

COMMENTARY

Potential Risks of Blocking GDF15-Based Brain Energy Sensing

Alan A. Cohen^{1,2}   | Martin Picard^{2,3}

¹Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA | ²The Butler Columbia Aging Center, Mailman School of Public Health, Columbia University, New York, New York, USA | ³Department of Psychiatry and Neurology, Columbia University Irving Medical Center, New York, New York, USA

Correspondence: Alan A. Cohen (alan.cohen@columbia.edu)

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Growth differentiation factor 15 (GDF15) is rapidly becoming one of the most studied endogenous signaling proteins. Secreted from energetically stressed cells, GDF15 is known as a “metabokine.” GDF15 can be released into circulation by multiple organ systems across pathologies, making it the most robust pan-diagnostic illness marker [1]. Among ~3000 circulating proteins in 53,026 individuals from the UK Biobank, GDF15 was the strongest prognostic indicator of pathology, physical and cognitive disability, and all-cause mortality [1], calling clinical attention and inviting GDF15-targeting therapies, notably ponesegromab. As a monoclonal antibody therapeutic, ponesegromab acts by neutralizing GDF15 and preventing binding to its cognate receptor in the brainstem, where it would otherwise activate visceral malaise and stress cascades. As one of the circulating proteins most strongly associated with multimorbidity and aging, modulation of GDF15 levels might be expected *prima facie* to have benefits for a wide range of aging-related conditions, including heart failure, sarcopenia/cachexia, and frailty, and indeed various clinical trials are underway.

Despite this promise, there is also reason for caution in the use of ponesegromab and other GDF15 signaling antagonists. We recently proposed the brain–body energy conservation (BEC) model of aging, which suggests that many adverse aspects of aging are compensatory responses to other pathologies, and more specifically that the energetic distress indicated by GDF15 and other cytokines is a signal that the brain uses to reallocate energy to where it is most needed in times of scarcity, such as during frailty in aging [2]. GDF15 appears to trigger a dual energy conservation/mobilization response [3]. In mice, GDF15 signaling on the brain stimulates a torpor-like sickness

behavior phenotype that *conserves energy*, promoting survival. Simultaneously, GDF15 stimulates both the hypothalamic–pituitary–adrenal axis and sympathetic arm of the autonomic nervous system that elevate blood glucose/lipids to fuel the increase in energy expenditure that comes with turning on stress responses [4]. In humans, blood GDF15 increases with unsustainable exercise training load (i.e., overtraining), correlating with reduced maximal heart rate—presumably a response to limit damage from excessively intense activity [5].

The central role of GDF15 as an energy-regulating hormone [3] is consistent with our emerging understanding of inflammation and cytokine/chemokine/metabokine networks not as problematic actors in and of themselves, but as messengers signaling a wide diversity of stressors to the brain and the rest of the body, thereby facilitating appropriate physiological and behavioral responses [6]. Cytokine and metabolite signaling on the brain is a form of “metaboception”—similar to interoception and nociception—which enables the brain to receive information and respond to internal threats, including energy deficits [3]. Analogous to austerity measures governments may take under fiscal stress, many of these responses may result in adverse effects; nonetheless, they are foreseeable and generally acceptable adverse effects that are triggered to avoid more severe outcomes, including death.

The BEC model leads to several clear predictions: under conditions of energetic stress such as frailty, cancer, and pregnancy, suppression of GDF15 should lead to marked improvements in primary endpoints such as weight or muscle loss, nausea, vomiting, physical activity, and feeling of energy. However, these

improvements are expected to come at a price: the brain is no longer detecting a severe energy shortage in the body, and therefore stops making the kinds of energy rationing and reallocation decisions that may be needed to stave off disaster (i.e., death or accelerating decline). Side effects are thus predicted to be potentially severe, but also to appear at longer timescales and at off-target aspects of physiology, which may be hard to predict. Because clinical trials are generally powered to detect benefits in short-term primary endpoints, not in unknown, off-target, long-term side effects, clinical trials would be expected to show clear benefits of GDF15 suppression. However, they may fail to show relevant long-term harms from treatment. Such an approach emphasizing short-term gain but blind to potential harmful consequences would lead to approvals and clinical guidelines that lack a full, balanced picture of risks and benefits, including the potential for harm of patients.

Indeed, two recent studies appear to confirm this concern. In a recent article, Groarke et al. [7] demonstrated substantial benefits of ponesegromab for the treatment of cancer cachexia. The Phase 2, randomized, double-blind, 12-week trial with four arms (placebo, 100, 200, 400 mg Ponesegromab) appears well conducted and the results are convincing. The study showed improvement in the treatment groups in the primary endpoint, dose-dependent weight gain, as well as moderate improvements in secondary endpoints such as physical activity, and trends toward decreases in cachexia-associated adverse events such as nausea, vomiting, and diarrhea; all anticipated biobehavioral effects of GDF15 signaling on the brain [8]. The trial also reported adverse events in 70% of the ponesegromab-treated

patients, compared to 80% in placebo-treated patients, generating enthusiasm to pursue subsequent drug development phases.

The results of the Groarke et al. study are as predicted by the BEC model of aging, and therein lies the worry. The team carefully measured the short-term benefits predicted by suppression of the GDF15 response mechanism, observing the predictable physiological, behavioral, and subjective consequences of preventing the brain from sensing systemic energetic stress. However, the trial was underpowered and its follow-up period naturally insufficient to detect the longer-term, more severe adverse events that are also predicted by the BEC model. Indeed, though not statistically significant, treatment groups exhibited 33% higher rates of both severe adverse events (32% all ponesegromab groups vs. 24% placebo) and mortality (14.8% vs. 11.1%). In the 400 mg group specifically, 9 of the 50 (18%) patients died, compared to 5 of the 45 (11.1%) placebo-treated patients—a 7% absolute higher mortality risk, or a 62% elevation relative the placebo-treated group.

Supporting our concerns, the enthusiasm in the case of cancer cachexia was not replicated in a second study when ponesegromab was used to treat heart failure [9]. Although weight gain was observed in the treatment group, there was a hazard ratio of 2.24 for the primary outcome—worsening of heart failure events or death—largely driven by the heart failure events. In this case, power seems to have been sufficient to detect the harms relative to the benefits. In both studies, harms and benefits align perfectly with BEC predictions, which we outline in Figure 1.

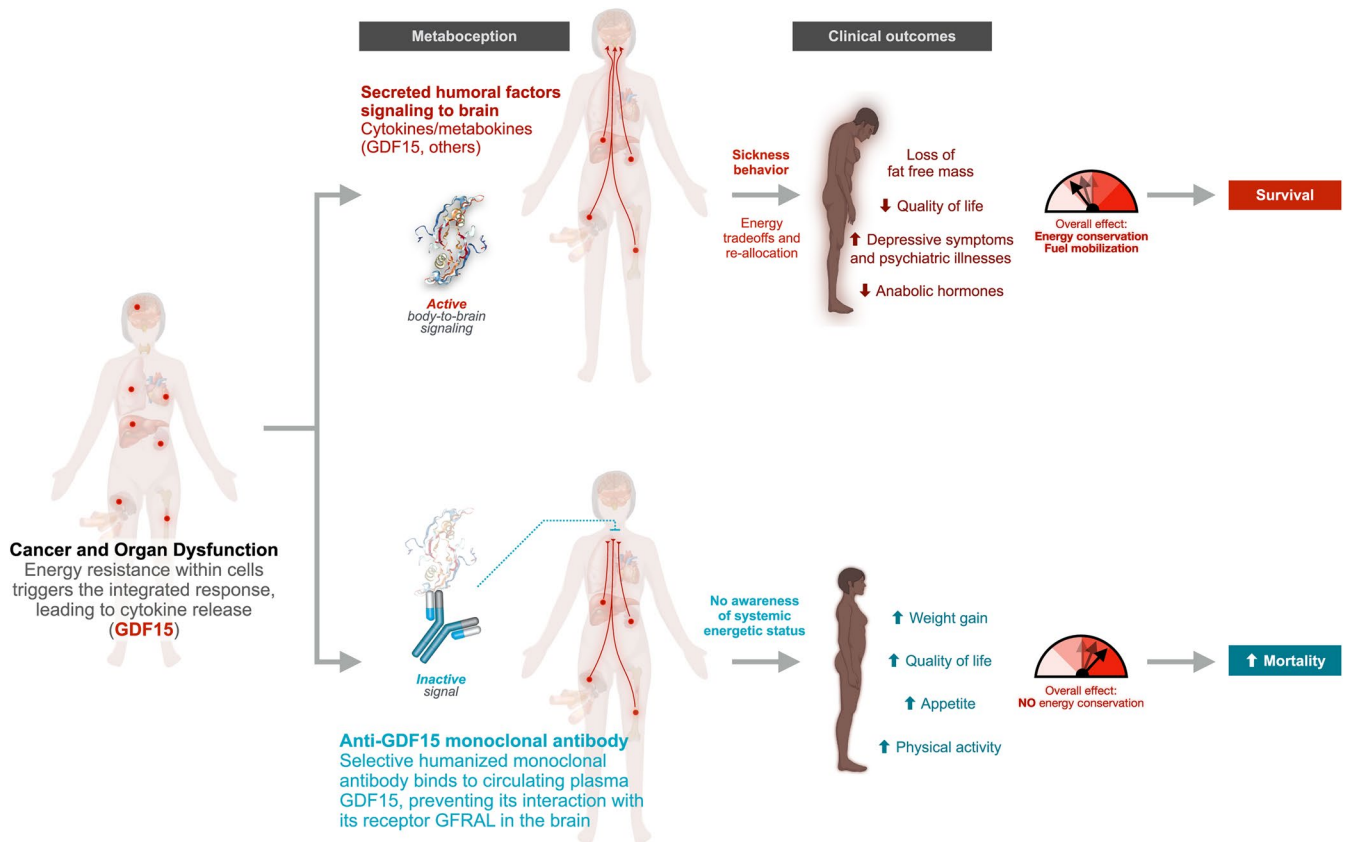


FIGURE 1 | Predicted harms and benefits of GDF15 suppression under the BEC model.

As with aging more generally [10], research on GDF15 suppression should aim to balance the risks of long-term, harder-to-detect harm with short-term gain. This balance is particularly salient given the strong mechanistic reasons to suspect that such trade-offs are being regulated by the targeted biological pathways [10]. Indeed, various examples are emerging of cases where aggressive treatment to restore “optimal” or “normal” function may short-circuit adaptive mechanisms that help prevent death or severe adverse outcomes, either harming or failing to improve on less-aggressive strategies. Examples include aggressive vasopressor treatment to restore blood pressure after traumatic injury [11] and early parenteral nutrition in children and adults in the ICU that does not improve outcomes, but, in fact, increases mortality [12].

Although we raise questions around the insufficiently characterized long-term effects of anti-GDF15 therapies, we applaud and align with Groarke et al.’s enthusiasm regarding the potential acute functional and biobehavioral effects of ponesegromab. For example, in the context of palliative care, increased weight and decreased nausea and vomiting would often be valuable, even at the expense of a potentially shorter lifespan. Moreover, the body’s internal homeostatic mechanisms may not always make the “right” decisions, particularly in the context of advanced cancer, where natural selection is usually blind and may not have optimized every detail of the regulation. Nonetheless, it is precisely in these life-or-death situations where we need to be cautious about alleviating symptoms at the expense of survival, particularly as we begin to understand how the body itself is employing sophisticated internal algorithms to balance competing priorities and make necessary sacrifices to ensure survival. Treated patients and regulators should have access to data from adequately powered studies that can reveal and balance the risk–benefit tradeoffs that new treatments offer.

Accordingly, we call for larger trials with considerably longer follow ups to holistically evaluate the full effects of anti-GDF15 therapies on muscle mass and weight, biobehavioral outcomes, and mortality. Data from larger trials would provide higher-precision evidence to help non-palliative patients and families make decisions about the short-term gains relative to potential risks. For example, should the numbers from Groarke et al.’s Phase 2 trial hold up, patients and families offered the 400 mg ponesegromab treatment would need to accept a 62% increase in mortality risk in return for potential improvements in cachexia symptoms. Thus, we additionally recommend that severe adverse events and death continue to be monitored in the open label extension of Groarke et al.’s study, including with intention-to-treat analyses.

There is a common conception that inflammation and related signals such as GDF15 are simply nefarious. This conception makes the age-old error of confounding correlation and causation—GDF15 is indeed strongly associated with a wide variety of adverse health outcomes, both cross-sectionally and longitudinally [1]. It also fails to understand the evolutionary origins of these signaling networks and the crucial role they play in maintaining homeostasis, particularly under adverse conditions [2]. Similar principles underlie recent changes in thinking around the roles of reactive oxygen species in aging [13] and amyloid β in neurodegeneration [14, 15]. Our argument

here builds upon a first-principles, energetic rationale that recognizes the energy tradeoffs that support health and resilience. Clinical trials are rarely designed with sufficient breadth and time to measure the complex priorities being balanced by the energetically challenged systems we seek to manipulate in the hopes of returning the patient to health. On this basis, we call for caution to avoid shooting the messenger, the body-to-brain signaling metabolite GDF15.

Author Contributions

A.A.C. and M.P. jointly conceived of and wrote the manuscript.

Disclosure

No role for any sponsors.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Y. T. Deng, J. You, Y. He, et al., “Atlas of the Plasma Proteome in Health and Disease in 53,026 Adults,” *Cell* 188, no. 1 (2025): 253–271.e7.
2. E. D. Shaulson, A. A. Cohen, and M. Picard, “The Brain–Body Energy Conservation Model of Aging,” *Nature Aging* 4, no. 10 (2024): 1354–1371.
3. C. Liu, M. Picard, E. Epel, T. Wager, L. Barrett, and Q. Huang, “Mitocaption via the Metabokine GDF15 Drives Human Health and Behaviors,” [osf.io, https://osf.io/preprints/osf/ekj54](https://osf.io/preprints/osf/ekj54).
4. L. Engström Ruud, F. Font-Gironès, J. Zajdel, et al., “Activation of GFRAL+ Neurons Induces Hypothermia and Glucoregulatory Responses Associated With Nausea and Torpor,” *Cell Reports* 43, no. 4 (2024): 113960.
5. C. Poffé, M. Ramaekers, R. Van Thienen, and P. Hespel, “Ketone Ester Supplementation Blunts Overreaching Symptoms During Endurance Training Overload,” *Journal of Physiology* 597, no. 12 (2019): 3009–3027.
6. R. Medzhitov, “The Spectrum of Inflammatory Responses,” *Science* 374, no. 6571 (2021): 1070–1075.
7. J. D. Groarke, J. Crawford, S. M. Collins, et al., “Ponesegromab for the Treatment of Cancer Cachexia,” *New England Journal of Medicine* 391, no. 24 (2024): 2291–2303.
8. S. M. Lockhart, V. Saudek, and S. O’Rahilly, “GDF15: A Hormone Conveying Somatic Distress to the Brain,” *Endocrine Reviews* 41, no. 4 (2020): 610–642.
9. D. Berg, *GARDEN-TIMI 74: GDF-15 Neutralization in Heart Failure* (Heart Failure Society of America, 2025).
10. A. A. Cohen, J. R. Beard, L. Ferrucci, et al., “Balancing the Promise and Risks of Geroscience Interventions,” *Nature Aging* 5, no. 1 (2025): 4–8.
11. F. Lamontagne, F. Lamontagne, A. Richards-Belle, et al., “Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial,” *JAMA* 323, no. 10 (2020): 938–949.
12. T. Fizev, D. Kerklaan, D. Mesotten, et al., “Early Versus Late Parenteral Nutrition in Critically Ill Children,” *New England Journal of Medicine* 374, no. 12 (2016): 1111–1122.
13. J. P. de Magalhaes and G. M. Church, “Cells Discover Fire: Employing Reactive Oxygen Species in Development and Consequences for Aging,” *Experimental Gerontology* 41, no. 1 (2006): 1–10.

14. T. Fulop, C. Ramassamy, S. Lévesque, et al., “Viruses—A Major Cause of Amyloid Deposition in the Brain,” *Expert Review of Neurotherapeutics* 23, no. 9 (2023): 775–790.
15. D. K. V. Kumar, S. H. Choi, K. J. Washicosky, et al., “Amyloid- β Peptide Protects Against Microbial Infection in Mouse and Worm Models of Alzheimer’s Disease,” *Science Translational Medicine* 8, no. 340 (2016): 340ra72.