To: Athamanatha (Daniel Davies)

Dear Athamanatha,

[redacted] We have carefully considered your response to our letter dated October 26, 2022, and the Board would like to take some time to shed further light and elaborate on some of the points that were raised.

[redacted]

[redacted]

[redacted]

Overview of our position regarding involvement or interaction with Vulpine Labs

For your involvement with Vulpine Labs (VL), we want to add further clarity, and also raise some additional concerns after the Directors recently became aware of several newer documents describing VL's objectives. You raised a point that "what [redacted] decides to do with his time and money when discussing matters with me in PMs is on him as a responsible adult to weigh up". [redacted] is a new member of the FFF's community (joined [redacted]), and he shows promise as a potential volunteer, as you suggested briefly in the community moderation channel.

The reality is, what [redacted] or any current or future FFF volunteer does with their time and money is highly influenced by what they are told by senior FFF leadership. If a new person hears a Director speak passionately about another project, they may very well surmise that the project is effectively endorsed by FFF. They will also likely believe a leadership figure by default when making statements on scientific feasibility. We as leaders are trusted sources of scientific

knowledge, and that trust was hard-earned. As we've emphasized, you are perceived continuously as a member of senior FFF leadership, no matter which space you work in.

We feel that it's also important to clarify that we don't necessarily believe that your actions and (mis)use of influence are deliberate. None of us are questioning your character, and we've all worked with you for a long time. The issue is more with that you are perceived as an FFF leader no matter what space you operate in, and that your representation can create unintentional undue influence on other members that cannot be condoned.

We want to emphasize that the FFF is supportive of entrepreneurship, innovation, and empowering our stakeholders. These are important to us, because we know the FFF itself cannot solve all the challenges for accomplishing freedom of form. However, these must be balanced with needs for truths in science, medicine, and even in balancing optimistic, yet realistic, expectations of our stakeholders. Therefore, while we may be receptive in many cases to collaborating on talent recruitment, promotion, resource sharing, and even technology/license sharing, we cannot accept any such collaboration with Vulpine Labs at this time.

In this matter, we intend to model our guidelines to you from standard industry expectations regarding solicitation - where the result of discussing an organization may be expected to lead to any recruitment or other positive outcomes for that organization - as a general guide. It is important to remember this is a Board discussion, which carries greater levels of concern and exposure than the types of solicitation traditionally covered in employment contracts. Thus, we ask you to refrain from mentioning Vulpine Labs in spaces such as the FFF server, direct messages with current and prospective FFF server members, and spaces where you could reasonably be expected to be viewed as an FFF leader, with a limited exception for the #vulpine-designs-and-labs channel in the Morphological Freedom server.

Details that have informed our position on Vulpine Labs

In your response, you asked us whether you are to be prohibited from discussing Vulpine Labs in FFF-associated spaces. It took us some time to arrive at an answer for this, and we were prompted to review VL's materials in order to do so. Unfortunately, after this review, we are seriously concerned by the statements made in VL documentation, and for reasons outlined below, we have concluded that yes, you should not discuss it while in FFF spaces where you are likely to be viewed as a leader of our organization.

Most of our review centered around statements made in the 2022 version of your official Business Plan aimed at recruiting investors. We have found several areas that we have serious concerns about, pertaining to your representations of scientific feasibility and timelines of projects. These include statements made about VL's putative "Geneticiser" device that are simply not rooted in scientific fact. When you make these statements, especially to potential FFF volunteers you've encountered through the FFF's community, it reflects very poorly on us, and

also presents false hope to our community by disregarding both physically impossible barriers as well as many more substantial scientific challenges that would take time to solve.

Furthermore, it raises serious concerns about your general approach to science. Making grand statements about scientific ideas, while placing the responsibility on others to evaluate and do a reality check, is not responsible or acceptable. While we welcome creative, forward-thinking ideas about scientific methods of achieving our goals, these ideas must come with solid scientific reasoning and a factual basis, especially when coming from members of FFF leadership.

We would like to highlight examples pertaining to the Geneticiser to show the issues in some detail, though we have similar concerns about the GUESS and other activities that are beyond the scope to discuss here.

A. The proposed Geneticiser is fundamentally impossible for numerous reasons.
In your Business Plan, you state that "Our Geneticiser device [...] is designed to be capable of reading and writing DNA in the same device, and *without reagents*". Furthermore, on page 8, you claim that “current designs hold the sample with acoustic levitation & read, manipulate & ‘write’ the molecules therein via hollow laser beams.” This is factually impossible for the following reasons:

1. **Limitations of optical resolution**
   DNA is well below the diffraction limit of visible light, which is given by the Abbe diffraction limit:

$$d = \frac{\lambda}{2n \sin\theta} = \frac{\lambda}{2\mathrm{NA}}$$

   Where λ is the wavelength of light, n is the refraction index of the medium used, θ is the maximum half-angle for the cone of light that can enter the lens, and NA is the numerical aperture. In modern optics, NA (i.e. 2n sin θ) can reach 1.4-1.6. The refractive index *n* has a theoretical maximum of about 1.7, and the best possible value for θ is 90°, corresponding to a perfect lens that accepts 180° of light, making the maximum theoretical NA about 1.7 as well. Given a minimum wavelength of 380 nm (violet) before the sample would be rapidly chemically damaged, that puts the diffraction limit in near-perfect circumstances at around 380/(2x1.7) = about 112 nm. It is important to note, though, that even in state-of-the-art devices, the theoretical limit is not practically achievable, and the true diffraction limit will be substantially worse.

   Conversely, a DNA strand (in B-DNA conformation) is about 2.0 nm wide - 56x smaller than the theoretical resolution limit. The space between bases in B-DNA is almost another order of magnitude smaller, at 0.34 nm.

Other methods, like higher energy light or electron beams, will destroy the sample, and still fail due to diffraction in an unpurified sample containing many other components.

There are a variety of super-resolution methods for deconvolution based on known characteristics of the Airy functions and by collecting many images of the same sample followed by post-processing. Notably, these only work for detection and not for sample manipulation with a collimated laser beam. Such methods include STORM (stochastic optical reconstruction microscopy), for example, but even under perfect conditions with near-perfect lenses and ultra-pure light sources, the resolution limit is still about 20 nm, an order of magnitude greater than the width of a DNA strand.

It is important to also note that even if you could observe individual bases, you would still need to identify what they are (A/C/T/G). Without the benefit of dyes or biochemical tools added to the system, which are excluded in your proposal, this would require either the use of the intrinsic fluorescence of DNA bases (which, in addition to suffering from crosstalk from neighboring bases and other molecules due to excitation beam resolution limits, would also require long imaging times due to low quantum yields, allowing the sample to shift and preventing using a STORM-like imaging technique), or otherwise achieving angstrom-level resolution to directly observe base shape (1 Å = 0.1 nm).

No super-resolution method can achieve this, and it most certainly cannot be achieved in a DIY device built by end users at home. Super-resolution instruments are multimillion-dollar devices that require precision engineering, and even these expertly-developed devices are incapable of achieving this kind of resolution. Based on our hands-on experience with various microscopy formats including super-resolution, we can confidently say it is naive to propose optical equipment with a resolving power that is orders of magnitude better than the current state-of-the-art and established physical limits.

2. **Shear forces and beam cohesion/diffusion in the microenvironment**
   The proposed method of stabilizing the DNA, via laser or acoustic waves, would result in turbulence and tend to spin the molecule from radiation pressure, causing shear within its microenvironment. As well, any sample of biological material in the laser beam's path, such as cells as proposed, would rapidly disrupt beam cohesion. Similar issues occur for acoustic waves such as are used in acoustic force spectroscopy, the method of manipulating biomolecules with acoustic tweezers. It is misleading to suggest that *"Current designs hold the sample with acoustic levitation & read, manipulate & 'write' the molecules therein via hollow laser beams"* without addressing these fundamental physical constraints.

3. **Illumination is an unsuitable mechanism for editing DNA**
   High energy illumination, even if it is not in the UV spectrum, is likely to result in oxidative DNA damage, possible formation of dipyrimidine photodimers, single and double strand breaks, buildup of reactive oxygen species, etc. Even if target molecules in the core of a

hollow laser beam are not excessively illuminated at any given time, the surrounding biological matter will be exposed to damaging levels of illumination.

Separately, it is inconceivable how an illumination-based mechanism would allow arbitrary editing of DNA. There are no existing reactions, even theoretically, that permit mutating nucleobases using only light (or electrons, for that matter), especially between purines and pyrimidines. Purines contain a double ring structure with additional carbon atoms that must come from somewhere. Even if larger-scale molecular assemblies are used instead, illumination cannot be expected to precisely control which bonds are broken or rearranged in DNA to a level sufficient for the Geneticiser's needs. There are no indications that consideration has been given to the relative bond strengths in DNA, or how these compare with the forces and energetics being proposed by the Geneticiser's illumination methods. Moreover, it is difficult to imagine how, even if intermediate products could be produced in such an illumination-mediated reaction, those products could be contained so as to avoid countless side-reactions.

4. **Low structural accessibility and high concentration of contaminants during proposed reactions on DNA in unpurified samples**
   Genes are wrapped around histones and bound by hundreds to thousands of proteins, along with RNA and other biomolecules nearby. Without purification - which requires reagents and more steps with equipment - your sample will be so contaminated by other molecules that even if you circumvented the uncircumventable problems above, you wouldn't gain any useful sequence information due to so many confounders.

   We do not dispute that precisely editing DNA in cells is becoming routine. However, enzyme-based tools are very well developed, and there are countless exciting possibilities for engineering even better enzyme-based systems. Enzymes allow you to target specific sequences, catalyze specific reactions, exclude surrounding contaminants, and incorporate, remove, or edit arbitrary DNA. Today's enzymes already address many of the fundamental limitations the Geneticiser succumbs to. It is odd that DNA-modifying enzymes such as CRISPR are not mentioned in the Business Plan.

5. **Lack of input reagents for *de novo* synthesis of DNA**
   De novo gene synthesis, in the manner you propose, is intractable without reagents. Reagents are needed for direct consumption as building blocks and for controlling the correct order of assembly, along with the biochemical environment, because something must guide the synthesis of the correct order of nucleotides, and this cannot be laser light due to resolution limits as discussed above. (Short wavelength light or electron beams do not solve this issue, as they would cause oxidative DNA damage and single and double strand breaks.)

   In practice, it would require either:
   a. Direct synthesis of oligonucleotides in rounds of nucleotide addition, usually performed by phosphoramidite synthesis, using several reagents such as artificial

nucleotides with cleavable protecting groups, and other buffers and chemicals. This approach has a practical limitation to a few hundred bases.

b. Stitched oligonucleotide synthesis, required for genes longer than a few hundred base pairs. This might use several oligos produced via phosphoramidite synthesis, which would then need to be assembled and ligated using some combination of external polymerases, endonucleases, exonucleases, and ligase.
c. An exotic chemical DNA synthesis method supporting longer lengths that has yet to be discovered, but that will still rely on cleavable protecting groups and require a variety of intermediate chemicals.
d. Enzyme-based synthesis (theoretical), which would require a tunable polymerase that adds nucleotides sequentially based on external input (e.g. optogenetic mechanisms and the like). While this is theoretically possible, it would involve extensive protein engineering, and also involve the provisioning of an external, artificial polymerase enzyme, or a gene encoding the enzyme - either way, requiring reagents.

6. **Quality control for the output**
   If the sample is ultimately destined for human use, you will require purity well in excess of 99% to ensure patient safety. No technique, even current state-of-the-art ones, can be 100% efficient in every instance, and as such, the sample will require substantial purification and sequence verification if the DNA is intended for functional use in patients. Depending on the method, the synthesis process itself also introduces many chemical byproducts that can be toxic and must be removed by post-synthesis purification. While other nucleotide synthesis methods are almost certainly possible, quality control will be a central theme.

   Notably, it is at least possible with current techniques to do quality control on output DNA without risking damage to the sample through direct, illumination-based observation, and without asking to overcome the other intractable issues already discussed.

7. **Device stability**
   Even ignoring all of the fundamental issues listed above, you still have the problem that devices working at the nanoscale are extremely sensitive to motion. Cutting-edge super-resolution microscopes, which again are orders of magnitude less precise than the proposed Geneticiser, are placed on vibration-isolation tables. Molecule-level manipulations are even more sensitive, requiring highly precise motion-canceling tables and often being held in buildings with warnings to outsiders not to make excessive vibrations. Thus, we see no reason to accept the claim that a device operating at this scale will ever be practical for an end-user outside a highly controlled environment.

B. Unawareness of competitive landscape

It is surprising that Illumina, Oxford Nanopore, Thermo Fisher/Ion Torrent, Zeiss, Perkin Elmer, and Olympus are not listed as competitors, since many of their business activities overlap VL's proposed Geneticiser activities, even ignoring the other proposed activities by VL. While we

would not expect a complete competitive analysis, the omission of mentioning any of the above names and the multitude of their platforms on the market suggest a lack of awareness or lack of interest in the current state-of-the-art for sequencing and optical equipment.

It is also surprising that the likes of Moderna, Pfizer/BioNTech, Novartis, and many others are not presented as competitors for bio/pharma companies, or indeed, why integrated health systems such as Partners Healthcare, HCA Healthcare, or the NHS, are not listed. These organizations collectively have tens of thousands of doctors and scientists. While we would support additional competition in the healthcare space to bring down prices and improve care and patient choice, the current landscape is continuously improving patient outcomes, and collectively integrates diagnostics and treatments. Parts of the existing healthcare system can be improved or replaced, but it is hubris to suggest that a single device, at home, can both diagnose and treat patients across all existing and new areas of healthcare.

C. Inattentiveness towards patient needs, including safety

When describing the Geneticiser in section 3.3 of your Business Plan, you mention that the device might work on “a sample of the patient’s cells”. There are no meaningful details about the types of cells that would be worked with, the target patient populations and their disease areas, how cells will be safely collected by the end user, or how the Geneticiser will help safely alleviate their diseases.

While we appreciate that platforms can be applied to several patient areas, it comes across as misleading to describe the deep motivations by VL for improving patient lives without providing credible steps that will be taken towards their benefit. One could imagine that a new gene editing technology, such as the proposed Geneticiser, would involve substantial risks. Extensive preclinical and clinical validation would be required to avoid causing patient harm. For example, see previous retrovirus clinical trials for SCID patients. It is essential to be aware of, and make allowances to test for, potential harms to patients, but there are no indications you have done this.

Interestingly, neither the FDA, nor any specific regulatory approval process, or even an equivalent self-directed process to ensure safety, is mentioned in your proposal. While we do not expect such a proposal to be comprehensive, this is a clear omission.

Considering the rapid progress of clinical trials and approvals for gene therapies, cell-based therapies, and other biological therapies, especially in light of clearly demonstrated efficacy and safety in many cases, it is irresponsible to propose an entirely new gene editing method - dramatically less mature in development than when retroviruses were tried in patients - without presenting clear criteria on why it would be more efficacious and safe than the current state-of-the-art, as well as clear steps to address sources of risk.

Conclusions regarding our position on Vulpine Labs

We understand and empathize with your personal and professional investment in Vulpine Labs. However, after carefully reviewing your claims, we have the professional opinion that VL is not

capable of delivering on what it promises at this time, due to theoretical, practical, and personnel-based constraints. Moreover, we have substantial concerns that rise above technical issues, to include creating false hope, making misleading statements (regardless of whether they are intended as such), and an unsatisfactory approach to patient needs.

We do not believe it is appropriate or realistic to place the onus on readers to evaluate VL's claims. VL's claims have taken substantial theoretical understanding and professional experience to disprove in a fair and factual way, and we would not have expended this effort if we did not believe it was important to do so. We have to imagine that skeptics would simply dismiss your claims as being too-good-to-be-true, whereas people who are more receptive to your claims are giving VL unearned trust that the proposal comes from a solid basis. This situation is very difficult to reconcile with how we approach not just science, but how we represent our goals and communicate what our stakeholders can look forward to.

At this time, it would represent an unacceptable reputational risk for the FFF to have any association to VL, especially through one of our senior members of leadership. The continuing public availability of materials, which we have shown lack factual basis, is an aggravating factor.

Our requests in this message

We are directing you to:

1. [redacted]
2. Cease any and all promotion of VL's activities in FFF-associated spaces and/or to our members.
3. Do not make false, misleading, or scientifically unsound statements in any context where you are perceived as acting as a professional, even within the specific spaces for VL (e.g. #vulpine-designs-and-labs in the Morphological Freedom server), because these still represent a credible reputational risk to the FFF by association. It is not the responsibility of readers or stakeholders to critically evaluate your claims.

Additionally, we are strongly suggesting that you:

4. Take to heart our technical and strategic criticisms of VL's business plan, and go back to the drawing board with a blank slate to build a sound technical and medical basis.
5. Retract existing misleading or scientifically unsound statements that are currently posted in any view of the public, until VL materials can be comprehensively revised with sound basis.

As always, please feel free to ask any questions that you may have.This is indeed a difficult matter for all of us, and we sincerely hope that you are willing to make the necessary changes to be able to continue serving on our Board of Directors.