Professor Grant Guilford
Vice-Chancellor
Victoria University
PO Box 600
Wellington 6140
New Zealand

April 24th, 2019.

Re. The use of the Forced Swim Test by Victoria University

Dear Vice-Chancellor Professor Grant Guilford,

Thank you in advance for your time. I am writing on behalf of the New Zealand Anti-Vivisection Society (NZAVS) and Save Animals from Exploitation (SAFE), and our combined, more than 65,000 members and supporters. **Based on the information presented below, we ask that Victoria University discontinue the use of the Forced Swim Test (FST) in manipulations involving animals conducted and funded by your institute.**

I have tried contacting you via email on the 9th of April 2019. It's been over two weeks and unfortunately, I haven't received a response from you. I therefore felt it was necessary to come and deliver this letter to you in person, with Debra Ashton, the CEO of SAFE so that we can be 100% certain you have heard our concerns.

Since 2009, staff and students at Victoria University have published at least seven manuscripts (references below) that describe the use of mice and rats in FST experiments.
In these publications, Victoria University-affiliated authors have described the FST as a way to assess for "pro-depressive effects,[1,2,3] and "depressive behaviours,"[4] and a way to evaluate "depressive-like effects."[5,6]

However, the applicability of an animal's behaviour during the FST to their mood, or to human depression, or to the utility of a compound for treating human depression has been scientifically refuted, as thoroughly discussed in the attached document by Dr Trunnell titled, *"The Invalidity of the Forced Swim Test.*"

During the FST, animals (typically mice or rats) are forced to swim in a cylinder of water. They swim frantically, trying to find an escape, until they stop struggling and subsequently float. The claim is that when mice spend more time floating, they are deemed to be more "depressed." The FST is fundamentally flawed, however, since evidence shows that floating is actually a learned and adaptive behaviour, one that saves energy and is beneficial for survival.[7] Individual animals who are quicker to float also save energy and

[1] Kivell, B., Paton, K., Kumar, N., Morani, A., Culverhouse, A., Shepherd, A., ... & Prisinzano, T. (2018). Kappa Opioid Receptor Agonist Mesyl Sal B Attenuates Behavioral Sensitization to Cocaine with Fewer Aversive Side-Effects than Salvinorin A in Rodents. *Molecules*, *23*(10), 2602.
[2] Morani, A. S., Schenk, S., Prisinzano, T. E., & Kivell, B. (2012). Single injection of novel kappa opioid receptor agonist salvinorin A attenuates expression of cocaine induced behavioral sensitization in rats. *Behavioural pharmacology*, *23*(2), 162.
[3] Young, D. (2015). Pre-clinical anti-addictive and side-effect profiles of novel kappa-opioid agonists.
[4] Morani, A. S. (2011). Behavioural pharmacology of novel kappa opioid compounds.
[5] Mathew, S. et al. (2016). *Breaking the Cycle of Addiction; Investigating the side-effects of 16-Ethynyl Sal A (a potential anti-addiction drug).* Retrieved from https://www.victoria.ac.nz/news/2016/04/summer-gold-competition-2016-winners/MEDoR-SBS-109-Mathew,-Stephen.pdf
[6] Ewald, A. W., Bosch, P. J., Culverhouse, A., Crowley, R. S., Neuenswander, B., Prisinzano, T. E., & Kivell, B. M. (2017). The C-2 derivatives of salvinorin A, ethoxymethyl ether Sal B and β-tetrahydropyran Sal B, have anti-cocaine properties with minimal side effects. *Psychopharmacology*, *234*(16), 2499-2514.
[7] Molendijk, M. L., & de Kloet, E. R. (2015). Immobility in the forced swim test is adaptive and does not reflect depression. *Psychoneuroendocrinology*, *62*, 389-391.

are less likely to sink, meaning that animals who more rapidly pick up on this reality, and spend less time struggling, are simply learning this adaptive behaviour more readily.

Some claim that the Forced Swim Test is a screening tool for antidepressant activity, since sometimes mice who are given human antidepressant drugs will swim more and float less. However, the immobility response has also been documented to reduce after treatment with drugs that do not have antidepressant effects, such as antihistamines, anticholinergics, and other miscellaneous drugs.[8] Time spent swimming vs. floating is also influenced by the genetic strain of an animal and experimental variances, such as water depth or temperature.[9]

There is a clear need to develop new therapeutics to treat human depression. Only small numbers of patients respond to available treatments, which themselves have severe shortcomings.[10] However, the use of animal experiments in an effort to generate these treatments has been criticised by scientists as a major contributor to failure rates in this area.[11] Animals are poor models of human depression and lack many important aspects of model validity. Hendrie and Pickles (2013), argue that multiple failures on the part of animal experimenters are to blame for lack of progress in this field, namely falling trap to "logical flaws" and "false assumptions."[12]

The FST is so traumatic to animals that the test is often used as a stressor in itself,[13] in an effort to create a sense of helplessness. This test has also been conducted by affiliates of Victoria University for this reason.[14] To quote Dutch animal behaviourists Franz Josef van der Staay, Saskia S. Arndt, and Rebecca E. Nordquist, "If evidence accumulates that the intended goal/purpose cannot be reached, then one should consider abandoning further development of the model."[15]

In summary, the FST does not reliably predict successful novel treatments for human depression—nullifying any scientific justification for carrying out the test; and it causes acute suffering and distress to the animals who are used—presenting a compelling ethical argument against using the test. We therefore ask Victoria University to immediately **discontinue its use of the Forced Swim Test in any research, testing or teaching manipulation involving animals.**

In December 2018 pharmaceutical Giant AbbVie committed to no longer funding or conducting the FST. In March 2019 Johnson and Johnson made the same commitment. There is currently a lot of international attention on this test (mainly due to the launch of a campaign by People for the Ethical Treatment of Animals who have a supporter base of 6.5 million people strong) and it would be a shame to see a prestigious university in New Zealand miss an opportunity to meet improving global standards.

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[8] Arai, I., Tsuyuki, Y., Shiomoto, H., Satoh, M., & Otomo, S. (2000). Decreased body temperature dependent appearance of behavioral despair in the forced swimming test in mice. *Pharmacological research*, *42*(2), 171-176.

[9] De Pablo, J. M., Parra, A., Segovia, S., & Guillamón, A. (1989). Learned immobility explains the behavior of rats in the forced swimming test. *Physiology & behavior*, *46*(2), 229-237; Jefferys, D., & Funder, J. (1994). The effect of water temperature on immobility in the forced swimming test in rats. *European journal of pharmacology*, *253*(1-2), 91-94; Lucki, I., Dalvi, A., & Mayorga, A. J. (2001). Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. *Psychopharmacology*, *155*(3), 315-322.

[10] Hendrie, C., & Pickles, A. (2013). The failure of the antidepressant drug discovery process is systemic. *Journal of Psychopharmacology*, *27*(5), 407-416.

[11] Garner, J. P. (2014). The significance of meaning: why do over 90% of behavioral neuroscience results fail to translate to humans, and what can we do to fix it?. *ILAR journal*, *55*(3), 438-456.

[12] Hendrie 2013

[13] De Kloet, E. R., & Molendijk, M. L. (2016). Coping with the forced swim stressor: towards understanding an adaptive mechanism. *Neural plasticity*, *2016*.

[14] Welsh, S. A. (2017). The effect of novel kappa opioid peptide receptor agonists on learning and memory in rats.

[15] van der Staay, F. J., Arndt, S. S., & Nordquist, R. E. (2009). Evaluation of animal models of neurobehavioral disorders. *Behavioral and Brain Functions*, *5*(1), 11.

We hope to see Victoria University head in the same progressive direction as these massive corporate companies and become the first university in New Zealand to **commit to no longer funding or conducting this irrelevant and cruel test.**

We also hope that by delivering this letter directly to you, you'll understand just how important this issue is to us and our thousands of supporters.

You may contact me by e-mail at tara@nzavs.org.nz or via phone, 027 816 1926. Thank you for your consideration, and I look forward to your response.

Kindly,

Tara Jackson
Executive Director
New Zealand Anti-Vivisection Society Inc.

With expert advice provided by Dr Emily Trunnell, Neuroscientist and Research Associate.

Use of the Forced Swim Test in Victoria University-affiliated publications:

a) Kivell, B., Paton, K., Kumar, N., Morani, A., Culverhouse, A., Shepherd, A., ... & Prisinzano, T. (2018). Kappa Opioid Receptor Agonist Mesyl Sal B Attenuates Behavioral Sensitization to Cocaine with Fewer Aversive Side-Effects than Salvinorin A in Rodents. *Molecules*, *23*(10), 2602.
b) Morani, A. S., Schenk, S., Prisinzano, T. E., & Kivell, B. (2012). Single injection of novel kappa opioid receptor agonist salvinorin A attenuates expression of cocaine induced behavioral sensitization in rats. *Behavioural pharmacology*, *23*(2), 162.
c) Young, D. (2015). Pre-clinical anti-addictive and side-effect profiles of novel kappa-opioid agonists.
d) Morani, A. S. (2011). Behavioural pharmacology of novel kappa opioid compounds.
e) Welsh, S. A. (2017). The effect of novel kappa opioid peptide receptor agonists on learning and memory in rats.
f) Mathew, S. et al. (2016). *Breaking the Cycle of Addiction; Investigating the side-effects of 16-Ethynyl Sal A (a potential anti-addiction drug).* Retrieved from https://www.victoria.ac.nz/news/2016/04/summer-gold-competition-2016-winners/MEDoR-SBS-109-Mathew,-Stephen.pdf
g) Ewald, A. W., Bosch, P. J., Culverhouse, A., Crowley, R. S., Neuenswander, B., Prisinzano, T. E., & Kivell, B. M. (2017). The C-2 derivatives of salvinorin A, ethoxymethyl ether Sal B and β-tetrahydropyran Sal B, have anti-cocaine properties with minimal side effects. *Psychopharmacology*, *234*(16), 2499-2514.