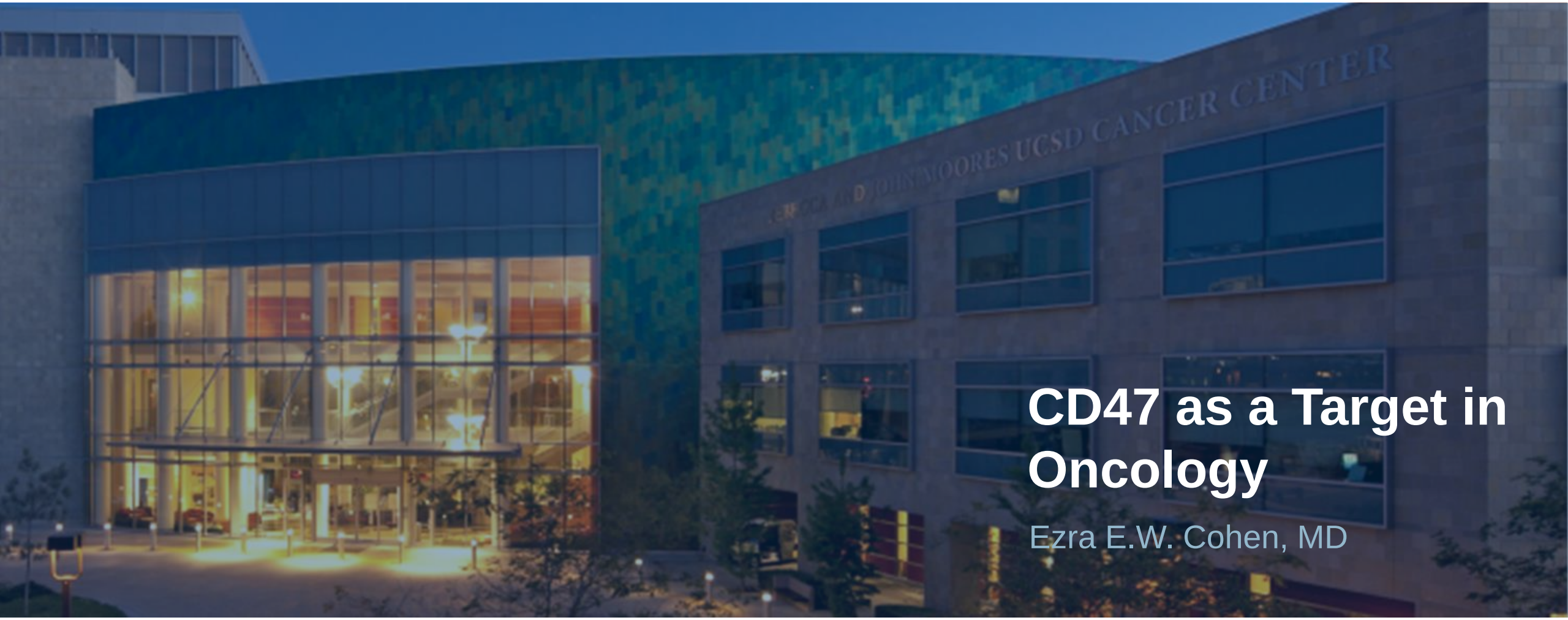

CD47 as a Target in Oncology

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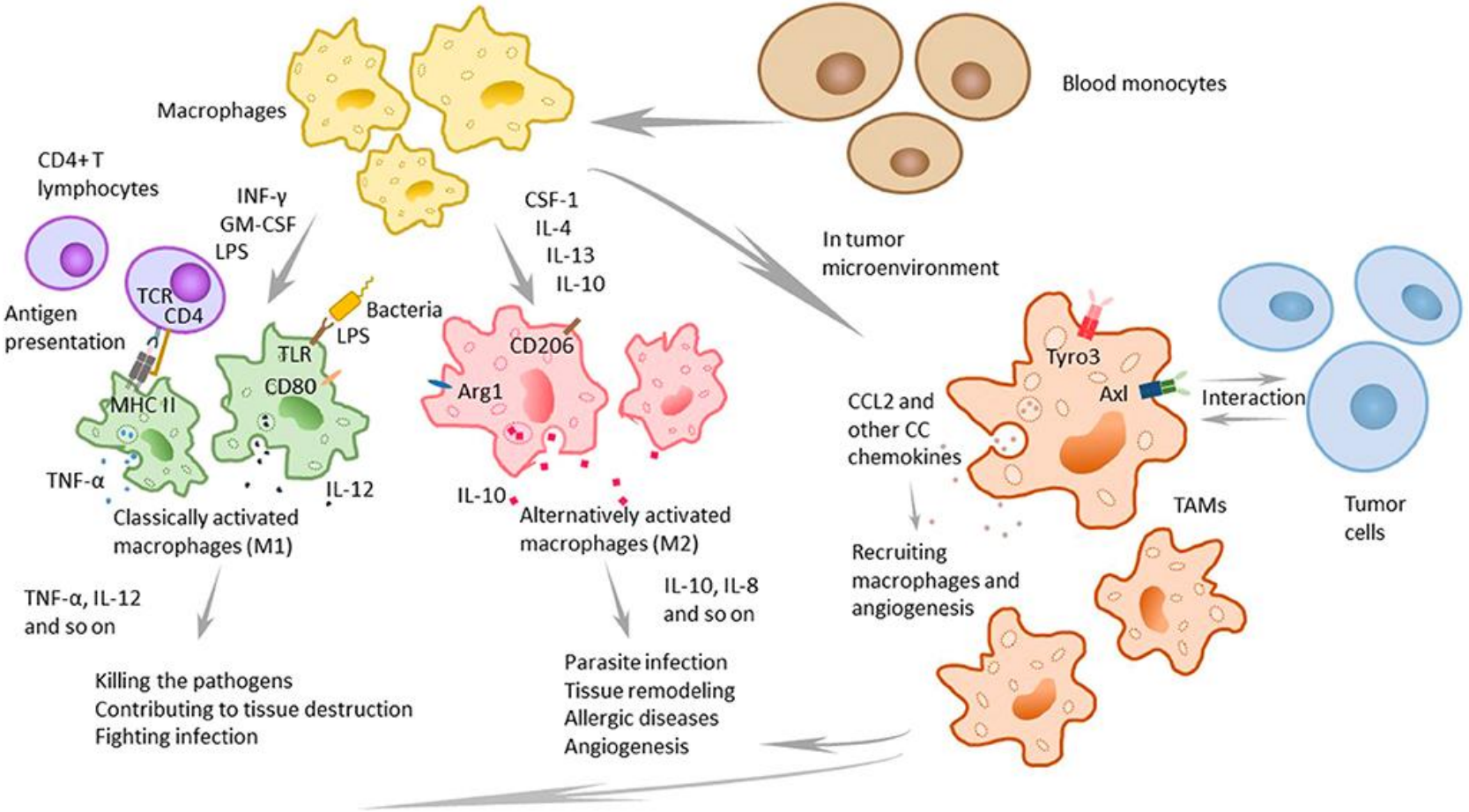
NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

UC San Diego
Moores Cancer Center

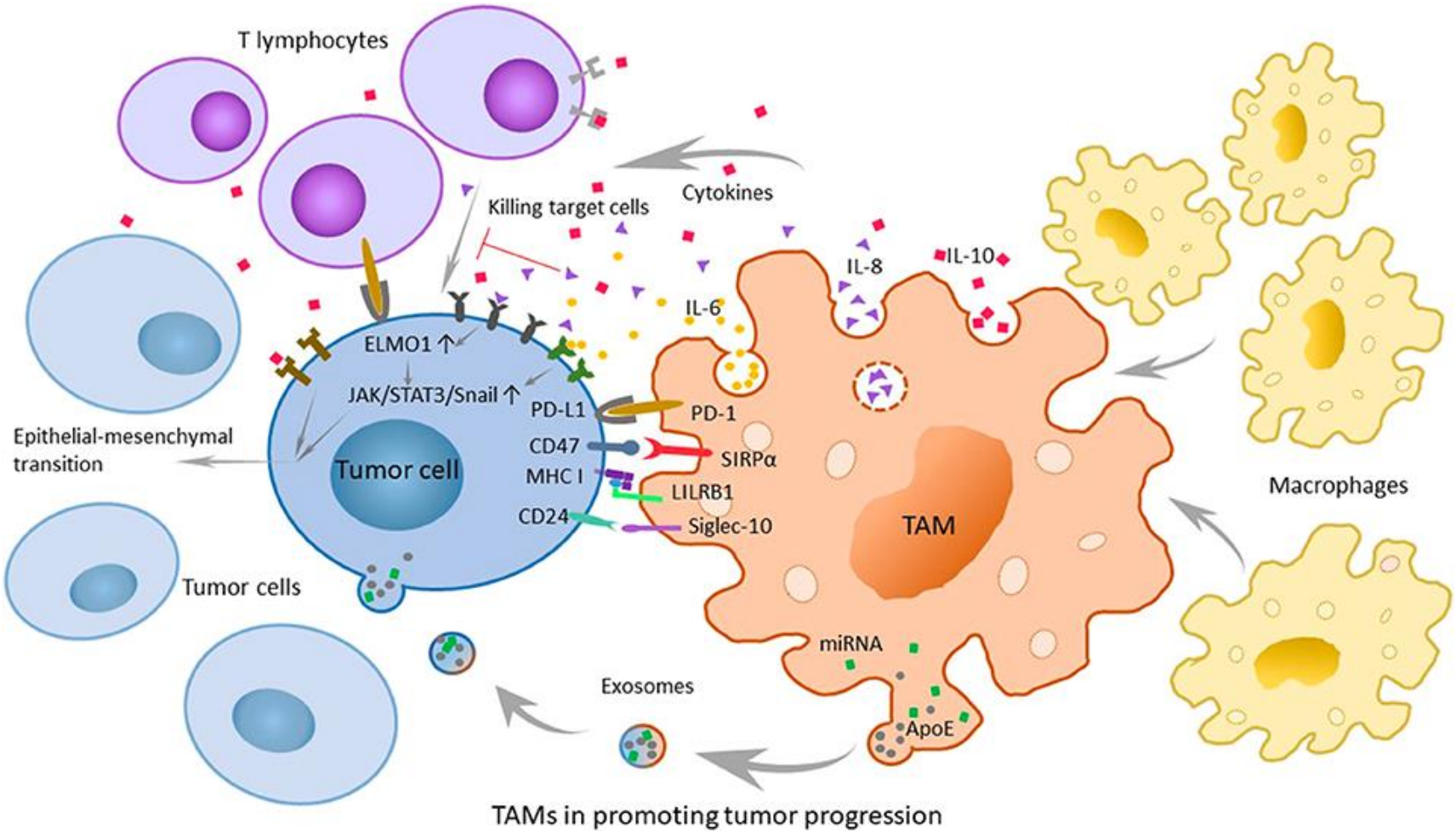
The Innate Immune System

Two of the main subpopulations of macrophages (M1 and M2) and tumor associated macrophages (TAMs)



Front. Oncol., 25 February 2020 | https://doi.org/10.3389/fonc.2020.00188

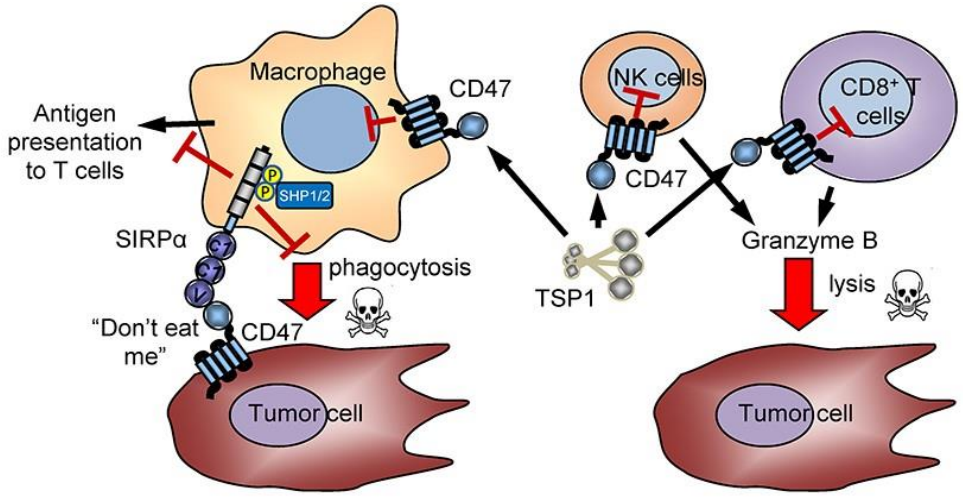
Tumor-Associated Macrophages: Insights and Therapies



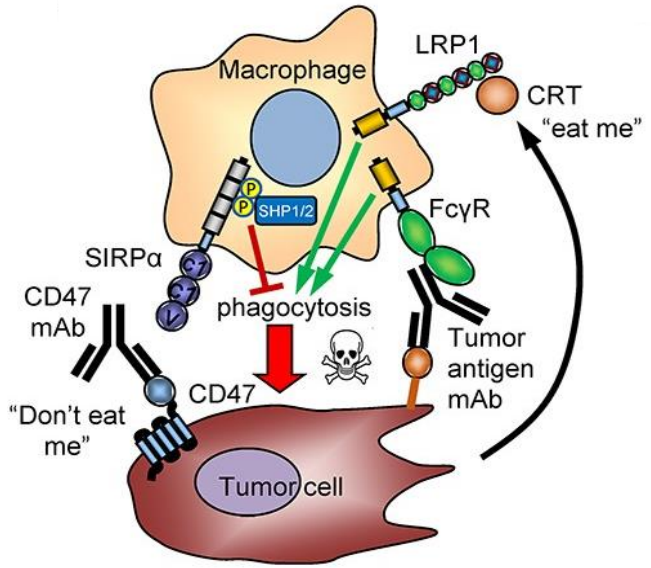
Front. Oncol., 25 February 2020 | https://doi.org/10.3389/fonc.2020.00188

CD47 Functions In The Tumor Microenvironment

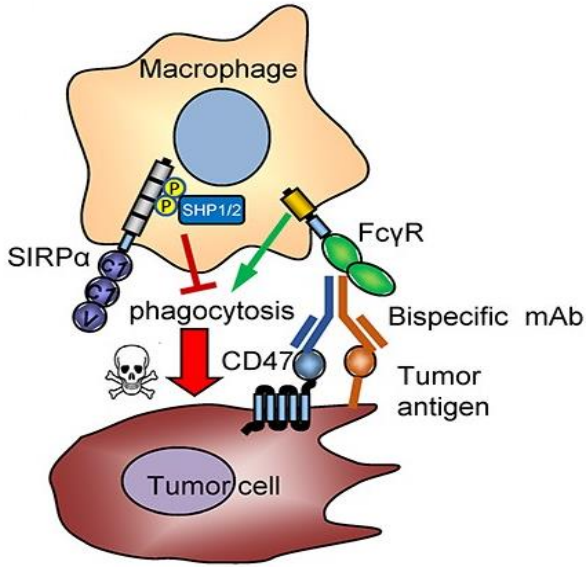
CD47-dependent inhibition of phagocytosis and antigen presentation



Anti-CD47-antibody-dependent phagocytosis and ADCP/ADCC



Bispecific CD47 antibody-dependent ADCP and/or ADCC

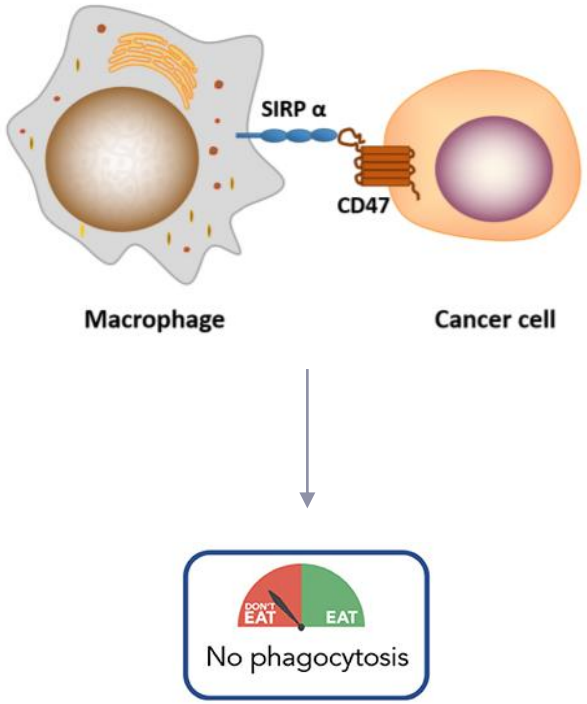


CD47 Interaction With SIRPα Prevents Innate Immune Cells From Attacking Host Cells

Healthy Cells

CD47 protects healthy cells from destruction

- CD47 is a surface protein widely expressed on healthy cells
- Interacts with SIRPα expressed on macrophages and dendritic cells
- Regulates innate immune cell phagocytic activity and cell migration



Tumor Cells

CD47 overexpression evades immune destruction of tumor cells

- CD47 is over-expressed across solid tumors and hematological malignancies
- Serves as a camouflage to avoid clearance by macrophages
- Elevated CD47 is associated with a poor prognosis

Lu Q et al.; Onco Targets Ther. 2020; Chao MP et al.; Front. Oncol., 2020

CD47 Is A Clinically Validated Innate Immunity Check Point Inhibitor

CD47 inhibition impairs tumor growth, inhibits metastatic spread, and leads to tumor regression in preclinical models

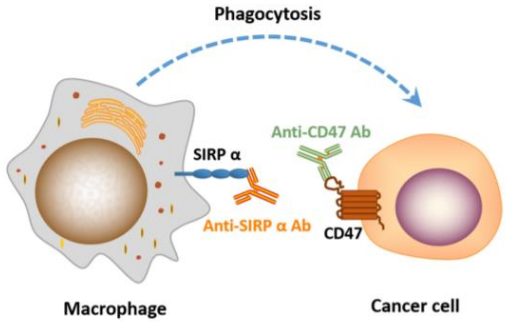
Evidence supports CD47 blockade may help **bridge innate and adaptive immunity** by

1. Reactivating macrophages against cancer cells
2. Enhancing APC presentation of tumor antigens
3. Inducing anti-tumor T-cell activity

Therapeutic considerations for targeting CD47

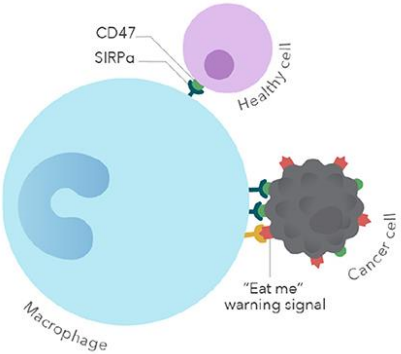
Enhanced activity in combination

CD47 inhibition in combination with antibodies targeting macrophages **enhances phagocytosis and anti-tumor activity** in preclinical models



Healthy cells are spared

An **additional 'eat me signal'** expressed on cancer cells and RBC is required for phagocytosis during CD47 blockade



Lu Q et al.; Onco Targets Ther. 2020; Chao MP et al.; Front. Oncol., 2020; Jalil et al., Antibody Therapeutics, 2020; Takimoto et al., Annals of Oncology, 2019; Tseng T et al., PNAS, 2013

CD47i Monotherapy: Lack of Clinical Responses In Solid Tumors

Company	I-MAB Biopharma/ AbbVie	Innovent	Gilead/ Forty Seven	Surface Oncology	ALX Oncology
Candidate	Lemzoparlimab	Letaplimab	Magrolimab	SRF231	ALX148
MOA	Anti-CD47 Monoclonal Antibody	Anti-CD47 Monoclonal Antibody	Anti-CD47 Monoclonal antibody	Anti-CD47 Monoclonal Antibody	SIRPα-Fc fusion protein
Clinical stage	Phase 1	Phase 1	Phase 1	Phase 1	Phase 1
Indication	Solid Tumors	Solid Tumors	Solid Tumors	Solid Tumors	Solid tumors
N	20	20	62	46	25
Efficacy	6% ORR (1/16)	0% ORR (0/15)	6% ORR (2/35)	0% ORR (0/38)	0% ORR (0/25)
Anemia	30%	15%	57%	24%	-

CD47 Therapies For Solid Tumors – Future Directions

1. Combination with therapeutic mAb's (IgG1-based preferred)

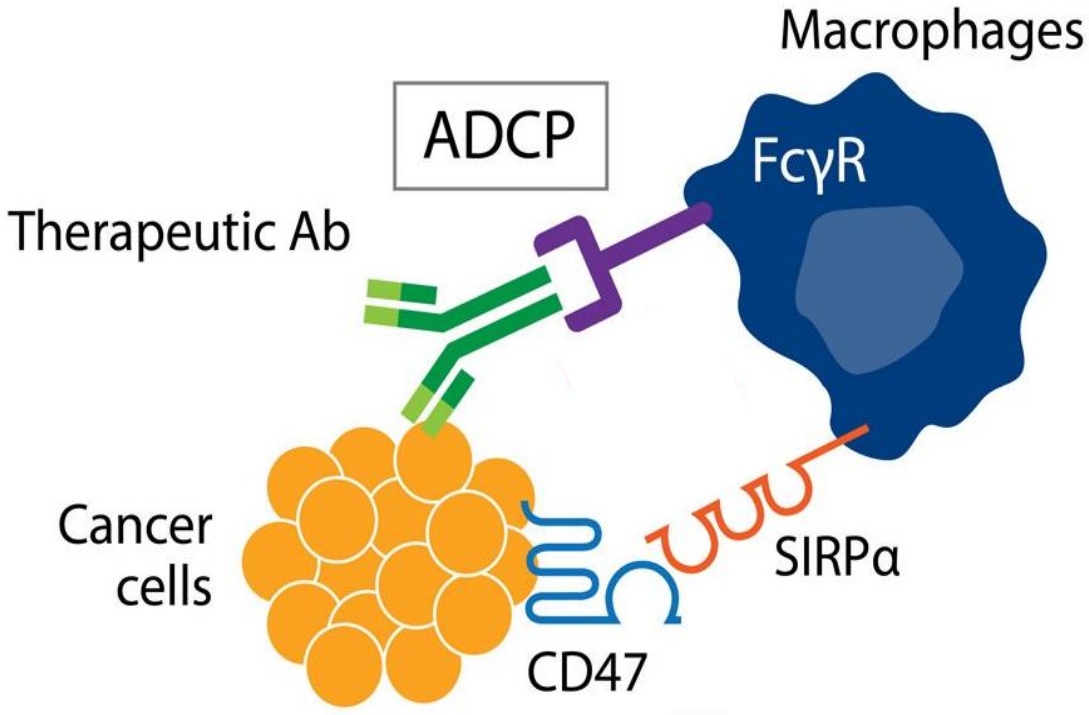
2. Combination of innate and adaptive immunity

3. Combination with Chemotherapy/ Radiotherapy

Combination With Therapeutic mAb's

Combination With Therapeutic mAb's

- CD47 blockade on tumor cells triggers phagocytosis by macrophages which may be opsonized with tumor antigen-specific therapeutic Abs such as cetuximab or trastuzumab
- The mechanism is called antibody-dependent cellular phagocytosis (ADCP) elicited by the interaction of the Fc region of tumor-bound Abs with the macrophage Fcγ receptor (FcγR)



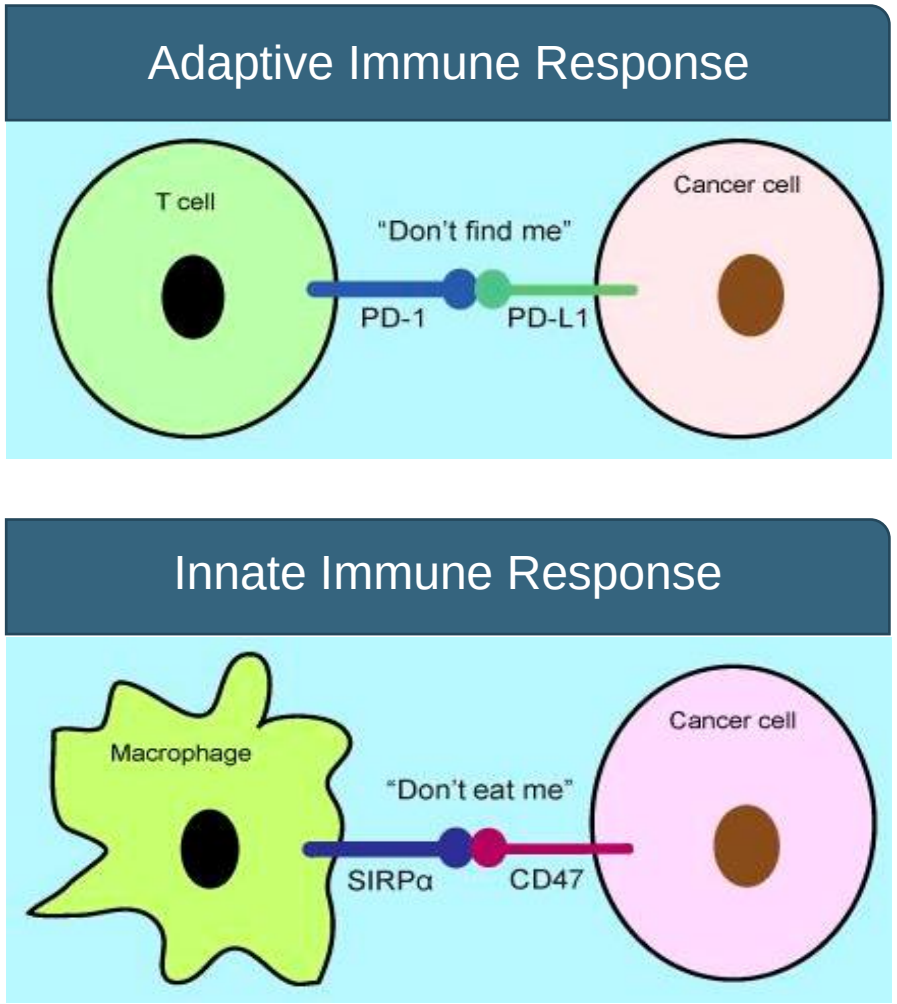
https://doi.org/10.1111/cas.13663

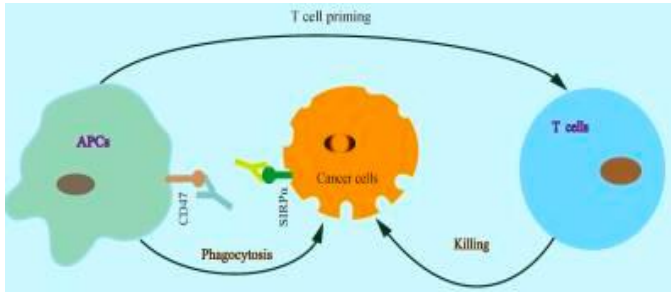
CD47i Combinations: Therapeutic mAb's Improve Clinical Responses

Company	Gilead/ Forty Seven	Gilead/ Forty Seven	Alx Oncology	Alx Oncology	Alx Oncology
Candidate	Magrolimab	Magrolimab	Evorpacept	Evorpacept	Evorpacept
MOA	Anti-CD47 Monoclonal Antibody	Anti-CD47 Monoclonal Antibody	SIRPα-Fc Fusion Protein	SIRPα-Fc Fusion Protein	SIRPα-Fc Fusion Protein
Clinical stage	Phase 1	Phase 1	Phase 1b	Phase 1b	Phase 1b
Additional drug	Cetuximab	Avelumab	Pembrolizumab + 5FU + Platinum	Trastuzumab	Trastuzumab Ramucirumab Paclitaxel
Indication	KRASwt, KRASmut Colorectal Cancer	Ovarian Cancer	HNSCC	HER2+ G/GEJ	HER2+ G/GEJ
N	30	18	13	19	18
Efficacy	7% ORR	6% ORR	**38.5% ORR**	21% ORR	**72% ORR**
Anemia	22%	24%	10%	7%	6%

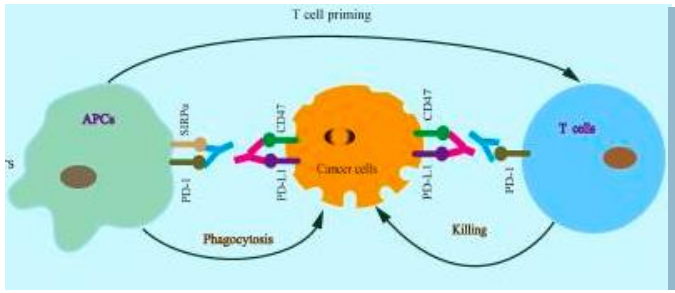
Combination Of Innate And Adaptive Immunity

Combination Of Innate And Adaptive Immunity

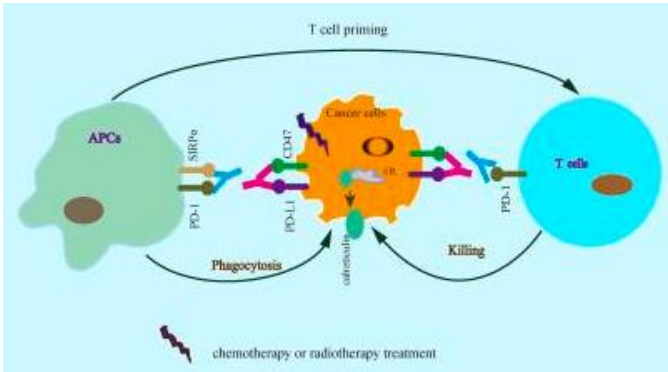




I: SIRPα/CD47 inhibitors



II: Combination with PD-1/PD-L1 inhibitors



III: Combination with chemotherapy or radiotherapy

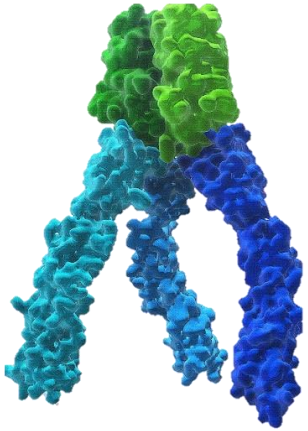
Int J Biol Sci. 2021; 17(13): 3281–3287

Combination Of Innate And Adaptive Immunity In Clinical Development

- Bi-specific fusion proteins combining anti-CD47 and TNF superfamily ligand for immune co-stimulation
- Combination of anti-CD47 and other immune checkpoint inhibitors such as PD-1/PD-L1
- Bi-specific Ab's aiming to both CD47 and PD-1/PD-L1

DSP107
CD47x41BB

Trimeric 4-1BBL for
T cell co-stimulation



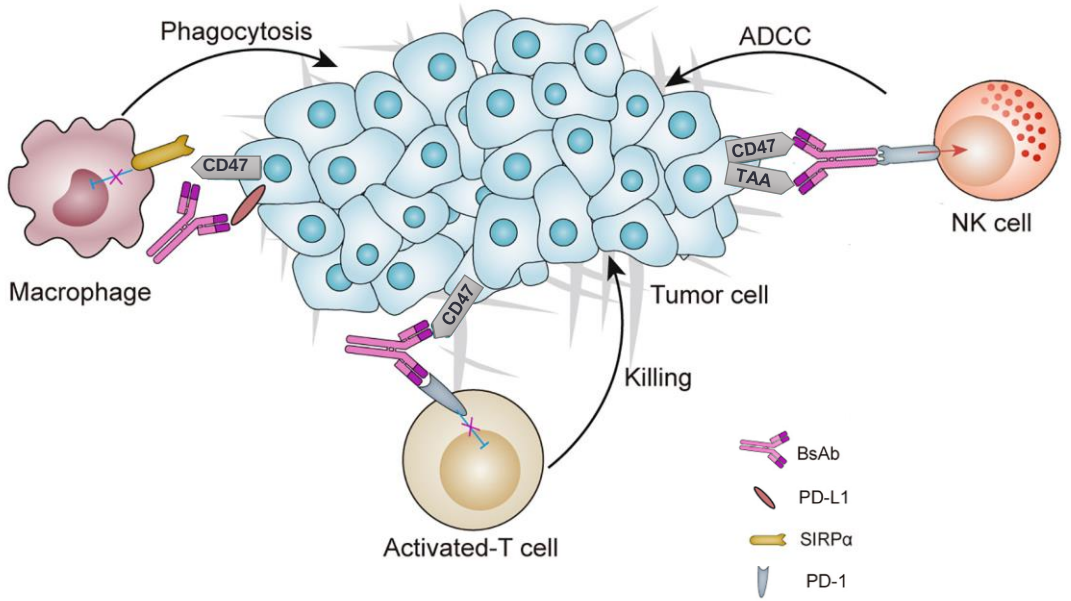
3 SIRPα for CD47 blockade

SL-172154
CD47xCD40

Hexameric CD40L for
antigen presentation

6 SIRPα for CD47 blockade

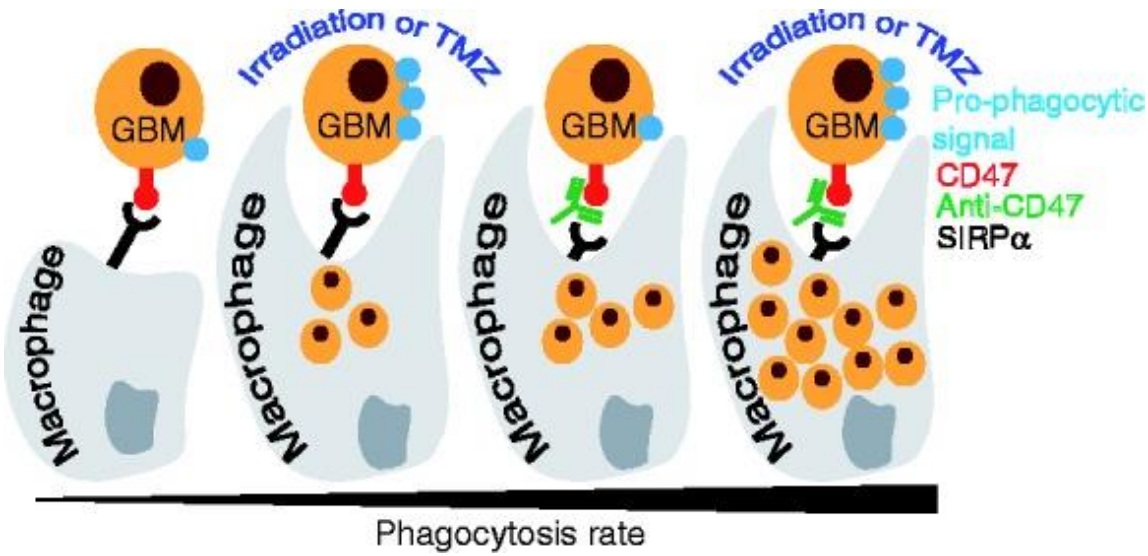
HX009, PF-07257876, IBI322
CD47xPD-1/PD-L1



Combination With Chemotherapy/Radiotherapy

Combination With Chemotherapy/Radiotherapy

- Anti-CD47 immunotherapy in combination with irradiation or chemotherapy may enhance macrophage-dependent phagocytosis and antigen presentation
- Tumor cell death triggered by immunogenic chemotherapeutic such as anthracyclines, cyclophosphamide and taxanes may lead to exposure of calreticulin on the cell surface where it serves as a de novo “eat-me” signal enhancing phagocytosis



Innate Immun. 2020 Feb; 26(2): 130–137.
doi: 10.1177/1753425919876690

Summary and Conclusions

- CD47 is well-established as a critical immune mediator within the tumor microenvironment, as CD47 overexpression leads to poor clinical outcomes across solid tumors and hematologic malignancies
- CD47 is a clinically validated innate immunity checkpoint inhibitor, but lacks robust clinical responses as a monotherapy
- Combination of anti-CD47 antibodies with therapeutic monoclonal antibodies have shown improved clinical efficacy
- Several CD47-targeted therapeutic considerations are currently in development, including SIRPα/CD47 bi-specific inhibitors, combination with adaptive immune activators, and combination with chemotherapy or radiotherapy