
INNBC
Whitepaper
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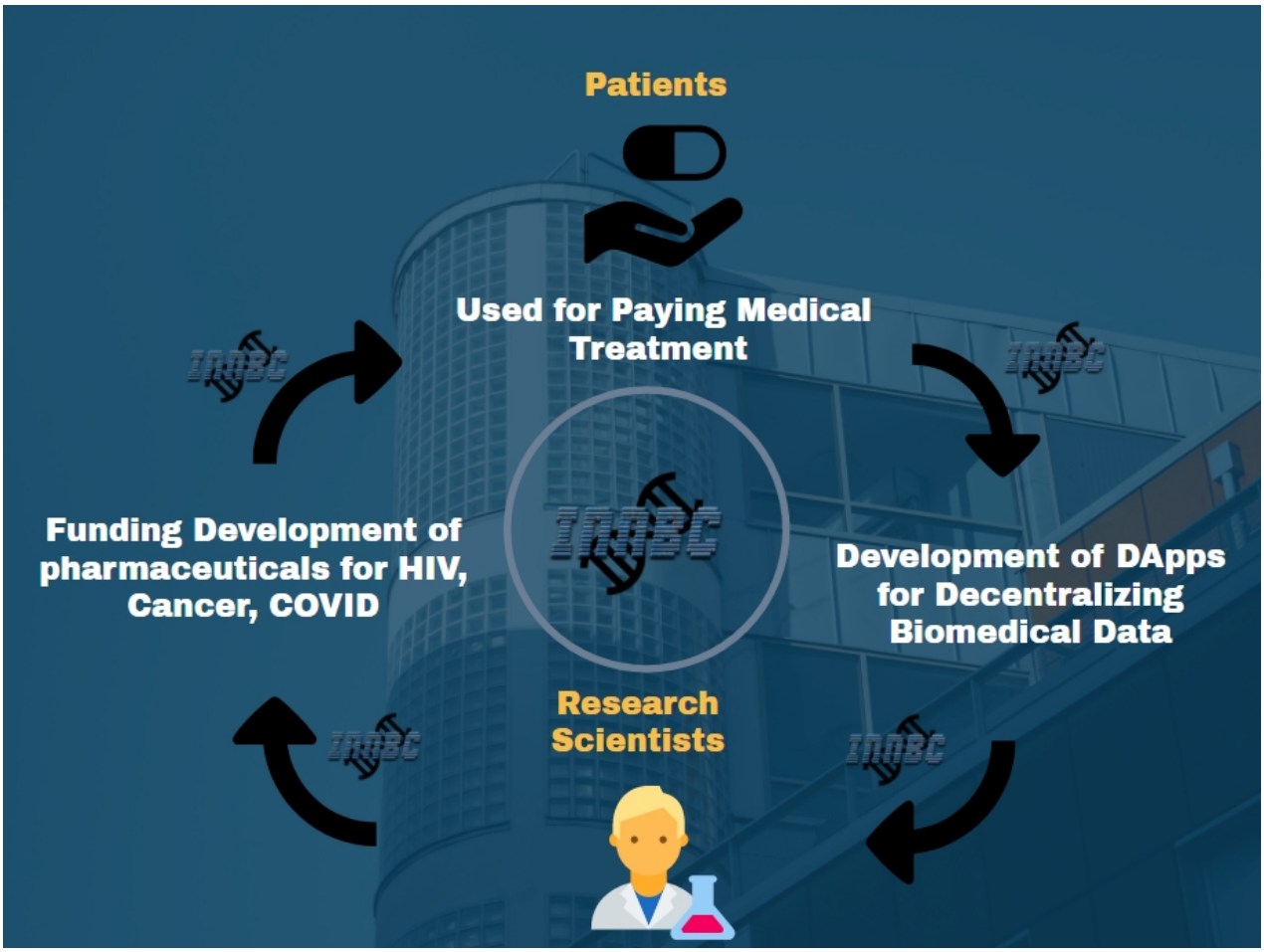
# INTRODUCTION

Innovative Bioresearch Ltd is a biotech company founded by Italian research scientist Dr. Jonathan Fior with the goal of bringing innovation to the field of HIV, cancer and regeneration research. The INNBC (InnovativeBioresearchCoin) token was issued in 2018 to support our biomedical research and to be used as a means of payment to access all our pharmaceutical products and services. As such, INNBC is the first token to decentralize biomedical research, from the funding aspect of the research, to data sharing, using blockchain technology to decentralize biomedical data. Such a process involves on one side the actual biomedical research to develop pharmaceuticals for diseases such as HIV, Cancer and more recently COVID, and on the other side the development of applications using blockchain technology (decentralized applications, Dapps) for storing and sharing on chain the data produced by research studies.

# TOKEN UTILITY AND ECONOMY




At its core, INNBC is meant to be used as a means of payment to access our pharmaceutical products. Therefore, by owning INNBC you own access to such products, with a token backed by actual pharmaceuticals. Accordingly, as a first step in the process, INNBC funds the actual biomedical research to develop novel pharmaceuticals for HIV, cancer and COVID, which are then accessed by the patients through the token. At the same time, INNBC also funds the development of decentralized applications that use blockchain technology for recording and sharing the data produced by the research studies on chain. This means that for the first time, we bring the peer reviewed scientific standard into crypto, as we publish all our work in peer reviewed scientific journals.

## INNBC DeFi-Science Model and Ecosystem

INNBC is the first token to combine DeFi (decentralized finance) and science, introducing, for the first time, a "DeFi-Science" model. In such a model, some supply is allocated for supporting development of pharmaceuticals for HIV, cancer, COVID, as well as development of decentralized applications for biomedical research. This is what, in turn, can really back the value of the token, besides speculation on the markets. As such, Innovative Bioresearch reserves the right to issue additional tokens to support the development of pharmaceutical products, as well as for traditional DeFi features such as staking and farming. Here, you would not just be farming a token, but actively contributing to "farming" actual drugs and therapies. Just by simply using our DApps, you are actively contributing to provide more exposure and visibility to the INNBC project, and therefore supporting our vaccine research. Isn't this amazing? This is something unprecedented in DeFi and crypto. We call this "DeFi-Science". Understanding the dynamics of the development of a pharmaceutical product is therefore extremely important before purchasing INNBC. INNBC did not have an ICO, the token initial distribution was to the participants of the bounty contests launched when we issued the token, after which INNBC was directly listed on the exchange markets where users are free to purchase the token. The token can be used right after purchasing, and all holders of INNBC are free to sell their tokens to users who need those for access to our platform.

**INNBC TOKEN TECHNICAL INFO**

Token name: InnovativeBioresearchCoin

Symbol: INNBC

Type: ERC20 Token

Token adress: 0xB67718b98d52318240c52E71A898335da4A28c42

Decimals: 6

Block Explorer: https://etherscan.io/token/0xB67718b98d52318240c52E71A898335da4A28c42

Along with INNBC, the main token, we later issued INNBCL (InnovativeBioresearchClassic), a sister bonus token that makes you elegible for additional INNBC airdrop and bonses, just like when we first listed INNBC on the global crypto exchange BigOne, and INNBCL token holders were rewarded with INNBC bonuses.

**INNBCL TOKEN TECHNICAL INFO**

Token name: InnovativeBioresearchClassic

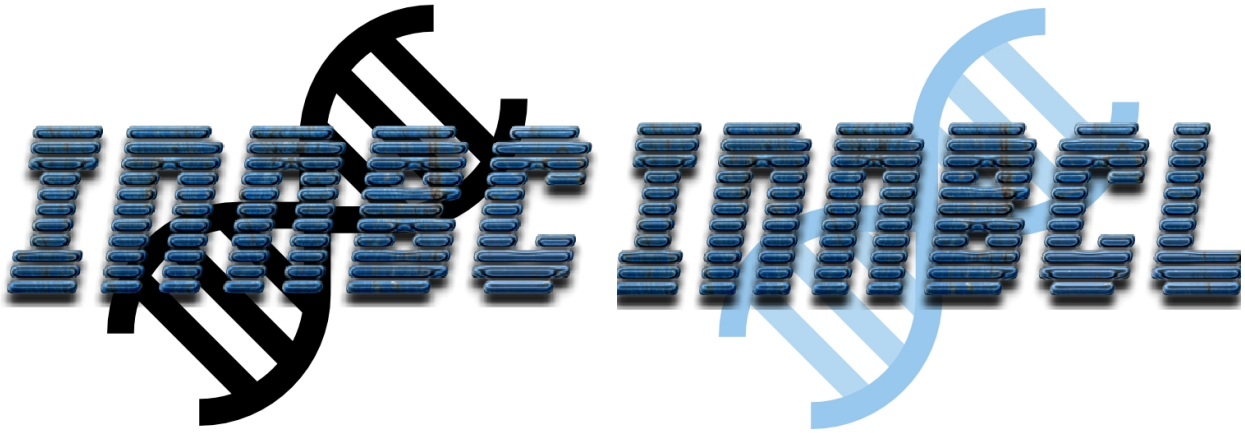
Symbol: INNBCL

Type: ERC20 Token

Token adress: 0x0Cc9FCCFF81252F4bd8C5c6b359B14ae2Ed851cf

Decimals: 6

Block Explorer: https://etherscan.io/token/0x0Cc9FCCFF81252F4bd8C5c6b359B14ae2Ed851cf



# INNBC DAPP, A REAL USE CASE IN SCIENCE

One of the goals of the project is to bring mass adoption of blockchain technology for science. This involves first the development of tools such as decentralized applications (DApps), providing utility and real use cases in biomedical research. When we started our study and research on which areas of scientific research could provide a suitable application for blockchain technology, we concluded that decentralization of scientific data is a very useful area, especially in terms of permanently recording and sharing the data using a blockchain. In fact, there are several specific features of blockchain technology that are very well suited for such a purpose:

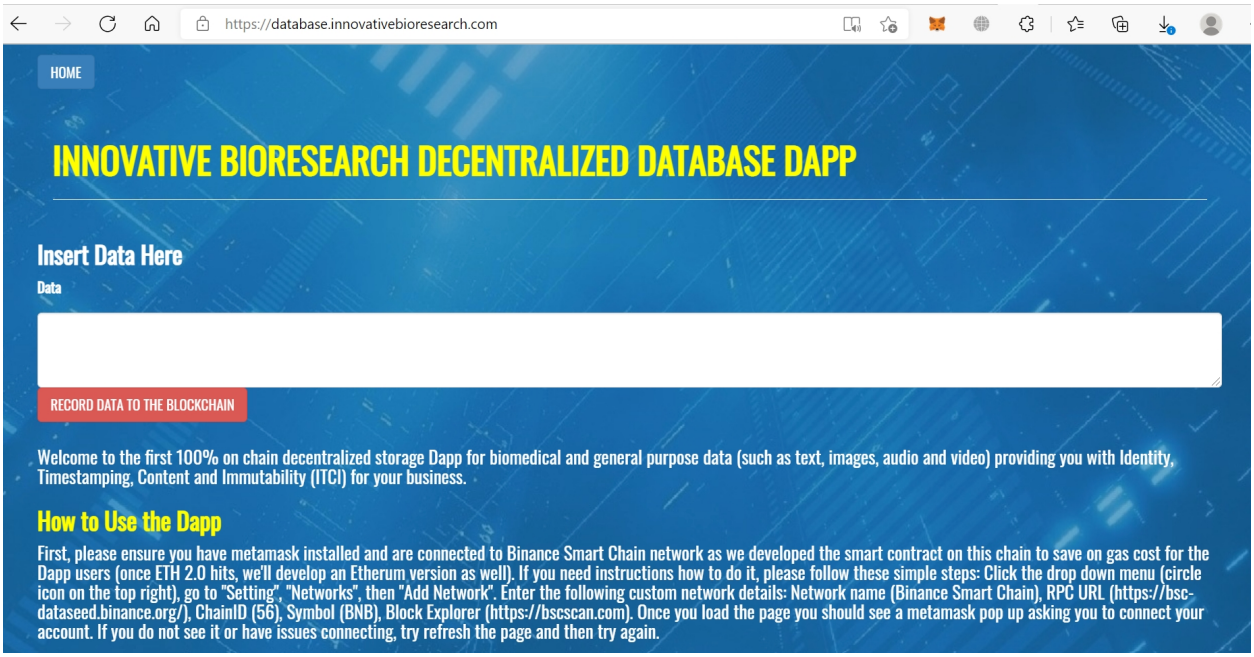
•**Immutability.** Scientific data need to be immutable. Once a study is peer reviewed and published, its data must be permanently stored and never altered. In the blockchain, all data is stored in every single node, never ceasing to exist, and always staying on the blockchain. It is immutability that gives the blockchain its openness and BFT (Byzantine Fault Tolerance).

•**Decentralization.** The blockchain is designed to be distributed and synchronized across networks, making data freely available to anyone. We believe that scientific data should be shared and not being hidden behind a firewall.

•**Security.** The kind of transactions that can be performed are strictly defined in advance and stored in the blockchain as “smart contracts”; this prevents fraudulent data from being added to the blockchain thus ensuring integrity of the database. By contrast, it would be much easier to compromise a centralized database.

•**Proof of Authorship and identity.** Say you make an important discovery and want an undeniable proof that you are the author. If you want to defend your work and claim in court to be the author, you must be able to prove it. This evidence can be difficult to provide. However, if you record the data on a blockchain, including a detailed description of your work, along with authorship information, the timestamp can prove that the data was generated at a certain point in time and have not been changed since. Such data recorded on the blockchain can legally represent an unambiguous reference to the author. A specific wallet can also be linked to the author and his institution, providing the author with a “digital identity” such as that only the transactions associated with that specific wallet would be considered legit data belonging to the author and his institution.

We developed the INNBC DApp to be a very pratical and straightforward tool for research scientists, accessible with no coding knowledge, featuring a simple, clean and intuitive front end UI (user interface) where users just need to paste their data as a text in the input field and press a button to store the data on chain.




The DApp is live and accessible at [https://database.innovativebioresearch.com/](https://database.innovativebioresearch.com/)

One of the most important features of the DApp is that all data is stored 100% on chain. We developed the first true on chain decentralized storage Dapp for biomedical research, which can also be used for general purpose data (such as text, images, audio and video) providing you with Identity, Timestamping, Content and Immutability (ITCI) for your business. What this means is that our Dapp has a wide range of applications in many different fields in addition to science. Below just a few examples:

•Application for Commercial Activities. Timestamping will allow you to record any relevant event for your business. Say for instance that you sold a product to a customer; you can record the event to the blockchain and include the tx as a QR code on the product itself as a proof of product authenticity and to keep track of the item.

•Application for Entertainment, Art and Software Development industries. Identity and Timestamping will protect the intellectual property of your work, providing you with proof of authorship. This is important for a large number of fields. For instance, it would work perfectly

well for NFTs where you could store your digital images on chain adding author information, instead than being stored on a centralized server as it currently happens. You could store a lower resolution version of the image or you could store it in different chunks in case of very large images.

•Application for Decentralized Messaging, News Releases, and Social Networking. Decentralization and Immutability provide a censorship resistant environment for posting content unlike traditional centralized platforms that can be controlled by the issuer (e.g., Twitter, Facebook) limiting your access to the platform, whereas this control does not exist in a decentralized platform.

We build this application on Binance Smart Chain initially due to lower gas fees, and we plant to launch an Etherum version as well once ETH 2.0 is released.

# INNBC HIV CURE RESEARCH

## SUPT1 CELL INFUSION THERAPY

This is an overview providing an introduction to SupT1 cell infusion therapy, our novel HIV therapy, currently in development by Innovative Bioresearch. HIV infection usually leads to a progressive decline in number and functionality of CD4+ T lymphocytes, resulting in AIDS development. As explained in Dr. Jonathan Fior's research papers [1–3], the HIV virus has a higher tropism for SupT1 cells than for primary CD4+ T cells. Several hypotheses have been proposed as an explanation, most notably the higher surface expression of CD4 and CXCR4 receptors in SupT1 cells. In addition, in vitro studies of HIV evolution show that persistent growth in the SupT1 cell line results in a less cytopathic virus with a reduced capacity for syncytium formation, a higher sensitivity to neutralization, improved replication in SupT1 cells and impaired infection of primary CD4+ T cells [4–6]. Accordingly, Jonathan Fior proposed the infusion of irradiated SupT1 cells as a cell-based HIV therapy to exploit the therapeutic potential of these phenomena [1–3]. The rationale behind this approach is that moving infection toward the inoculated cells should prevent infection and depletion of the patient's own CD4+ T cells and, therefore, AIDS. In such a strategy, SupT1 cells would act as a "decoy target" for the HIV virus to prevent CD4+ T cell depletion as well as to render the virus less cytopathic. As previously mentioned, in vitro studies of HIV evolution show that prolonged replication in SupT1 cells renders the virus less cytopathic and more sensitive to neutralization. Accordingly, replication of the virus in the inoculated SupT1 cells should also have a vaccination effect; that

is, the therapy should also induce the virus to become progressively less aggressive and harmful for the patient. The use of SupT1 cells as a decoy target for HIV has been investigated in vitro and in vivo, with interesting results [1,3]. In vitro data showed that, when primary CD4+ T cells are infected with HIV in the presence of SupT1 cells, the preferential infection of SupT1 cells can spare primary CD4+ T cells from infection and depletion. In vivo data in humanized mice showed that significantly lower viral replication (~10-fold) and potentially preserved CD4+ T cell frequency at Week 1 was scored in animals treated with SupT1 cell infusion. Of note, one animal exhibited a sustained decrease in HIV replication and CD4+ T cell depletion (no virus detected anymore at Weeks 3 and 4), a result that may hold the key to future HIV treatments. Given the urgent and global need for a cost effective cure for HIV, we believe that the millions of people infected by this terrible disease deserve highly innovative HIV cure research strategies, such as SupT1 cell infusion therapy.

***In summary, these are some of the potential therapeutic benefits of this cell-based treatment that go beyond what can be achievable with traditional antiretroviral therapy (cART):***

1)The vaccination effect. As previously mentioned, SupT1 cells have been shown to have a very powerful vaccination effect in vitro [4–6]. In this regard, in vitro studies of HIV evolution showed that upon prolonged replication in SupT1 cells, the X4 HIV-1 LAI virus evolves toward a less virulent phenotype with a reduced capacity for syncytium formation, thus losing the main cytopathic feature characterizing X4 strains, and most notably the virus adaptation to replicate in SupT1 cells results in gradually losing the ability to replicate in primary CD4+ T cells [4]. In addition, the variation to neutralization sensitivity after viral growth in tumor T cell lines has also been examined. Interestingly, one study reported that primary isolates that were initially resistant to neutralization acquired sensitivity to neutralization after continuous growth in tumor T cell lines, and that the sensitivity to neutralization progressively increased during the days of culturing [5]. Specifically, it was shown that after 14 days in continuous culture, 100 micrograms/mL of rsCD4 (recombinant soluble CD4) were needed to neutralize 1 TCID of primary isolate, while only 0.3 micrograms/mL of rsCD4 were needed to neutralize 1 TCID of the virus after 75 days in continuous culture. This means that there was a 300 fold increase in virus sensitivity to neutralization after prolonged replication in a tumor T cell line, which is really something remarkable. All these phenomena could therefore harbor a significant therapeutic potential that could be exploited with SupT1 cell infusion therapy to induce HIV infection to evolve into a more tractable state for therapy.

2)Potentially no organ toxicity; cART is a drug based treatment and as such is associated with organ toxicity because the drugs are metabolized by various organs. By contrast, SupT1 cell infusion is a cell-based treatment and there is no chemical substance injected into the body that needs to be metabolized, which could significantly improve the quality of the patient's life.

3)Be effective in patients in a terminal state of disease that developed drug resistant and very aggressive HIV strains. When a patient is treated with cART, the virus fights back because it strives to survive, which can result in the development of very aggressive and drug resistant HIV

strains, especially in the terminal stage of the disease and in such cases cART becomes ineffective. By contrast, SupT1 cell infusion therapy provides the virus with a permissive cell-line in which it can preferentially replicate, so that a peaceful coexistence between virus and host becomes possible, which could dramatically improve the patient's health as the virus infection progressively moves toward the inoculated SupT1 cells and the virus becomes increasingly less pathogenic for its host.

4)Possible association of the treatment with novel molecular compounds such as a Vif-inhibitor to act on HIV reservoirs. The HIV-1 Vif protein is essential for viral replication in primary CD4+ T cells but not in SupT1 cells [1]. Accordingly, pharmacologic inhibition of Vif could be combined with SupT1 cell infusion to further restrict viral replication to the inoculated SupT1 cells. Considering that APOBEC3G is expressed by different cell types, such as neuronal cells, astrocytes, and macrophages [2], pharmacologic inhibition of Vif may also have the benefit of acting on HIV reservoirs in the brain and other body areas. There are several molecules with promising anti-Vif activity currently being tested [2]. Similarly, other HIV-1 accessory proteins that are not essential for replication in SupT1 cells (e.g., Vpr, Vpu, and Nef [3]) may also be the target of pharmacologic inhibition. It is important to point out that these drugs would not affect virus replication in the inoculated SupT1 cells, and therefore in combination with SupT1 cell infusion therapy, there should not be development of drug resistance normally associated with drug based treatments.

5)A cost effective AIDS cure solution. Our mission is to provide a cost effective cure solution for AIDS. In contrast with traditional cell-based and gene-based therapies that make use of modified autologous cells and are therefore very expensive and often unpractical for a large scale application, using a standardized T cell line such as the SupT1 cell line should significantly reduce the treatment costs associated with SupT1 cell infusion therapy, allowing access to the therapy where access to traditional HIV therapies is restricted by economic and social limitations. The social and economical impacts of a low cost HIV cure solution would be enormous.

***Below some considerations with regard to potential issues:***

1)Safety. We take this issue very seriously and are committed to performing very rigorous preclinical research to ensure there is enough data on safety to obtain approval from regulatory agencies for human experimentation. In this regard, injection of irradiated tumor cells as a therapy is already performed in cancer vaccination. In such cases, irradiating the cells prior to inoculation has been shown to ensure treatment safety both in animal and clinical studies [7]. We used the same protocol used in cancer vaccination studies (i.e., 30 Gy of radiation dose for the cells), which resulted in safe in vivo inoculation in our animal study as well [3]. Specifically, all animals successfully survived the treatment and presence of SupT1 cells was almost undetectable at late time points, which means that irradiating the cells prior to inoculation efficiently prevented SupT1 cell replication. Furthermore, we infused high doses of cells (40 million SupT1 cells were infused weekly), which in a highly immunodeficient mouse strain

would rapidly lead to animal death in case of tumor development. Therefore, based on the clinical data we already have from cancer vaccination studies, and from the results of our first animal study, we believe that meeting the safety standards required for human trials is something feasible.

2)Rejection issues. Tumors can develop because tumor cells are able to evade immune recognition. For example, SupT1 cells do not express HLA-DR, which is an antigen highly associated with immune recognition [8]. Accordingly, given the tumoral nature of SupT1 cells, they should be significantly less immunogenic than normal cells and as such should survive in the patient long enough to provide a therapeutic effect. However, it is possible that the HIV virus will eradicate the cells faster and more efficiently than the immune system itself in any case.

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# INNBC CANCER AND REGENERATION RESEARCH

*The following article is a peer reviewed scientific paper written by Dr. Jonathan Fior and published in Journal of Cancer (available at http://www.jcancer.org/v05p0715.htm) representing our directions for developing novel cancer and regenerative therapies given that, as you will discover by reading this paper on the amazing salamander regeneration process and how it compares with human healing, cancer and regeneration can be considered two sides of the same coin…*

## Salamander Regeneration as a Model for Developing Novel Regenerative and Anticancer Therapies

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*J Cancer. 2014; 5(8): 715–719*

### Abstract

Among vertebrates, urodele amphibians are the only tetrapods with the ability to regenerate complex structures such as limbs, tail, and spinal cord throughout their lives. Furthermore, the

salamander regeneration process has been shown to reverse tumorigenicity. Fibroblasts are essential for salamander regeneration, but the mechanisms underlying their role in the formation of a regeneration blastema remain unclear. Here, I review the role of fibroblasts in salamander limb regeneration and how their activity compares with that of human fibroblasts. In addition, the question of whether salamander blastema tissue could induce regeneration and tumor regression in animals with a limited regeneration ability is discussed. A deeper understanding of these processes may lead to the development of novel regenerative and anticancer therapies.

*Keywords: salamander regeneration, wound healing, tumor progression, fibroblasts*

**Introduction**

Fibroblasts are prototypical mesenchymal cells responsible for synthesizing the extracellular matrix, thus preserving the structural integrity of connective tissues [1]. In addition, fibroblasts play a crucial role in wound healing and tumor development [1]; therefore, these cells are of great interest for the study of these processes. Among vertebrates, urodele amphibians are the only tetrapods with the ability to regenerate complex structures such as limbs, tail, and spinal cord throughout their lives [2]. However, this remarkable turnover does not result in a high incidence of tumor formation [3], suggesting that a tight control system is in place that prevents uncontrolled cell proliferation and therefore cancer.

A possible hypothesis for the origin of human cancer is that during the course of evolution, humans lost an advanced regeneration ability as well as the associated control system, resulting in a more permissive environment for cancer development. Interestingly, humans seem to retain a silent regeneration potential in the form of quiescent stem cells. For example, humans cannot regenerate cardiac tissue after myocardial infarction, despite the presence of adult cardiac stem cells [4]. One of the most striking differences between human and salamander healing is the nature of fibroblast activity after tissue injury. In contrast with human fibroblasts, salamander fibroblasts initiate a dedifferentiation program following injury. Fibroblast dedifferentiation is a crucial step for the formation of a regeneration blastema, a mass of undifferentiated proliferating cells responsible for the regeneration of complex structures such as limbs. Although other cell types contribute to blastema formation, fibroblasts appear to play a central role [5, 6]. Here, I review the role of fibroblasts in salamander limb regeneration and how their activity compares with that of human fibroblasts. In addition, the question of whether salamander blastema tissue could induce regeneration and tumor regression in animals with limited regeneration ability is discussed. A deeper understanding of these processes may lead to the development of novel regenerative and anticancer therapies.

**The Role of Fibroblasts in Salamander Limb Regeneration**

The regeneration of a complex body structure like a salamander limb can be divided into three different phases [6]. Following limb amputation, in the first phase epithelial cells migrate to cover the exposed underlying tissue, forming an epithelium that closes the wound. This wound

epithelium then thickens, forming an apical epidermal cap (AEC). After wound closure, the regeneration process proceeds to the second phase, in which a population of undifferentiated cells migrates under the wound epidermis, leading to the formation of a structure called a blastema. Finally, in the third phase, the blastema grows in a proximodistal direction, regenerating the missing limb. Previous studies suggest that the most abundant cells in the blastema are connective tissue fibroblasts that have undergone dedifferentiation [5, 6]. The other identified cell types seem to act as lineage-restricted tissue-specific stem cells [5]; however, it was reported that muscle satellite cells may act as a multipotent cell population [7]. Interestingly, muscle tissue appears to originate from both resident muscle satellite cells and dedifferentiated muscle cells [5]. Thus, along with dedifferentiation of mature cells, activation of reserve stem cell populations may also contribute to blastema formation.

The underlying reason for the significant presence of fibroblast-derived cells in the blastema remains unclear, however. It was suggested that these cells act as multipotent stem cells and are therefore involved in the regeneration of various tissues [6]. In this regard, fibroblast-derived blastema cells may play important structural roles. Limb regeneration in adult salamanders likely involves precise repetition of specific embryonic developmental steps to perfectly regenerate a limb. This precise process may be achieved by creating an embryonic-like environment at the site of regeneration. Therefore, it is possible that dedifferentiated fibroblasts in the blastema may also function to generate embryonic-like scaffolds, thus providing structural support for embryonic-like limb development. Interestingly, the information required to recreate the limb pattern is carried by dermal fibroblasts. This was shown by experiments in which regeneration was induced in irradiated limbs that received a graft of unirradiated skin [8]. Because irradiation inhibits cell proliferation, cellular contribution from the limb is blocked; thus, the grafted skin provides the only source of cells for the blastema. Surprisingly, this results in regeneration of a muscleless but otherwise normally patterned limb [8]. An important characteristic of blastema cells is positional identity, which ensures the correct pattern of tissue growth. A blastema only regenerates structures that are distal to the amputation level; accordingly, only the missing structures are regenerated [8]. Retinoic acid treatment can affect this positional identity by proximalizing blastema positional values [8]. For example, retinoic acid treatment of a blastema formed at the wrist level can result in a whole new limb regenerating from the wrist (with duplication of structures that are proximal to the amputation level). HOX genes seem to be involved in positional identity [8]. In fact, analysis of HOX expression in human fibroblasts suggests that these cells play an important role in defining skin positional identity [9]. Therefore, fibroblasts may constitute a positional identity map of the whole organism; accordingly, fibroblast-derived blastema cells may carry the positional information, thus directing blastema differentiation into appropriate mature tissues.

Dedifferentiated fibroblasts are the earliest blastema cells [5]; therefore, resident fibroblasts may be the earliest target of signals that initiate blastema formation. There are two main sources of signals that drive the formation of a blastema and then maintain its growth: the

nerves and the AEC. Evidence suggests that fibroblast growth factors such as FGF-1, FGF-2, FGF-8, and FGF-10 are mediators of AEC signals [8], while FGF-2, glial growth factor 2 (GGF-2), substance P, tranferrin, and newt anterior gradient protein (nAG) act as mediators of nerve signals [8, 10]. Interactions between the AEC and the severed limb nerves are essential for blastema formation. However, once formed and innervated, a blastema can produce its own neural factors; in fact, a blastema is an autonomous, self-organizing structure [8]. Interestingly, if a limb is denervated and then amputated, it is possible to rescue limb regeneration by artificially inducing nAG expression; however, the regenerated limb is usually atrophic [10]. As previously mentioned, regenerated structures are always formed in a proximodistal direction, and the most distal structure of a blastema is the AEC. This suggests that beneath the AEC there is a reservoir of proliferating blastema cells, which are maintained in an undifferentiated state by signals from the AEC. It is thought that during limb regeneration, these cells give rise to blastema cells that are at more proximal levels [5]; however, the blastema cells that grow in these more proximal regions are not under the influence of AEC signals and therefore differentiate into mature tissues [5]. In fact, evidence suggests that AEC signaling is spatially restricted [5]. The stem cell-like plasticity of fibroblast cells seems to be the key to the advanced regeneration ability of salamanders. In this regard, the limited regeneration ability of mammals may reflect an evolutionary loss of this fibroblast characteristic. Although human fibroblasts do not have the ability to dedifferentiate and initiate blastema formation, they are essential for promoting and supporting cancer stemness [11]. This shows that human fibroblasts retain the ability to support cell dedifferentiation processes.

**Salamander Regeneration and Cancer**

Salamander regeneration involves dedifferentiation of mature tissue into a mass of stem-cell like cells, which then redifferentiate into appropriate mature tissues to perfectly repair the damage. This precise process can be repeated indefinitely without resulting in abnormal tissue growth, whereas in mammals constant repair of tissue exposed to chronic damage has been linked to cancer [3]. Thus, many authors hypothesized that salamanders are resistant to cancer formation, leading to the use of salamanders as an in vivo animal model for cancer studies. These experiments involved transplantation of frog tumor tissue [12] as well as the use of cancer-inducing agents such as chemical carcinogens [3]. In one study [12], frog renal tumor tissue was transplanted subcutaneously into the salamander forelimb and began to grow and invade tissues. The limb was then amputated through the tumor mass, leading to regeneration of a normal limb and disappearance of the cancer. Histological studies indicated that frog tumor cells in the regenerated limb reverted to a normal phenotype and generated different tissues, such as muscle and cartilage [12]. This important result suggested that the salamander regeneration process can reverse tumorigenicity. Another study showed that in salamanders, chemically induced epithelial cancer can spontaneously revert to a normal phenotype [13], further supporting the idea that regeneration can reverse tumorigenicity. As previously mentioned, salamanders may be able to create an embryonic-like environment at the site of regeneration, thus allowing precise repetition of specific embryonic developmental steps to

perfectly regenerate complex structures such as limbs. Considering that embryonic environments can reverse tumorigenicity by reprogramming tumor cells [14], the resistance to cancer of these animals may simply be a consequence of their regeneration ability rather than a specialized defense mechanism against cancer. In fact, administration of chemical carcinogens has been reported to induce cancer in regeneration-incompetent tissues but not in tissues capable of regeneration [3]. In particular, because the lens is regenerated from the dorsal but not the ventral iris, a few studies investigated tumor formation in these tissues after lens removal [3]. The results showed that administration of chemical carcinogens was able to induce formation of malignant tissue from the ventral but not the dorsal iris [3].

**Human Fibroblasts and Their Role in Wound Healing and Cancer**

Solid tumors have been described as “wounds that do not heal” [15]. In fact, wound healing and cancer share a number of common features, such as cell proliferation, angiogenesis, tissue remodeling, and a heavy involvement of fibroblasts. The physiological wound healing process can be divided into four different phases: hemostasis, inflammation, proliferation, and tissue remodeling [16]. The main function of the hemostasis phase is to stop bleeding, which is accomplished through the process of coagulation. Following wounding, the first response of damaged blood vessels is vasoconstriction, which is induced by different mediators, such as endothelin (produced by the vascular endothelium) and noradrenaline (released by sympathetic nerves) [17]. Next, blood contact with the exposed endothelial collagen triggers the coagulation process; platelets adhere to the damaged surface to form a plug that seals the vessel, and a fibrin matrix is deposited to further strengthen the platelet plug [17, 18]. The fibrin clot is not only important to stop blood loss, but also to provide a provisional matrix for granulation tissue formation and wound re-epithelization [17, 18]. In addition, activated platelets release growth factors and cytokines for the activation and recruitment of leukocytes, endothelial cells, and fibroblasts [18]. The main function of the inflammation phase is to clean and sterilize the wound; pathogens, cellular debris, and foreign materials are removed by phagocytic cells such as neutrophils and macrophages [17]. During this phase, mediators such as kinins, histamine, prostaglandins, and leukotrienes stimulate vasodilatation to facilitate the extravasation of circulating cells [17]. Neutrophils are mainly present during the inflammation phase and are then removed by apoptosis, while macrophages remain until wound healing is complete [17]. Macrophages play an essential role during the successive phases of wound healing, especially in supporting fibroblast activity though the release of important molecules such as transforming growth factor-beta (TGF-beta) [19]. Once the inflammatory response begins to subside, the proliferation phase of healing begins. Resolution of the inflammatory response is essential for successful healing [20]. The main function of the proliferation phase is to repair the damaged tissue; this starts with the formation of granulation tissue, which consists essentially of infiltrating cells (e.g., fibroblasts and macrophages), proliferating blood vessels, and loose connective tissue [21]. As previously mentioned the fibrin clot provides a provisional matrix for granulation tissue formation and wound re-epithelization. In particular, the fibrin clot is rich in fibronectin, which appears to be an important protein that supports the infiltration of

fibroblasts and keratinocytes [22, 23]. During the proliferation phase, fibroblasts infiltrate the wound and release matrix metalloproteinases (MMPs) to degrade the fibrin clot, allowing deposition of newly synthesized extracellular matrix [21]; this initial matrix is weaker than that of later stages, probably to facilitate angiogenesis and cell invasion. Specifically, the early matrix is rich in fibronectin and hyaluronic acid, while the later matrix is rich in collagens and proteoglycans [21]. Under the influence of factors such as TGF-beta, a portion of fibroblasts then acquire the myofibroblast phenotype, which is characterized by the expression of alpha-smooth muscle actin (alpha-SMA) [24]. Myofibroblasts greatly contribute to the synthesis of new extracellular matrix [25]. In addition, these cells generate contractile force to narrow the gap between the wound edges [25]. In vitro studies indicate that in fibroblasts, alpha-SMA expression enhances the generation of contractile force [26]. Increased contractile force appears to be a hallmark of scar formation. In fact, scarless wound healing in salamanders is characterized by the presence of a very small number of myofibroblasts in the wound [27], indicating a reduced need for wound contraction; by contrast, when macrophages are artificially depleted after wounding, which hampers salamander limb regeneration and leads to scar formation, an increased number of myofibroblasts is observed in the wound [28]. Interestingly, scarless wound healing in mammalian fetuses is also characterized by an evident lack of myofibroblasts [29, 30]. At the end of the proliferation phase, myofibroblasts undergo apoptosis and are cleared by macrophages, leading to scar formation [31]. The final phase of wound healing is tissue remodeling, which aims to maximize restoring of the pre-existing tissue [17]. In this phase, fibroblasts continue to remodel the extracellular matrix, and the duration of this process depends on the type of wound [18]. The healed tissue can usually regain approximately 80% of its original strength [17, 18].

In contrast with physiological wound healing, a process at the end of which myofibroblasts undergo apoptosis and are cleared from the healed tissue, in cancer the myofibroblasts present in the tumor stroma are maintained in a state of persistent activation by the tumor [32]. These cells in the tumor stroma are called cancer-associated fibroblasts (CAFs) [32]. Activated CAFs support tumor growth by secreting important molecules such as growth factors, cytokines, and proteases; the reciprocal interplay between CAFs and tumor cells forms the basis for tumor progression and metastasis. Among the tumor-supporting molecules produced by CAFs, TGF-beta, stromal cell-derived factor-1 (SDF-1), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and proteases such as MMPs play a crucial role in tumorigenesis [32]. TGF-beta appears to increase the levels of CXCR4 expression in tumor cells, thus enhancing tumor cell sensitivity to SDF-1, a growth factor that specifically binds to the CXCR4 receptor [33]. However, TGF-beta has also been reported to inhibit tumor growth, while at the same time promoting metastasis [34]. HGF promotes invasion by binding to c-MET, a tyrosine kinase receptor typically expressed by epithelial-derived tumors such as esophageal squamous cell carcinoma [35]. VEGF promotes angiogenesis, an essential process that provides oxygen and nutrients to the tumor [36]. FGF has been shown to be associated with cancer progression in several experimental models. For

example, binding of FGF-2 to its receptor activates the progesterone receptor in mouse mammary tumor cells, thus promoting tumor proliferation [37]; in addition, FGF-2 stimulates proliferation of human breast cancer cells as well [37]. MMPs cause proteolytic degradation of the extracellular matrix, allowing the tumor to grow and metastasize [38]. Furthermore, cleavage of the extracellular matrix by MMPs can cause additional release of tumor-supporting molecules such as VEGF [32]. In addition to providing tumor-supporting molecules, CAFs are thought to actively participate in the tumor metabolism. Specifically, evidence suggests that CAFs are induced by the tumor to undergo aerobic glycolysis, thus providing energy-rich metabolites such as lactate and pyruvate, which are then used by cancer cells in the Krebs cycle [32].

**Conclusions and Future Directions**

Salamanders are a valuable animal model to study phenomena such as cancer and regeneration. The ability of salamanders to regenerate tissue provides a model for regenerative medicine. The ability of salamanders to reverse tumorigenicity can help us understand how to manipulate the biological conditions that cause and maintain cancer. Considering that signaling pathways involved in regeneration may be highly conserved among all vertebrates, an interesting question is whether salamander blastema tissue could induce regeneration and tumor regression in animals with limited generation ability. However, considering mammals as potential hosts, there are a number of possible limitations. A first issue is that host body temperature will probably dictate whether salamander blastema cells can successfully grow in the host. However, it may be possible to engineer blastema cells to grow at different temperatures, while initial studies could be conducted using ectothermic animals such as frogs as hosts. A second issue is the host immune system reaction against the transplanted tissue. However, this problem may be addressed by using immunosuppressive agents. Another vital question is whether host tissues can support the regeneration process of a salamander blastema. Interestingly, blastema autografting and homografting experiments show that, once developed, a blastema can act as an autonomous, self-organizing structure [8]; thus, a xenotransplanted blastema may successfully grow, provided that it can rely on the host tissues for nutrients. Furthermore, addition of the nAG protein may facilitate the process. However, using an already developed blastema poses the additional problem of whether the regenerated limb will be a salamander limb, a normal limb, or a chimeric limb. This is a crucial aspect because the host immune system may reject the new limb. In this regard, an alternative could be to induce blastema formation directly in the host. Considering their essential role in blastema formation, salamander fibroblasts may be able to initiate blastema formation at the site of the host tissue wound, resulting in a blastema composed mainly of undifferentiated host cells. Furthermore, bone marrow-derived cells could act as a source of fibroblasts for wounds and tumors [39]. Therefore, it may also be worthwhile to investigate xenotransplantation of engineered salamander bone marrow stem cells as a therapeutic strategy for inducing a salamander-like regenerative and anticancer response.

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**Competing Interests**

The author has declared that no competing interest exists.

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**HOW WE OPERATE**

For research projects, Dr. Jonathan Fior works as PI (principal investigator), conceiving the experiments and writing the experiment protocol. The work is then commissioned to a Contract Research Organization (CRO), which physically performs the experiments. Jonathan Fior then supervises all aspects related to the research communicating closely with the CRO. Once the experiments are completed, he analyzes the results and writes a scientific paper, which is published in a peer reviewed scientific journal. This means that although our team is not a large team, we actually have companies with 100+ people working for us. For example, for our HIV study in humanized mice we used a state-of-the-art CRO company such as AXENIS, a spin-off of the Institut Pasteur (Paris, France), which has now been acquired by Genoway. This way we can keep a small, yet strong and great, team. We only publish on open access scientific journals as we believe in free information and don't want our data being hidden behind a paywall. For our cryptocurrency, we are also working with some very high profile personalities of the blockchain industry as advisors.

**CORE TEAM**


Dr. Jonathan Fior is a research scientist specialized in the field of virology, immunology, cancer and regeneration*. He founded Innovative Bioresearch Ltd and conceived SupT1 cell infusion therapy, a novel cell-based therapy for HIV that uses SupT1 cells as a decoy target for HIV-1 to prevent CD4+ T cell depletion as well as to render the virus less cytopathic. In addition to his expertise in science, Jonathan Fior has advanced coding skills as a blockchain developer, as well as a great financial competence being a successful and experienced stock trader.

***Jonathan Fior's publications***

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Enrico Durante is an experienced marketer specialized in Management, Growth Hacking, Business Development, Marketing, and blockchain knowledge. One of his strongest qualities is that he always puts myself in the client's shoes. Every project has its own target audience with their needs, expectations, taste, etc. When starting a project, he always takes his time to carefully plan, research and experiment, before kicking off with the final strategies to work. He also operates locally to provide direct assistance to Italian commercial activities using INNBC as a means of payment; you can see him in action in this video filmed in one of the largest construction companies in Messina, Italy, accepting INNBC as a means of payment.


Alessandro Gatti is a legal expert and he ensures that everything we do is in accordance with the law.


Michael is our strong and hard working community manager, doing his best to also moderate our very active Telegram group (https://t.me/innovativebioresearch), which can get very wild sometimes!

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**RISK FACTORS**

The purchase of INNBC token (hereinafter in this article “Risk Factors” referred to as the "Token" or "Tokens") may be associated with a high degree of risk. To protect the interests of Tokens’ potential purchasers, the Innovative Bioresearch (hereinafter in this article “Risk Factors” referred to as the "Company") team conducted an analysis of such potential risks and outlined the result of this analysis in this chapter of the Whitepaper. IMPORTANT: THE LIST OF RISK FACTORS DESCRIBED BELOW IS NOT EXHAUSTIVE. IN ADDITION TO THE RISKS DISCLOSED IN THIS WHITEPAPER, THERE MAY BE EXISTING OTHER RISKS WHICH THE COMPANY'S TEAM AT

PRESENT CAN NOT REASONABLY FORECAST. These risks can materialize in other forms of risk than those specified here. Prior to acquiring Tokens, each potential Token purchaser is advised to carefully review all the information and assess the risks of such purchase, including but not limited to, the risks set forth in this Whitepaper and to decide upon purchase of Tokens based on such assessment.

**1. Technical and technological risks:**

1.1. Risks of the blockchain. Tokens are released on Ethereum blockchain. In this regard, any malfunction of the Ethereum protocol may lead to a restriction in the use of Tokens, and / or to the fact that Tokens or the platform will function in an unforeseen manner.

1.2. Risk of hacker attacks on the platform, smart contracts, or Tokens. Tokens can be expropriated and / or stolen, by hacking Tokens, or otherwise. Hackers or other groups or organizations may attempt to intervene in a smart contract or Tokens in various ways, including, but not limited to, virus attacks, DDOS attacks, concerted attacks, network attacks, and denial of service attacks, and others. In addition, since the Ethereum platform is based on open source software, there is a risk that Ethereum smart contracts may contain intentional or unintentional errors or shortcomings that could adversely affect Tokens or lead to loss of Tokens, or loss of access or control Tokens. In the event of such an error or weakness of the software, there can be no remedy, and tokens owners are not guaranteed any compensation or compensation.

1.3. Risk of hacker attack on the computer of tokenholder, or loss of passwords / of private keys. Purchased Tokens can be stored by the tokenholder in her\his digital wallet or safe, for which a password, a digital key or a combination of digital keys is required. Accordingly, the loss of the necessary keys associated with such digital wallet or safe, can lead to loss of access to Tokens. In addition, any third party that gets access to such passwords and / or private keys (by way of getting (through hacking, or negligence of tokenholder) access to login credentials of tokenholders' hosting-wallet, or otherwise), will be able to use Tokens of the tokenholder. Company assumes no liability for such losses.

1.4. Risk of using new technologies, and changes in technology in the future. Tokens and blockchain are fairly new and relatively untested technologies. Although at the moment they have largely proven their efficiency, reliability and security, there is no guarantee that in future these technologies do not fail in any way. Further, as technological progress develops, flaws can be found in these technologies, which flaws will prevent their functioning in the way that they function at the moment.

Finally, there is no guarantee that these technologies will be compatible with any new technologies invented in future. In the event of such incompatibility, use of Tokens and blockchain can be found unreasonable and stopped.

1.5. Risk of incompatibility of the cryptowallet service. An electronic cryptowallet or wallet service provider that tokenholder has chosen \ will choose for obtaining and storing Tokens, must be technically compatible with Tokens. Failure to comply with this condition may lead to the fact that the tokenholder will not be able to get access to her\his Tokens. Tokenholders must independently determine the fact of the compatibility of the cryptowallet she\he registered, with the Tokens. Company assumes no responsibility for any errors related to wrong determination of the above fact.

**2. Regulatory Risks:**

2.1. Risk of regulatory uncertainty. Regulatory status of cryptographic tokens, digital assets and blockchain technology, is unclear or not defined in many jurisdictions. It cannot be excluded that such technologies, and, in particular, Tokens, will in future become subject to one or more (adopted or new) interpretations of laws (or other regulations), court judgments, or actions by various regulatory bodies around the world, including, but not limited to, the imposition of restrictions on the use or possession of digital tokens, such as Tokens. Such changes can adversely affect Tokens in various ways, including, for example, by determining that Tokens are regulated financial instruments that require registration or compliance with other legal requirements and procedures. Company may stop distributing Tokens, developing a platform or terminating operations in a particular jurisdiction if the actions of regulatory authorities of the relevant jurisdiction make it illegal or not commercially viable to proceed.

2.2. Risk of inability to obtain, maintain or renew licenses and permits. As of the date of Tokens sale, there are no statutory requirements requiring Company to obtain any licenses and permits necessary for the sale of the Tokens, but the risk that such legislative requirements may be enacted in the future cannot be ruled out. In this event, possibility of sale and further use of Tokens will depend on the procedure of issuing such licenses and permits, and on compliance with their terms. We cannot exclude that requirements of the law will be technically or economically unachievable for Company. Company may stop distribution of Tokens, develop a platform or terminate operations in a particular jurisdiction in the event of economic, technological or other inability to obtain the required licenses or permits under such jurisdiction.

2.3. The risk of governmental action. The industry of blocking and reversing tokens is new, and simply by virtue of novelty can be subject to increased supervision and regulatory control, including investigations or enforcement actions. There can be no guarantee that the government will not study the activities of the parties. All this can be investigated, which in turn can have a significant negative impact on Tokens and / or platform development.

**3. Business risks:**

3.1. Risk of failure in development. It cannot be excluded that for various reasons, including but not limited to, for reasons of insolvency of business or technological strategies or business arrangements, technological problems, emergence of new technologies, etc., that the model

that Company developed and described in this Whitepaper, will not achieve the desired functionality, be inoperative, or work in a way different from what developers designed it for. Also, we cannot exclude the risk that for these or different reasons, development and implementation of the model can take longer than Company predicts at the moment, and when the model is ready, it will appear to be outdated and\or irrelevant.

3.2. Risk of insufficient implementation. It cannot be excluded that, for various reasons, including, but not limited to, for reasons of insolvency of marketing strategies, external constraints, or competitors' actions, the model developed by Company and described in this Whitepaper model may appear to be unpopular and\or unclaimed, lacking use and application.

3.3. Risk of dependence on third parties. Even after the launch, the model developed by Company and described in this Whitepaper will rely, wholly or partially, on third parties, for adoption and implementation of certain functions, as well as for continuing its development, maintenance and support. Though above-mentioned third parties are carefully selected by Company's team, there is no insurance or guarantee that these third parties will do their job properly, or otherwise meet users' needs, and this can have a significant adverse impact on the platform.

3.4. Risk of loss of cash. The project described in this Whitepaper, the model developed by Company, the platform being created, as well as any funds collected within the framework of the Token sale described, are not insured. In case of failure of the project for any reason, loss of functionality of the Token or platform, there is no private or public insurance representative to whom token holders can apply for reimbursement.

3.5. Risk of force majeure. In the future, there may be extraordinary circumstances that Company cannot reasonably anticipate or prevent and that may be subject to restrictions or impediments to the operation of the Company or Token platform. Company performance may be interrupted, suspended or delayed due to force majeure circumstances. For the purposes of this Whitepaper, force majeure shall mean extraordinary events and circumstances which could not be prevented by Company and shall include: acts of nature, wars, armed conflicts, mass civil disorders, industrial actions, epidemics, lockouts, slowdowns, prolonged shortage or other failures of energy supplies or communication service, acts of municipal, state or federal governmental agencies, other circumstances beyond Company's control, which were not in existence at the time of Whitepaper release.

3.6. Value of Tokens. Once purchased, the value of Tokens may significantly fluctuate due to various reasons. Company does not guarantee any specific value of the Tokens over any specific period of time. Company shall not be held responsible for any change in the value of Tokens.

**4. Other risks:**

4.1. Taxes. Token holders are solely responsible for determining if the transactions contemplated herein are subject to any applicable taxes whether in their home country or in another jurisdiction. It will be the sole responsibility of Token holders to comply with the tax laws of any jurisdictions applicable to them and pay all relevant taxes.

4.2. Disclosure of Information. Personal information received from Tokens holders, the information about the number of tokens owned, the wallet addresses used, and any other relevant information may be disclosed to law enforcement, government officials, and other third parties when Company is required to disclose such information by law, subpoena, or court order. Company shall at no time be held responsible for such information disclosure.

4.3. Risk of Insufficient information. Tokens are at a very early developmental stage and its philosophy, consensus mechanism, algorithm, code and other technical specifications and parameters could be updated and changed frequently and constantly. While the Whitepaper contains the up-to-date key information related to Tokens at the date of the Whitepaper, it is not complete nor is final and is subject to adjustments and updates that Company may make from time to time. Company is not in a position, nor obliged to report on every detail of the development of Tokens and other elements of the system presented by Company and therefore will not necessarily provide timely or full access to all the information relating to the Tokens, but will use reasonable efforts.