Innate Immune Signaling in Breast Cancer

MATOS

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Session IX

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Objectives

- What is the Innate Immune System?
- How is the Innate Immune System Altered in Breast Cancer?
- Strategies to Harness the Innate Immune System for Improved Treatments

Adaptive and Innate Immunity

Adaptive Immunity

Endogenous

B Cells

T Cells

Synthetic

Therapeutic Abs
ADCs

CAR-T Cells

Innate Immunity

Myeloid Cells

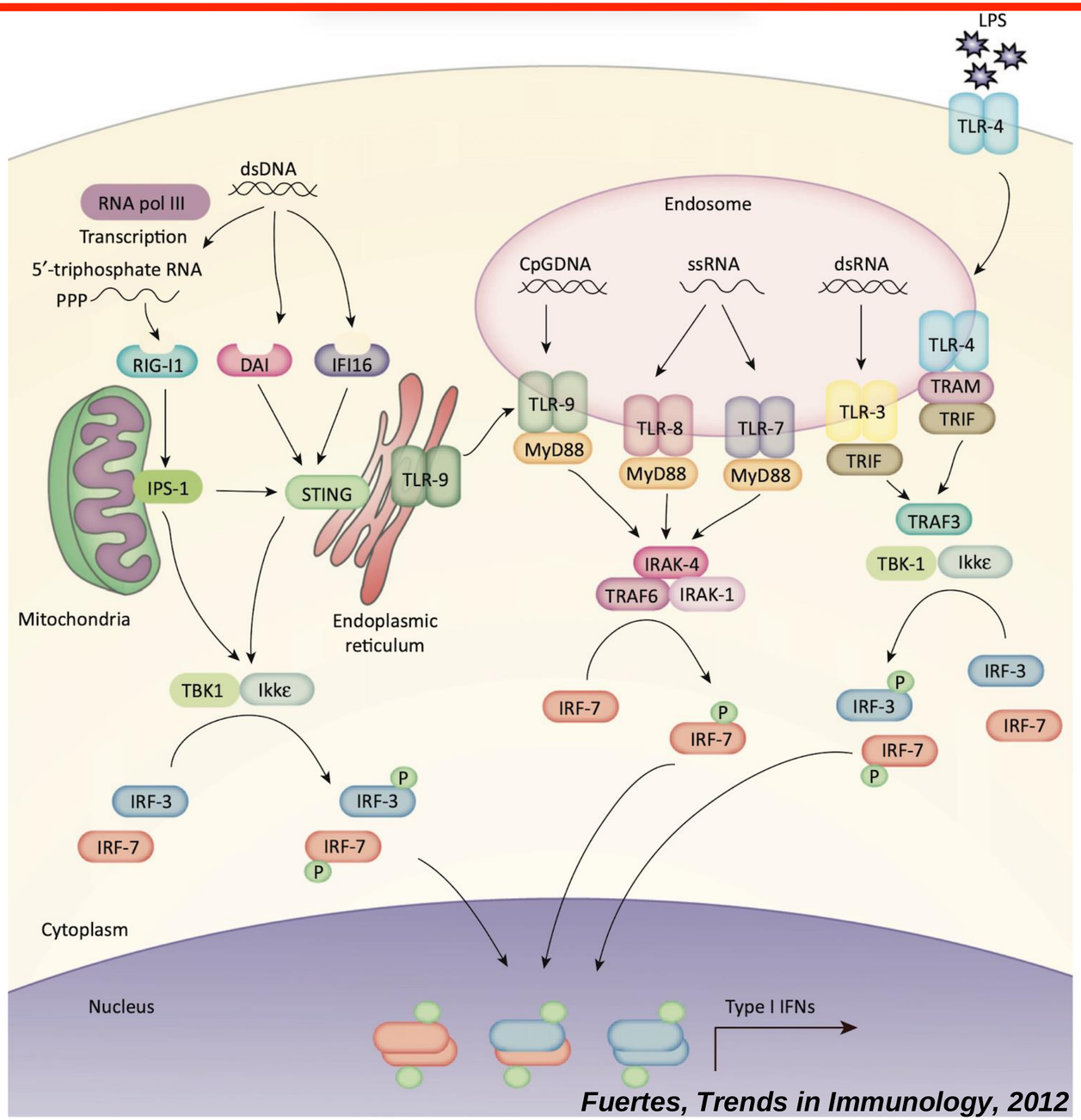
Macrophages
Monocytes
Dendritic Cells
Neutrophils
Mast Cells
Eosinophils

NK Cells

Role of Innate Immunity

1. Rapidly detect and kill pathogens and tumor cells
2. Activate or suppress the adaptive immune system - (long-term immune surveillance)
3. Alter the tumor microenvironment - cytokines / metabolism / ECM
4. Can contribute to immune suppression, therapy resistance, and metastasis
5. Can stimulate anti-tumor immunity and mediate therapeutic activity

The Innate Immune System Responds to Various Cues



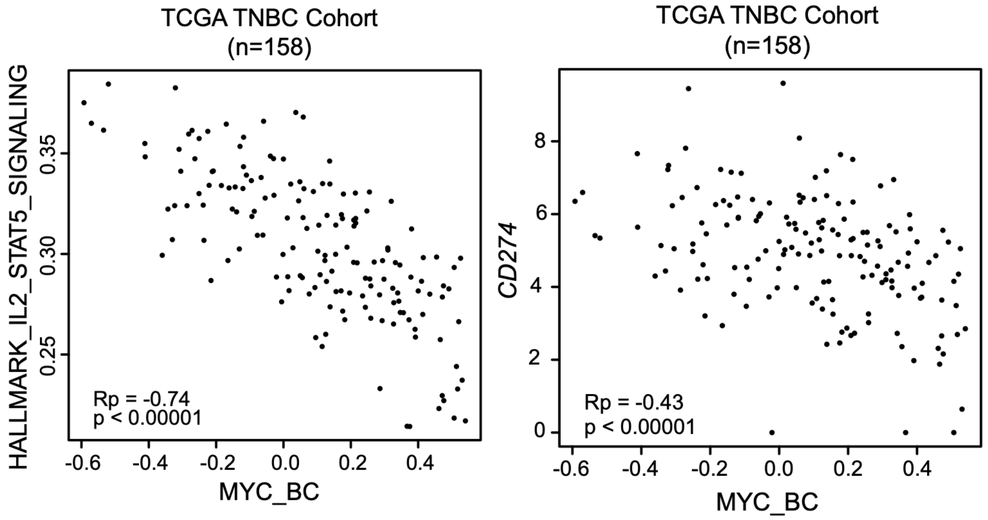
Fuertes, Trends in Immunology, 2012

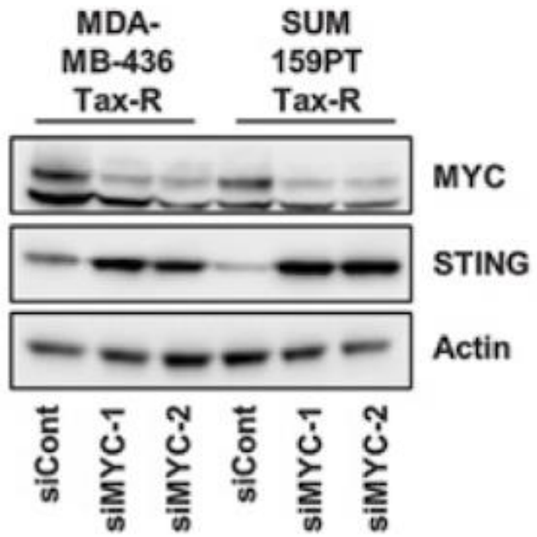
1. Innate immune and other cells can respond to diverse internal and external signals
2. Include distinct forms of nucleic acids and lipopolysaccharides
3. Signals converge on increased IFN signaling
4. IFN activates antigen presentation (MHC expression)
5. Regulates activity of innate (eg. macrophage and NK cells) and T cells
6. Components of these sensing pathways are targets for suppression in cancer
7. Components are also basis of new therapies

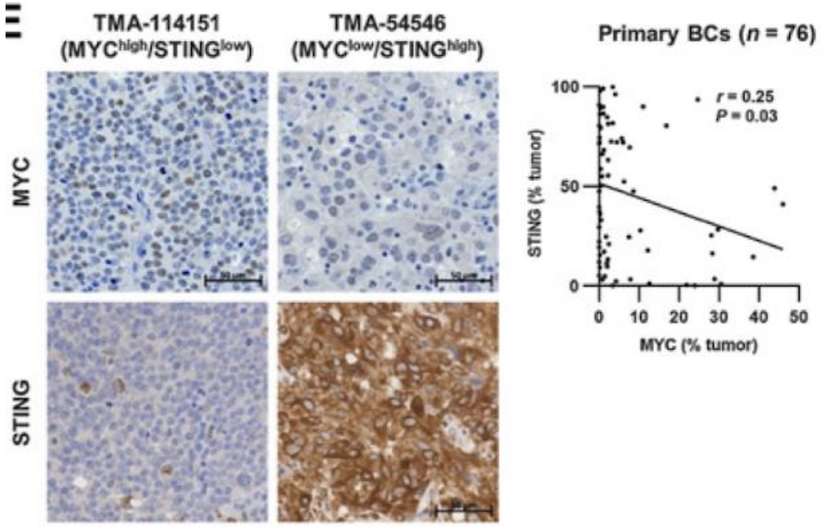
Alterations of Innate Immunity in Breast Cancer

1. Tumor Cell Death -> activation of TLR signaling pathways
2. Chromosomal Instability -> cGAS-STING pathways
3. Tumor and Myeloid cell expression of PD-L1
4. CD47 and other signals that block phagocytosis / innate immune activity
5. Oncogene signaling -> antigen presentation / other immune evasion

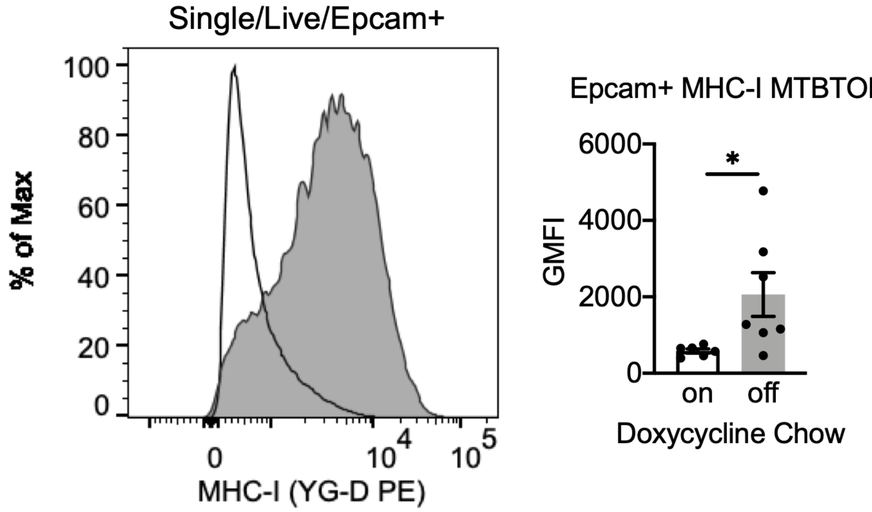
MYC Oncogene Suppress Innate Immune Responses in TNBC







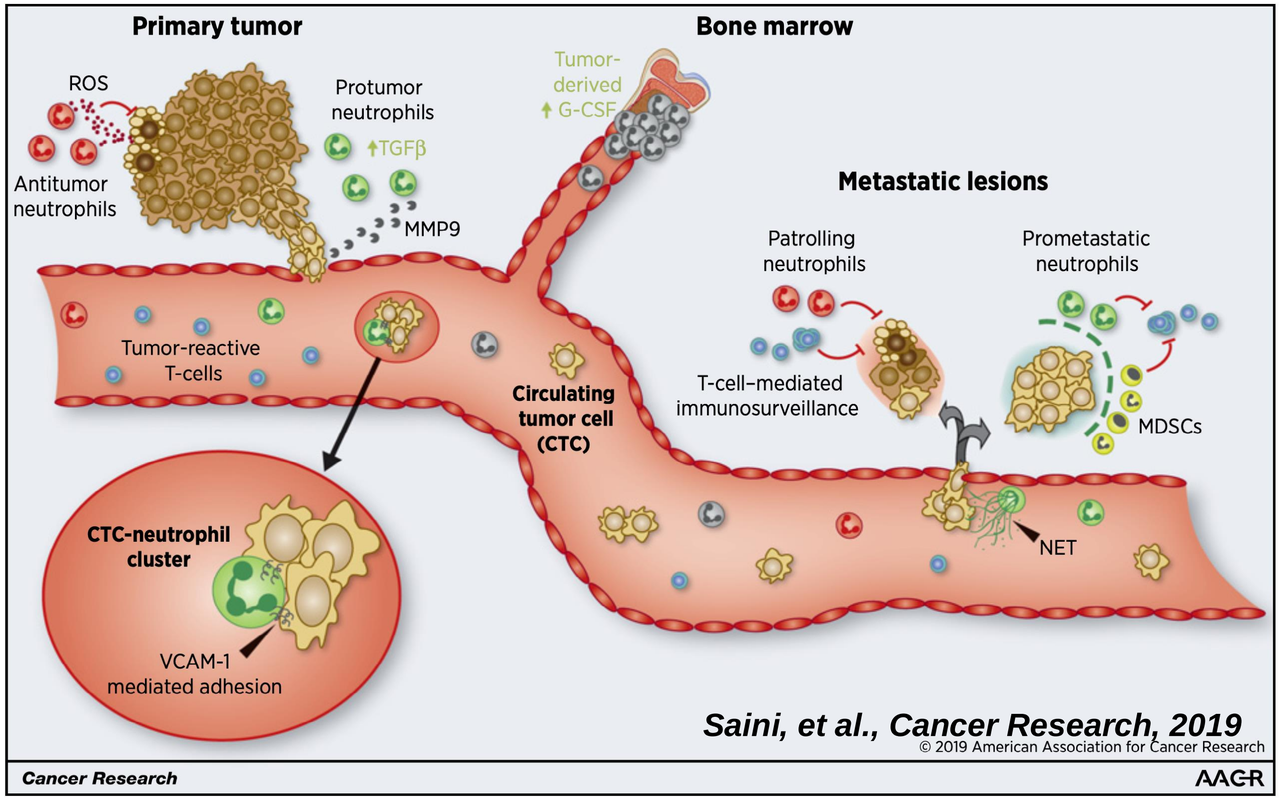
Lee, et al., Cancer Immunology Res., 2022

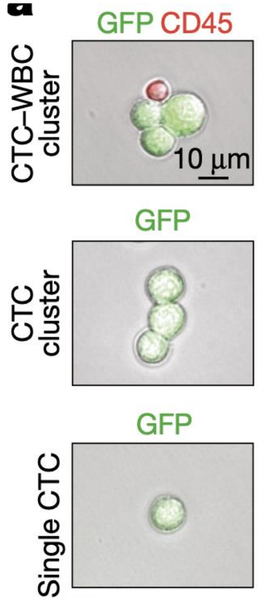


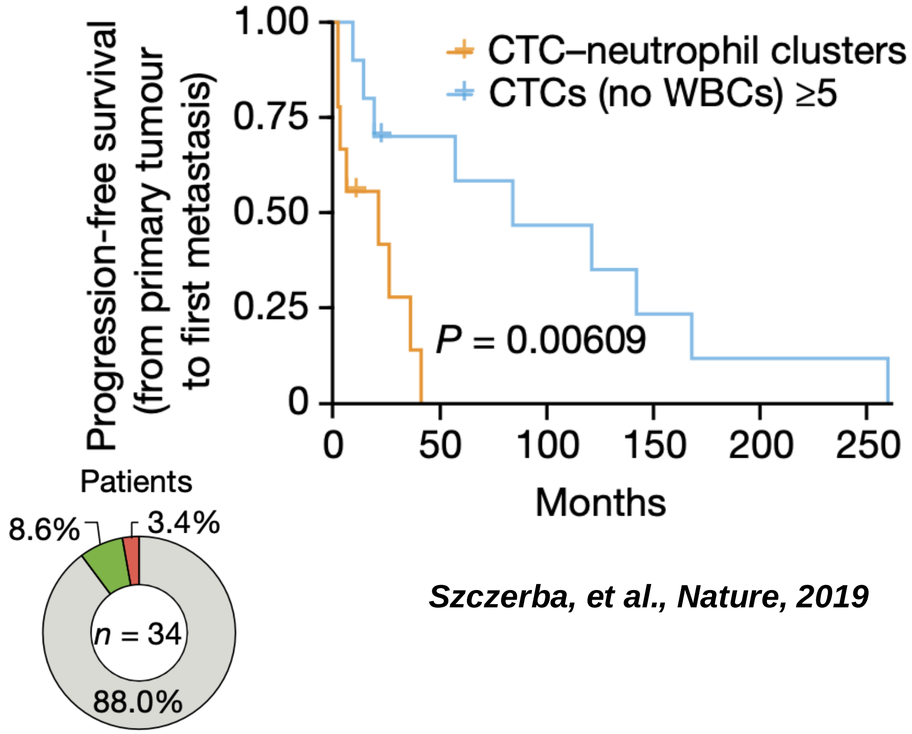
1. Overexpression of a single oncogene MYC drives multiple forms of immune evasion
2. Decrease tumor cell PD-L1
3. Decreased tumor cell MHC-I (antigen presentation)
4. Decreased cGAS-STING pathway activation

Lee, Housley et al., Nature Comm., 2022

Neutrophils have Opposing Roles in Breast Cancer Metastasis





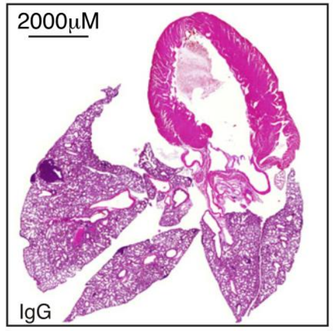


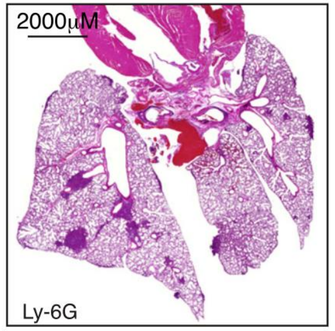
Szczerba, et al., Nature, 2019

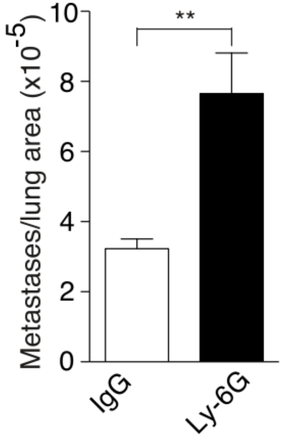
Tumor Entrained Neutrophils Inhibit Seeding in the Premetastatic Lung

Zvi Granot,[1] Erik Henke,[1] Elizabeth A. Comen,[2] Tari A. King,[3] Larry Norton,[2] and Robert Benezra[1,*]

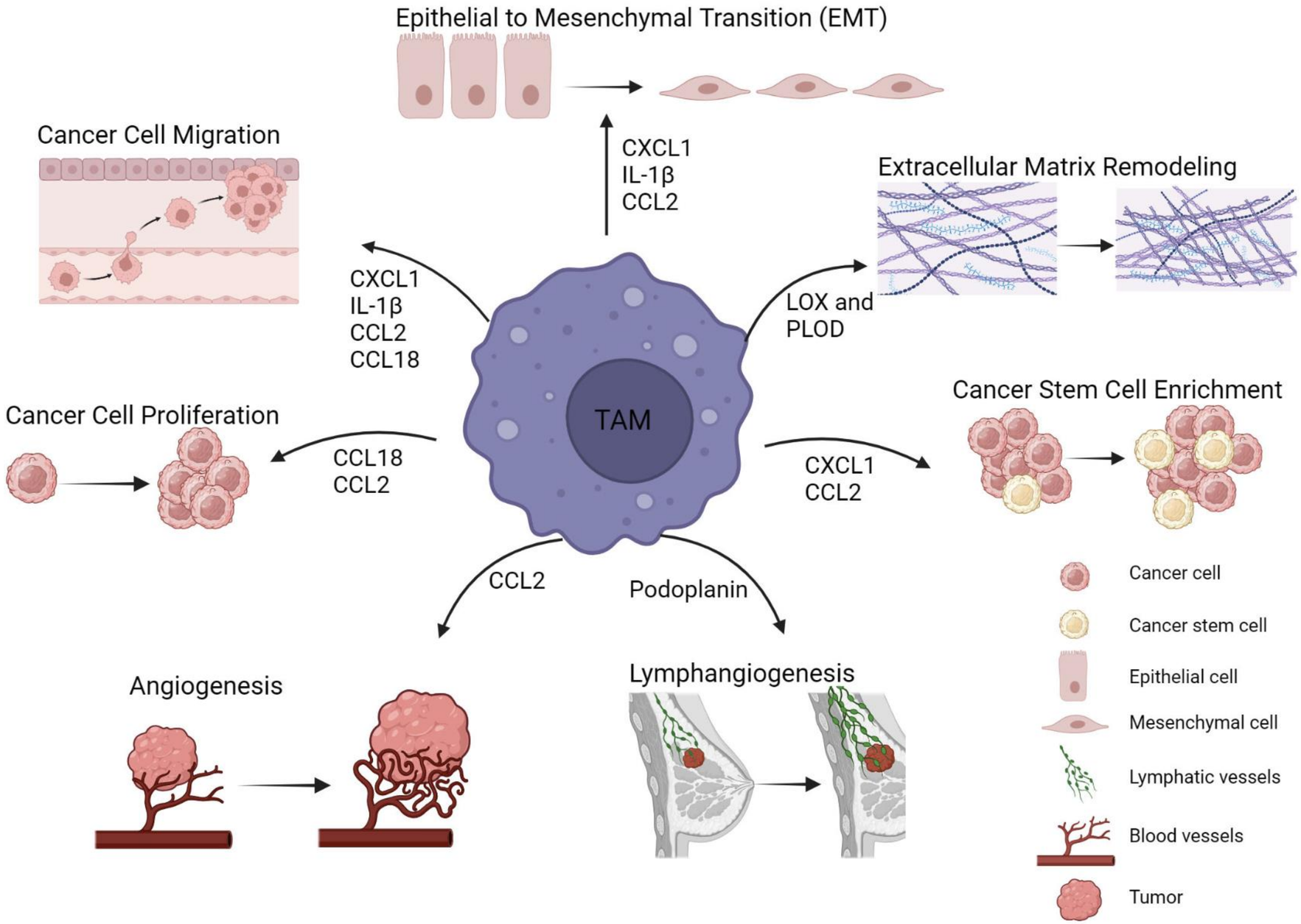
Granot, et al., Cancer Cell, 2011





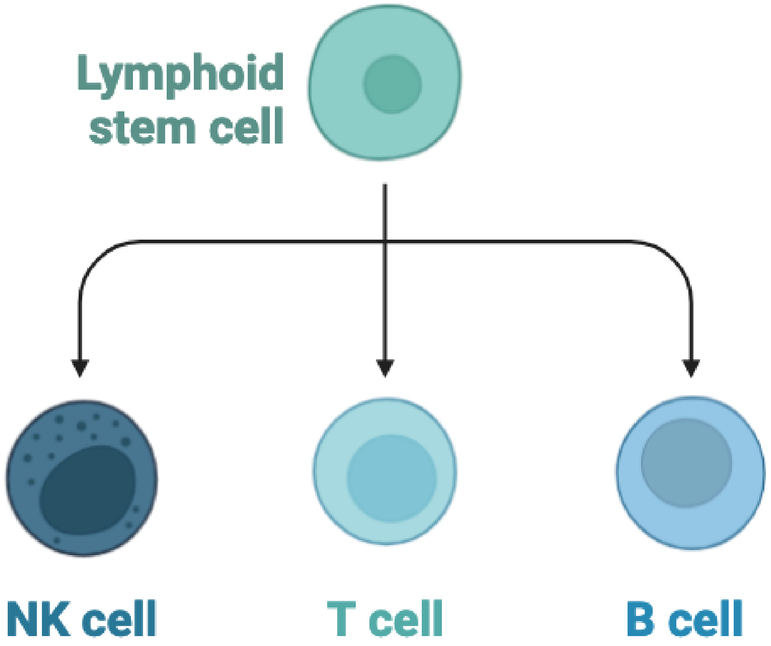


Macrophages are Reprogrammed to Support Tumorigenesis and Metastasis



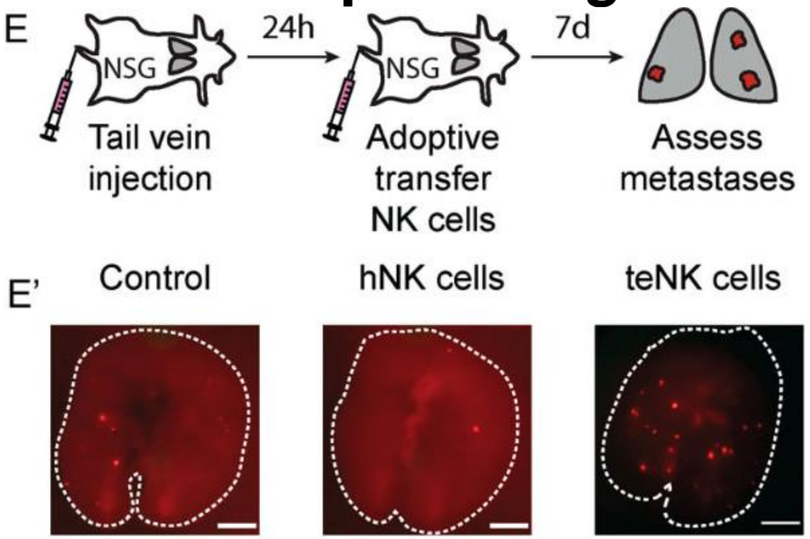
Stavrou, et al., Front Immunology, 2024

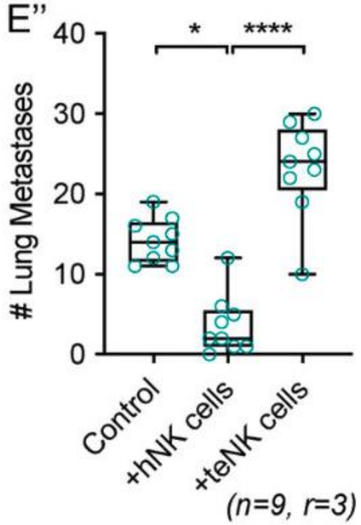
NK Cells Can Eliminate or Assist Breast Cancer



Kill MHC-I Deficient Cancer Cells

Cancer cells educate natural killer cells to a metastasis-promoting cell state





Chan, et al., J Cell Biol, 2020

CellPress

Cancer Cell

Article

The temporal progression of lung immune remodeling during breast cancer metastasis

Cytotoxic NK cell proportions increase during metastasis, unlike in primary tumor

McGinnis, et al., Cancer Cell, 2024

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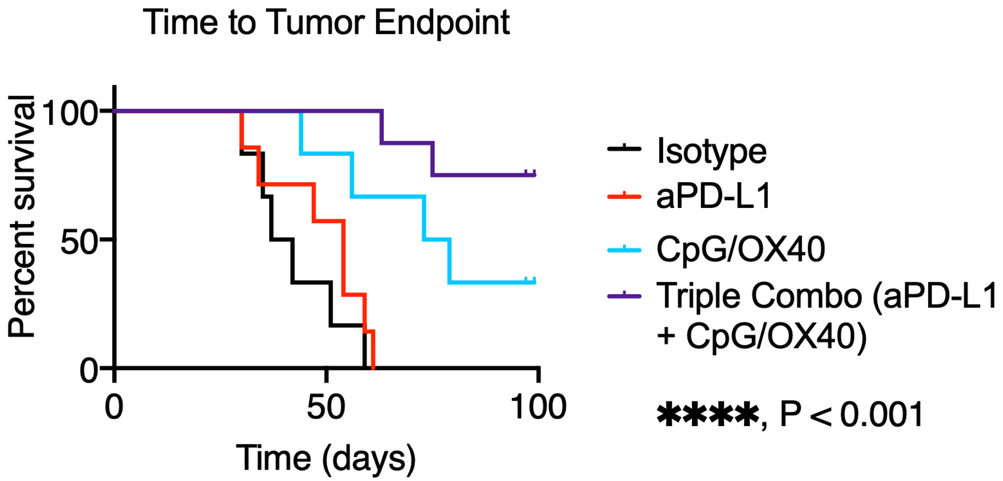
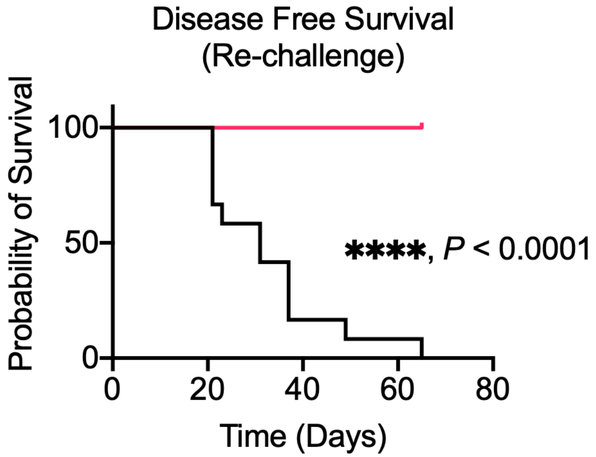
Innate Immunity and Therapeutics

1. TLR9 / cGAS-STING - small molecule agonists
2. Anti-CD47 - improving anticancer phagocytosis
3. mRNA vaccines - require DCs / personalized cancer vaccines

TLR9 / cGAS-STING Agonists Activate INF Signaling

In Preclinical TNBC Models TLR9 Agonists Can Synergize with Anti-PD-L1 Therapy





Lee, Housley et al., Nature Comm., 2022

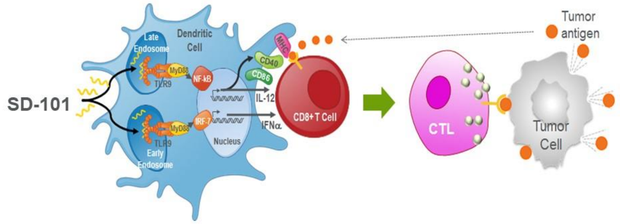
Evaluation of Intra-Tumoral SD-101 and Pembrolizumab in Combination with Paclitaxel Followed by AC in High-Risk HER2-negative Stage II/III Breast Cancer: Results From the I-SPY 2 Trial

Jo Chien, Hatem Soliman, Cheryl Ewing, Judy C Boughey, Michael J. Campbell, Hope S.Rugo, Anne Wallace, Kathy S. Albain, Erica Stringer-Reasor, An L. Church, Kevin Kalinsky, Anthony Elias, Zahi Mitri, Amy S.Clark, Rita Nanda, Alexandra Thomas, Christina Yau, Denise Wolf, Donald A Berry, and Laura J Esserman

on behalf of the I-SPY 2 TRIAL Consortium

SD-101

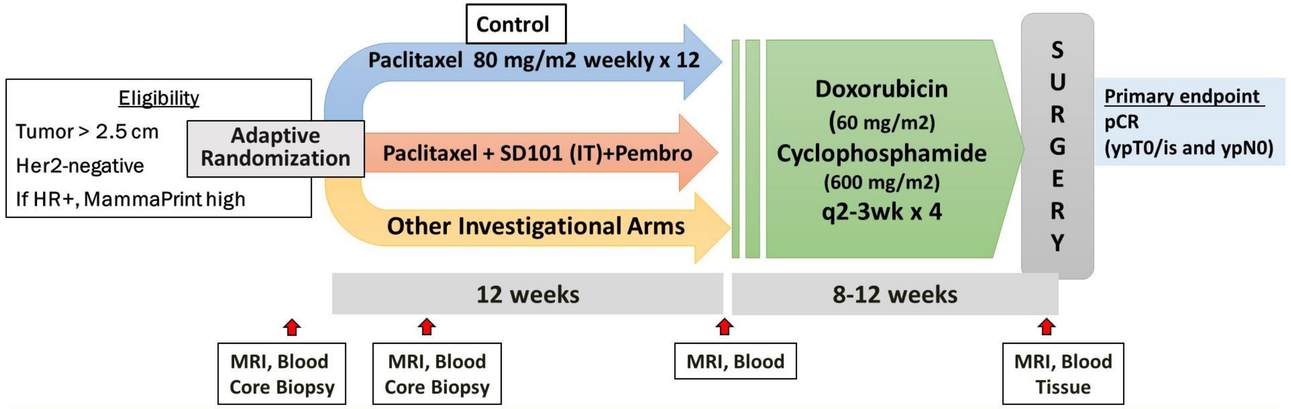
- Toll-like receptor 9 (TLR9) is a member of the TLR family which plays a key role in recognizing pathogen-expressed molecules
- SD-101 is a synthetic oligonucleotide with cytosine-phosphate-guanine (CpG) motifs
  - Binds and activates TLR9 in plasmacytoid dendritic cells (pDCs)
  - pDCs release IFN-alpha, mature into efficient APCs, and stimulate cytotoxic T cells
- Delivery of SD-101 directly to tumors focuses action on tumor-reactive T cells



Chien, et al., ASCO, 2021

TLR9 / cGAS-STING Agonists Activate INF Signal

I-SPY 2 TRIAL Design



- SD-101+Pembrolizumab was studied in 3 HER2-negative biomarker signatures: All HER2-, HR+HER2-, HR- HER2- (TN)
- Agent Graduation:
  - ≥85% predicted probability of success in a 300-patient phase 3 neoadjuvant trial
- Graduation is assessed for each pre-specified biomarker signature

Selected Treatment-Related Adverse Events (non-immune)

No safety signals seen in the 10-patient safety run-in for SD-101+Pembro arm

Adverse Event	SD101+ Pembro+Paclitaxel (n=75 subjects)		Paclitaxel (n=329 subjects)	
	≥ Grade 3	All Grade	≥ Grade 3	All Grade
Blood and lymphatic system disorders				
Anemia	5 (6.7%)	23 (30.7%)	13 (4.0%)	58 (17.6%)
Febrile neutropenia	9 (12%)	9 (12%)	21 (6.4%)	21 (6.4%)
Neutropenia	21 (28%)	31 (41.3%)	28 (8.5%)	47 (14.3%)
General disorders and administratio				
Infusion related reaction	0 (0%)	13 (17.3%)	0 (0%)	24 (7.3%)
Injection site reaction	0 (0%)	**17 (22.7%)**	0 (0%)	5 (1.5%)
Fever	1 (1.3%)	**44 (58.7%)**	1 (0.3%)	37 (11.2%)
Flu like symptoms	1 (1.3%)	**9 (12%)**	0 (0%)	17 (5.2%)
Fatigue	4 (5.3%)	59 (78.6%)	4 (1.2%)	208 (63.2%)
Infections				
Skin infection/Soft tissue infection	**5 (6.7%)**	**12 (16%)**	0 (0%)	9 (2.7%)
Liver Enzymes				
Alanine aminotransferase increased	4 (5.3%)	**24 (32%)**	4 (1.2%)	30 (9.1%)
Aspartate aminotransferase increased	1 (1.3%)	**18 (24%)**	2 (0.6%)	21 (6.4%)
Gastrointestinal disorders				
Diarrhea	2 (2.7%)	37 (49.3%)	4 (1.2%)	105 (31.9%)
Nausea	0 (0%)	47 (62.6%)	1 (0.3%)	179 (54.4%)
Vomiting	0 (0%)	12 (16%)	2 (0.6%)	52 (15.8%)

Efficacy Analysis

SD-101+Pembrolizumab arm increased estimated pCR rates compared to control arm.

- This did not meet the pre-specified threshold for graduation

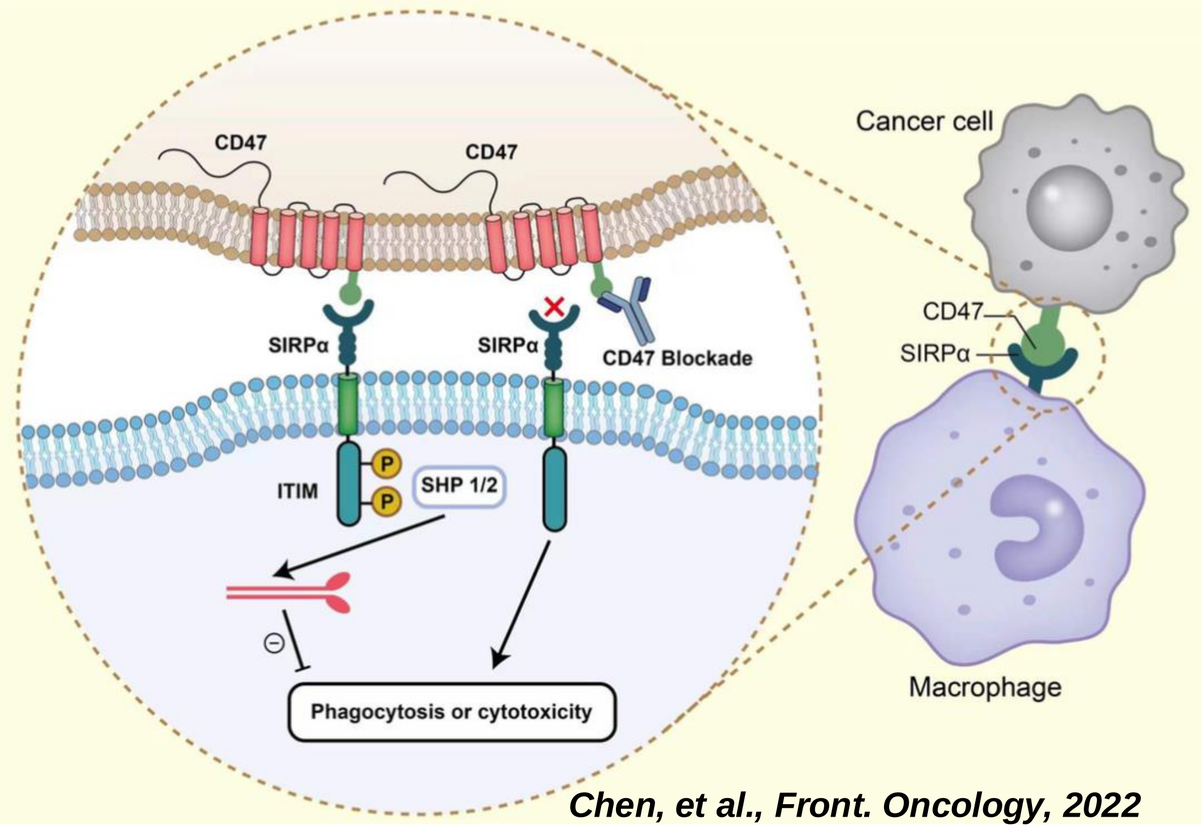
Signature	Estimated pCR Rate (95% Probability Interval)		Probability SD101+P Superior to Control	Predictive Probability of Success in Phase 3 (relative to Control)
	SD101+P (n=75)	Control (n-329)		
HER2-	**0.341 (0.24-0.44)**	**0.199 (0.16-0.24)**	0.997	0.717
HR-HER2-	0.437 (0.28- 0.6)	0.275 (0.21-0.34)	0.973	0.707
HR+HER2-	0.259 (0.14- 0.37)	0.135 (0.09- 0.18)	0.986	0.679

SD-101 does not appear to further increase tumor response when added to pembrolizumab in both HR+ HER2- and TN subtypes.

Chien, et al., ASCO, 2021

Targeting CD47 (Don’t Eat Me)

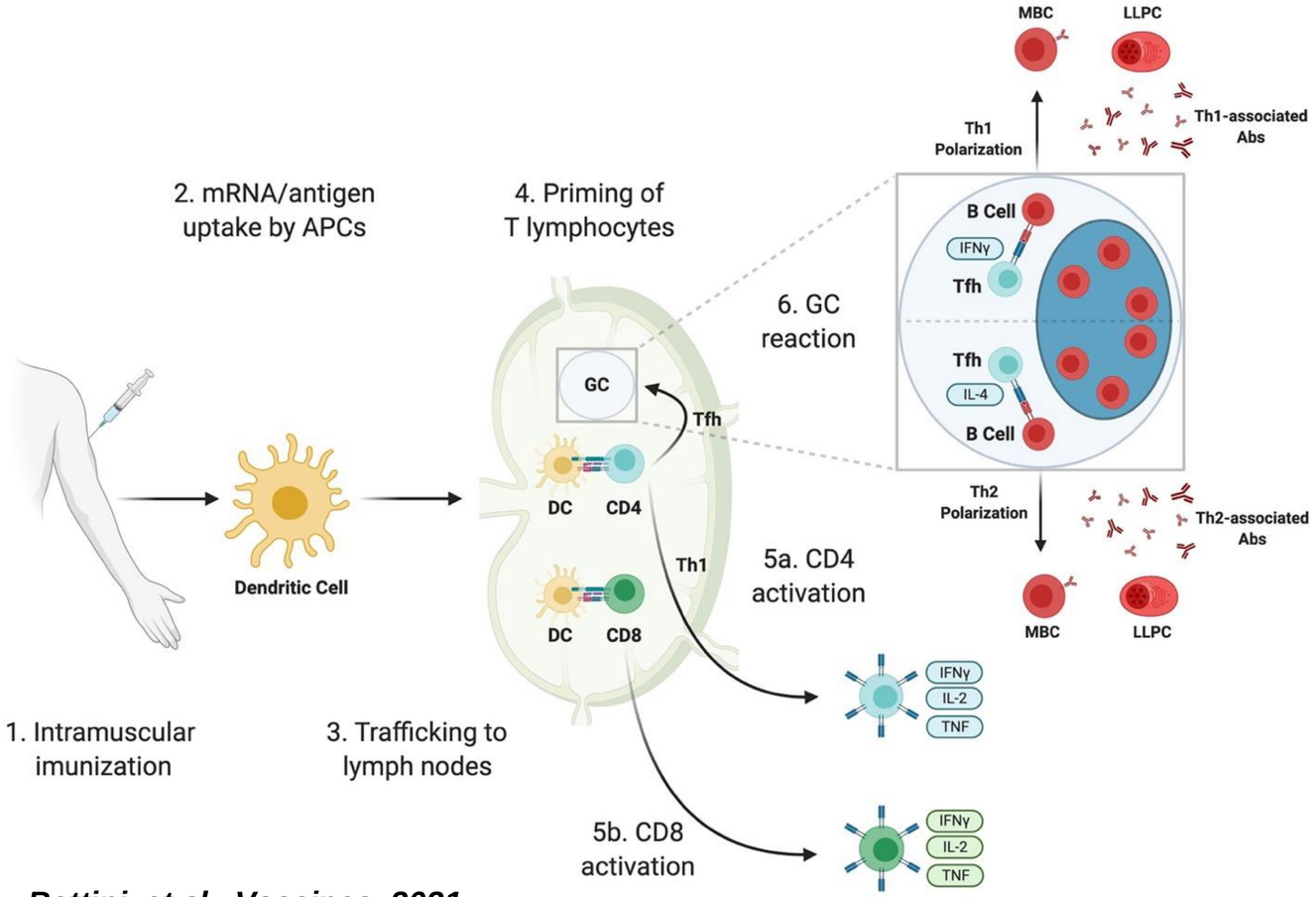
CD47 Block Macrophage Phagocytosis of Cancer Cells



Chen, et al., Front. Oncology, 2022

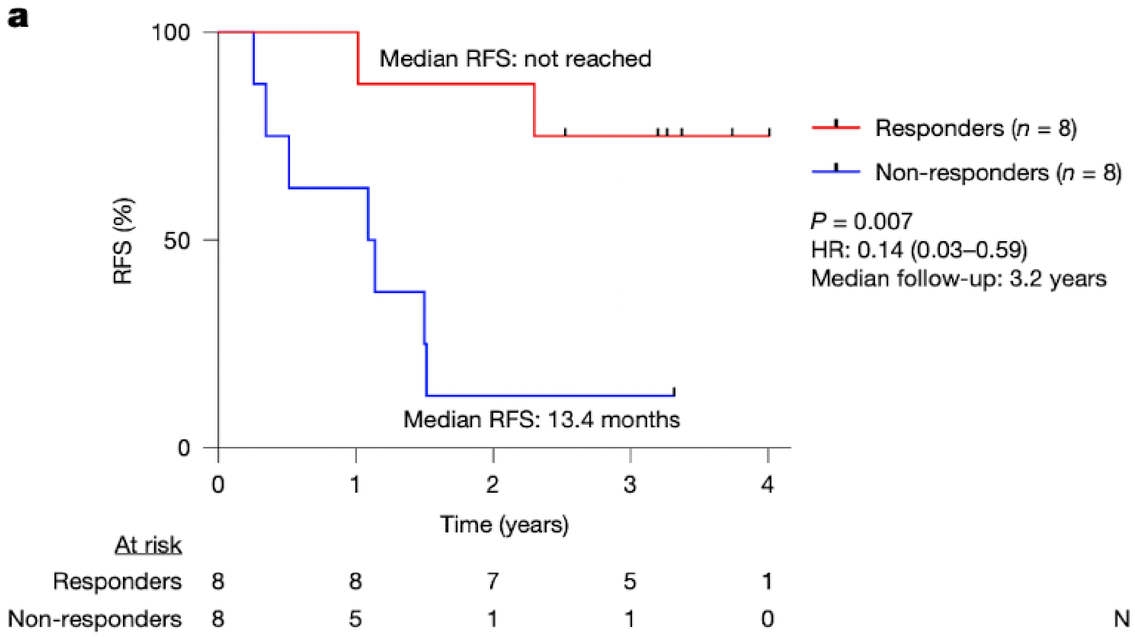
1. Increased phagocytosis of tumor cells
2. Increased antigen presentation to activate T cells
3. ADCC
4. Caspase-independent cell death
5. Preclinical studies have indicated that CD47-SIRPα blockade synergizes with anti-HER2 or anthracyclines.
6. Widely expressed on normal cells causing concern about anemia
7. Dual targeting CD47 + PD-L1 bispecifics showed synergistic activity in preclinical models
8. More that two dozen trials of CD47 blockade are ongoing in various solid tumors
9. Montero, et al. presented at SABCS 2024 trial of HER2 bispecific + CD47 targeting (PS8-09) for metastatic BrCA. Among 19 evaluable HER+; ORR = 37%, DCR 75%, median duration of response 6 months
10. Phase 3 ENHANCE trial of AML; magrolimab - first in class CD47 full clinical hold for futility and increased risk of death

mRNA Vaccines Rely on Antigen Presenting Cells for Stimulation of B and T Cells & Application to Personalized Cancer Vaccines



Bettini, et al., Vaccines, 2021

Atezolizumab + mRNA Vaccine for Neoantigens (up to 20) + modified FOLFIRINOX chemotherapy



Sethna, et al., Nature, 2024

Summary

- The innate immune system responds to breast cancer and can prepare the adaptive immune system for long term anticancer immunity.
- Components of the innate immune system are often altered or co-opted to elicit tumor therapy resistance and metastasis.
- Strategies to leverage the innate immune system are under investigation
  - TLR9 / cGAS-STING agonists (multiple immune cells)
  - anti-CD47 (macrophages)
  - mRNA vacines (dendritic cells)