# CAXXÖN LABS

## **Informed Consent Form**

(in alignment with World Health Organization – Research Ethics Review Committee Guidelines)

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Name of Organization:	Caxxon Labs, a research and development entity jointly incorporated in Germany and Taiwan R.O.C.
Sponsor:	Global Citizen Capital, an investment vehicle wholly incorporated in British Virgin Islands
Co-Sponsors:	Asian World Anti-Aging and Well-Being Association ("AWAWA")
	Better Together Foundation
Name of Program and Version:	Telomeres Rejuvenation 3.0 (Phase 3)
Dates of Program:	Registration: 09/01/2019, on a first come, first serve basis. Program will close when capacity is reached

#### Synopsis

Since 2000, more than USD 100 billion has been spent collectively towards research and development of drugs, both pharmaceutical and non-pharmaceutical, curing lifethreatening diseases such as cancer. Even then, the success rate of these drugs on average, as measured by the industry standard of five-year survival rate, is 30-40% for early detection and 5-15% for late detection.

In the same period, less than USD 10 billion has been allocated towards regenerative medicine and its proven scientific ability to prevent or delay the onset of such life-threatening diseases.

It is time we take charge and change this development path for health. Welcome to our Program 3.0, whereby a group of German and Taiwanese scientists have taken an approved, non-pharmaceutical and cancer-treating drug, and converted its formula towards preventive healthcare purposes. This Informed Consent Form has two parts:

- Information Sheet
- Provision Consent

## **PART I: Information Sheet**

#### **Introduction on Telomeres**

The 2009 Nobel Prize in Physiology or Medicine was awarded to Dr. Elizabeth H Blackburn and her team for their discovery of how chromosomes are protected by telomeres and the enzyme telomerase. Inside the nucleus of virtually all of our cells are 46 chromosomes, the thread-like packages that carry our genes. At the tips of these chromosomes, like the hard ends of shoelaces, are structures called telomeres. While they do not contain genes, telomeres are important for replication or duplication of the chromosomes during cell division. They are made up of approximately 1,000 to 2,500 copies of a repeated DNA sequence (the order of chemical building blocks in a stretch of DNA), TTAGGG.

When humans are born, we do not have every cell our bodies will ever need. As we grow, we need new skin, bone, blood, and many other kinds of cells. Even as adults, we need to make new cells. For example, skin cells and those cells that line our intestines are constantly replaced. All of these reproducing cells need their telomeres for cell division. Without their telomeres, our cells would be unable to reproduce at all.

Telomeres also play an important protective role in our cells. Their presence prevents important genetic material from being lost during cell division. They also serve as a "cap" on the ends of chromosomes, protecting chromosome ends from appearing broken. This is an important function, because broken chromosomes trigger unwanted biological responses.



Accumulation of DNA damage with age appears to affect the genome near to randomly, but there are some chromosomal regions, such as telomeres, that are particularly susceptible to age-related deterioration (Blackburn et al., 2006), (Figure A). Replicative DNA polymerases lack the capacity to replicate completely the terminal ends of linear DNA molecules, a function that is proprietary of a specialized DNA polymerase known as telomerase. However, most mammalian somatic cells do not express telomerase, and this leads to the progressive and cumulative loss of telomere-protective sequences from chromosome ends. Telomere exhaustion explains the limited proliferative capacity of some types of in-vitro-cultured cells, the so-called replicative senescence, or Hayflick limit (Hayflick and Moorhead, 1961; Olovnikov, 1996).

Indeed, ectopic expression of telomerase is sufficient to confer immortality to otherwise mortal cells without causing oncogenic transformation (Bodnar et al., 1998). Importantly, telomere shortening is also observed during normal aging both in human and in mice (Blasco, 2007a).

Telomeres are bound by a characteristic multiprotein complex known as shelterin (Palm and de Lange, 2008). A main function of this complex is to prevent the access of DNA repair proteins to the telomeres. Otherwise, telomeres would be "repaired" as DNA breaks leading to chromosome fusions. Due to their restricted DNA repair, DNA damage at telomeres is notably persistent and highly efficient in inducing senescence and/or apoptosis (Fumagalli et al., 2012; Hewitt et al., 2012).

Telomerase deficiency in humans is associated with premature development of diseases, such as pulmonary fibrosis, dyskeratosis congenita, and aplastic anaemia, which involve the loss of the regenerative capacity of different tissues (Armanios and Blackburn, 2012). Telomere uncapping and rampant chromo- some fusions can also result from deficiencies in shelterin components (Palm and de Lange, 2008). Shelterin mutations have been found in some cases of aplastic anaemia and dyskeratosis congenita (Savage et al., 2008; Walne et al., 2008; Zhong et al., 2011). Various loss-of-function models for shelterin components are characterized by rapid decline of the regenerative capacity of tissues and accelerated aging, a phenomenon that occurs even in presence of telomeres with normal length (Martinez and Blasco, 2010).

Genetically modified animal models have established causal links between telomere loss, cellular senescence, and organismal aging. Thus, mice with shortened or lengthened telomeres exhibit decreased or increased lifespans, respectively (Armanios et al., 2009; Blasco et al., 1997; Herrera et al., 1999; Rudolph et al., 1999; Toma' s-Loba et al., 2008). Recent evidence also indicates that aging can be reverted by telomerase activation. In particular, the premature aging of telomerase-deficient mice can be reverted when telomerase is genetically reactivated in these aged mice (Jaskelioff et al., 2011). Moreover, normal physiological aging can be delayed without increasing the incidence of cancer in adult wild-type mice by systemic viral transduction of telomerase (Bernardes de Jesus et al., 2012). In humans, recent meta-analyses have supported the existence of a strong relation between short telomeres and mortality risk, particularly at younger ages (Boonekamp et al., 2013).

#### **Information of Telomerase**

Some cells have the ability to reverse telomere shortening by expressing telomerase, an enzyme that extends the telomeres of chromosomes. Telomerase is an RNA-dependent DNA polymerase, meaning an enzyme that can make DNA using RNA as a template.

For telomerase to be functional, the enzyme binds to a special RNA molecule that contains a sequence complementary to the telomeric repeat. It extends (adds nucleotides to) the overhanging strand of the telomere DNA using this complementary RNA as a template. When the overhang is long enough, a matching strand can be made by the normal DNA replication machinery (using an RNA primer and DNA polymerase), producing double-stranded DNA. The primer may not be positioned right at the chromosome end and cannot be replaced with DNA, so an overhang will still be present. However, the overall telomere length will be greater.



At the leading edge of cancer research, scientists are currently looking at ways to help the immune system identify and target malignant cells by way of their telomerase expression, leaving normal cells unharmed. In one clinical trial, 50 patients with advanced prostate cancer were vaccinated with immune cells that could do just that. All patients with detectable levels of circulating tumour cells showed declines ranging from six to a thousand fold.

Another approach uses oncolytic viruses to attack telomerase-expressing cells. These are genetically engineered viruses that specifically infect and destroy cancer and other mutated cells by penetrating their membranes and replicating inside them. The replication is triggered by the presence of telomerase.

#### **Purpose of the Research**

The evidence that activation of telomerase is necessary for most cancers and other major diseases arising from cellular aging to thrive is strong. Indeed, some scientists believe that telomerase activation is the main pathway by which cancer cells become immortal, that is, able to reproduce forever without limits. Cancer cells generally need to acquire four-to-six mutations to become malignant. On average, a cell with a mutation would need to expand to at least a million cells (20 doublings) before it had a chance for another rare mutation to occur. If a cell can divide 30 to 80 times, pre-malignant cells can only acquire one-to-three mutations before they stop dividing. Replicative aging is thus a barrier against the formation of malignant cancer cells. Thus, say researchers, telomerase activation is necessary for most, but not all, cancers and major life-threatening diseases to grow.

Based on the award-winning research carried out by Dr. Jaw-Ji Yang and his team since 2006, prostaglandins are formed from arachidonic acid through the activities of cyclooxygenase and subsequent downstream enzymes. Two closed related forms of cyclooxygenases were discovered, identified as  $COX_1$  and  $COX_2$ , and both isoenzymes can transform arachidonic acid into prostaglandins, despite differing in their physiological roles.  $COX_1$  is the constitutively expressed enzyme, and on the other hand,  $COX_2$  is an inducible form and is expressed in response to growth factors or physiological stimuli as well as inflammatory resultant in the synthesis of prostaglandins, which mediate pain and support the inflammation process. Furthermore,  $COX_2$  also plays a role in angiogenesis among certain cancers and in the development of Alzheimer's Disease (AD), according to recent studies indicating that  $COX_2$  is expressed abundantly in these diseases.

Studies also suggest that  $COX_2$  inhibitors could effectively reduce the risk of developing Alzheimer's Disease. Recent studies demonstrating that overexpression of  $COX_2$  is associated with the development of cancers and a rise of  $COX_2$  levels is a common finding of cancer formation.  $COX_2$  inhibitors, such as non-steroidal anti-inflammatory drugs (NSAID's), embody anti-cancer effect and also are able to prevent cancer development according to numerous clinical therapy studies. Therefore, there is new hope to treat or prevent cancers through the inhibition of  $COX_2$  functions or decreasing  $COX_2$  protein expression levels. (Mazhar, Ang et al. 2006) Nowadays, despite many  $COX_2$  inhibitors have been discovered, it became a mission to search for and locate natural  $COX_2$  inhibitors existence in plants.

After many in-depth studies spanning close to a decade, it was discovered that five out of more than 500 DNA genetic variations of Boehmeria Nivea Extract (BNE) could effectively decrease  $COX_2$  protein expression levels in cancer cell lines. BNE is a wild herb first documented 4,000 years ago in the Emperor's Guide for Herbal Remedies for curing diseases related to the heart, lungs and intestines. Combined with molecular scientific approach, BNE suppresses the production of signal molecule related to tumour cells growth, such as  $\beta$ -catenin, and decrease the activities of growth regulatory proteins, such as phospho-AKT. These data suggest that BNE could play roles to inhibit tumour cells growth. We performed the soft agar assay and proved that BNE could inhibit tumour cells growth in an anchorage-independent growth condition. One genetic variation of the BNE DNA is shown below.



In this study, it was also discovered that BNE decreases the protein expression levels of P-glycoprotein (P-gp), an efflux pump, which is located on cell membrane to regulate multidrug resistance (MDR) and recognizes different chemotherapeutic agents and transports them out of membrane. Therefore, BNE has great potential to attribute its action on P-gp protein expression levels and to reduce drug resistance in cancer cells. Overall, we found that BNE could effectively decrease inflammation, inhibit cancer cell growth as well as reduce P-gp proteins mediated MDR. It is therefore that BNE is effective in the prevention and treatment of cancer in additional to overall cellular-aging. The below figure highlights a specific test where oral cancer cell line, KB, treated with BNE at different concentrations over time and apoptotic cells were observed.



# Information on Telomeres Malfunctioning

As mentioned above, telomeres serve as protective caps on the ends of chromosomes. From time to time, defects in this capping function can occur, and may be related to the end loops unravelling. The capping function can be lost if the telomere becomes too short or is deleted entirely, or if a telomere protein is missing or mutated. The body perceives uncapped chromosomes as broken ends. These broken DNA ends spark one of two repair mechanisms.

The first is called *homologous recombination* (HR), in which a broken DNA end is fixed by copying the sequence from a similar, unbroken DNA molecule. In some situations, recombination between malfunctioning telomeres can be frequent enough to keep cells alive and keep telomeres very long.

In a second mechanism, the broken ends of two chromosomes with telomere failure simply fuse together. This is called *non-homologous end joining* (NHEJ). Under most circumstances, this end joining is an effective and useful DNA repair process. With malfunctioning human telomeres, however, it can have devastating consequences.



If two different chromosomes are fused by way of telomere end joining, they cannot separate properly during replication. During cell division, a tug of war between the two daughter cells over the fused chromosome usually results in it being broken into two uneven pieces. Each daughter cell then inherits a chromosome with missing or extra DNA and has one (newly broken) end missing a telomere. That end is free to potentially cause another round of chromosome fusion and breakage. Through this mechanism, uncapped telomeres can wreak havoc, killing cells and rendering those that survive genetically abnormal.

In addition to causing DNA repair in the form of recombination or end joining, broken DNA ends or uncapped telomeres can trigger other cellular responses. Because broken chromosomes are a severe form of DNA damage, cells are often exquisitely sensitive to their presence. Unrepaired broken DNA ends will often trigger cellular growth arrest, thereby preventing any cell division as long as the broken ends persist. In some human cells, broken DNA ends can trigger cellular suicide, a process known as apoptosis. Because short telomeres are more common in older cells, telomere capping problems may be related to the development of cancer and other age-related diseases.

#### **Type of Research Intervention**

The shortening of telomeres has been associated with a number of diseases, many of them age-related. Shortened telomeres have been identified in aging skin, blood, and cardiovascular cells. And the cells of people with a variety of diseases—from atherosclerosis to hepatitis to blood disorders—have been found to have shortened telomeres.

In addition, COX<sub>2</sub>, an intracellular regulatory protein, and AKT / protein kinase B (PKB) is also involved in the biological response of cells, including cell growth, division and survival. Phosphorylated in position 308 and 473 plays a role for the regulation AKT protein activity, and the phosphorylation in 308 position plays a more important role in the development of cancer. Lots of studies indicate that AKT proteins are overexpressed in a large amount of cancer cells (Gallay, Dos Santos et al. 2009), therefore, AKT could be a target for immune system and anti-cancer therapy. Amongst these, we employed BNE to block mutated cells growth, and we found this product can effectively inhibit a variety of cancer cell growth, including oral cancer, liver cancer, lung cancer, osteosarcoma, colorectal cancer, and other cancer cell lines. BNE works on cancer cells through pleiotropic mechanisms, including the inhibition on the inflammatory COX<sub>2</sub> proteins, cancer development regulation protein,  $\beta$ catenin, cancer cell survival protein, AKT, anti-apoptotic protein, GRP78, and invasion associated protein, MMP9. Beside cancer, chronic inflammation results in many such as immune, cardiovascular and nerve diseases are applicable. Since BNE can inhibit COX<sub>2</sub>, therefore, we infer BNE can be applied to prevent these diseases.



#### Information on the Program

Through completed research from Programs 1.0 and 2.0, Program 3.0 for telomeres rejuvenation purposes will consist of oral intake of three types of capsules on a daily basis.

To reduce the probability of telomeres malfunctioning and to increase telomerase productivity, supported by improved cellular-level health, three types of capsules are involved in this program. Each type of capsule and its formula is drawn from a different DNA composition of BNE, isolated with molecular science-based technology with 99.2% and above genetic specificity.

As mentioned before, there are more than 500 DNA genetic compositions associated with BNE, of which only five have proven so far (over the past decade of research) to innately carry medical-level telomeres-rejuvenating benefits. Given the source material is 100% grown in the wild across Asia, searching, harvesting, verifying, extracting and formulating

the qualified DNA composition at the aforementioned 99.2% accuracy is a costly (both time and money) exercise.

Each capsule seeks to improve on different bodily functions which assist cardiovascular health, mental capacity and immunity strength, which in combination suppresses telomeres malfunctioning and improves telomerase productivity. In combination, BNE inhibits the free radical oxidization of proteins, thereby supporting the defense against telomeres deterioration, and prevents accumulation of oxidized proteins,

# **Voluntary Participation**

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive will continue and nothing will change. If you choose not to participate in this program you have the right to do.

# **Procedures and Protocol**

# A. Program Procedures

Program 3.0 is focused on the concentration of BNE and synergistic herbs for results maximization.

Participants in the Program will be given capsules representing 82.5% concentration level (vs 100% which represent the level corresponding to the medicinal drug and its equivalent). This has, from results of previous studies, demonstrated to have best results in terms of optimization of cellular-level health across various age categories.

The team will do all in its power to look after you and the other participants very carefully during the program. If we are concerned about what the drug is doing, we will find out which changes need to be made. If there is anything of concern or that is unclear about the procedures, please reach out to the program operator.

# **B.** Description of the Program

Prior to the commencement of Program 3.0, a blood test must be taken either at our Institute or at a health check-up center in your local jurisdiction. A checklist of items to be tested for will be distributed to those who choose the latter option of carrying out the blood test in their home country.

After the blood test is completed, we ask for them to be scanned and emailed to our scientific team for a review by the medical team. Subsequently, upon the go-ahead is provided, an administrator of Program 3.0 will contact you and the capsules will be delivered to a predetermined address.

If doing the blood test review, the results demonstrate that your body has a system outside of cardiovascular, nervous and immune which require more immediate attention, you will be contacted to discuss the addition or substitute of one or two of the three capsule types.

At the end of Program 3.0, we ask that a second blood best covering the same checklist of items be conducted, and also scanned and emailed back to our clinical team for scientific research and benchmarking purposes.

## Duration

Program 3.0 will take place over 180 days in total. During that time, it will be necessary for you to take the capsules, on a daily basis, each morning on an empty stomach. If one daily intake is missed, please stagger the intake to complete the full cycle of 180 days. If for some reason more than three consecutive days are missed, please alert the program team. At the end of six months, Program 3.0 will be completed.

During this time, it is recommended that other chemically-based supplements be halted. Please reach out to the administration team on queries relating to a specific product.

## Side Effects

As the main ingredient, BNE is a 100% natural wild herb, found generally at high-altitude across Asia. In addition, the entire scientific formula for each capsule contains zero pharmaceutical component. There have been zero reports of any negative side effects from both Programs 1.0 and 2.0.

Nonetheless, it is possible that the capsules may cause some problems that we are not aware of. We will follow you closely and keep track of any unwanted effects or any problems. If it is necessary, we will discuss it together with you and you will always be consulted before we move to the next step.

#### Risks

By participating in this program, you are agreeing to consuming capsules with BNE, a natural wild herb, as the main ingredient. While the possibility of this happening is very low, you should still be aware of the possibility of an allergic reaction. As such, we suggest running an allergy panel test if any negative symptoms surface after the commencement of Program 3.0. We also strongly encourage cessation of intake of other herb-based supplements during the program. If there is any query, please contact the program team.

#### Benefits

Based on the results of Programs 1.0 and 2.0, on average 76% and 51% of subjects, exclusive and inclusive of those on placebo, experience a statistically significant improvement in their holistic health, in particularly in areas of circulatory system, nervous system and immune system. These three systems in combination is instrumental to promoting and maintaining cellular health. Mitochondrial restoration was also evident in many cases.



\* Based on 50 participants in a double-blind setting



\* Based on 100 participants in a double-blind setting

With Program 3.0 which itself has no placebo role, it is envisioned that the percentage of cellular rejuvenation will increase compared to the prior two programs.

#### **Financial Terms and Assistance**

Unlike super majority of programs which are designed by pharmaceutical companies and are meant to research on a targeted disease, this rejuvenation program is associated with regenerative medicine. It is hence neither eligible to receive any government or NGO grants nor sponsored by pharmaceutical companies, despite the potential impact of its findings in relation to cure of cancer and other major diseases.

With the financial patronage of Global Citizen Capital, 75% of the operating, research and development, legal and license costs associated with Program 3.0 has been covered.

All volunteers are asked to cover their individual share of costs for Program 3.0, which will be capped at no more than USD 500 per month, assuming 0% financial assistance.

Furthermore, with the sponsorship of the Asia World Anti-Aging and Well-Being Association ("AWAWA") and the Better Together Foundation, up to 100% financial assistance is offered for those who qualify based on income parameters. A separate form will be sent upon request for the application for financial sponsorship.

We solemnly express our gratitude for your contribution towards our team of scientists and their ongoing research into meaningful pro-active and pre-emptive healthcare.

# Confidentiality

With this telomeres-oriented research, something out of the ordinary is being accomplished. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no one but the researchers will be able to see it. It will not be shared with or given to anyone until the entire program is completed and information is prepared for scientific research purposes. At the end of the program, all individual-based data will be deleted.

# PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been responded and answered to my satisfaction.

I therefore consent voluntarily to participate as a participant in this research.

Print Name of Participant: \_\_\_\_\_

Signature of Participant: \_\_\_\_\_

Citizenship:

Country of Residence:

Date:

Day/Month/Year