecular information and its autophagy-inducing effects of AUTEN-67 can be transferred into a living tissue, the Drosophila fat body, by a non-invasive way, using TRIOMED MM device. A-A'', Fat body cells from an untreated control (**A**) and an AUTEN-67-treated (**A'**) animal. AUTEN-67 was added to the yeast extract the animals fed. (**A''**) Quantification of autophagic structures in control vs. treated animals. Animals were transgenic for an autophagy reporter, mCherry::Atg8a (red dots). Hoechst staining (blue) indicates nuclei.

On panels **A''**, bars indicate S.D., *. P<0.5, **: P<0.01, unpaired Student's t-test. **B**, Fat body cells from an animal treated with the molecular information of air. **B'**, Fat body cells from an animal treated with the molecular information of yeast extract. Both samples show no elevation in autophagic activity (positive controls). **C**, Fat body cells from an animal treated with the molecular information of rapamycin. A significant increase in autophagic activity can be seen, as compared with positive controls. **D**, Fat body cells from an animal treated with the molecular information of AUTEN-67. The amount of autophagic structures is comparable with those found in rapamycin-treated animals.

Animals expressing a human mutant Huntingtin protein (128QhHTT) were treated with the molecular information of AUTEN-67 and tested for their ability to climb up on the wall of the glass vial (an endogenous negative geotaxis reflex). The presence of the toxic protein (128QhHTT) largely decreased the movement of animals tested (**Figure 6**). However, transferring the molecular information of AUTEN-67 into the animals by using a TRIOMED MMW device significantly restored their climbing ability. We can conclude that this non-invasive treatment of AUTEN-67 increases autophagy and prevents the animal from the adverse effects of toxic proteins.

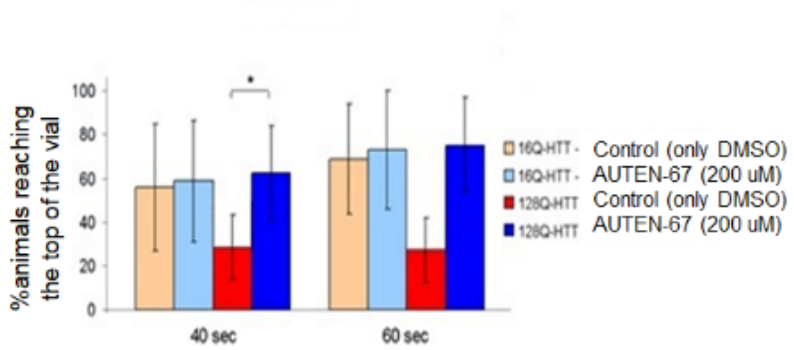


Figure 6. Transferring the molecular information of the autophagy enhancer AUTEN-67 into animals transgenic for a human mutant Huntingtin protein (128QhHTT) in a non-invasive manner can significantly restore their movement ability to normal levels. Animals were shaken down to the bottom of the vial, and let them to climb up on the wall for 40 and 60 seconds. Percentage of animals that reached the top of the vial was determined. Bars represent SD, *: P<0.05; unpaired t-test.

5 Potential Additional Outcomes

Based on the model we formulated for explaining the mechanism of ageing, we intend to establish the following biotechnological goals.

1, We recognized and proved that cancer cells have an indefinite proliferation capacity due to the ectopic expression of Piwi proteins. These proteins are required for inhibiting MGEs, thereby ensuring genetic integrity of subsequent cell clones. We wish to identify small molecules (drug candidates) that potently inhibit Piwi proteins. These agents will act as potent anticancer compound.

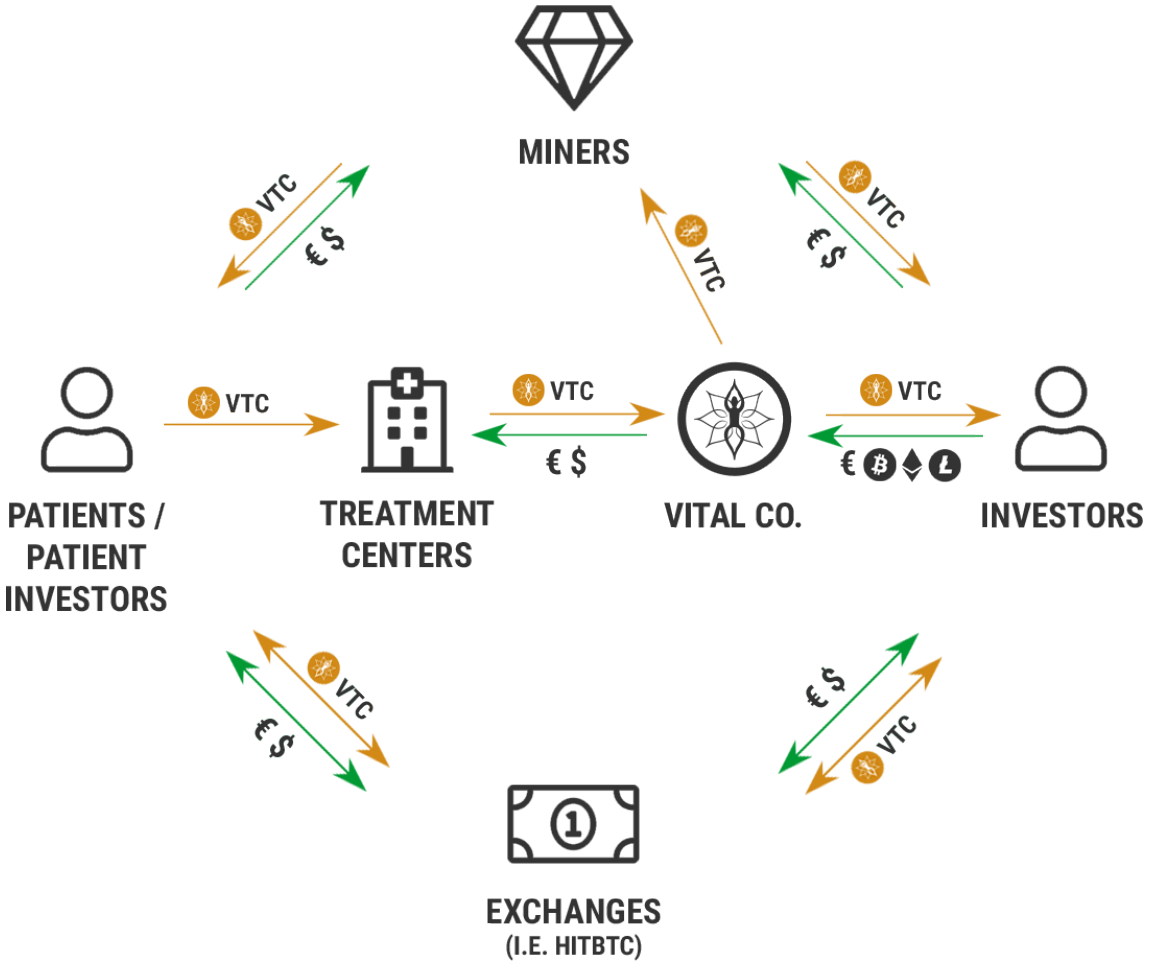
2, We intend to develop small molecules that are capable of inhibiting reverse transcription in human cells. The enzymes' reverse transcriptases are encoded by MGEs sequences and ensures the mobilization of retrotransposons. Thus, these inhibitors (functioning as anti-ageing agents) will block MGE activity, thereby slowing down significantly the ageing process.

3, We will develop a novel diagnostic toll, by which one can determine age from DNA sample. As we explored, ageing is driven by the progressive mobilization of MGEs in somatic cells. Their mobilization is catalysed by a specific chromatin modification (Sturm et al., manuscript under evaluation). The relative level of this chromatin change is proportional to the age of the organism. Thus, determining relative chromatin state by a simple PCR (polymerase chain reaction) experiment will allow to determine age from DNA sample. This can be widely used in forensic science.

4, At advanced ages, our novel method (see the above point 3) is capable of determining the biological age of an individual. This will be informative for an early stage of a degenerative process that has not yet been manifested phenotypically. Uncovering early stages of these pathologies is crucial for their effective treatment (when the pathology is recognized phenotypically, large parts of the brain have already undergone intense degenerative processes (a large amount of neuronal cell death can be detected in the affected patients).

6 Usage of Vitalcoins

An enhanced bitcoin forked crypto currency, Vitalcoin, as a utility coin, has been developed in which all of the mentioned services will be denoted. This will provide a framework for an anonymously transferrable asset that can be utilized infinitely for the delivery of these revolutionary medical solutions across the globe. The services-based model consists of recurring subscription and some non-recurring services, centered on early diagnostics and treatments of diseases within approved treatment centers.



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