Molecules of *Discovering Novel Autophagy Activators* IP-NFT from Korolchuk Lab at Newcastle University

1. Executive Summary

This whitepaper presents an examination of the unique approach by VitaDAO, a decentralized autonomous organization, in allocating funding for longevity research through the sale of VITA-FAST Molecules, ERC-20 tokens on Ethereum representing fractions of the *Discovering Novel Autophagy Activators* Intellectual Property Non-Fungible Token (IP-NFT) funding the work of the Viktor Korolchuk lab at Newcastle University.

VITA-FAST tokens confer governance rights over IP generated by the Korolchuk Lab's longevity research funded by VitaDAO, offering a novel mechanism for public involvement in the decision-making processes. This approach is intended to support the longevity research activities of the Korolchuk Lab at Newcastle University.

The sale of VITA-FAST tokens represents an innovative approach to democratizing funding for scientific research. It demands thorough understanding and careful consideration of potential risks from potential VITA-FAST token buyers.

The purchase of VITA-FAST tokens inherently carries risks including the unpredictable nature of research outcomes which may impact the future value of the project, regulatory changes and uncertainties, and challenges related to intellectual property rights enforcement. The VITA-FAST token is issued in compliance with the laws of Switzerland.

The subsequent sections of this whitepaper will delve deeper into the various aspects to offer a comprehensive view of this research funding initiative.

2. Project Overview

VitaDAO owns the IP rights to research and development into activators of autophagy by the Korolchuk Lab at Newcastle University. The Korolchuk Lab research focuses on understanding the molecular mechanisms that control cellular homeostasis and aging. The lab looks to identify new therapeutic targets for age-related diseases and develop interventions to improve human healthspan. The lab is led by Dr. Viktor Korolchuk, a highly regarded researcher with extensive experience in autophagy and lysosomal biology. The lab is affiliated with Newcastle University and has collaborations with several international institutions.

VitaDAO initially supported the Korolchuk Lab via a Sponsored Research Agreement (SRA) to accelerate their research and expand their impact. The SRA was created to fund the lab's investigations into cellular mechanisms of aging and provide resources for drug discovery and development.

The sale and funds aim to continue to support the work initiated by Dr. Korolchuk and Newcastle University to advance the field of aging research by empowering people to govern the Korolchuk Lab longevity therapeutics development through the use of cryptographic tokens representing fractions of the Korolchuk IP-NFT.

3. Project Background

Aging is associated with a decline in the capacity of the autophagy pathway. Therefore, activation of autophagy is considered a promising therapeutic approach to combat aging and age-related diseases. While we are aware of how crucial autophagy is to the body, we still need to understand the mechanism through which autophagy becomes deficient with age, and how to rectify this.

Autophagy, colloquially known as a cell’s ‘waste-management’ system, is a highly selective biological process that is essential to cell metabolism and thus ultimately, survival. By sequestering, degrading, and recycling faulty cellular components, autophagy ensures that harmful components, such as dysfunctional organelles, misfolded proteins, defective DNA, and reactive oxygen species (ROS) are eliminated and/or prepared for re-use. When issues arise in the process, there are far-reaching consequences. Tissue deterioration due to cell dysfunction and death impacts our longevity, immunity, cardiac health, muscle function, metabolism, and brain function. Notably, impaired autophagy is strongly linked to neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS).

Dr. Korolchuk’s project focuses on autophagy activators, with specific attention to the lysosome. The lysosome is the vesicle that binds with the membrane-bound ‘junk’, and carries enzymes that serve to degrade said ‘junk’. Alzheimer’s and Parkinson’s have a very high incidence of lysosomal dysfunction, along with other lysosomal storage disorders such as Niemann-Pick Type C (NPC). For this study, NPC was chosen as the disease model as it is a monogenetic orphan disease, meaning that the biological causes are better understood, and any therapeutics

developed will have a much shorter path to drug approval compared to other complex diseases. Once the drug is approved, it has the potential to become a recognized therapeutic for more lysosomal storage disorders, and diseases that have a high incidence of lysosomal dysfunction, such as Alzheimer's and Parkinson's.

Previously, Dr. Korolchuk made contributions to the team that established the mechanism by which faulty autophagy leads to cell death:

1. Dysfunctional mitochondria accumulate within cells due to inadequate recycling caused by faulty autophagy.
2. Accumulation of reactive oxygen species (ROS) and DNA damage induces cellular stress.
3. Stress response pathways are activated (PARP & SIRT)
4. Depletion of NAD+ and NADH which are essential to cellular metabolic pathways.
5. Mitochondria lose their ability to generate ATP as they become depolarized.
6. Apoptosis (programmed cell death) begins.

To model lysosomal dysfunction, the Korolchuk Lab has used cells with a mutation in a lysosomal protein, Niemann-Pick C1 (Npc1 -/-), associated with said neurodegenerative diseases. When these cells are subjected to metabolic stress, they suffer cell death due to dysfunctional autophagy, providing an easy readout for an autophagy assay (cells dead/cells alive). To identify true autophagy activators, the Korolchuk Lab also uses cells that lack initiation of autophagy (Atg5 -/-) and are therefore not rescuable by autophagy inducers in parallel with Npc1 knockout cells. By testing the compounds in Atg5 -/-, one can differentiate between compounds that specifically activate autophagy (successful in Npc1-/-) and compounds that induce cell survival unrelated to autophagy (successful in Atg5-/-).

Approximately 4000 bioactive molecules and commercial small molecules will be screened. The naturally occurring molecules consist of a unique library of plant and animal compounds from the KVP lab. The bioavailability of the bioactive compounds is useful for drug translation.

The experimental plan is as follows:

1. Assay optimization and screening of compounds in cell survival assays (Atg5-/- vs Npc1-/-) and dose-response effects, using mouse embryonic fibroblasts (MEFs).
2. Luciferase-p62 clearance assay
3. Halo orthogonal assay
4. Selection and purchase of derivatives of lead series.
5. Screening of commercial derivatives in cell survival assays, p62 clearance, and Halo assay (as done in steps 1-3)
6. Synthesis of lead series at a Contract Research Organisation (CRO) and determination of the mechanism of action.
7. Structure-activity relationship (SAR) and validation in vitro autophagy assays.

Cell survival assay

The bioactive molecules and commercial small molecules will be screened in a cell survival assay to find which molecules can reactivate autophagy in NPC1 -/- cells. This assay also ensures that all molecules moved to further rounds of screening are not cytotoxic, and therefore not suitable for a therapeutic.

Luciferase-p6 clearance

Generation and optimization of Npc1 -/- MEFs with an inducible tet-on-tet-off expression of a luciferase-tagged autophagy flux reporter p62. Clearance of the p62 protein is only possible with proper autophagy. By quantifying clearance, the lab will be able to confirm that autophagy is indeed occurring, and at what level it occurs.

Halo-GFP-LC3 orthogonal assay

Generation and optimized Npc1 -/- cells stably expressing “traffic-light” EGFP-RFP-LC3 for high throughput high content screening. Automated image analysis gives information about the number of autophagosomes, the number of autolysosomes, as well as if autophagy has been activated.

For more information, view the public data room here.

4. Project Status and Future Plans

To date, Dr. Korolchuk and his team have generated data on thousands of compounds from an initial library using the assays described above. From the initial screen, several compounds have emerged as having potential autophagic properties. Lead series have been identified, a library of derivatives has been classified, and have been synthesized by external suppliers. The small molecules that have been screened have high chemical variability and no similarity to pre-existing autophagy inducers, representing a high possibility of novel IP.

At the time of publishing, the lab is screening the second generation of compounds that have been developed as lead series based on hits and is waiting on the delivery of additional chemical series of their leads. These derivatives will undergo the same screening process as before (cell survival, p62 clearance, and autolysosome quantification).

Once lead molecules have been identified, VitaDAO and Molecule will work with Newcastle University and Dr. Korolchuk's lab to start the process of drug translation. They will be required to consider things such as pharmacokinetics, target deconvolution, structure-activity relationships, scalability, and manufacturing.

Upon completion, further research in *in vitro* and *in vivo* models will need to be performed. Possibilities include using Neimann-Pick Type C patient-derived fibroblasts or CRISPR-Cas9 Npc1 knock-out cells to examine the efficacy of lead compounds in a human cell model. Induced Pluripotent Stem Cells (iPSCs) can be used to model disease progression in different cell types. Npc1-mutant mice and cats who display the same symptoms as humans with Niemann-Pick

Type C provide strong *in vivo* models to evaluate neurological outcomes as well as potential toxicity in large animal models.

From there, clinical studies would commence:

- Phase 1 Clinical Trials:
  Testing of the drug in a small group of healthy volunteers or patients (20-100) to evaluate safety, dosage, and side effects.

- Phase 2 Clinical Trials:
  For Niemann-Pick Type C, Orphan Drug designation could be sought at this stage, which may provide some benefits including tax credits for certain research and a waiver of the FDA user fee.

- Phase 3 Clinical Trials:
  In this stage, if successful in Niemann-Pick Type C, the drug could be tried for Alzheimer's disease as a future indication, although that would involve its own full set of clinical trials.

- FDA Review and Market:
  Once Phase 3 is complete, a New Drug Application (NDA) is submitted to the FDA. The FDA then reviews the application, which can take up to 2 years, but may be faster for drugs with a Breakthrough Therapy designation.

5. Introduction to Blockchain, NFTs, IP-NFTs, and Molecules

Blockchain is a decentralized digital ledger technology that allows for secure and transparent record-keeping of transactions. Since the publication of the Bitcoin whitepaper in 2008 by the pseudonymous person or group known as Satoshi Nakamoto, blockchain technology has gained significant attention and adoption and spawned a whole ecosystem of cryptocurrencies and blockchain technology, leading to new innovations and use cases beyond just currency.

Non-fungible tokens (NFTs) are a type of digital asset that uses blockchain technology to verify and authenticate ownership, uniqueness, and provenance. NFTs can be used to represent various forms of digital content, including art, virtual real property, scientific research and development (R&D) data, and intellectual property. They provide a new way to manage and protect intellectual property, allowing creators and owners to easily transfer ownership, establish authenticity, and control usage rights.

IP-NFTs (Intellectual Property Non-Fungible Tokens) are a specific type of NFT that represent intellectual property and data rights to scientific research. IP-NFTs attach legal contracts, such as sponsored research agreements, to smart contracts (NFTs) to create a new paradigm in the evolution of legal contracts for scientific research. As smart contracts on Ethereum, IP-NFTs can be permissionlessly transferred peer-to-peer, made composable with DeFi, used to distribute

governance to groups of stakeholders, built upon to unlock new ways to interact with and develop IP, R&D data, and NIPIA (Non-IP Intangible Assets, like trade secrets and publicity rights), used to empower crowd control of ethics in commercialization, and create unprecedented liquidity in IP markets through the development of this new asset class..

The first IP-NFTs were minted by Molecule for the VitaDAO community to register its longevity therapeutics IP and R&D data rights on Ethereum.

Now VitaDAO seeks to open up the development of an IP-NFT by minting new tokens in order to raise funds for additional scientific research and IP development. By distributing these new tokens, called Molecules, VitaDAO will distribute rights and responsibilities to the IP and R&D data of IP-NFTs to groups of token holders.

6. Tokenomics of VITA-FAST

These tokens, Molecules, represent membership in an IP pool containing the IP and R&D data attached to their parent IP-NFT.

Molecules of the Korolchuk IP-NFT are denoted by the token symbol “VITA-FAST.”

The rights of VITA-FAST token holders are governed by the Korolchuk-Free Association of Molecules (FAM) Membership Agreement. Those rights are:

- Governance: VITA-FAST token holders have the right to participate in the governance of the IP-NFT and its development. This includes voting on proposed licenses and uses of proceeds.

- Access to Intellectual Property: VITA-FAST token holders have access to relevant data and other Intellectual Property (IP) or future Intellectual Property arising from the development of the IP-NFT. This is necessary for due diligence and to govern the development of the IP-NFT intelligently. However, this does not grant any license to the IP.

- Duty of Care: VITA-FAST token holders have a Duty of Care to honor, support, and adhere to the terms and conditions of the Korolchuk FAM Membership Agreement, including any governance agreement made pursuant to it.

- Confidentiality: VITA-FAST token holders must not, without consent, use or disclose any confidential information or IP for any purpose or attempt to sell or register any Confidential Information, IP, or R&D data rights developed through participation in the IP pool.

A total of 1,000,000 VITA-FAST tokens will be minted using the Korolchuk IP-NFT.

10% of VITA-FAST tokens (100,000 VITA-FAST) will be sold to a maximum of 499 participants who are VITA tokenholders of VitaDAO, with the VITA-FAST tokens purchased in the sale vesting over 2 months with a 2 month cliff.

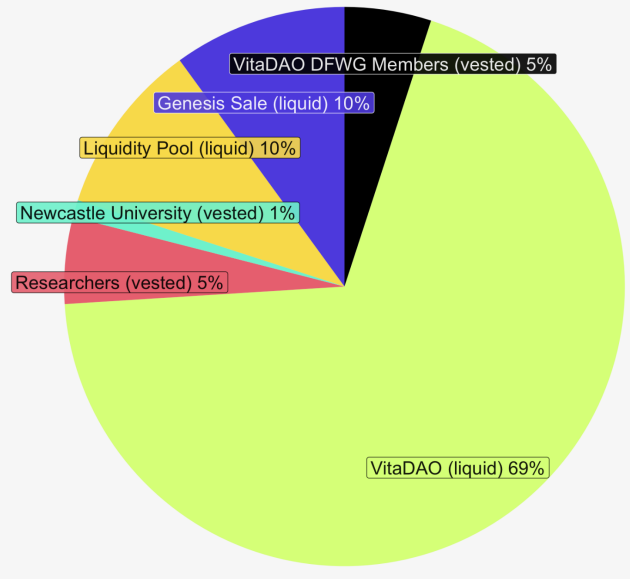
VitaDAO will retain 69% of the VITA-FAST tokens.

The Researchers will receive 5% of VITA-FAST tokens vested over 4 years with a 1 year cliff. The vesting period incentivizes long-term success of the project and discourages falsification of data.

Newcastle University will receive 1% of VITA-FAST tokens vested over 4 years with a 1 year cliff. This is not required in the contract, but is intended to be a strong signal to other University TTOs and an incentive to speed up the licensing process if completed by a deadline.

VitaDAO's dealflow working group contributors will receive 5% of VITA-FAST tokens vested over 4 years with a 1 year cliff. Vesting period incentivizes long-term success of the project, but must first be approved by VitaDAO governance..

Liquidity pool will receive 10% of VITA-FAST tokens. A Uniswap V3 liquidity pool will be created upon claiming the sale proceeds, matching 10% of the VITA-FAST tokens with 10% of the funds raised.



7. Genesis Sale Structure

The genesis VITA-FAST token sale will be a fixed-price sale with pro rata distribution, overflow refunds, and 2 month vesting.

10% of VITA-FAST tokens will be sold to VITA holders at a fixed price determined by a cost-based valuation as described below. The funds will be raised in wrapped ether (WETH) to

minimize the impact of USD(C) inflation and minimize the number of swaps required by participants.

Cost-based valuation

The price per VITA-FAST tokens is determined by a cost-based valuation which does not factor in any appreciation or depreciation in the value of the project based on the emergent data. VITA-FAST token buyers and sellers will have the power of price discovery in the open market once liquidity is seeded in the VITA-FAST-ETH paired liquidity pool at the conclusion of the sale.

The cost-based valuation is determined by adding together VitaDAO's committed research costs of 220,358 CHF (245,557 USD), incurred legal and operational costs of 38,563 CHF (43,295 USD), inflation of 23,865 USD (VitaDAO holds USDC so it makes sense to calculate inflation with regard to USDC). Calculated with the US Bureau of Statistics Inflation Calculator), for a total cost-based price of 312,717 USD for all 1,000,000 VITA-FAST tokens.

Given the final valuation, 10% of the Molecules would be valued at 31,271 USD and a price of 0.31271 USD per VITA-FAST token.

Bidding and locking (staking) VITA

The sale of VITA-FAST tokens will occur over a 2-day period, where members of VitaDAO may bid as much money as they are willing to contribute to the sale.

In order to bid, the bidder must lock (stake) VITA equivalent to the amount of ETH they want to bid. The value of the buyer's bid can be up to the maximum of their VITA holdings locked (staked) in the sales contract. The more VITA a buyer is willing to stake in the sales contract for the 60-day vesting period, the more that buyer may bid during the 2-day sale period. If the sales goal of 31,271 USD is not met, all funds will be returned to funders.

Pro rata distribution

If the sales goal is met or exceeded, then the final allocation of Molecules will be proportional to each bidder's fraction of the total bids.

For example, if Alice bids 40,000 USD and Bob bids 20,000 USD, and Alice and Bob are the only funders, then Alice will receive twice the allocation as Bob (this also means that Alice locked (staked) twice as much VITA as Bob).

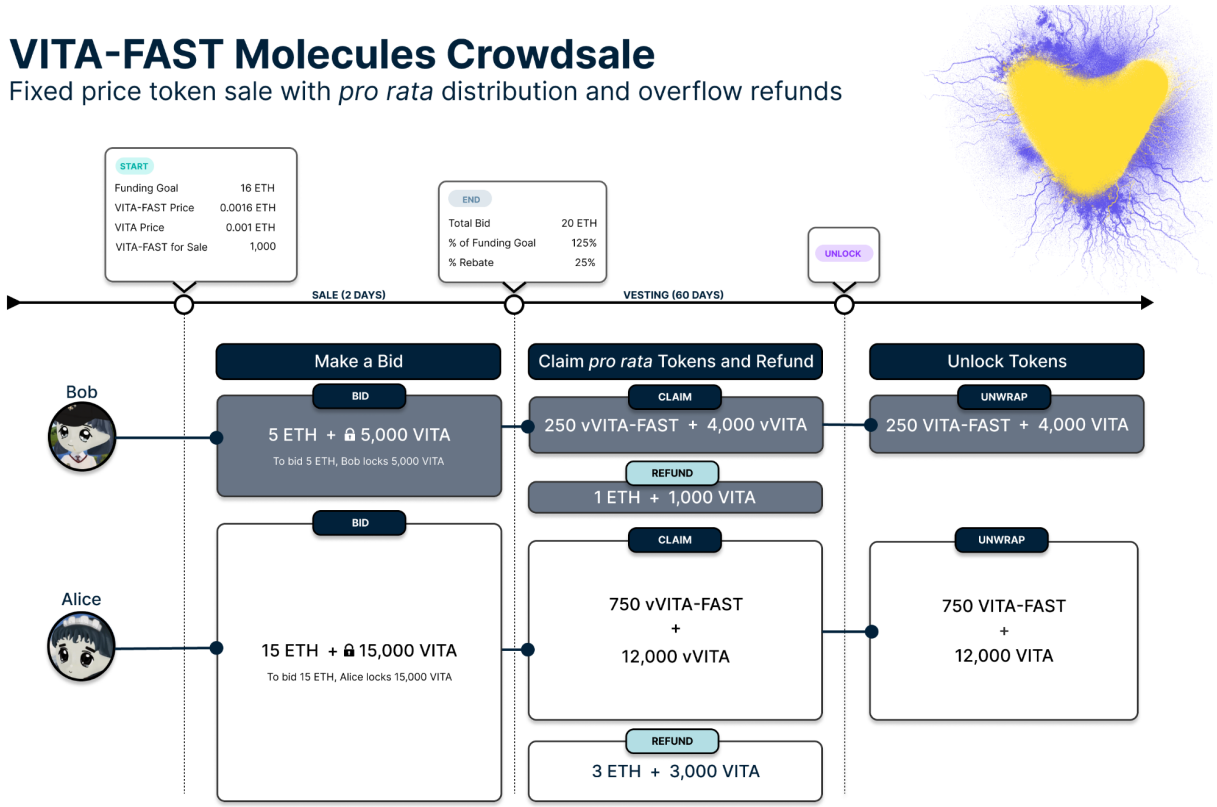
Overflow refunds

Any overflow is returned to bidders. If the amount bid exceeds the sales goal, then the excess amount is automatically returned via the token sale smart contract.

For example, VITA-FAST tokens sought to raise 31,271 USD, but Alice and Bob together bid 60,000 USD. The surplus of 28,279 USD overflows and is returned pro rata to Alice and Bob, so Alice gets back 19,153 USD and Bob gets back 9,576 USD.

2 month vesting

Sale participants receive vested VITA (vVITA) and vested VITA-FAST (vVITA-FAST), to ensure they can participate in governance while vesting. After the two-month (60 day) vesting period is over, sales participants will begin to be able to swap their vVITA for VITA and vVITA-FAST for VITA-FAST tokens. The tokens are locked for the full 2-month vesting period.



8. Use of Funds

The immediate application of the funds raised will be to establish liquidity for VITA-FAST. VITA-FAST holders have the power to decide how these funds will be subsequently used in advancing longevity research and IP development at the Korolchuk lab at Newcastle University.

For example, VITA-FAST holders could vote on the decentralization of Structure-Activity Relationship (SAR) analysis. The Korolchuk laboratory has a computational biologist on staff, yet the objective is to harness superior SAR expertise from a global pool. The aim is to identify promising compound scaffolds and design optimal candidates for further medicinal chemistry optimization. To facilitate this, as an example use case, LabDAO has proposed providing access

to its extensive network of computational chemists and creating hackathons centered around analyzing data generated by the Korolchuk lab. Considering the vast array of compounds identified as hits from the screening, both SAR analyses and medicinal chemistry will be indispensable in the selection of lead compounds. Another example would be engaging experienced medicinal chemists as another possible application of the capital. A further allocation of funds could be directed towards filing patents. Given the potential volume of novel compounds generated by this research, robust substance of matter patent protection for the most promising compounds will be vital to enhance the IP value.

In conclusion, while the short-term use of the raised capital will be for ensuring liquidity, through token holder governance there are various pathways to redirect this capital from liquidity to IP generation. This transition should be a community decision where VITA-FAST holders have the necessary data and context to facilitate informed decision-making.

9. Risk Factors

When purchasing Molecules to fund scientific research, several potential risks may apply. It's important to note that this list is not exhaustive and that the specific risks can vary depending on the nature of the project, the research being funded, the structure of the investment, the jurisdiction, and other factors.

- Liquidity Risk: The market for trading Molecules might be limited. This could mean you may not be able to resell your Molecules easily or at a price that you find satisfactory.

- Regulatory Risk: The regulatory landscape for Molecules and blockchain technology is still evolving. Changes in laws or regulations could have a material impact on the value or legality of your purchase.

- Project Risk: The success of the scientific research being funded is not guaranteed. There might be delays, cost overruns, or the research might not yield the expected results.

- Technological Risk: As with any digital asset, there is the risk of loss due to hacking, technical glitches, or issues with the underlying blockchain.

- Smart Contract Risk: The Molecules are governed by a smart contract and there is a risk that the contract could have bugs or security vulnerabilities that could be exploited.

- Market Risk: The value of Molecules could fluctuate due to changes in the broader market for NFTs, biotechnology intellectual property, or cryptocurrencies.

- Intellectual Property Risk: There may be disputes or uncertainties regarding the ownership or enforcement of the underlying intellectual property.

- Legal and Compliance Risk: Depending on your jurisdiction, owning and trading Molecules or other digital assets might have legal implications, including potential tax liabilities.

- Network Risk: The value and function of the Molecules could be impacted by changes or issues with the underlying blockchain network, Ethereum, such as changes in the consensus mechanism, forks, or network congestion.

- Operational Risk: The platforms or exchanges used to buy, sell, or store the Molecules could have operational issues, such as downtime, that could impact your ability to manage your purchase.

- Governance Risk: Molecules include governance rights and there may be disagreements or disputes among the token holders.

10. Legal Considerations

VITA-FAST represents membership in an IP pool containing the *Discovering Novel Autophagy Activators* IP-NFT and its attached IP and R&D data. IP pool membership enables token holders to govern the joint development and experimental use of the IP and R&D data in the pool.

VITA-FAST holders may have rights to govern issuance of licenses to use the underlying IP and R&D data attached to the IP-NFT. Control over the licensing function of the IP and R&D data is decentralized through token holder governance.

VITA-FAST holders may have rights to govern proceeds from licensing or sale of the IP and R&D data. Distribution of licensing or sale proceeds is not hard-coded. Given regulatory uncertainty, token holders must make a careful judgment in the future about whether, and how, to distribute licensing or sale proceeds, such as by forming a legal entity prior to making such distribution and it is recommended that such decisions include soliciting legal advice.

VITA-FAST holders may be granted information rights, entitling them to regular, non-confidential updates from the researchers and the ability to pose queries. This extends to accessing data rooms containing the IP and R&D data, including a continuously open, non-confidential data room. The latter is designed to aid the community's decision-making process through the provision of research results, with proprietary data being redacted to safeguard the IP's integrity. This data room also serves as the primary means for delivering non-confidential updates to holders of Molecules.

VITA-FAST holders may also have the opportunity to gain access to confidential data, subject to adherence to protocols such as Know-Your-Customer (KYC) and Non-Disclosure Agreements (NDA) as governed by token holders. This data will be highly confidential, thus requiring users to adhere to such protocols to safeguard the IP.

VITA-FAST will not be sold to U.S. persons in compliance with Regulation S of the United States

Securities Act of 1933. In accordance with this regulation, VITA-FAST will not be made available to U.S. persons or within the United States,. Potential purchasers will be required to provide sufficient proof of their non-U.S. person status including IP address checks, geofencing, and attestations.

11. Team

Viktor Korolchuk is a cell biologist and researcher who currently leads the Korolchuk Lab at Newcastle University. He obtained his PhD from the University of Cambridge in 2007 and subsequently held postdoctoral positions at the University of California, San Diego, and the University of Cambridge.

Dr. Korolchuk's research focuses on the molecular mechanisms that regulate cellular homeostasis, particularly in the context of neurodegenerative diseases and cancer. He has published numerous articles in high-impact scientific journals and is recognized as an expert in the field.
In addition to his academic work, Dr. Korolchuk is involved in several industry collaborations and has received funding from a variety of sources, including the UK Medical Research Council, the European Research Council, and the Wellcome Trust. He is also a member of several professional organizations, including the Biochemical Society and the Royal Society of Biology.

Peter Banks trained as a geneticist during his undergraduate degree at Newcastle University. He gained his PhD studying the role of cohesins in Caenorhabditis elegans, also at Newcastle University before starting a postdoctoral role with David Lydall. It was whilst working on the role of chromatin modifications in budding yeast that Peter became interested in the use of robotics in Genetic research. Utilizing the unique setup that David Lydall had developed within the Centre for Integrated Systems Biology of Ageing and Nutrition, Peter developed the skills that would allow him to move into high throughput screening.

In 2011, Peter was appointed to run a new facility set up within the Faculty of Medical Sciences at Newcastle University. Initially offering to run genome wide yeast screens, the faculty invested significant funds to develop mammalian siRNA screening in 2012. Over the following years the screening facility has continued to develop recruiting a new member of staff Adrian Blackburn incorporating bacteria and alternative yeasts such as Candida albicans.

Jóhannes Reynisson is a drug discovery expert and a research lead at VitaDAO, where he oversees projects related to drug discovery and leads collaborations with academic institutions and industry partners. He holds a PhD in chemistry from the University of Copenhagen and has extensive experience in the pharmaceutical industry, including working as a medicinal chemist and project leader at Novartis and AstraZeneca. He holds a PhD in from the University of Copenhagen in chemical biology and has extensive experience in drug discovery projects, including working as a molecular modeler at the Institute of Cancer Research, London, UK and project leader at the University of Auckland, NZ. He has authored more than 150 peer-reviewed

publications and patents. His research focuses on the discovery of new drug candidates and the development of novel therapeutic strategies for various diseases, including cancer, infectious diseases, and neurodegenerative disorders.

In addition to the core team outlined above, the project has support from the entire VitaDAO community of contributors.

Resources:
Korolchuk Lab - VitaDAO

Discovering Novel Autophagy Activators - Molecule

Funding Science Through Blockchain Technology and Cryptocurrencies - Newcastle University

Newcastle fractionalization proposal to VitaDAO (VDP-100)

VitaDAO snapshot proposal approving VDP-100

Korolchuk-Free Association of Molecules (FAM) Membership Agreement