Tumor tissue architecture, immune cells and molecular characteristics in relation to immune escape in colon cancer: what rises must fall

Zhu, H.

Chapter 6

General discussion

General considerations and systems biology framework

The work presented in this thesis supports the view that colon cancer outcome is strongly influenced by the balance between immune control and immune escape. Conventional staging captures tumor burden and pattern of spread but does not reflect the complexity of tumor immune interactions[1,2]. By integrating spatial T cell organization, HLA class Ia and HLA class Ib tissue expression, germline HLA class I diversity, transcriptomic immune signatures, and clinical outcome, this work links molecular variation to tissue architecture and patient level phenotypes.

From a systems biology perspective, colon cancer can be regarded as a network of interacting components that operate across organizational levels. DNA variation at HLA loci and in tumor genomes shapes antigen processing and presentation [3]. These molecular processes influence the phenotype of tumor cells and immune cells and contribute to emergent properties at the tissue level, such as immune inflamed or immune desert microenvironments[4–6]. In turn, tissue level events, including necrosis, cytokine release and therapeutic intervention, feedback to molecular and cellular pathways[7,8]. This combination of upward and downward causation results in dynamic trajectories of immune control and immune escape. The measurements performed in this thesis capture selected emergent properties of this system, in particular spatial T cell organization and HLA class I expression patterns.

Chapter 2 frames tumor immunity in colon cancer within a systems biology perspective. It defines immune contexture as an emergent property generated by coupled tumor intrinsic programs, antigen presentation capacity, and microenvironmental constraints, and it formalizes upward causation, downward causation, and multiple realizability as a causal scaffold. This framework motivates why spatial immune architecture and HLA class I axis measurements are mechanistically informative and why integration across molecular, cellular, tissue, and patient levels is required to interpret outcome associated immune control and immune escape trajectories.

Biological implications of spatial T cell patterns

The findings in **Chapter 3** highlight that spatial T cell patterns capture functionally relevant information. Proliferative Ki67+ and cytotoxical Granzyme B+ T cells localized predominantly in tumor epithelium, consistent with efficient effector function requiring close contact between T cells and malignant cells[9–11]. Short distances between CD3+CD8+ T cells and tumor cells and high

Immunologic Constant of Rejection (ICR) scores were associated with improved survival, suggesting that spatial metrics capture an engaged cytotoxic response rather than simple presence of T cells[12].

The association between higher stromal densities of FoxP3+T cells and favorable outcome suggests that regulatory T cells in colon cancer can mark organized immune niches rather than pure suppression. This is in line with observations that FoxP3+T cells often colocalize with effector T cells and antigen presenting cells in tertiary lymphoid structures[13–16]. These spatial patterns likely reflect the net effect of multiple coordinated mechanisms, including chemokine driven recruitment, local cell migration, antigen dependent activation, and constraints imposed by tissue structure. They are shaped both by tumor intrinsic molecular programs and by microenvironmental forces such as hypoxia, necrosis, stromal remodeling, vascular organization, and treatment induced inflammation, which together reconfigure immune cell positioning and function[17–20].

Antigen presentation, immune infiltration and immune escape

Chapter 4 provides insight into how antigen presentation and immune infiltration interact to shape the tumor immune contexture. Tumors with preserved HLA class Ia expression and high CD45+ cell density displayed immune active gene signatures and better outcome. Tumors with reduced HLA class Ia expression showed sparse immune infiltrates and immune cold transcriptional profiles. These patterns are compatible with immunoediting, in which tumors that have undergone intense immune pressure acquire defects in antigen presentation machinery and thereby lower their visibility to CD8+ T cells[21–23].

The context dependent associations of HLA class Ib molecules with immune infiltrates and outcome suggest that HLA-E, HLA-F and HLA-G act as modulators of innate and adaptive responses. Their expression likely influences natural killer cell activity, dendritic cell function and recruitment of regulatory cell populations[24–28]. Within a systems biology framework, HLA class Ia and HLA class Ib molecules are part of a regulatory network that links tumor intrinsic changes to the composition and activation state of the infiltrating immune system. Defects in one component of this network can propagate across levels, leading to emergent properties such as ineffective immune surveillance or profound local immune suppression.

Contribution of germline HLA class I diversity

Furthermore, **Chapter 5** extends the analysis to germline HLA class I diversity. HLA evolutionary divergence, in particular at HLA-B, associated with immune gene signatures in immune active tumors. This suggests that individuals with broader HLA-B immunopeptidomes are more likely to mount diverse and sustained T cell responses that leave a durable imprint on the tumor microenvironment[29,30]. At the same time, the scale and direction of these associations varied across clinical and molecular contexts, consistent with germline HLA features acting in concert with tumor intrinsic factors such as mutational burden, microsatellite status, and oncogenic signaling pathways[5,31,32,32,33].

Locus specific mapping of HLA-A, HLA-B and HLA-C expression showed that selective loss of individual loci can occur without complete HLA class I downregulation. Such patterns fit models in which tumor cells evade dominant T cell clones restricted by a particular HLA molecule while maintaining enough HLA class I expression to avoid natural killer cell activation[34–36]. This fine tuning of antigen presentation represents an emergent strategy of immune escape that results from the interaction between germline HLA repertoire, tumor mutation landscape and immune selection pressure.

Systems biology interpretation of the thesis

Across **Chapters 3** to **5**, the data support a coherent multilevel model. At the molecular level, germline HLA class I polymorphisms and tumor derived alterations in antigen processing and presentation pathways determine which peptides can be displayed on HLA class I molecules[37–39]. At the cellular level, these processes influence recognition of tumor cells by CD8 positive T cells and natural killer cells and shape the differentiation and activation state of immune cells[40–42]. At the tissue level, this results in specific spatial patterns of T cell infiltration, HLA class I expression mosaics and stromal remodeling[12,43,43]. At the patient level, these emergent properties translate into clinical phenotypes such as immune active or immune cold tumors and favorable or poor outcome[44–46].

In this systems biology view, immune contexture is an emergent property that arises from many interacting elements rather than from a single driver. Similar clinical phenotypes can result from different combinations of underlying changes, reflecting multiple realizability of tumor immune states[47–49]. For

example, an immune cold tumor may result from low mutational load, from defects in antigen presentation, from absence of priming at distant sites or from local exclusion of T cells by stromal barriers[50–52]. Conversely, immune inflamed tumors may share features such as high ICR scores and dense T cell infiltrates despite different combinations of HLA alleles and oncogenic events. The measurements in this thesis capture three key components of this system and help to position colon tumors along a continuum of immune control and immune escape.

Clinical implications and future directions

Immunotherapy is clinically established for a biologically defined subset of colon cancers, with the most consistent benefit in microsatellite instability high or mismatch repair deficient advanced disease[53]. Immune checkpoint blockade shows the most consistent benefit in microsatellite instability high or mismatch repair deficient advanced disease, where PD-1 blockade with pembrolizumab is an established first line option and nivolumab combined with ipilimumab is an approved regimen[54]. However, the majority of colon cancers are microsatellite stable and display primary resistance to single agent checkpoint blockade[55]. This clinical reality indicates that patient selection should incorporate tissue level readouts of immune engagement and antigen presentation capacity rather than relying on one genomic label[56].

The findings of this thesis support a stratification concept built on three coupled layers. In Chapter 3, spatial metrics that capture short distances between CD8 positive T cells and tumor cells, and enrichment of proliferative or Granzyme B positive T cells within tumor epithelium, provide evidence for effective effector deployment that may complement immune gene signatures in identifying actionable immune inflamed states. In Chapter 4, preserved HLA class Ia expression together with high CD45 density marks an immune active contexture with strong rejection related transcriptomic activity, which is the biological setting where PD-1 based therapy is most likely to amplify a pre-existing tumor reactive T cell response[57]. In Chapter 5, germline and locus specific HLA features refine the antigen presentation landscape. HLA evolutionary divergence at HLA-B associated with immune activation within immune active tumors, and selective loss of individual HLA loci indicates ongoing immune editing, both of which can inform patient enrichment for T cell based immunotherapy or for combination strategies that counter immune escape[58].

Tumors with reduced HLA class Ia expression implicate antigen presentation as a mechanistic constraint on T cell mediated immunity and may inform treatment

selection, even when associations with survival are not observed. Prognostic associations describe outcome in a given cohort, whereas predictive value refers to differential benefit from a specific therapy[59]. In such cases, rational approaches include therapeutic restoration of antigen presentation through reinforcement of interferon signaling, epigenetic reactivation of antigen processing machinery, and local inflammatory priming, followed by PD-1 blockade[60–62]. In parallel, immune modalities that do not rely on HLA restricted peptide presentation may be considered, including antibody based T cell redirecting strategies, chimeric antigen receptor T cells[63], or innate immune agonists, in order to bypass defects in the HLA class Ia axis[64]. The heterogeneous patterns of HLA class Ib molecules observed in this thesis suggest additional therapeutic hypotheses. Increased expression of HLA-E, HLA-F or HLA-G can bias the local immune circuit toward inhibitory signaling in natural killer cells and other innate effectors[65,66]. These tumors may be candidates for strategies that enhance natural killer cell activity, such as targeting the NKG2A axis, IL-15 based stimulation, or adoptive natural killer cell transfer, ideally guided by tissue level profiling of HLA class Ib together with classical HLA class Ia status[67].

Future studies should continue along two complementary lines. One line is prospective clinical validation in cohorts treated with contemporary immunotherapy, with pre-specified endpoints for response and survival and with harmonized assays for HLA class I and spatial T cell metrics. The other line is mechanistic resolution. Integration of locus specific HLA loss patterns with immunopeptidomics, single cell spatial profiling and T cell receptor sequencing can directly link antigen presentation to clonal selection and immune editing. Longitudinal sampling of primary tumors, metastases and blood will be needed to model how immune contexture trajectories change under therapy and to identify actionable points of intervention.

Conclusion

This thesis shows that spatial T cell organization, HLA class I tissue expression and locus specific HLA class I diversity together define key aspects of the immune contexture in colon cancer. These features intersect with molecular subtypes and immune gene signatures and are related to clinical outcome. By dissecting these layers and embedding them in a systems biology framework that considers multilevel causation and emergent properties, the work contributes to a more nuanced understanding of immune control and immune escape in colon cancer. It illustrates how multiscale thinking can be translated into concrete tissue based biomarkers and provides a foundation for future studies that aim to

develop integrated, predictive models for personalized immunotherapy in this disease.

References:

1. Roelands J, Kuppen PJK, Ahmed EI, Mall R, Masoodi T, Singh P, et al. An integrated tumor, immune and microbiome atlas of colon cancer. Nat Med. 2023;29:1273–86.

2. Taube JM, Galon J, Sholl LM, Rodig SJ, Cottrell TR, Giraldo NA, et al. Implications of the tumor immune microenvironment for staging and therapeutics. Mod Pathol Off J U S Can Acad Pathol Inc. 2018;31:214–34.

3. Kelly A, Trowsdale J. Genetics of antigen processing and presentation. Immunogenetics. 2019;71:161–70.

4. Hegde PS, Chen DS. Top 10 Challenges in Cancer Immunotherapy. Immunity. 2020;52:17–35.

5. Li Q, Geng S, Luo H, Wang W, Mo Y-Q, Luo Q, et al. Signaling pathways involved in colorectal cancer: pathogenesis and targeted therapy. Signal Transduct Target Ther. 2024;9:266.

6. Zheng S, Wang W, Shen L, Yao Y, Xia W, Ni C. Tumor battlefield within inflamed, excluded or desert immune phenotypes: the mechanisms and strategies. Exp Hematol Oncol. 2024;13:80.

7. Karki R, Kanneganti T-D. The "cytokine storm": molecular mechanisms and therapeutic prospects. Trends Immunol. 2021;42:681–705.

8. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9:7204–18.

9. Corgnac S, Malenica I, Mezquita L, Auclin E, Voilin E, Kacher J, et al. CD103+CD8+ TRM Cells Accumulate in Tumors of Anti-PD-1-Responder Lung Cancer Patients and Are Tumor-Reactive Lymphocytes Enriched with Tc17. Cell Rep Med. 2020;1:100127.

10. Tsujikawa T, Kumar S, Borkar RN, Azimi V, Thibault G, Chang YH, et al. Quantitative Multiplex Immunohistochemistry Reveals Myeloid-Inflamed Tumor-Immune Complexity Associated with Poor Prognosis. Cell Rep. 2017;19:203–17

11. Prizment AE, Vierkant RA, Smyrk TC, Tillmans LS, Nelson HH, Lynch CF, et al. Cytotoxic T Cells and Granzyme B Associated with Improved Colorectal Cancer Survival in a Prospective Cohort of Older Women. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol. 2017;26:622–31.

12. Zhu H, Roelands J, Ahmed EI, Stouten I, Hoorntje R, van Vlierberghe RLP, et al. Location matters: spatial dynamics of tumor-infiltrating T cell subsets is prognostic in colon cancer. Front Immunol. 2024;15:1293618.

13. Wing JB, Tanaka A, Sakaguchi S. Human FOXP3+ Regulatory T Cell Heterogeneity and Function in Autoimmunity and Cancer. Immunity. 2019;50:302–16.

14. Sharma A, Rudra D. Emerging Functions of Regulatory T Cells in Tissue Homeostasis. Front Immunol. 2018;9:883.

15. Zhao L, Jin S, Wang S, Zhang Z, Wang X, Chen Z, et al. Tertiary lymphoid structures in diseases: immune mechanisms and therapeutic advances. Signal Transduct Target Ther. 2024;9:225.

16. Colbeck EJ, Ager A, Gallimore A, Jones GW. Tertiary Lymphoid Structures in Cancer: Drivers of Antitumor Immunity, Immunosuppression, or Bystander Sentinels in Disease? Front Immunol. 2017;8:1830.

17. Greco Song H-H, Rumma RT, Ozaki CK, Edelman ER, Chen CS. Vascular Tissue Engineering: Progress, Challenges, and Clinical Promise. Cell Stem Cell. 2018;22:608.

18. de Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell. 2023;41:374–403.

19. Duarte D, Hawkins ED, Akinduro O, Ang H, De Filippo K, Kong IY, et al. Inhibition of Endosteal Vascular Niche Remodeling Rescues Hematopoietic Stem Cell Loss in AML. Cell Stem Cell. 2018;22:64-77.e6.

20. Zhao Y, Shen M, Wu L, Yang H, Yao Y, Yang Q, et al. Stromal cells in the tumor microenvironment: accomplices of tumor progression? Cell Death Dis. 2023;14:587.

21. Tufail M, Jiang C-H, Li N. Immune evasion in cancer: mechanisms and cutting-edge therapeutic approaches. Signal Transduct Target Ther. 2025;10:227.

22. Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer Immune Evasion Through Loss of MHC Class I Antigen Presentation. Front Immunol. 2021;12:636568.

23. Mortezaee K, Majidpoor J. Mechanisms of CD8+ T cell exclusion and dysfunction in cancer resistance to anti-PD-(L)1. Biomed Pharmacother Biomedecine Pharmacother. 2023;163:114824.

24. Morandi F, Pistoia V. Interactions between HLA-G and HLA-E in Physiological and Pathological Conditions. Front Immunol. 2014;5:394.

25. Krijgsman D, Roelands J, Hendrickx W, Bedognetti D, Kuppen PJK. HLA-G: A New Immune Checkpoint in Cancer? Int J Mol Sci. 2020;21:4528.

26. van de Water RB, Krijgsman D, Houvast RD, Vahrmeijer AL, Kuppen PJK. A Critical Assessment of the Association between HLA-G Expression by Carcinomas and Clinical Outcome. Int J Mol Sci. 2021;22:8265.

27. de Kruijf EM, Sajet A, van Nes JGH, Natanov R, Putter H, Smit VTHBM, et al. HLA-E and HLA-G Expression in Classical HLA Class I-Negative Tumors Is of Prognostic Value for Clinical Outcome of Early Breast Cancer Patients. J Immunol [Internet]. 2010 [cited 2025 Feb 1];185:7452–9.

28. Lin A, Yan W-H. The Emerging Roles of Human Leukocyte Antigen-F in Immune Modulation and Viral Infection. Front Immunol. 2019;10:964.

29. Nelde A, Maringer Y, Bilich T, Salih HR, Roerden M, Heitmann JS, et al. Immunopeptidomics-Guided Warehouse Design for Peptide-Based Immunotherapy in Chronic Lymphocytic Leukemia. Front Immunol. 2021;12:705974.

30. Kraemer AI, Chong C, Huber F, Pak H, Stevenson BJ, Müller M, et al. The immunopeptidome landscape associated with T cell infiltration, inflammation and immune editing in lung cancer. Nat Cancer. 2023;4:608–28.

31. Lu Z, Chen H, Jiao X, Wang Y, Wu L, Sun H, et al. Germline HLA-B evolutionary divergence influences the efficacy of immune checkpoint blockade therapy in gastrointestinal cancer. Genome Med. 2021;13:175.

32. Sayaman RW, Saad M, Thorsson V, Hu D, Hendrickx W, Roelands J, et al. Germline genetic contribution to the immune landscape of cancer. Immunity. 2021;54:367-386.e8.

33. Picard E, Verschoor CP, Ma GW, Pawelec G. Relationships Between Immune Landscapes, Genetic Subtypes and Responses to Immunotherapy in Colorectal Cancer. Front Immunol. 2020;11:369.

34. Hazini A, Fisher K, Seymour L. Deregulation of HLA-I in cancer and its central importance for immunotherapy. J Immunother Cancer. 2021;9:e002899.

35. Hiura S, Kuwasaki Y, Nishikawa Y, Kimura T, Yoshida S, Nakayama M, et al. Selective agonists of KIR and NKG2A to evade missing self response of natural killer cells. Sci Rep. 2025;15:33550.

36. Rodríguez JA. HLA-mediated tumor escape mechanisms that may impair immunotherapy clinical outcomes via T-cell activation. Oncol Lett. 2017;14:4415–27.

37. Concha-Benavente F, Srivastava R, Ferrone S, Ferris RL. Immunological and clinical significance of HLA class I antigen processing machinery component defects in malignant cells. Oral Oncol. 2016;58:52–8.

38. Shraibman B, Kadosh DM, Barnea E, Admon A. Human Leukocyte Antigen (HLA) Peptides Derived from Tumor Antigens Induced by Inhibition of DNA Methylation for Development of Drug-facilitated Immunotherapy. Mol Cell Proteomics MCP. 2016;15:3058–70.

39. Bassani-Sternberg M, Pletscher-Frankild S, Jensen LJ, Mann M. Mass spectrometry of human leukocyte antigen class I peptidomes reveals strong effects of protein abundance and turnover on antigen presentation. Mol Cell Proteomics MCP. 2015;14:658–73.

40. Marcus A, Gowen BG, Thompson TW, Iannello A, Ardolino M, Deng W, et al. Recognition of tumors by the innate immune system and natural killer cells. Adv Immunol. 2014;122:91–128.

41. Giles JR, Globig A-M, Kaech SM, Wherry EJ. CD8+ T cells in the cancer-immunity cycle. Immunity. 2023;56:2231–53.

42. Rosenberg J, Huang J. CD8+ T Cells and NK Cells: Parallel and Complementary Soldiers of Immunotherapy. Curr Opin Chem Eng. 2018;19:9–20.

43. Li C, Guo H, Zhai P, Yan M, Liu C, Wang X, et al. Spatial and Single-Cell Transcriptomics Reveal a Cancer-Associated Fibroblast Subset in HNSCC That Restricts Infiltration and Antitumor Activity of CD8+ T Cells. Cancer Res. 2024;84:258–75.

44. Zhang J, Huang D, Saw PE, Song E. Turning cold tumors hot: from molecular mechanisms to clinical applications. Trends Immunol. 2022;43:523–45.

45. Wu B, Zhang B, Li B, Wu H, Jiang M. Cold and hot tumors: from molecular mechanisms to targeted therapy. Signal Transduct Target Ther. 2024;9:274.

46. Wang L, Geng H, Liu Y, Liu L, Chen Y, Wu F, et al. Hot and cold tumors: Immunological features and the therapeutic strategies. MedComm. 2023;4:e343.

47. De Sousa E Melo F, Vermeulen L, Fessler E, Medema JP. Cancer heterogeneity--a multifaceted view. EMBO Rep. 2013;14:686–95.

48. Galon J, Bruni D. Tumor Immunology and Tumor Evolution: Intertwined Histories. Immunity. 2020;52:55–81.

49. Guo M, Peng Y, Gao A, Du C, Herman JG. Epigenetic heterogeneity in cancer. Biomark Res. 2019;7:23.

50. Wu B, Zhang B, Li B, Wu H, Jiang M. Cold and hot tumors: from molecular mechanisms to targeted therapy. Signal Transduct Target Ther. 2024;9:274.

51. Liu Y-T, Sun Z-J. Turning cold tumors into hot tumors by improving T-cell infiltration. Theranostics. 2021;11:5365–86.

52. Mellman I, Chen DS, Powles T, Turley SJ. The cancer-immunity cycle: Indication, genotype, and immunotype. Immunity. 2023;56:2188–205.

53. Asaoka Y, Ijichi H, Koike K. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med. 2015;373:1979.

54. Casak SJ, Marcus L, Fashoyin-Aje L, Mushti SL, Cheng J, Shen Y-L, et al. FDA Approval Summary: Pembrolizumab for the First-line Treatment of Patients with MSI-H/dMMR Advanced Unresectable or Metastatic Colorectal Carcinoma. Clin Cancer Res Off J Am Assoc Cancer Res. 2021;27:4680–4.

55. Buchler T. Microsatellite Instability and Metastatic Colorectal Cancer - A Clinical Perspective. Front Oncol. 2022;12:888181.

56. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science. New York, N.Y.; 2006;313:1960–4.

57. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJM, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515:568–71.

58. Chowell D, Krishna C, Pierini F, Makarov V, Rizvi NA, Kuo F, et al. Evolutionary divergence of HLA class I genotype impacts efficacy of cancer immunotherapy. Nat Med. 2019;25:1715–20.

59. Dhatchinamoorthy K, Colbert JD, Rock KL. Cancer Immune Evasion Through Loss of MHC Class I Antigen Presentation. Front Immunol. 2021;12:636568.

60. Appleton E, Hassan J, Chan Wah Hak C, Sivamanoharan N, Wilkins A, Samson A, et al. Kickstarting Immunity in Cold Tumours: Localised Tumour

Therapy Combinations With Immune Checkpoint Blockade. Front Immunol. 2021;12:754436.

61. Maffei A, Papadopoulos K, Harris PE. MHC class I antigen processing pathways. Hum Immunol. 1997;54:91–103.

62. Serrano A, Tanzarella S, Lionello I, Mendez R, Traversari C, Ruiz-Cabello F, et al. Rexpression of HLA class I antigens and restoration of antigen-specific CTL response in melanoma cells following 5-aza-2'-deoxycytidine treatment. Int J Cancer. 2001;94:243–51.

63. Qin X, Ning W, Liu H, Liu X, Luo W, Xia N. Stepping forward: T-cell redirecting bispecific antibodies in cancer therapy. Acta Pharm Sin B. 2024;14:2361–77.

64. Appleton E, Hassan J, Chan Wah Hak C, Sivamanoharan N, Wilkins A, Samson A, et al. Kickstarting Immunity in Cold Tumours: Localised Tumour Therapy Combinations With Immune Checkpoint Blockade. Front Immunol. 2021;12:754436.

65. Braud VM, Allan DS, O'Callaghan CA, Söderström K, D'Andrea A, Ogg GS, et al. HLA-E binds to natural killer cell receptors CD94/NKG2A, B and C. Nature. 1998;391:795–9.

66. Dulberger CL, McMurtrey CP, Hölzemer A, Neu KE, Liu V, Steinbach AM, et al. Human Leukocyte Antigen F Presents Peptides and Regulates Immunity through Interactions with NK Cell Receptors. Immunity. 2017;46:1018-1029.e7.

67. van Hall T, André P, Horowitz A, Ruan DF, Borst L, Zerbib R, et al. Monalizumab: inhibiting the novel immune checkpoint NKG2A. J Immunother Cancer. 2019;7:263.