FLYKITT

Technical White Paper

Overview

This white paper describes new insights into jet lag and how the FlyKitt system leverages these to mitigate or eliminate jet lag for most travelers. It has been known for many decades that traversing multiple time zones causes a misalignment of the body's circadian rhythm. However, this does not explain the entirety of jet lag symptoms or their severity. Breakthrough research by Fount's CEO Andrew Herr has identified that circadian disruption is complicated by an inflammatory response resulting from the rapid transition to and extended time spent in the low-pressure, low oxygen environment of aircraft cabins.

The FlyKitt system is designed to mitigate both the inflammatory and circadian challenges behind jet lag. It was developed based on extensive work with Navy SEALs, fighter pilots, and executives who undertake long-distance travel immediately before high-skill activities like military operations and major negotiations. By taking into account the full spectrum of physiological factors and performance needs, Fount has created a comprehensive, integrated solution that dramatically improves how users feel and perform and which is effective in >93% of cases.[1]

Physiology of Jet Lag

The Canonical Understanding of Jet Lag is Not Comprehensive

The human sleep-wake cycle is governed by the central circadian rhythm, a roughly 24-hour cycle primarily controlled in the brain by the suprachiasmatic nucleus (SCN). The SCN relies on internal and external cues — zeitgebers — to maintain synchronization with the environment, aligning our sleep-wake cycle with night and day. Zeitgebers include cues such as temperature, eating, and particularly bright light sensed through visual and non-visual receptors in the eye. When stimulated, these receptors inhibit melatonin production, decrease sleepiness, and push off the onset of sleep, as is appropriate during daytime. As night comes and temperature and light decrease, at

[1] Based on a retrospective analysis of 110 sequential trips using FlyKitt from Fount internal data.

least in the natural environment, then these blocks are removed and our bodies prepare for sleep.[2]

The body's innate circadian system provides some flexibility. The consensus in the circadian biology field is that individuals can shift their clocks by about two hours later or one hour earlier per day without major disturbance to sleep quality and subsequent performance. With long-distance air travel, however, it is possible to traverse many more time zones in a single day, which can cause circadian misalignment, as evidenced by melatonin and cortisol rhythms that no longer match morning and evening and difficulty falling asleep and staying awake.

Traditional research on jet lag has highlighted this circadian mismatch as the cause of jet lag. However, we propose that these effects do not explain the magnitude of brain fog, gastrointestinal symptoms, joint pain, and other symptoms commonly described with jet lag. Studies also exist that contradict the circadian-only model. For example, in perhaps the most detailed study on the physiology of jet lag, researchers found no correlation between degree of cortisol rhythm alignment and subjective discomfort following a westward flight with a 7-hour time change and the return weeks later. Interestingly, in the same study, individuals whose cortisol rhythm adapted faster to the clock time had the lowest scores on a measure of anxiety and depression. Taken together, these two data points suggest that individuals who adjust faster may have fewer symptoms due to a separate causal factor.[3] We propose the missing influence is inflammation, which is known to cause anxiety, negative mood, sleepiness, and reduce alertness.[4]

Novel Insights into Jet Lag: Pressure Change, Low Oxygen, & Inflammation

When at cruising altitude, commercial airplanes typically pressurize the cabin to the equivalent of air at 5,000 - 8,000 ft due to mechanical constraints and cost. As a result, passengers experience lower pressure and lower oxygen levels than they are used to,

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[2] Robert L. Sack, "The Pathophysiology of Jet Lag," *Travel Medicine and Infectious Disease* 7, no. 2 (March 2009): 102–10, https://doi.org/10.1016/j.tmaid.2009.01.006; "Effects of Calibrated Blue–Yellow Changes in Light on the Human Circadian Clock | Nature Human Behaviour," accessed December 26, 2023, https://www.nature.com/articles/s41562-023-01791-7.
[3] DANIEL DÉSIR et al., "Effects of 'Jet Lag' on Hormonal Patterns. I. Procedures, Variations in Total Plasma Proteins, and Disruption of Adrenocorticotropin-Cortisol Periodicity*," *The Journal of Clinical Endocrinology & Metabolism* 52, no. 4 (April 1, 1981): 628–41, https://doi.org/10.1210/jcem-52-4-628.
[4] Harald Engler et al., "Endotoxin-Induced Physiological and Psychological Sickness Responses in Healthy Humans: Insights into the Post-Acute Phase," *Neuroimmunomodulation* 30, no. 1 (October 5, 2023): 268–76, https://doi.org/10.1159/000534444.

or hypobaric hypoxia.[5] Several streams of research tie airline travel and hypobaric hypoxia to inflammation, which we have identified as playing a key role in causing the symptoms of jet lag and amplifying the effects of circadian misalignment.

Observational studies find that airline travel is associated with the onset of or increased severity of various inflammatory conditions. While individuals sit at their desks or on the couch for just as many hours as they might sit on a plane, the risk of deep-vein thrombosis is elevated with air travel.[6] Studies also find that the risk of relapse for auto-immune disorders is substantially increased post air travel.[7] Importantly, this study did not require flights to be long distance, which should mitigate the known pro-inflammatory role of sleep disruption, suggesting a separate pro-inflammatory effect of air travel.

In-vivo human studies of hypobaric hypoxia also find dysregulation of various oxidative stress and immune pathways. While findings vary study-to-study, they include loss of diurnal variation in the cytokine IL-6 and the clotting marker D-Dimer, increases in the level of the prostaglandin PGE2, and lower-leg edema.[8] Even after just 30 minutes at 8,000 feet of relative oxygen and pressure, expression increases for a number of inflammation- and oxidative stress-related proteins.[9] In a group of 20 individuals in a hypobaric chamber simulating flight conditions, coagulation factors increased more than 2.5-fold within 2 hours, and interestingly, there was also an increase at return to ambient pressure, suggesting that not only does exposure to hypobaric hypoxia cause damage, but also reoxygenation, which is a known phenomenon with reperfusion injury and carbon monoxide poisoning.[10] Furthermore, very fast transitions to hypobaric hypoxic

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[5] Michael Bagshaw and Petra Illig, "The Aircraft Cabin Environment," in *Travel Medicine (Fourth Edition)*, ed. Jay S. Keystone et al. (London: Elsevier, 2019), 429–36, https://doi.org/10.1016/B978-0-323-54696-6.00047-1.

[6] Israel Gavish and Benjamin Brenner, "Air Travel and the Risk of Thromboembolism," *Internal and Emergency Medicine* 6, no. 2 (April 2011): 113–16, https://doi.org/10.1007/s11739-010-0474-6.

[7] Stephan R. Vavricka et al., "High Altitude Journeys and Flights Are Associated with an Increased Risk of Flares in Inflammatory Bowel Disease Patients," *Journal of Crohn's and Colitis* 8, no. 3 (March 1, 2014): 191–99, https://doi.org/10.1016/j.crohns.2013.07.011.

[8] ICE Research Consortium of the European Community 6th Framework Programme, "Health Effects of Airline Cabin Environments in Simulated 8-Hour Flights," *Aerospace Medicine and Human Performance* 88, no. 7 (July 1, 2017): 651–56, https://doi.org/10.3357/AMHP.4366.2017; Sebastian Bao Dinh Bui et al., "Simulated Airplane Headache: A Proxy towards Identification of Underlying Mechanisms," *The Journal of Headache and Pain* 18, no. 1 (December 2017): 9, https://doi.org/10.1186/s10194-017-0724-3; Gianni Belcaro et al., "Long-Haul Flights, Edema, and Thrombotic Events: Prevention with Stockings and Pycnogenol® Supplementation (LONFLIT Registry Study)," *Minerva Cardioangiologica* 66, no. 2 (April 2018): 152–59, https://doi.org/10.23736/S0026-4725.17.04577-7.

[9] Jochen Hinkelbein et al., "Thirty Minutes of Hypobaric Hypoxia Provokes Alterations of Immune Response, Haemostasis, and Metabolism Proteins in Human Serum," *International Journal of Molecular Sciences* 18, no. 9 (August 31, 2017): 1882, https://doi.org/10.3390/ijms18091882.

[10] Bjørn Bendz et al., "Association between Acute Hypobaric Hypoxia and Activation of Coagulation in Human Beings," *The Lancet* 356, no. 9242 (November 11, 2000): 1657–58, https://doi.org/10.1016/S0140-6736(00)03165-2; Yoav Keynan, Noemi Bitterman, and Haim Bitterman,

environments are well documented to exacerbate the impact on humans, and commercial airline flight can go from sea level to 8,000 ft in relative altitude in less than 30 minutes.[11]

Treatments known to influence the immune system can also have beneficial effects. For example, dietary and supplemental polyphenols can decrease inflammation, and a polyphenol extract of french pine bark lowered edema in flyers.[12] Doctors sometimes use corticosteroids to prevent ill effects from air travel in patients with autoimmune disease or who simply want to avoid feeling worse after.[13] And while anecdotal, fasting, which is known to have anti-inflammatory effects, is commonly reported as having beneficial effects during travel across a wide variety of symptoms associated with both jet lag and inflammation.

Another intriguing line of research initially funded by the Office of Naval Research and extended by our work with fighter pilots has identified a further pro-inflammatory pathway as potentially relevant to air travel. Over the past decade, Navy-funded research into dive physiology has demonstrated that rapid decreases in pressure after breathing high partial pressures of oxygen and nitrogen, such as surfacing too quickly after a dive, can initiate an inflammatory process. Breathing compressed gas can generate oxidative stress, which increases the number of circulating microparticles. In this condition, rapid decompression can activate cytokines in the microparticles and initiate an interleukin-1b (IL-1b) inflammatory cascade. Some of the leading researchers in the field argue that this inflammatory mechanism is the primary cause of decompression sickness (DCS) in divers, not direct effects of nitrogen bubbles.[14]

While flyers are not breathing high-partial pressures of gas before flight, they do experience rapid decompression. Furthermore, it is well documented that the rapid

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"Hypoxia–Reoxygenation Contributes to Increased Frequency of Venous Thromboembolism in Air Travellers," *Medical Hypotheses* 66, no. 1 (January 1, 2006): 165–68, https://doi.org/10.1016/j.mehy.2005.05.048.

[11] Claudia M. Toussaint et al., "Altitude, Acute Mountain Sickness, and Acetazolamide: Recommendations for Rapid Ascent," *High Altitude Medicine & Biology* 22, no. 1 (March 2021): 5–13, https://doi.org/10.1089/ham.2019.0123.

[12] Belcaro et al., "Long-Haul Flights, Edema, and Thrombotic Events"; Joanna Bowtell and Vincent Kelly, "Fruit-Derived Polyphenol Supplementation for Athlete Recovery and Performance," *Sports Medicine* 49, no. 1 (February 1, 2019): 3–23, https://doi.org/10.1007/s40279-018-0998-x.

[13] Andrew Herr, "Private Communication with Medical Doctors."

[14] S. E. Bearden et al., "Oxidative Stress during a 3.5-Hour Exposure to 120 kPa(a) PO2 in Human Divers," *Undersea & Hyperbaric Medicine: Journal of the Undersea and Hyperbaric Medical Society, Inc* 26, no. 3 (1999): 159–64; Stephen R. Thom et al., "Association of Microparticles and Neutrophil Activation with Decompression Sickness," *Journal of Applied Physiology (Bethesda, Md.: 1985)* 119, no. 5 (September 1, 2015): 427–34, https://doi.org/10.1152/japplphysiol.00380.2015; Ante Obad et al., "The Effects of Acute Oral Antioxidants on Diving-Induced Alterations in Human Cardiovascular Function," *The Journal of Physiology* 578, no. Pt 3 (February 1, 2007): 859–70, https://doi.org/10.1113/jphysiol.2006.122218.

decompression and mild hypobaric hypoxia in commercial airplanes is sufficient to induce DCS when flying within 24 hours of a dive, showing that the pressure change and cabin environment in a standard commercial aircraft is sufficient to induce major inflammatory symptoms in a sensitized individual.[15] We propose that flying without diving can cause a much smaller, but still meaningful inflammatory effect along these lines, likely exacerbated by the subsequent exposure to hypobaric hypoxia for the remainder of the flight.

While the magnitude of inflammatory changes seen in studies of the hypobaric hypoxia experienced in commercial air travel is relatively small, they can still contribute to a larger effect due to amplification from sleep and circadian disruption secondary to circadian misalignment. Experimentally disrupted sleep causes increases in IL-6, TNF-α, IL-1β and other cytokines.[16] Circadian clock genes and the rhythmic release of hormones, including cortisol, also play important roles in modulating the immune system, leaving them dysregulated when in a state of circadian mismatch.[17] Thus, pro-inflammatory effects of sleep and circadian disruption can create a positive feedback loop with the pro-inflammatory effects of air travel, amplifying the overall inflammatory burden dramatically.

Identifying the role of inflammation and the potential for a positive feedback loop with the circadian elements of jet lag finally offers a model that can explain the severity of symptoms seen in travelers who suffer from jet lag for a week or more. A central role for the immune response can also explain the high degree of variability between how much jet lag individuals experience, with huge effects for some people and de minimis effects for others. Pro-inflammatory insults are known to cause highly variable effects depending on factors ranging from individuals' diets to the state of their immune system, such as relative Th1/Th2 activation, so a highly variable impact from jet lag is as expected.[18]

Altogether, existing data paint a strong picture that inflammation plays a critical role in jet lag. Perhaps the most impactful evidence, however, is that a protocol designed to mitigate the pro-inflammatory aspects of flight delivers dramatic benefits. The FlyKitt protocol uses multiple approaches to reduce inflammation, described below, and in a

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[15] J. J. Freiberger et al., "The Relative Risk of Decompression Sickness during and after Air Travel Following Diving," *Aviation, Space, and Environmental Medicine* 73, no. 10 (October 2002): 980–84.
[16] "Normative Variation in Self-Reported Sleep Quality and Sleep Debt Is Associated with Stimulated pro-Inflammatory Cytokine Production," *Biological Psychology* 82, no. 1 (September 1, 2009): 12–17, https://doi.org/10.1016/j.biopsycho.2009.04.008.
[17] J. Torres-Ruiz et al., "Air Travel, Circadian Rhythms/Hormones, and Autoimmunity," *Clinical Reviews in Allergy & Immunology* 53, no. 1 (August 1, 2017): 117–25, https://doi.org/10.1007/s12016-017-8599-2.
[18] Jun Jaekal et al., "Individual LPS Responsiveness Depends on the Variation of Toll-like Receptor (TLR) Expression Level.," 2007, https://repository.ubn.ru.nl/bitstream/handle/2066/53150/53150.pdf.

retrospective analysis, 93% of FlyKitt users described having a dramatic reduction in or full elimination of jet lag.

FlyKitt: A Novel Countermeasure System

Using our novel and patented approach, FlyKitt effectively mitigates both the inflammatory and circadian effects of long-distance travel and can do so without requiring individuals to change their schedule before the day of departure. It accomplishes this feat by providing a synergistic suite of tools:

Circadian Control Algorithm
Our artificial intelligence-driven algorithm uses data from a simple set of questions about sleep sensitivity, diet, caffeine usage, sleep timing preferences, and flight information to generate a protocol for when to eat, sleep, maximize and minimize light exposure, and use the supplements in the FlyKitt Pack, while taking into account flight schedules and times the user can sleep. The FlyKitt App gives the results as a simple, step-by-step plan with notifications and clear instructions when it's time to take an action.

Providing a customized plan is critical because the optimal schedule is often not intuitive, and following conventional advice can be detrimental. For example, depending on the direction of travel, individuals often mismanage light exposure based on recommendations to "get sunlight during the daytime at your destination." If individuals are exposed to bright blue light at their destination in the three hours before their typical wake time at their point of departure, their circadian clocks will shift backwards (earlier), which can make it difficult to stay awake until the new preferred bedtime.[19] Thus, while the advice to get light during the morning and afternoon at destination is beneficial outside of this special period, it leaves out a key caveat which can unwittingly make the time change more difficult. The FlyKitt plan includes this and many other nuances seamlessly in the user's plan.

FlyKitt Protect Supplement
FlyKitt contains two ingredients designed to block the oxidative stress and inflammation from air travel. The first is ascorbic acid, a form of Vitamin C, which is an antioxidant that can detoxify free radicals and protect from the in-flight environment. Interestingly, ascorbic acid has been shown to be especially effective at protecting from the dive-induced inflammation discussed above.[20] The second is a high-polyphenol extract

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[19] Bhanu P. Kolla and R. Robert Auger, "Jet Lag and Shift Work Sleep Disorders: How to Help Reset the Internal Clock," *Cleve Clin J Med* 78, no. 10 (2011): 675–84.
[20] Obad et al., "The Effects of Acute Oral Antioxidants on Diving-Induced Alterations in Human Cardiovascular Function."

of tart cherries. Tart cherries naturally contain polyphenols that can signal to our cells to boost their natural protective mechanisms. When these compounds are administered before a pro-inflammatory insult, cells are more resilient, produce fewer pro-inflammatory signals, and are less susceptible to the effects of inflammation.[21]

FlyKitt Sustain Supplement

In addition to blocking the proinflammatory effects of air travel, FlyKitt also includes a specially concentrated mixture of the omega-3 fatty acids EPA and DHA to tamp down inflammation that escapes the Protect supplementation and to manage the pro-inflammatory effects of shortened periods of sleep. Omega-3 fatty acids are used by the body as precursors to anti-inflammatory compounds and to support the activity of the brain's prefrontal cortex, so having a ready supply of them in the blood can enable the body to maintain healthy levels of inflammation and sustain energy and mood.[22]

FlyKitt Advance Supplement

FlyKitt also uses supplements to shift your circadian rhythm more effectively and increase the feeling of alignment with the time at your destination. Methylcobalamin and Pyridoxal 5'-Phosphate are activated forms of vitamin B12 and vitamin B6 that increase the sensitivity of the brain's circadian rhythm centers to light, temporarily decrease the amount of melatonin produced, and increase alertness. Together, these support the speed of circadian realignment, mental performance, and energy levels when you want to be awake.[23]

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[21] Jessica Amie Hill et al., "Tart Cherry Supplementation and Recovery From Strenuous Exercise: A Systematic Review and Meta-Analysis," *International Journal of Sport Nutrition and Exercise Metabolism* 31, no. 2 (January 13, 2021): 154–67, https://doi.org/10.1123/ijsnem.2020-0145; Anthony Lynn et al., "Effect of a Tart Cherry Juice Supplement on Arterial Stiffness and Inflammation in Healthy Adults: A Randomised Controlled Trial," *Plant Foods for Human Nutrition* 69, no. 2 (June 1, 2014): 122–27, https://doi.org/10.1007/s11130-014-0409-x; Keith R. Martin, Lacey Burrell, and Jennifer Bopp, "Authentic Tart Cherry Juice Reduces Markers of Inflammation in Overweight and Obese Subjects: A Randomized, Crossover Pilot Study," *Food & Function* 9, no. 10 (October 17, 2018): 5290–5300, https://doi.org/10.1039/C8FO01492B; Phillip G. Bell et al., "Recovery Facilitation with Montmorency Cherries Following High-Intensity, Metabolically Challenging Exercise," *Applied Physiology, Nutrition, and Metabolism = Physiologie Appliquee, Nutrition Et Metabolisme* 40, no. 4 (April 2015): 414–23, https://doi.org/10.1139/apnm-2014-0244.

[22] Magnus Bäck and Göran K. Hansson, "Omega-3 Fatty Acids, Cardiovascular Risk, and the Resolution of Inflammation," *The FASEB Journal* 33, no. 2 (2019): 1536–39, https://doi.org/10.1096/fj.201802445R; R. Johnsons, "Mitigating Sleep Loss: Assessment of Omega-3 Fatty Acids" (Defense Technical Information Center, 2011), https://apps.dtic.mil/sti/citations/ADA545126; Grace E. Giles et al., "Omega-3 Fatty Acids and Stress-Induced Changes to Mood and Cognition in Healthy Individuals," *Pharmacology, Biochemistry, and Behavior* 132 (May 2015): 10–19, https://doi.org/10.1016/j.pbb.2015.02.018; "Nutrition and the Circadian System - PubMed," accessed December 25, 2023, https://pubmed.ncbi.nlm.nih.gov/27221157/.

[23] S. Hashimoto et al., "Vitamin B12 Enhances the Phase-Response of Circadian Melatonin Rhythm to a Single Bright Light Exposure in Humans," *Neuroscience Letters* 220, no. 2 (December 13, 1996): 129–32, https://doi.org/10.1016/s0304-3940(96)13247-x; G. Mayer, M. Kröger, and K. Meier-Ewert, "Effects of Vitamin B12 on Performance and Circadian Rhythm in Normal Subjects," *Neuropsychopharmacology:*

FlyKitt Mellow Supplement
FlyKitt includes melatonin and magnesium glycinate to further enable the circadian shift and to make it easier to fall asleep at the appropriate time. As described above, melatonin is a natural hormone involved in maintaining your circadian rhythm and sleep quality. It does so by acting as a timing signal to the brain's sleep processes, and providing it as a supplement at the appropriate time can help to shift your circadian rhythm backwards and make it easier to fall asleep. Magnesium glycinate acts in a complimentary fashion, as it can decrease hyperactivity in the nervous system to make it easier to fall asleep when desired.[24]

Circadian Control Glasses
These blue-light-filtering glasses are designed for comfort during travel, while reducing total light exposure and blocking 99% of blue wavelengths that cause particularly strong alerting effects and shifts in the circadian phase. Wearing them at appropriate times, as directed by the Circadian Control Algorithm, can enable a faster circadian shift, easier sleep onset, and improved sleep quality.[25]

Circadian Reset Mix: This specially formulated drink mix is designed to be added to coffee to create a "hard reset" for the user's circadian rhythm. The mix of organic cane sugar, the methylcobalamin form of vitamin B12, the pyridoxal-5-phosphate form of vitamin B6, and coffee synergistically set and solidify the circadian rhythm in both the brain and body via provoking an intentional insulin release, influencing the suprachiasmatic nucleus's circadian pacemaker, decreasing adenosine signaling, and decreasing plasma melatonin. While we rarely recommend consuming added sugar, in this case the benefits of resetting the circadian rhythm outweigh the consequences from using it, especially when followed by the FlyKitt Protect and Sustain supplements at the proper time point as directed in the user's plan.[26]

Official Publication of the American College of Neuropsychopharmacology 15, no. 5 (November 1996): 456–64, https://doi.org/10.1016/S0893-133X(96)00055-3.

[24] Gregory M. Brown et al., "Melatonin and Its Relevance to Jet Lag," *Travel Medicine and Infectious Disease* 7, no. 2 (March 2009): 69–81, https://doi.org/10.1016/j.tmaid.2008.09.004; Forrest H. Nielsen, LuAnn K. Johnson, and Huawei Zeng, "Magnesium Supplementation Improves Indicators of Low Magnesium Status and Inflammatory Stress in Adults Older than 51 Years with Poor Quality Sleep," *Magnesium Research* 23, no. 4 (December 2010): 158–68, https://doi.org/10.1684/mrh.2010.0220.

[25] Kolla and Auger, "Jet Lag and Shift Work Sleep Disorders."

[26] Tiffany Fougeray et al., "The Hepatocyte Insulin Receptor Is Required to Program the Liver Clock and Rhythmic Gene Expression," *Cell Reports* 39, no. 2 (April 12, 2022): 110674, https://doi.org/10.1016/j.celrep.2022.110674; Tina M. Burke et al., "Effects of Caffeine on the Human Circadian Clock in Vivo and in Vitro," *Science Translational Medicine* 7, no. 305 (September 16, 2015): 305ra146, https://doi.org/10.1126/scitranslmed.aac5125; Hashimoto et al., "Vitamin B12 Enhances the Phase-Response of Circadian Melatonin Rhythm to a Single Bright Light Exposure in Humans"; Mayer, Kröger, and Meier-Ewert, "Effects of Vitamin B12 on Performance and Circadian Rhythm in Normal Subjects."

For the user’s safety, all of the dietary supplements in the FlyKitt system are FDA cleared, independently tested and validated by the NSF Certified for Sport program, produced in the USA, and non-prescription.

The integration of the diverse tools above explains the exceptional benefits of the FlyKitt system. In studies, less than 10% of people can typically travel long distances without jet lag. In comparison, a retrospective review of 110 trips using FlyKitt showed that more than 93% of travelers experienced minimal to no jet lag.

For more information, please contact Fount at flykittsupport@fount.bio.