Reply to: Postbiotics — when simplification fails to clarify

Seppo Salminen, Maria Carmen Collado, Akihito Endo, Colin Hill, Sarah Lebeer, Eamonn M. M. Quigley, Mary Ellen Sanders, Raanan Shamir, Jonathan R. Swann, Hania Szajewska and Gabriel Vinderola

Science thrives on open debate, which is particularly true when it comes to novel concepts, such as the emerging field of postbiotics. We have carefully considered the opinion of Aguilar-Toalá et al. in their Correspondence on our Consensus Statement[1] (Salminen, S. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 649–667 (2021)), and, although they raise important points (Aguilar-Toalá, J. E. et al. Postbiotics — when simplification fails to clarify. *Nat. Rev. Gastroenterol. Hepatol.* https://doi.org/10.1038/s41575-021-00521-6 (2021))[2], respectfully, we stand by the arguments made in our original paper.

Aguilar-Toalá et al.[2] state that the term 'postbiotic' was already adequately defined in 2013 (REF.[2]) and the ISAPP definition added confusion, not clarity, to the field. However, six definitions of postbiotics had been published prior to our paper[3–8], all of which differed on some important aspects (Supplementary Table 1), indicating that consensus around a single definition had not been achieved by the scientific community. The ISAPP panel had several concerns with the 2013 (REF.[3]) definition: it requires a probiotic as a progenitor, creating the untenable situation in which a metabolite produced by an established probiotic is considered a postbiotic whereas the same metabolite produced by a non-probiotic microorganism is not; it does not distinguish between a product administered to a host and microbial metabolites that could be produced in situ; and it uses the phrase "beneficial effects to the host in a direct or indirect way" and does not specify a health benefit, leaving the door open to further debate on what types of benefit could be encompassed. Aguilar-Toalá et al. state that the 2013 definition requires a "demonstrated benefit for the host (which would encompass health benefits)"; it does not encompass inanimate microorganisms, a topic of intense research, which we considered essential to capture under the latest postbiotic definition, to maintain broad and meaningful '-biotic' categories.

We disagree that valid markers of efficacy in products containing inactivated microorganisms are needed. Probiotics, prebiotics and synbiotics are all defined by their composition and function. The only markers of efficacy that are required are properly conducted efficacy trials and sufficient description of the '-biotic' substance. For each product, it is incumbent upon product developers to define parameters needed for consistent production, methods for quantification and approaches to quality assurance.

The ISAPP definition of postbiotic focuses on inanimate (a term explained in our paper) microbial cells as we believe this approach is the best use of the term 'postbiotic' (meaning 'after life', not 'from life') and further embraces innovation in a growing and evolving scientificconcept that encompasses the potential health-conferring benefits of dead and/or inactivated cells. We did not see value in generating a term for molecules, which typically are already well-defined and named. We recognize that microbial metabolites are important, albeit not essential, components of postbiotics, and our definition encompasses their inclusion. If specific metabolites are not identified, then the term cell-free supernatant is sufficient. We remain convinced that the complex preparations with dead and/or inactivated cells that provide a health benefit are well described by the term 'postbiotics'.

This field is in its infancy and we feel we have an opportunity now to coalesce around a more encompassing term. First definitions are not necessarily the best — consider the first definition published for probiotics in 1965 was "substances secreted by one microorganism that stimulate another microorganism"[9]. In the case of postbiotics, we felt that available definitions were not sufficient and we proposed an alternative that encompasses current science[2]. The final decision on the most appropriate and useful definition will rest with the scientific community and regulatory authorities.

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1. Salminen, S. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 649–667 (2021).
2. Aguilar-Toalá, J. E. et al. Postbiotics — when simplification fails to clarify. *Nat. Rev. Gastroenterol. Hepatol.* https://doi.org/10.1038/s41575-021-00521-6 (2021).
3. Tsilingiri, K. & Rescigno, M. Postbiotics: what else? *Benef. Microbes* **4**, 101–107 (2013).
4. Aguilar-Toalá, J. E. et al. Postbiotics: an evolving term within the functional foods field. *Trends Food Sci. Technol.* **75**, 105–114 (2018).
5. Collado, M. C., Vinderola, G. & Salminen, S. Postbiotics: facts and open questions. A position paper on the need for a consensus definition. *Benef. Microbes* **10**, 711–719 (2019).
6. Foo, H. L., Loh, T. C., Mutalib, N. E. A. & Rahim, R. A. in *Microbiome and Metabolome in Diagnosis, Therapy, and other Strategic Applications* Ch. 21 (eds Faintuch, J. & Faintuch, S.) 201–211 (Academic Press, 2019).
7. Johnson, C. N. et al. Administration of a postbiotic causes immunomodulatory responses in broiler gut and reduces disease pathogenesis following challenge. *Microorganisms* **7**, 268 (2019).
8. Wegh, C. A. M., Geerlings, S. Y., Knol, J., Roeselers, G. & Belzer, C. Postbiotics and their potential applications in early life nutrition and beyond. *Int. J. Mol. Sci.* **20**, 4673 (2019).
9. Lilly, D. M. & Stillwell, R. H. Probiotics: growth-promoting factors produced by microorganisms. *Science* **147**, 747–748 (1965).

Competing interests
S.S. serves on the board of ISAPP and has been a speaker in meetings funded by Industry, Nestle Nutrition and Institute Danone. M.C.C. has participated as a speaker for HIPP, Danone, Nutricia, Nestlé Nutrition Institute and Mead Johnson. A.E. has led industry-sponsored research projects with supports from B Food Science and Takanashi Milk Products, Japan, and has been a speaker for the companies. C.H. serves on the board of ISAPP, is a consultant to Artugen Therapeutics developing a live biotherapeutic, and has research grants with several industry partners, including ADARE Pharmaceuticals, manufacturers of Lacteol. S.L. serves on the academic board of ISAPP and has research grants with several industry partners, such as Yun. She has been

compensated for speaking by Yakult. E.M.M.Q. serves on the board of ISAPP and holds equity in Alimentary Health, serves as a consultant to 4D Pharma, Alimentary Health, Allergan, Biocodex, Ironwood, Salix, Takeda and Vibrant and has research support from 4D Pharma, Biomerica and Vibrant. M.E.S. has been compensated for speaking engagements or for consulting from Associated British Foods, Bayer, California Dairy Research Foundation, Cargill, Danone Research, Danone USA, Fairlife, General Mills, GlaxoSmithKline, JJ Heimbach, Kellogg, Kerry, Mead Johnson, Medscape, PepsiCo, Pfizer, Probi, Procter & Gamble, Trouw Nutrition, Visalia Dairy Company, Winclove Probiotics and Yakult. R.S. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott, Danone, and Nestlé. J.R.S. has led industry-sponsored research projects with support from AstraZeneca, Danone, Servier and Vitacress. H.S. has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Arla, Biogaia, Biocodex, Ch. Hansen, Danone, Nestlé, Nestlé Nutrition Institute, Nutricia and Merck. G.V. has led industry-sponsored research projects on dairy products and probiotics. These projects were independently carried out and had no influence on the content of this manuscript. He is member of the Argentinian board of the Yoghurt in Nutrition Initiative (YINI, Danone Argentina) and serves on the board of ISAPP.

Supplementary information

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