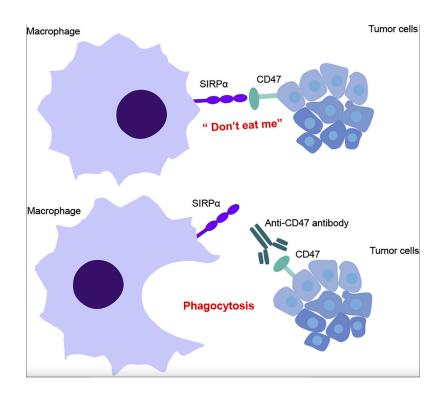
# A Natural Approach to Immunotherapy

By Mark Simon, Director Nutritional Oncology Research Institute July 2024

#### Introduction

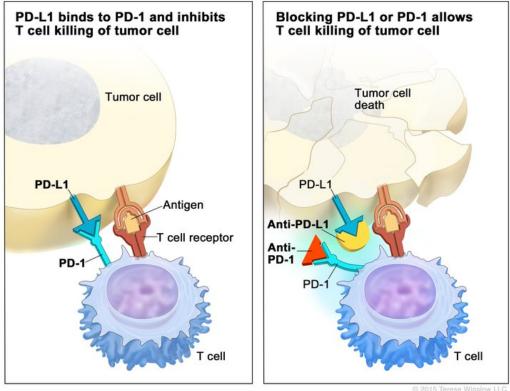
The immune system plays a highly complex role in cancer as both friend and foe. Since cancer originates from our own cells and the immune system is designed to only destroy cells infected with a pathogen, cancer cells are left untouched by the immune system. Cancer cells actually hijack the immune system to their advantage.

One of the hallmarks of cancer is immune evasion. Cancer cells express a variety of signals on their outer membrane that alert immune cells not to attack or destroy. All normal cells express these signals but cancer cells express them much more powerfully. One signal is called the "don't eat me signal" or otherwise known as CD47. Unsuccessful attempts have been made to block CD47 to allow macrophages to devour cancer cells.



Any attempt to build, boost or stimulate the immune system will not change the course of cancer progression. Cancer develops and progresses in individuals who have a normally functioning immune system. Paradoxically, immunosuppression offers benefit in cancer treatment by calming inflammation.

Blocking or degrading the signaling pathways that support immune evasion is a reasonable and scientifically supported approach. A new signaling system between cancer and immune cells was discovered which are called immune checkpoints. Blocking these checkpoints allows immune cells to kill cancer cells. Cancer cells express a checkpoint called PD-L1 while immune system T cells express PD-1. These checkpoints interact like a lock and key. This discovery has opened the path for the development of immune checkpoint inhibitors and immune checkpoint blockade therapy.



© 2015 Terese Winslow LLC U.S. Govt. has certain rights

The commonly administered immunotherapy drugs are designed to block the PD-1/ PD-L1 immune checkpoint pathway. These drugs are classified as immune checkpoint inhibitors and are specially engineered monoclonal antibodies Immunotherapy drugs are effective in about 10-15% of cases and can precipitate deadly side effects. A common reaction to immunotherapy drugs is an immune storm or a chronic autoimmune condition that causes damage to organs. Keytruda, Yervoy, Opdivo and Tecentriq represent the most commonly administered drugs that block the PD-L1/PD-1 signaling pathway.

As our understanding of the complex relationship between cancer and the immune system expands, a recent discovery has opened an opportunity for a drug free and non-toxic approach to implement immunotherapy. This discovery is so profoundly groundbreaking that the immunotherapy drugs in use today could become obsolete. First, a basic understanding of how immunotherapy drugs work is presented.

### PD-L1 and PD-1 Checkpoints

Cancer cells express PD-L1 much more strongly than normal cells to prevent cytotoxic T cells from killing them. Cytotoxic T cells express PD-1 to ensure that normal cells are not harmed by the immune system.

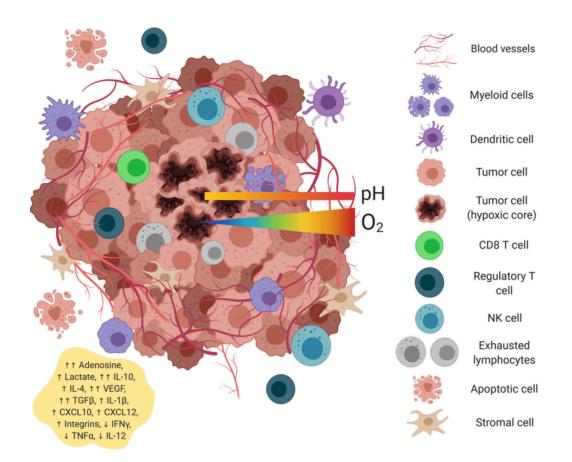
Immune checkpoint inhibitor drugs are designed to block the PD-L1/PD-1 signaling pathway by binding to either PD-L1 or PD-I. Sometimes a combination of immune checkpoint inhibitors are used to simultaneously block PD-L1 and PD-1.

A recently published scientific study discovered that a form of vitamin B6 effectively degrades and nearly eliminates the expression of PD-L1. Certain forms of vitamin B6 are known to trigger cancer cell death in cell culture. Also, high B6 levels correlate with reduced cancer risk. The required dosage of vitamin B6 is easily achievable with oral administration. This is a groundbreaking discovery that can be applied today, safely and effectively.

### **Tumor Microenvironment**

The tumor microenvironment is a complex landscape of tumor cells, immune cells, micro-vessels, lymphatic vessels, fibroblasts and extracellular fluid. However, studies on pH regulation of the TME have been mostly based on lactate, a metabolite of tumor cells. Notably, the Warburg effect results in the increased production of secreted lactate, thereby acidifying the extracellular microenvironment and affecting the surrounding cells. Lactate inhibits the activation and proliferation of CD8+ T cells, M1 macrophages, natural killer (NK) cells, and dendritic cells, contributing to tumor cell immune escape.

Acidity within the tumor microenvironment can be neutralized using alkalization therapy. Alkalization therapy combines an alkaline forming diet with pH buffers such as sodium bicarbonate. Alkalization therapy does not shift the blood or intracellular pH, only the extracellular fluid compartment.



### **Gut Microbiome**

The gut refers to the large intestine or colon. One can consider the gut to be a back end composter that breaks down fiber into health supportive metabolites. Absorption of water may be the primary function of the colon beyond elimination of waste.

Gut microbiome diversity influences immune response to infections and cancer. The details are far too complex to present here. What is important is the means by which one builds and maintains optimal gut microbiome diversity. Both friendly and pathogenic bacterial reside within the gut. What we eat dictates the balance between these bacteria.

Undigested protein is subject to bacterial fermentation. Metabolites produced from bacterial fermentation of protein create inflammation, toxicity and a compromised immune system.

A low-fat whole food plant-based diet offers the best approach to build and maintain a healthy gut. Probiotics along with proper food combining can be supportive

measures. High fiber is the most important characteristic of a gut health promoting diet so processed foods should be avoided. Fruits, vegetables and whole grains are the staples of a high fiber diet.

## A Natural Immunotherapy

For a successful response to a natural form of immunotherapy, several conditions must be met. Possibly the most important is neutralization of the acidic tumor microenvironment. Second is optimizing gut microbiome diversity. The final element is the right form and dosage of vitamin B6.

Therefore, a natural immunotherapy protocol must be comprised of a high fiber lowprotein plant-based diet, probiotics, alkalization therapy and high dose vitamin B6.

Natural killer cells are another defense against cancer. Cancer cells are protected from natural killer cells by the expression of HLA-E protein on the outer membrane. Sodium selenite decreases the expression of HLA-E in a dose dependent manner.

A hybrid approach is possible by combining natural immunotherapy with a natural cytotoxic protocol such as the NORI protocol. There is actually a 100% overlap between the NORI protocol and the natural immunotherapy approach presented here.

## Conclusion

An opportunity to advance a natural approach to immunotherapy has arrived. By addressing tumor acidity, gut microbiome diversity and utilizing vitamin B6 to degrade PD-L1, a viable natural immunotherapy protocol can be applied at very low cost and no risk of toxicity. Natural immunotherapy can be administered alone or with natural therapies.

## References

Deshmukh SK. Targeting "Do Not Eat Me" Signal CD47 in Cancer Immunotherapy. J Cell Immunol. 2019; 1(2): 50-52. <u>https://www.scientificarchives.com/article/targeting-do-not-eat-me-signal-cd47-incancer-immunotherapy</u>

Zhao , Shucheng Che , Junwei Ma , Hongwei Xie , Zhiyong Yan CD47 as a promising therapeutic target in oncology, Frontiers in Immunology, Vol.13, 2022. <u>https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.757480/</u> <u>full</u>

Gou, Q., Dong, C., Xu, H. *et al.* PD-L1 degradation pathway and immunotherapy for cancer. *Cell Death Dis* **11**, 955 (2020). <u>https://doi.org/10.1038/s41419-020-03140-2</u> <u>https://www.nature.com/articles/s41419-020-03140-2#citeas</u>

Jinwei Yuan, Jianlong Li, Man Shang, Yuan Fu, Ting Wang,

Identification of vitamin B6 as a PD-L1 suppressor and an adjuvant for cancer immunotherapy, Biochemical and Biophysical Research Communications, Volume 561, 2021, Pages 187-194,ISSN 0006-291X, https://doi.org/10.1016/j.bbrc.2021.05.022. https://www.sciencedirect.com/science/article/abs/pii/S0006291X21007932?

#### via%3Dihub

Monika Enqvist, Gustav Nilsonne, Oscar Hammarfjord, Robert P. A. Wallin, Niklas K. Björkström, Mikael Björnstedt, Anders Hjerpe, Hans-Gustaf Ljunggren, Katalin Dobra, Karl-Johan Malmberg, Mattias Carlsten; Selenite Induces Posttranscriptional Blockade of HLA-E Expression and Sensitizes Tumor Cells to CD94/NKG2A-Positive NK Cells. J Immunol 1 October 2011; 187 (7): 3546–3554. https://doi.org/10.4049/ jimmunol.1100610

https://journals.aai.org/jimmunol/article/187/7/3546/85238/Selenite-Induces-Posttranscriptional-Blockade-of

Sadeghi Rad H, Monkman J, Warkiani ME, Ladwa R, O'Byrne K, Rezaei N, Kulasinghe A. Understanding the tumor microenvironment for effective immunotherapy. Med Res Rev. 2021 May;41(3):1474-1498. doi: 10.1002/med.21765. Epub 2020 Dec 4. PMID: 33277742; PMCID: PMC8247330.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8247330/

Wang Q, Shao X, Zhang Y, Zhu M, Wang FXC, Mu J, Li J, Yao H, Chen K. Role of tumor microenvironment in cancer progression and therapeutic strategy. Cancer Med. 2023 May;12(10):11149-11165. doi: 10.1002/cam4.5698. Epub 2023 Feb 21. PMID: 36807772; PMCID: PMC10242329. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10242329/

Hosonuma M, Yoshimura K. Association between pH regulation of the tumor microenvironment and immunological state. Front Oncol. 2023 Jul 10;13:1175563. doi: 10.3389/fonc.2023.1175563. PMID: 37492477; PMCID: PMC10363976. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10363976/

Wada H, Hamaguchi R, Narui R, Morikawa H. Meaning and Significance of "Alkalization Therapy for Cancer". Front Oncol. 2022 Jul 14;12:920843. doi: 10.3389/ fonc.2022.920843. PMID: 35965526; PMCID: PMC9364696. <u>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9364696/#</u>

Hamaguchi R, Isowa M, Narui R, Morikawa H, Wada H. Clinical review of alkalization therapy in cancer treatment. Front Oncol. 2022 Sep 14;12:1003588. doi: 10.3389/fonc.2022.1003588. PMID: 36185175; PMCID: PMC9516301. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9516301/ Isowa, M.; Hamaguchi, R.; Narui, R.; Morikawa, H.; Okamoto, T.; Wada, H. Potential of Alkalization Therapy for the Management of Metastatic Pancreatic Cancer: A Retrospective Study. Cancers 2024, 16, 61. <u>https://doi.org/10.3390/cancers16010061</u> <u>https://www.mdpi.com/2072-6694/16/1/61</u>

Zhang, M., Liu, J. & Xia, Q. Role of gut microbiome in cancer immunotherapy: from predictive biomarker to therapeutic target. *Exp Hematol Oncol* **12**, 84 (2023). <u>https://doi.org/10.1186/s40164-023-00442-x</u> https://ehoonline.biomedcentral.com/articles/10.1186/s40164-023-00442-x

Björk, J.R., Bolte, L.A., Maltez Thomas, A. *et al.* Longitudinal gut microbiome changes in immune checkpoint blockade-treated advanced melanoma. *Nat Med* **30**, 785–796 (2024). <u>https://doi.org/10.1038/s41591-024-02803-3</u> <u>https://www.nature.com/articles/s41591-024-02803-3</u>

Kiousi DE, Kouroutzidou AZ, Neanidis K, Karavanis E, Matthaios D, Pappa A, Galanis A. The Role of the Gut Microbiome in Cancer Immunotherapy: Current Knowledge and Future Directions. Cancers (Basel). 2023 Mar 31;15(7):2101. doi: 10.3390/ cancers15072101. PMID: 37046762; PMCID: PMC10093606. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10093606/

Lu, Y., Yuan, X., Wang, M. et al. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. J Hematol Oncol 15, 47 (2022). https://doi.org/ 10.1186/s13045-022-01273-9 https://jhoonline.biomedcentral.com/articles/10.1186/s13045-022-01273-9

Gut Bacteria Influence Effectiveness of a Type of Immunotherapy, National Cancer Institute <u>https://www.cancer.gov/news-events/cancer-currents-blog/2018/gut-bacteria-checkpoint-inhibitors</u>