Commentary

Call for a holistic framework for cancer immunotherapy

Maximilian Boesch, PhD [1]; Florent Baty, PhD[1]; Tobias Kowatsch, PhD[2,3,4]; Dominik Wolf, MD[5]; Martin Früh, MD[6,7]; and Martin H. Brutsche, MD, PhD[1]

Cancer immunotherapy using immune checkpoint blockers (ICBs) has revolutionized clinical oncology. In exceptional responders, checkpoint inhibition enables long-term remission and potentially a cure, even in the metastatic setting, whereas there is still a significant proportion of patients without prolonged benefit. The complexity regulating the likelihood of ICB response can at least in part be explained by baseline variables such as tumor mutational burden,[1] immune checkpoint molecule expression levels (e.g., PD-1/PD-L1)[2] and tumor T-cell infiltration.[3] Unfortunately, these factors cannot be deliberately modulated therapeutically and therefore play only a minor role when envisioning treatment-enhancing strategies. Alternatively, emerging variables may easily be amenable to manipulation to optimize ICB response rates and durability. In this regard, nonpharmacological approaches such as specific health interventions and treatment timing have recently gained momentum, proposing a more holistic framework for cancer immunotherapy and management within an interdisciplinary, cross-functional environment.

Because diet influences the host microbiome,[4] which in turn affects ICB efficacy,[5,6] targeted dietary interventions represent a promising strategy to specifically modulate the microbial landscape and optimize cancer immunotherapy.[7] This concept is underscored by recent work in melanoma demonstrating an association of high fiber intake (i.e., ≥20 g/d) with improved progression-free survival under ICB therapy.[8] Mechanistically, a high-fiber diet promotes tumor T-cell infiltration as well as the expression of genes related to T-cell activation and effector function in murine models.[8] The concept of modulating ICB efficacy by dietary habits is further supported by prospective data from 101 patients with cancer on a fasting-mimicking diet (FMD) (NCT03340935).[9] The cyclic, 5-day dietary intervention was not only safe but also induced distinct metabolic changes and extensively reshaped the cancer immunome.[9] More specifically, FMD reduced blood glucose, insulin, and IGF1 levels, contracted circulating suppressive myeloid- and T-cell compartments, and enhanced intratumoral T-cell activation and cytotoxicity.[9] Notably, many of these effects were independent from the underlying tumor type and the particular cancer therapy used. This suggests that ICB-treated patients may also benefit from fasting/FMD. Importantly, because many cancer patients are cachectic or otherwise weak, the immune-modulatory and metabolic effects of fasting/FMD may, in the future, be more appropriately modeled by calorie restriction mimetics.[10]

In fit or only mildly impaired patients, physical activity, generally known to reduce cancer risk and cancer-specific morbidity and mortality,[11] may promote anticancer immunity and potentiate ICB efficacy. In preclinical models, aerobic exercise fosters systemic immune mobilization and induces the accumulation of activated, tumor-infiltrating T cells expressing IL-15Rα, finally leading to tumor growth retardation and sensitization to ICB treatment.[12] Higher T-cell infiltration and resensitization to checkpoint blockade were also observed in a recent preclinical study on exercise training in breast cancer.[13] Mechanistically, exercise-induced T-cell infiltration was mediated by CXCR3 signaling and associated with higher pericyte coverage, vessel normalization, and reduced hypoxia.[13] Notably, an exercise-dependent increase in tumor T-cell infiltration was also observed in men, suggesting clinical relevance.[12] Exercise training may further have a "conditioning effect" because prediagnostic physical activity correlates with higher T-cell infiltration in clinical cancer samples.[14] Importantly, physical activity also substantially improves quality of life and therapy tolerability in patients with cancer, thus having beneficial effects far beyond immune modulation.[15–17]

Accumulating evidence suggests that psychological distress negatively affects cancer outcomes. In murine models, stress-induced surges in glucocorticoid levels subvert type I interferon responses in certain immune cells, ultimately dampening anticancer immune surveillance and reducing therapeutic tumor control.[18] Similarly, a negative mood in cancer patients associates with plasma cortisol levels and expression of the glucocorticoid-inducible factor TSC22D3 in circulating leukocytes.[18] More broadly, stress-induced upregulation of glucocorticoids and other immunosuppressive factors blunts

Corresponding Author: Maximilian Boesch, Lung Center, Cantonal Hospital St. Gallen, Rorschacherstrasse 95, CH-9007 St. Gallen, Switzerland (maximilian.boesch@kssg.ch).

[1]Lung Center, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [2]Institute for Implementation Science in Health Care, University of Zurich, Zurich, Switzerland; [3]School of Medicine, University of St. Gallen, St. Gallen, Switzerland; [4]Centre for Digital Health Interventions, Department of Technology, Management, and Economics, ETH Zurich, Zurich, Switzerland; [5]Department of Internal Medicine V (Hematology and Oncology) and Comprehensive Cancer Center Innsbruck (CCCI), Medical University of Innsbruck, Innsbruck, Austria; [6]Department of Medical Oncology and Hematology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; [7]Department of Medical Oncology, University Hospital Bern, Bern, Switzerland

DOI: 10.1002/cncr.34467, **Received:** August 5, 2022; **Accepted:** August 22, 2022, **Published online** Month 00, 2022 in Wiley Online Library (wileyonlinelibrary.com)

immune responsiveness generally, which is supported by the observation that vaccine efficiency is reduced in stressed individuals.[19,20]

Finally, the immune system is tightly controlled by circadian rhythms, entailing oscillatory peaks of blood leukocyte numbers regulated by time-of-day-dependent variations in immune cell mobilization, trafficking, homing, and tissue drainage.[21] The relevance of circadian rhythmicity for cancer immunotherapy has recently been demonstrated in a retrospective, propensity score-matched analysis of 146 patients with melanoma showing that ICB infusions later than 4:30 pm were linked to inferior overall survival.[22] Again, these data are supported by other findings, including the observation that vaccine-induced immune responses are superior when vaccinating at earlier times in the day.[23–25]

We would like to raise awareness of the complexity of cancer immunotherapy and its dependence on various "soft variables," including physiological, environmental, behavioral, and psychological factors. Although the requirement for interdisciplinary, cross-functional cancer care has been partly considered (e.g., by installing interprofessional tumor boards under the umbrella of comprehensive cancer centers),[26,27] little focus has so far been put on collateral health factors such as diet, physical activity, mood improvement, and stress management. Thus, there is an urgent need to better embed cancer immunotherapy in a more holistic framework of patient-centric support interventions. Digital tools will help to achieve this goal and implement the required behavioral and lifestyle changes (e.g., diet, physical activity, mood/mindfulness, stress management apps).[28] Moreover, ICB infusion timing based on circadian rhythmicity represents a highly interesting concept that warrants further investigation in prospective clinical trials.

The holistic approach proposed here will advance the field of precision (immune-) oncology by broadening our view on the huge, yet untapped, potential to improve outcomes by modulating lifestyle-linked and psychological resilience-determining variables.

FUNDING INFORMATION

Original research inspiring this work was kindly supported by the Lungenliga St. Gallen-Appenzell based in St. Gallen, Switzerland (grant to Maximilian Boesch), and the Stiftung Propter Homines based in Vaduz, Principality of Liechtenstein (grant to Maximilian Boesch).

AUTHOR CONTRIBUTIONS

Maximilian Boesch: Writing – first draft and writing – final version. **Florent Baty:** writing – final version. **Tobias Kowatsch:** writing – final version. **Dominik Wolf:** writing – final version. **Martin Früh:** writing – final version. **Martin H. Brutsche:** Writing – first draft and writing – final version.

CONFLICTS OF INTEREST

Maximilian Boesch serves as an advisor for Pantec Biosolutions AG. The other authors declare no potential conflicts of interest.

REFERENCES

1. Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet*. 2019;51(2):202-206. doi:10.1038/s41588-018-0312-8
2. Doroshow DB, Bhalla S, Beasley MB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. *Nat Rev Clin Oncol*. 2021;18(6):345-362. doi:10.1038/s41571-021-00473-5
3. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568-571. doi:10.1038/nature13954
4. Wastyk HC, Fragiadakis GK, Perelman D, et al. Gut-microbiota-targeted diets modulate human immune status. *Cell*. 2021;184(16):4137-4153 e14. doi:10.1016/j.cell.2021.06.019
5. Boesch M, Baty F, Albrich WC, et al. Local tumor microbial signatures and response to checkpoint blockade in non–small cell lung cancer. *Onco Targets Ther*. 2021;10(1):1988403. doi:10.1080/2162402X.2021.1988403
6. Boesch M, Baty F, Rothschild SI, et al. Tumour neoantigen mimicry by microbial species in cancer immunotherapy. *Br J Cancer*. 2021;125:313-323. doi:10.1038/s41416-021-01365-2
7. Matson V, Gajewski TF. Dietary modulation of the gut microbiome as an immunoregulatory intervention. *Cancer Cell*. 2022;40(3):246-248. doi:10.1016/j.ccell.2022.02.014
8. Spencer CN, McQuade JL, Gopalakrishnan V, et al. Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response. *Science*. 2021;374(6575):1632-1640. doi:10.1126/science.aaz7015
9. Vernieri C, Fuca G, Ligorio F, et al. Fasting-mimicking diet is safe and reshapes metabolism and antitumor immunity in patients with cancer. *Cancer Discov*. 2022;12(1):90-107. doi:10.1158/2159-8290.CD-21-0030
10. Turbitt WJ, Demark-Wahnefried W, Peterson CM, Norian LA. Targeting glucose metabolism to enhance immunotherapy: emerging evidence on intermittent fasting and calorie restriction mimetics. *Front Immunol*. 2019;10:1402. doi:10.3389/fimmu.2019.01402
11. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical activity in cancer prevention and survival: a systematic review. *Med Sci Sports Exerc*. 2019;51(6):1252-1261. doi:10.1249/MSS.0000000000001937
12. Kurz E, Hirsch CA, Dalton T, et al. Exercise-induced engagement of the IL-15/IL-15Ralpha axis promotes antitumor immunity in pancreatic cancer. *Cancer Cell*. 2022;40:720-737.e5. doi:10.1016/j.ccell.2022.05.006
13. Gomes-Santos IL, Amoozgar Z, Kumar AS, et al. Exercise training improves tumor control by increasing CD8(+) T-cell infiltration via CXCR3 signaling and sensitizes breast cancer to immune checkpoint blockade. *Cancer Immunol Res*. 2021;9(7):765-778. doi:10.1158/2326-6066.CIR-20-0499
14. Renman D, Gylling B, Vidman L, et al. Density of CD3(+) and CD8(+) cells in the microenvironment of colorectal cancer according to prediagnostic physical activity. *Cancer Epidemiol Biomarkers Prev*. 2021;30(12):2317-2326. doi:10.1158/1055-9965.EPI-21-0508
15. Matzka M, Mayer H, Kock-Hodi S, et al. Relationship between resilience, psychological distress and physical activity in cancer patients: a cross-sectional observation study. *PLoS One*. 2016;11(4):e0154496. doi:10.1371/journal.pone.0154496
16. Groen WG, Naaktgeboren WR, van Harten WH, et al. Physical fitness and chemotherapy tolerance in patients with early-stage breast cancer. *Med Sci Sports Exerc*. 2022;54(4):537-542. doi:10.1249/MSS.0000000000002828
17. Gerritsen JK, Vincent AJ. Exercise improves quality of life in patients with cancer: a systematic review and meta-analysis of randomised controlled trials. *Br J Sports Med*. 2016;50(13):796-803. doi:10.1136/bjsports-2015-094787
18. Yang H, Xia L, Chen J, et al. Stress-glucocorticoid-TSC22D3 axis compromises therapy-induced antitumor immunity. *Nat Med*. 2019;25(9):1428-1441. doi:10.1038/s41591-019-0566-4

19. Glaser R, Kiecolt-Glaser JK, Bonneau RH, Malarkey W, Kennedy S, Hughes J. Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. *Psychosom Med*. 1992;54(1):22-29. doi:10.1097/00006842-199201000-00005
20. Madison AA, Shrout MR, Renna ME, Kiecolt-Glaser JK. Psychological and behavioral predictors of vaccine efficacy: considerations for COVID-19. *Perspect Psychol Sci*. 2021;16(2):191-203. doi:10.1177/1745691621989243
21. Wang C, Lutes LK, Barnoud C, Scheiermann C. The circadian immune system. *Sci Immunol* 2022;7(72):eabm2465. doi:10.1126/sciimmunol.abm2465
22. Qian DC, Kleber T, Brammer B, et al. Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): a propensity score-matched analysis of a single-centre, longitudinal study. *Lancet Oncol*. 2021;22(12):1777-1786. doi:10.1016/S1470-2045(21)00546-5
23. de Bree LCJ, Mourits VP, Koeken VA, et al. Circadian rhythm influences induction of trained immunity by BCG vaccination. *J Clin Invest*. 2020;130(10):5603-5617. doi:10.1172/JCI133934
24. Long JE, Drayson MT, Taylor AE, Toellner KM, Lord JM, Phillips AC. Morning vaccination enhances antibody response over afternoon vaccination: a cluster-randomised trial. *Vaccine*. 2016;34(24):2679-2685. doi:10.1016/j.vaccine.2016.04.032
25. Cermakian N, Stegeman SK, Tekade K, Labrecque N. Circadian rhythms in adaptive immunity and vaccination. *Semin Immunopathol*. 2022;44(2):193-207. doi:10.1007/s00281-021-00903-7
26. Soukup T, Lamb BW, Arora S, Darzi A, Sevdalis N, Green JS. Successful strategies in implementing a multidisciplinary team working in the care of patients with cancer: an overview and synthesis of the available literature. *J Multidiscip Healthc*. 2018;11:49-61. doi:10.2147/JMDH.S117945
27. Prabhu Das I, Baker M, Altice C, Castro KM, Brandys B, Mitchell SA. Outcomes of multidisciplinary treatment planning in US cancer care settings. *Cancer*. 2018;124(18):3656-3667. doi:10.1002/cncr.31394
28. Kowatsch T, Fleisch E. Digital health interventions. In: Gassmann O, Ferrandina F, eds. Connected Business: Create Value in a Networked Economy. Springer International Publishing; 2021:71-95.