



**I
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ISRAEL**

Mechanistische Wechselwirkungen und effektive Verknüpfungen von innate und adaptive immunity im TME

Hendrik Poeck



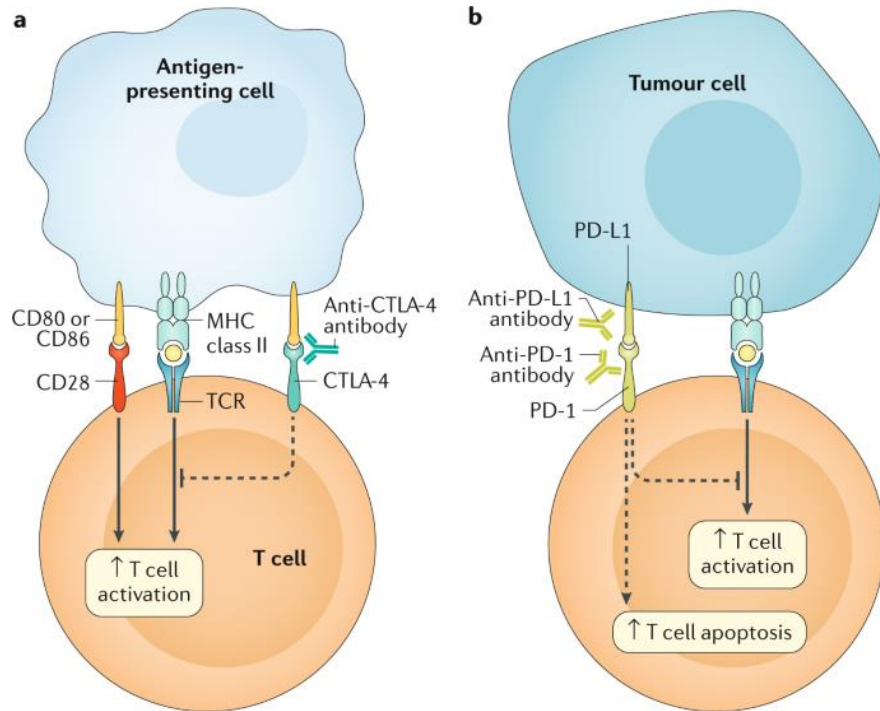
Offenlegung Interessenskonflikte

Beratungs-, Gutachtertätigkeit	Gilead/Kite; AbbVie; Pfizer; Bristol Myers-Squibb/Celgene, Servier
Honorare	Abbvie, Gilead/Kite, Novartis, Servier, Bristol Myers-Squibb/Celgene, Pfizer; Astellas, MSD, Janssen-Cilag
Finanzierung wissenschaftlicher Untersuchungen	Bristol Myers-Squibb/Celgene
Andere finanzielle Beziehungen	AbbVie, Gilead, Novartis, Bristol Myers-Squibb/Celgene, Pfizer; Janssen-Cilag, Amgen, Jazz

Cancer Immunotherapies: Nicht alle sprechen an

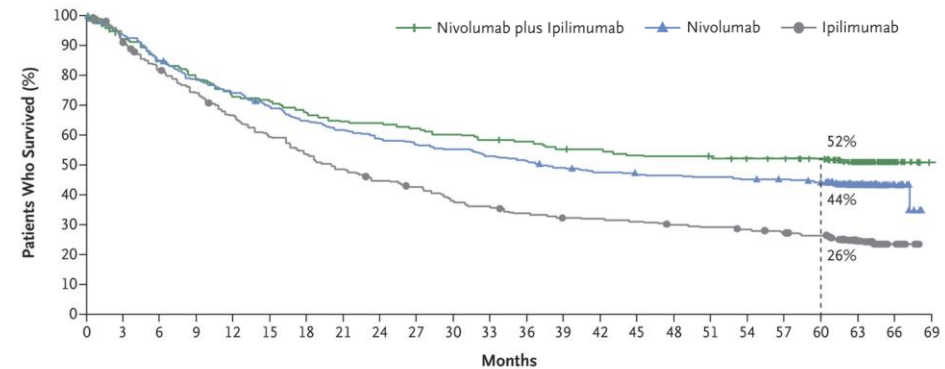
Immune Checkpoint Inhibitors (ICI)

Advanced melanoma



anti-CTLA-4 + anti-PD1 combination therapy:
 → ORR 57 %, mPFS 11.5 months, mOS > 36 months

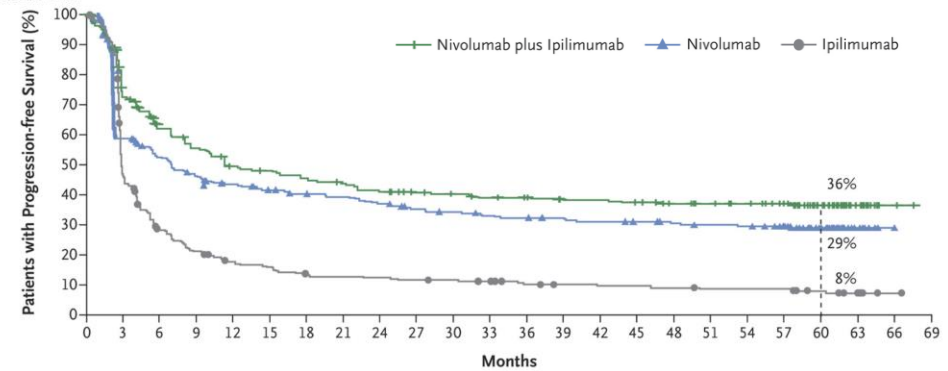
A Overall Survival



No. at Risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69
Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

B Progression-free Survival



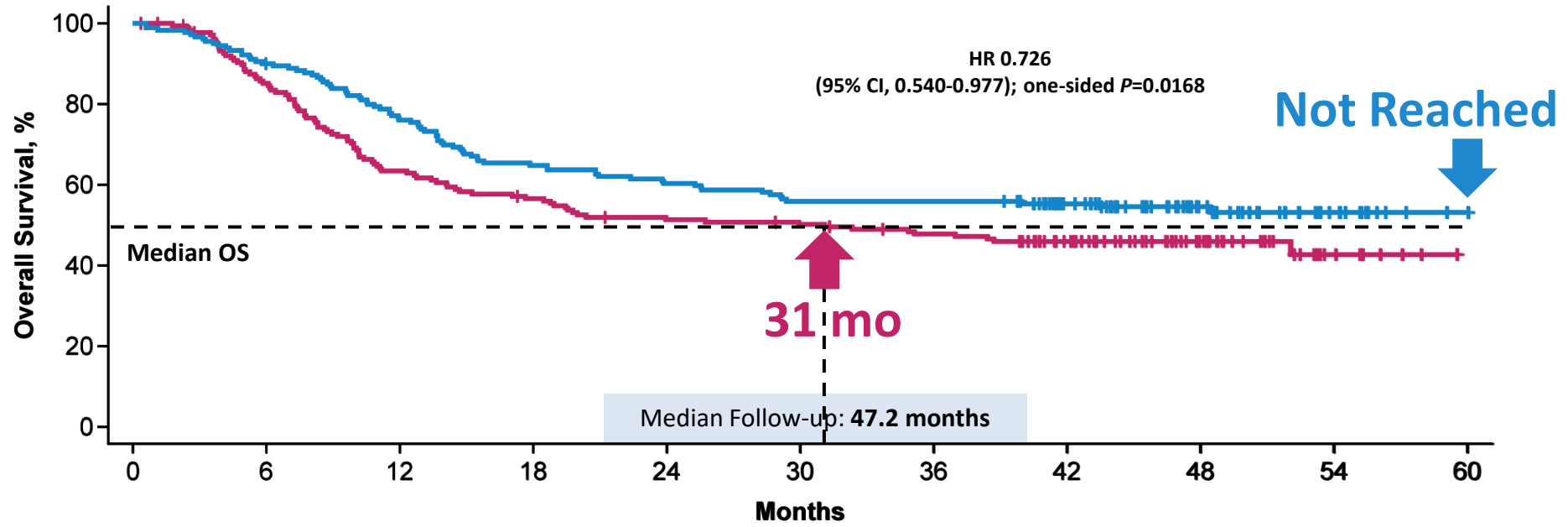
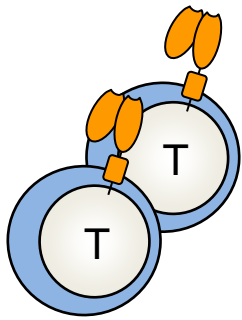
No. at Risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69
Nivolumab plus ipilimumab	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
Nivolumab	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
Ipilimumab	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

Cancer Immunotherapies: Nicht alle sprechen an

CAR T cells

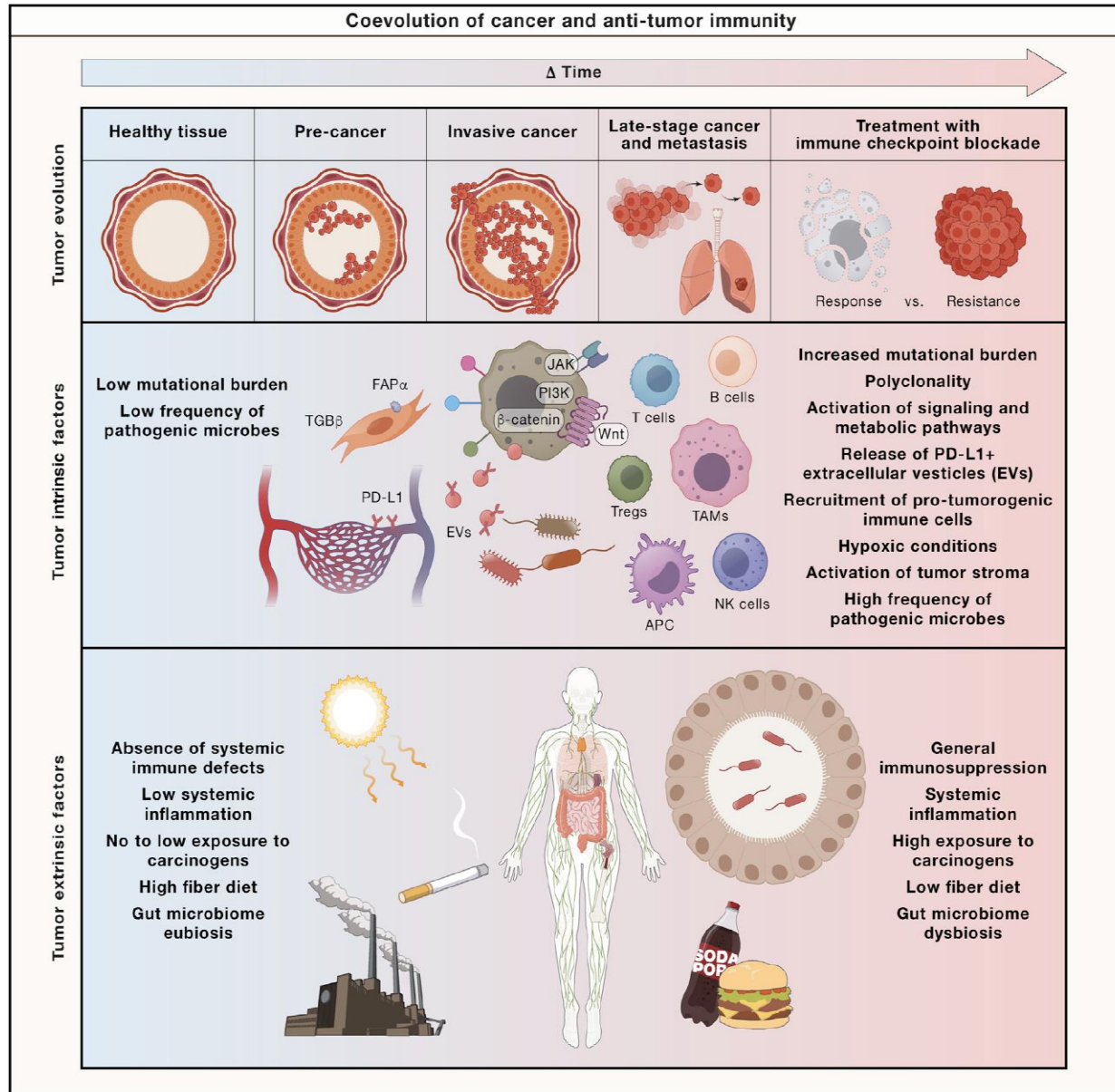
ZUMA-7: Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma



No. at Risk		0	6	12	18	24	30	36	42	48	54	60
Axi-Cel	180	161	136	116	108	100	100	80	41	14	1	
SOC	179	149	111	98	88	85	79	63	31	7	0	

Resistenzmechanismen

ICI



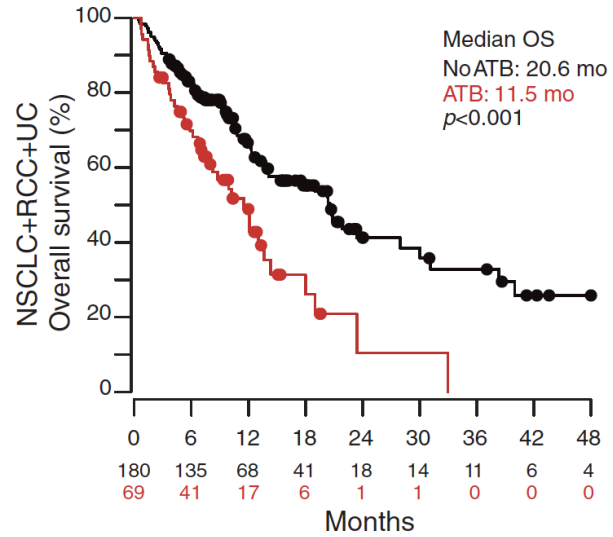
Adapted from Morad et al., *Cell* (2021)

Mikrobiom als Masterregulator für Cancer Immunotherapies

ICI

Routy et al., *Science* (2018)

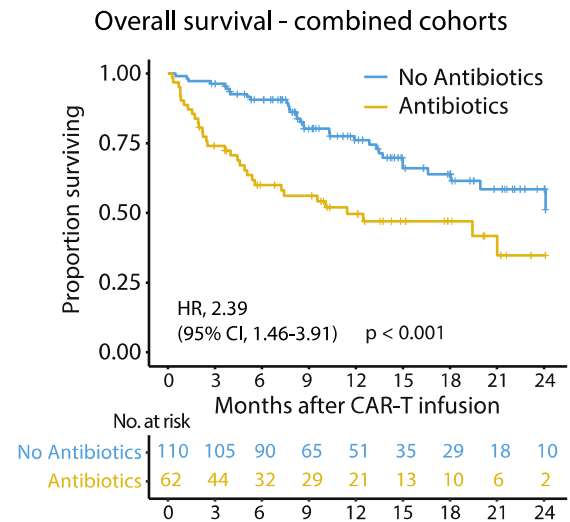
Derosa et al. *Cancer Discovery* (2021)



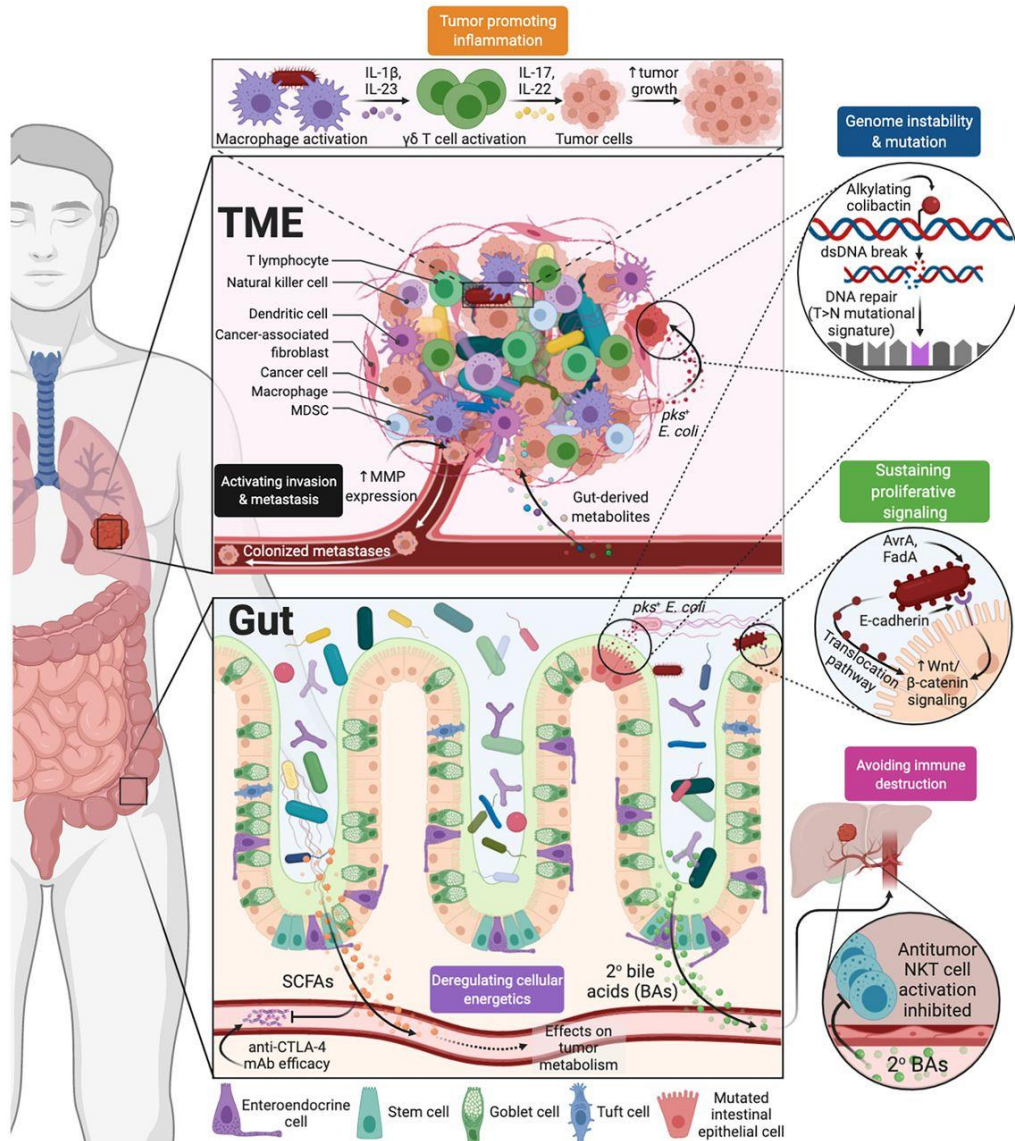
CAR T cells

Stein-Thoeringer et al., *Nat Med.* (2023)

Smith M et al., *Nat Med.* (2022)

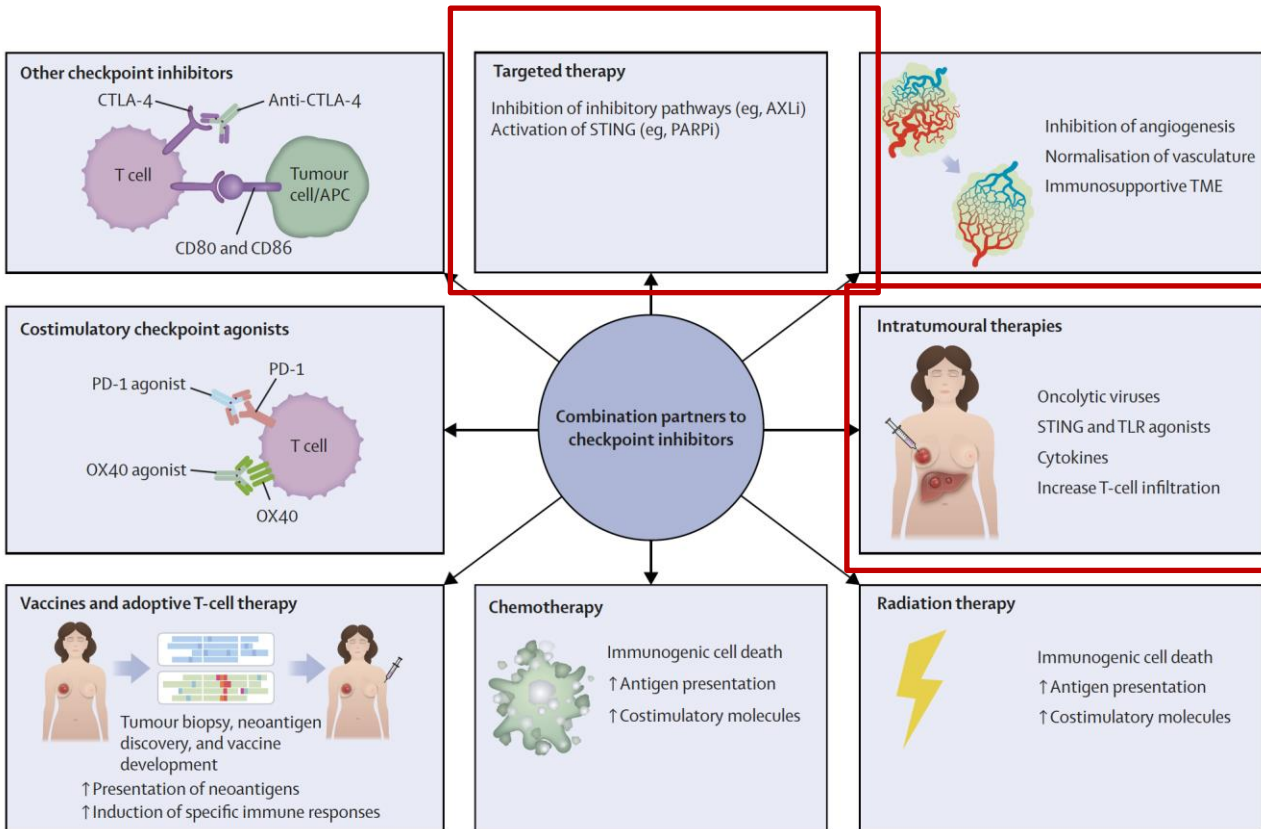


Wie beeinflusst das Mikrobiom Cancer Immunotherapies ?



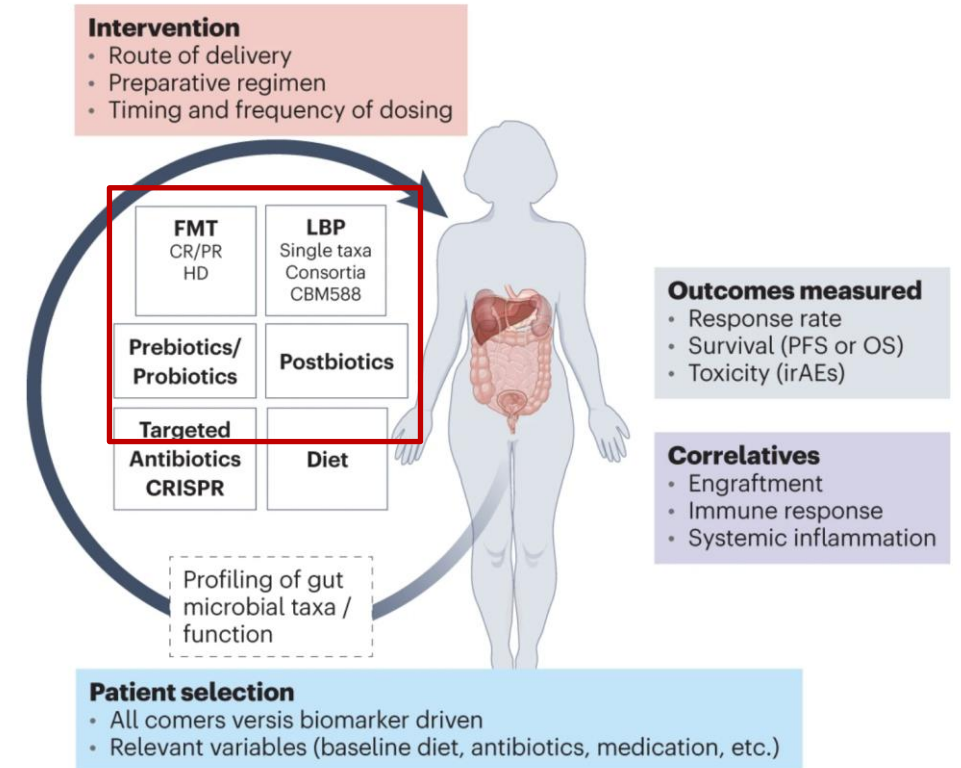
Adapted from Sepich-Poore et al., *Science* (2021)

Strategien zur Resistenzüberwindung: Modulation des TME



Adapted from Meric-Bernstam et al., *Lancet* (2021)

Microbiota-based therapeutic approaches



Adapted from Seo et al., *Nat Med* (2023)

Strategien zur Resistenzüberwindung: Modulation des TME

- I. Nucleic Acid Therapeutics**
- II. Immunstimulatorische Extracellular Vesicles(EVs)**
- III. Microbiome-derived strategies**

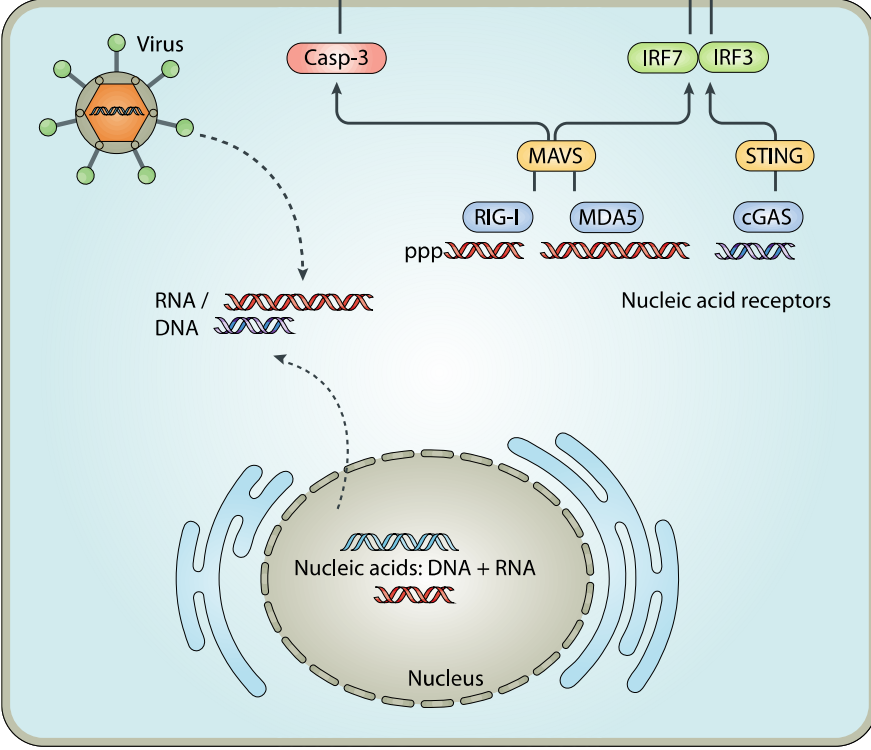
Nucleid acid therapeutics für cancer immunotherapies

Tumor cells

Immunogenic cell death

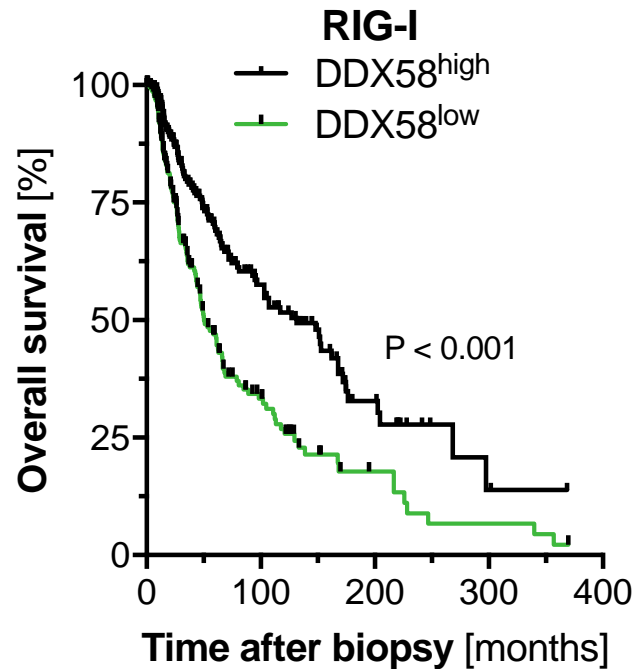
Type I Interferon + Inflammatory cytokines

Anti-tumor T-cell response



Immune cells

Hohe RIG-I expression im melanom geht mit einer verlängerten Gesamtüberlebenszeit einher



No. at risk	0	100	200	300	400			
High	228	113	60	32	14	4	2	1
Low	228	71	33	14	8	3	3	2

TCGA databank:

456 melanoma patients (primary, metastatic)
Therapy naive at biopsy

Selektives RIG-I Targeting fördert Anti-CTLA-4-vermittelte Antitumor-Immunität im Mausmodell

Tumors:

WT B16.OVA

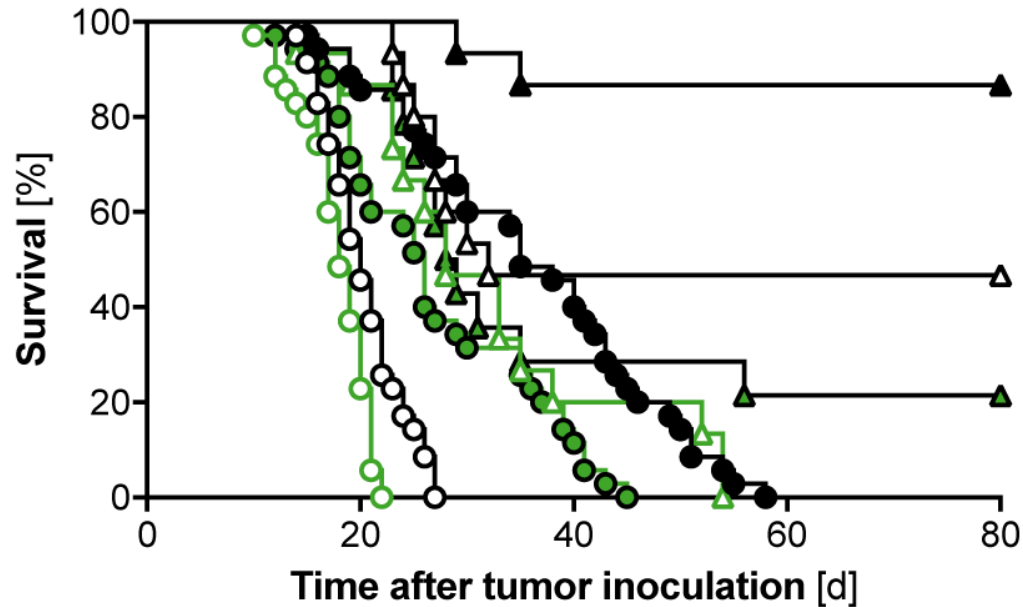
- Isotype
- △ Isotype + 3pRNA
- Anti-CTLA-4
- ▲ Anti-CTLA-4 + 3pRNA

Tumors:

RIG-I^{-/-} B16.OVA

- Isotype
- △ Isotype + 3pRNA
- Anti-CTLA-4
- ▲ Anti-CTLA-4 + 3pRNA

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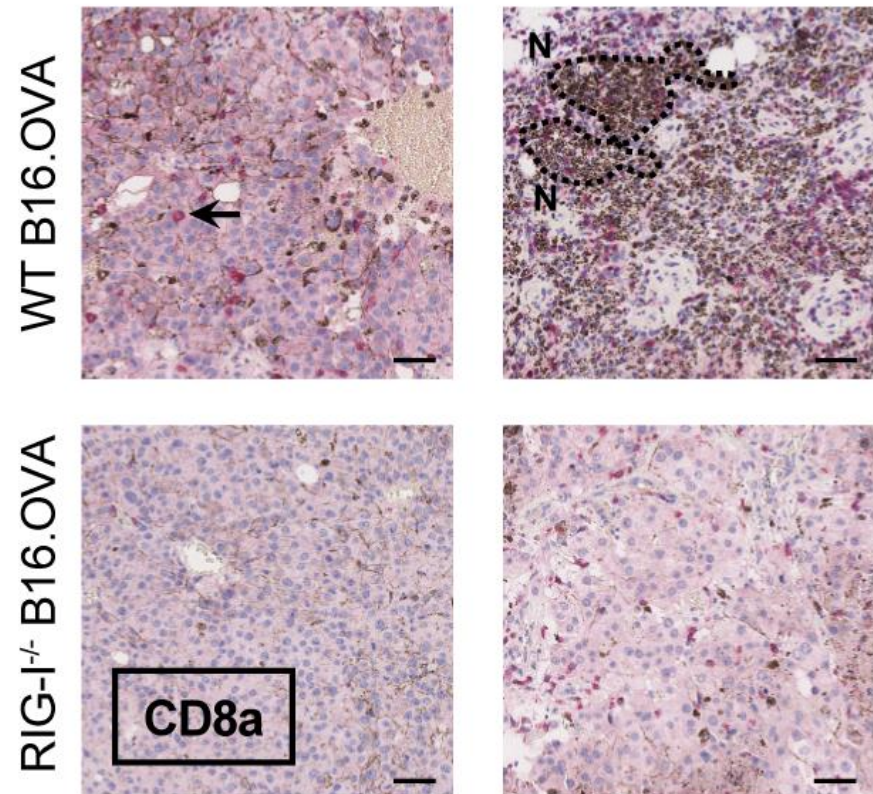


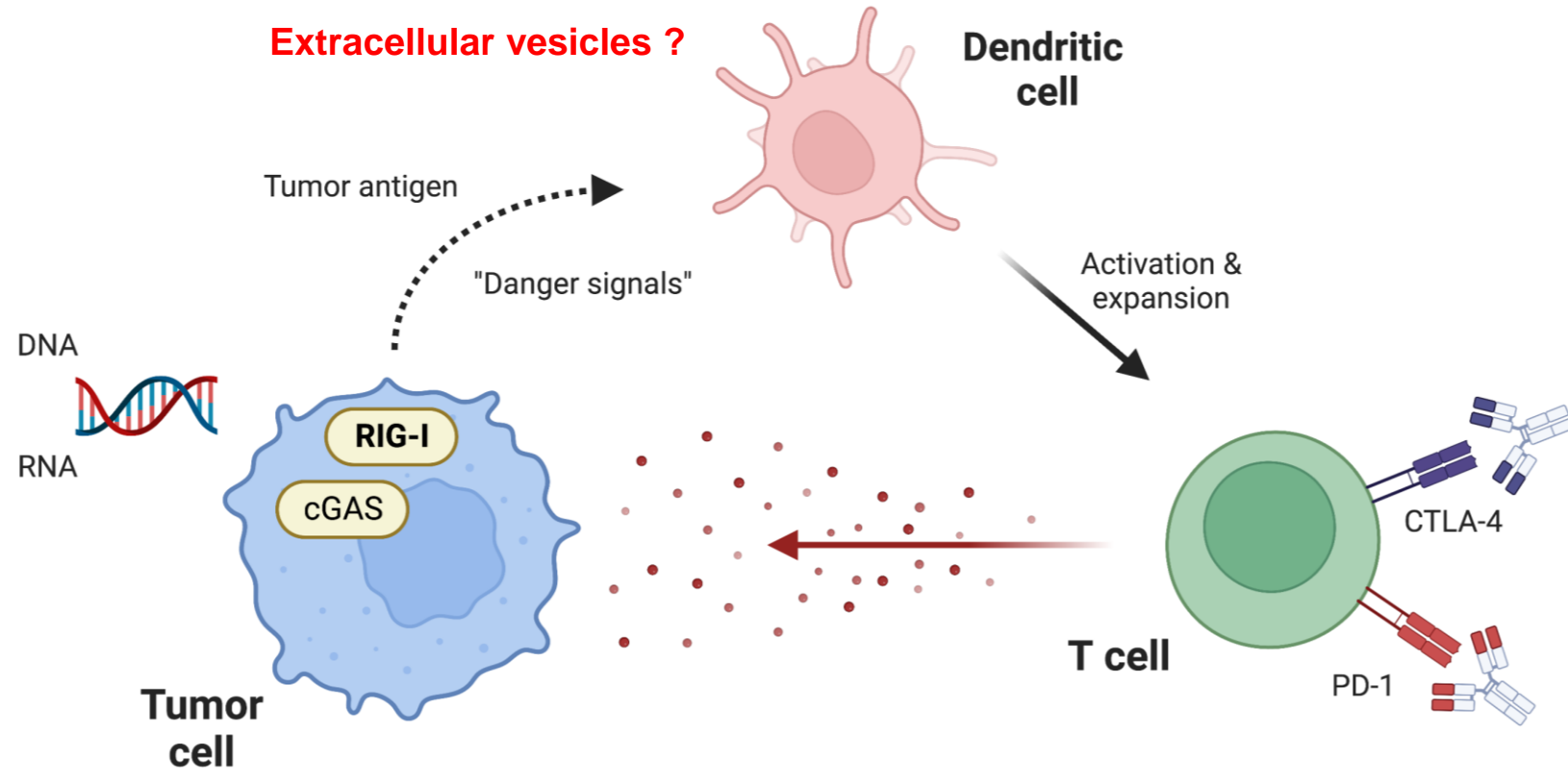
Heidegger et al., Sci Immunol (2019)

Injected tumor

Isotype

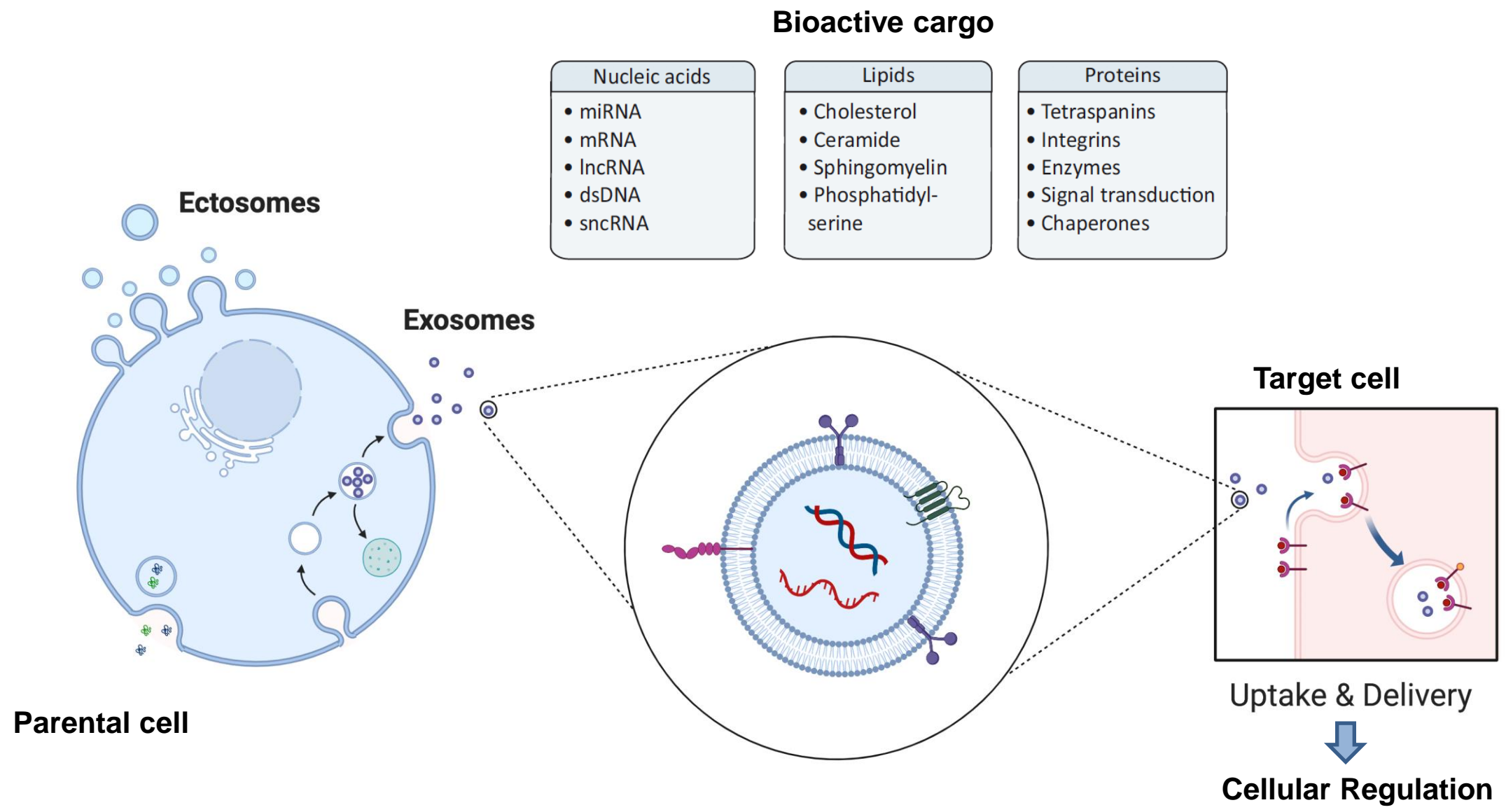
Anti-CTLA-4
+ 3pRNA



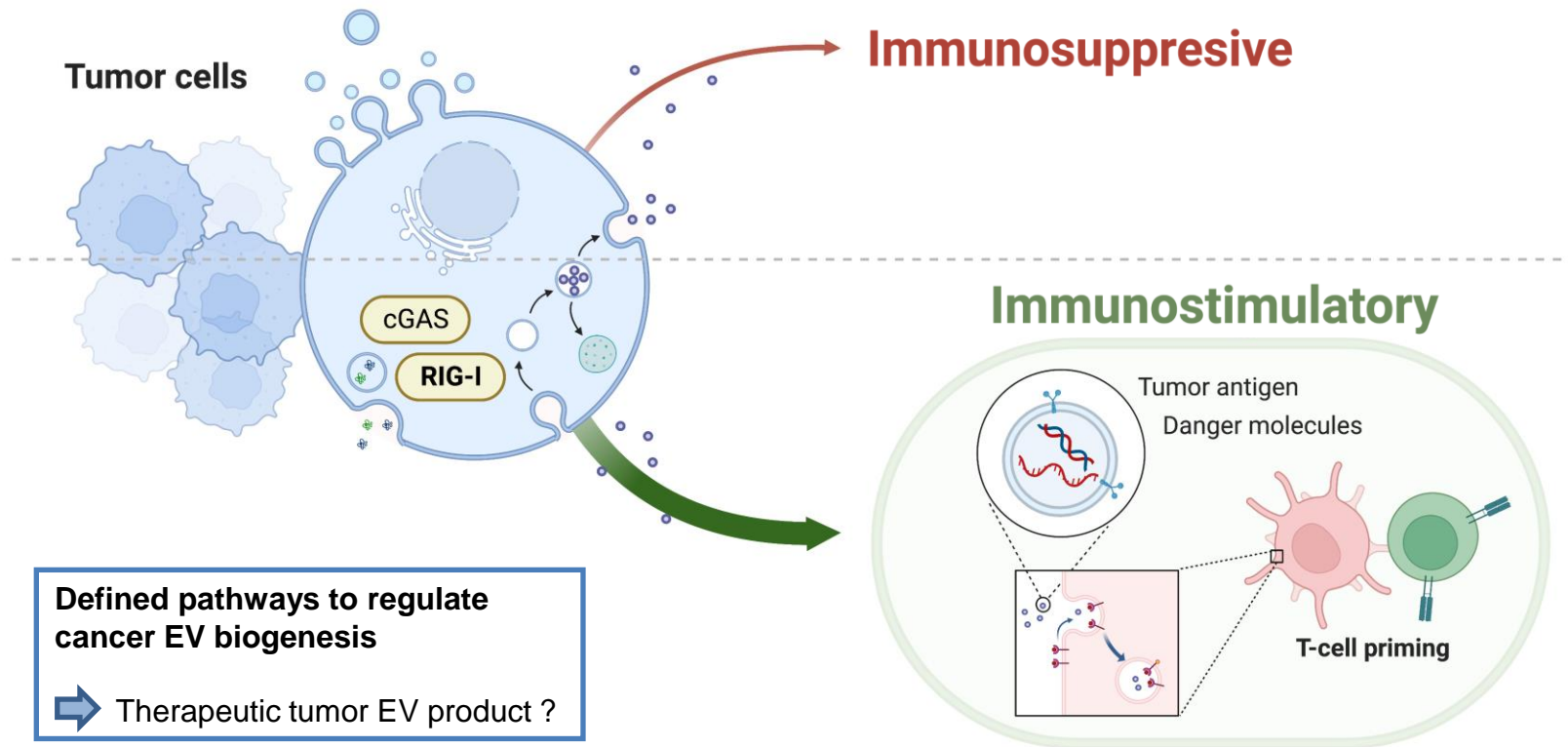


Heidegger et al., *Sci Immunol* (2019); Heidegger et al., *EBioMedicine* (2019);
 Bek et al., *Oncolimmunology* (2019); Poeck et al., *Eur J Immunol* (2021)

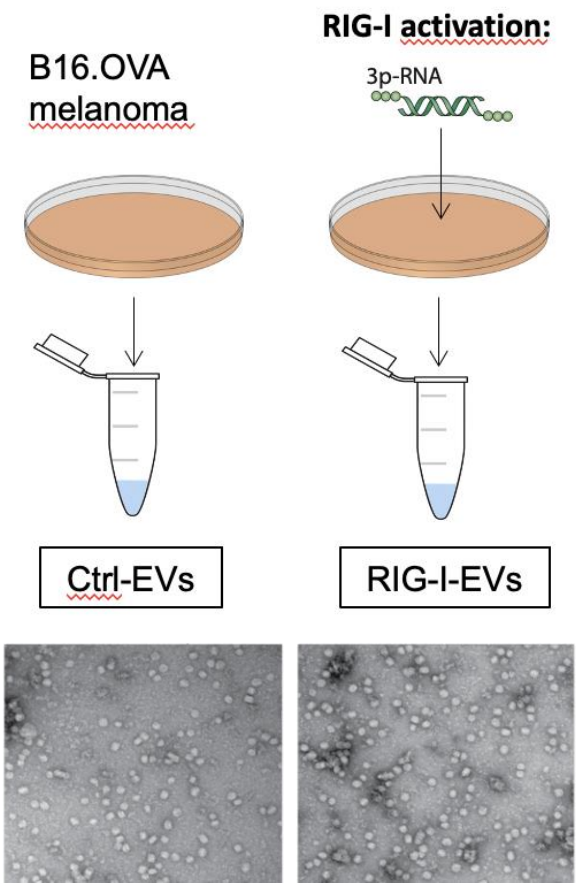
Extracellular vesicles (EVs): intercellular communication devices



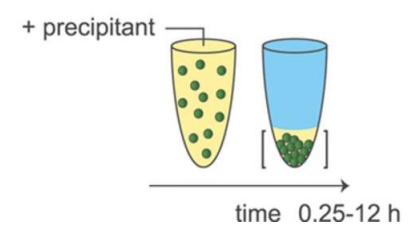
Dichotome Rolle von EVs in cancer



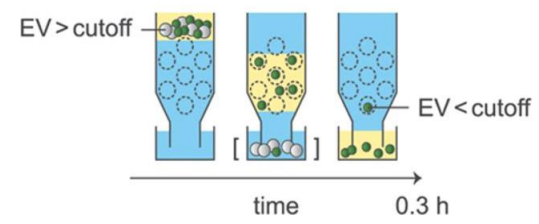
EVs aus Tumorzellen mit aktivem RIG-I signaling induzieren Interferone



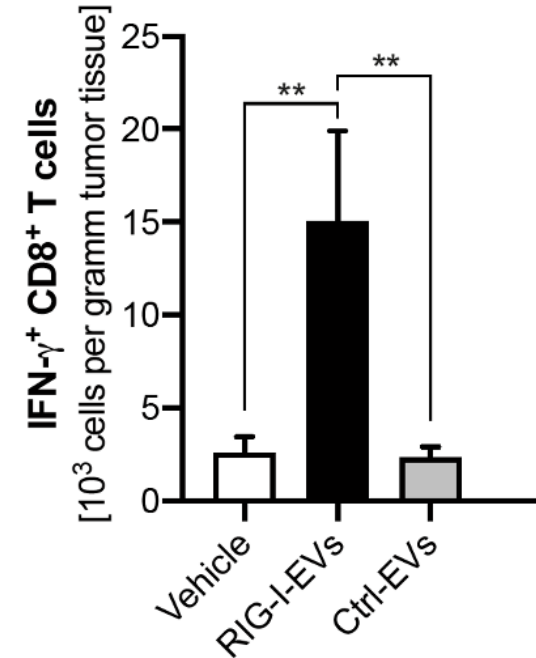
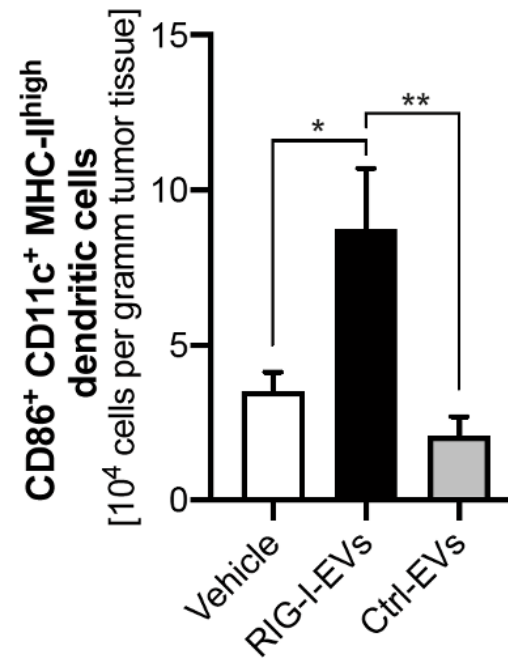
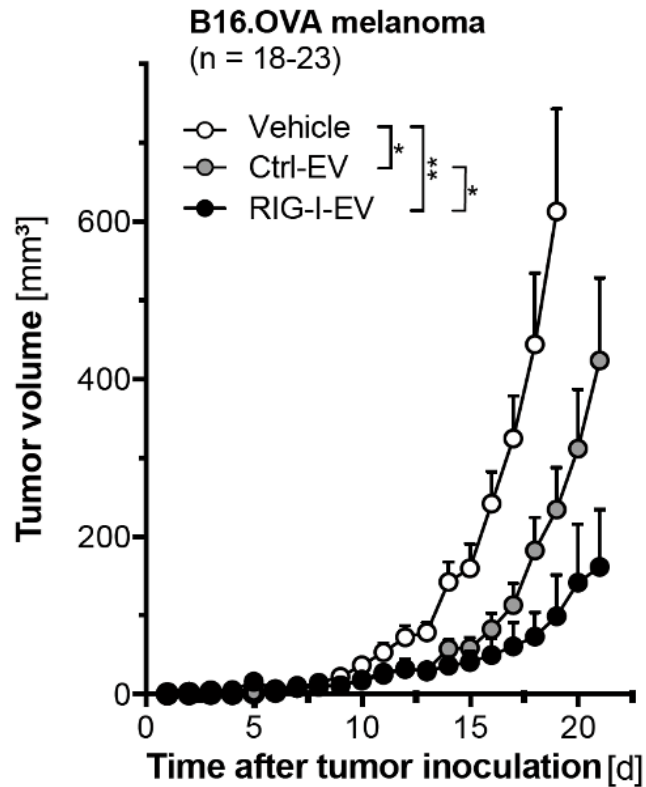
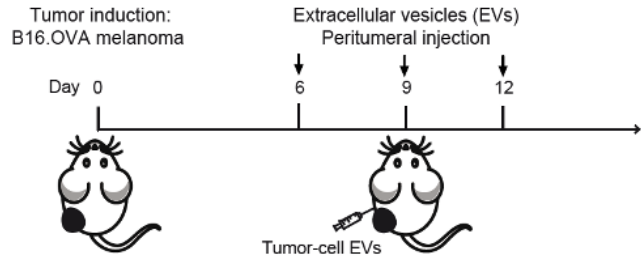
Conventional isolation method: **Precipitation-based**



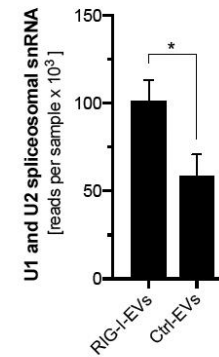
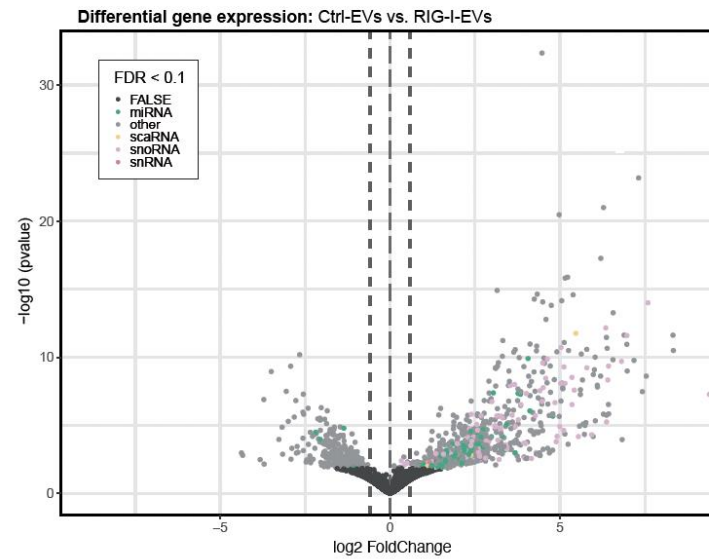
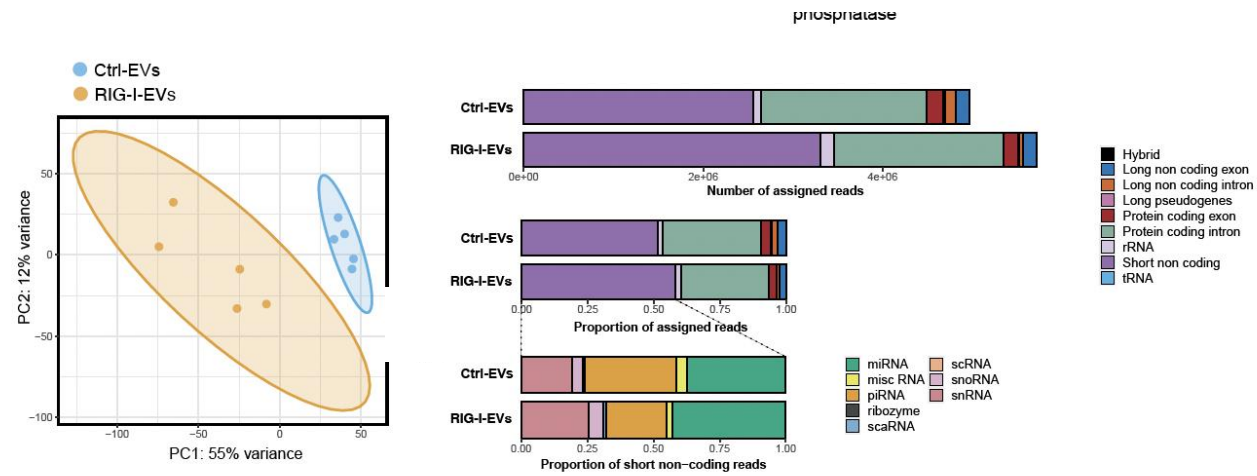
Complementary isolation method: **Size-exclusion chromatography**



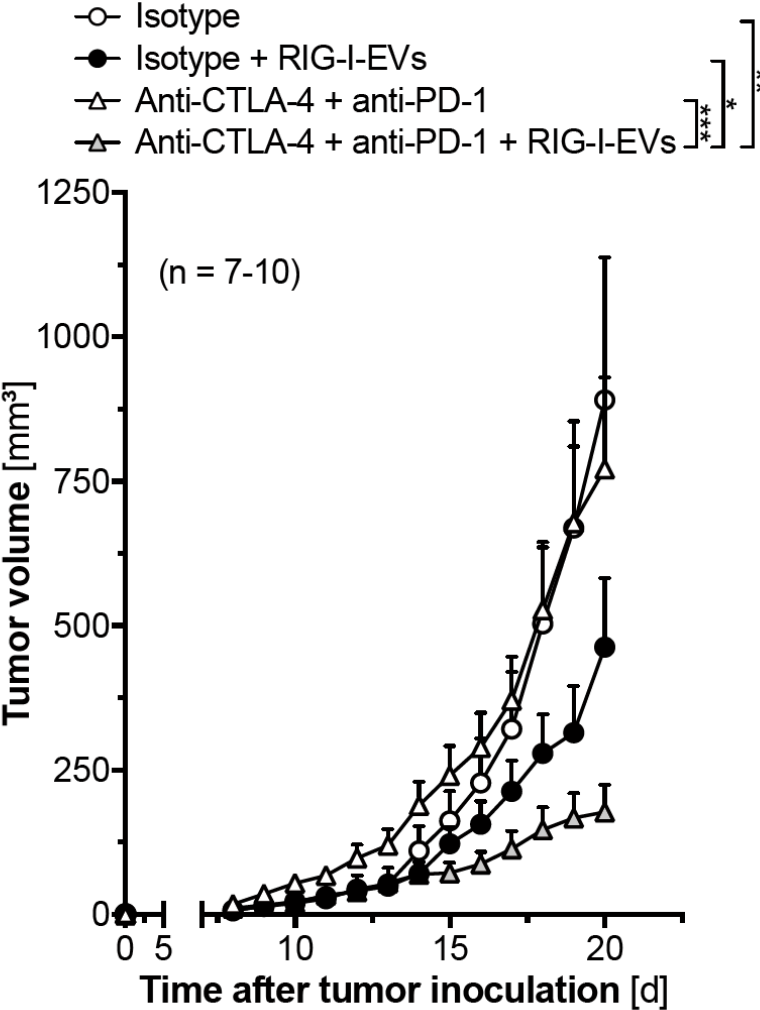
RIG-I EVs fördern T-zell-vermittelte Antitumor-Immunität



RIG-I Aktivierung in Tumorzellen reguliert das EV RNA cargo

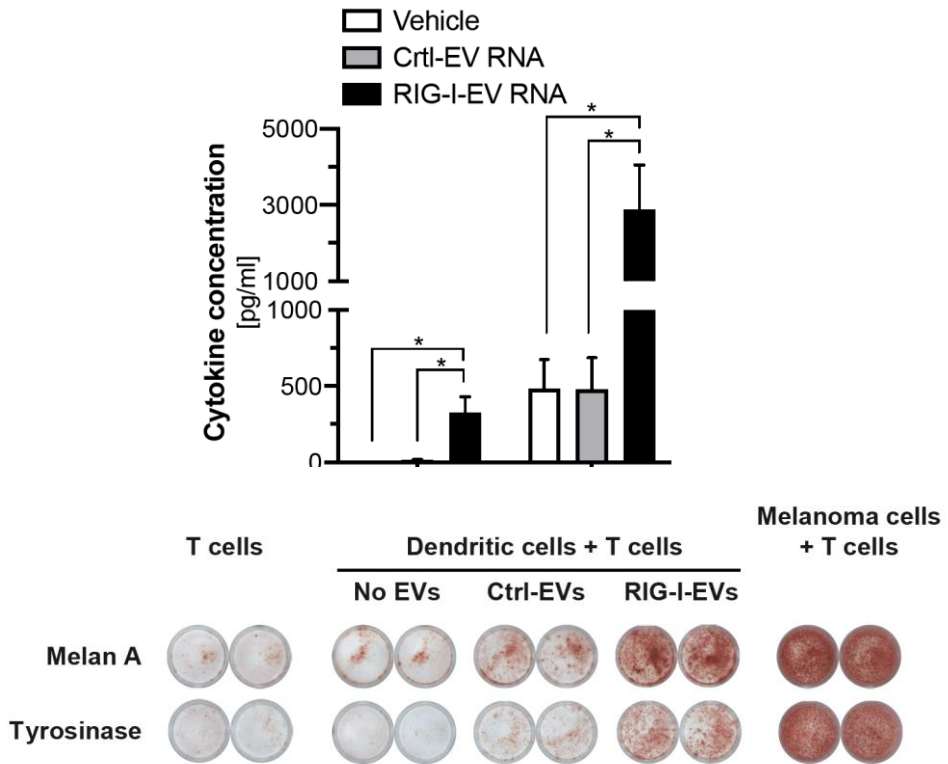


RIG-I EVs verstärken die Wirkung von Immun-Checkpoint-Inhibitoren in Mäusen und aktivieren menschliche T-Zellen

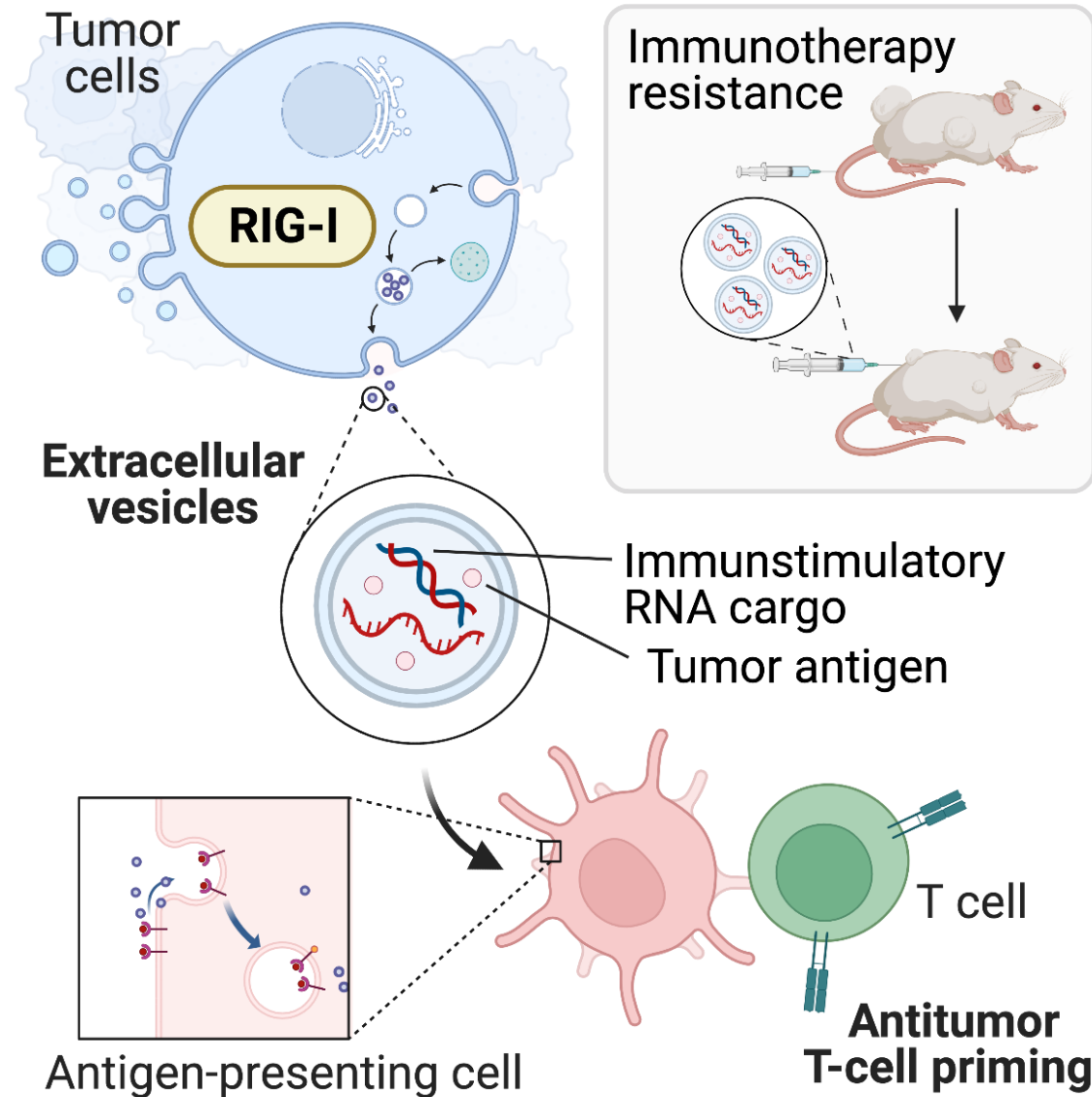


Heidegger et al., *Cell Rep Med* (2023)

EV source: Human melanoma cells (D04mel)
Target cells: PBMCs



Umprogrammierung von Tumor-EVs zur Modulation von T-Zell-Immunität

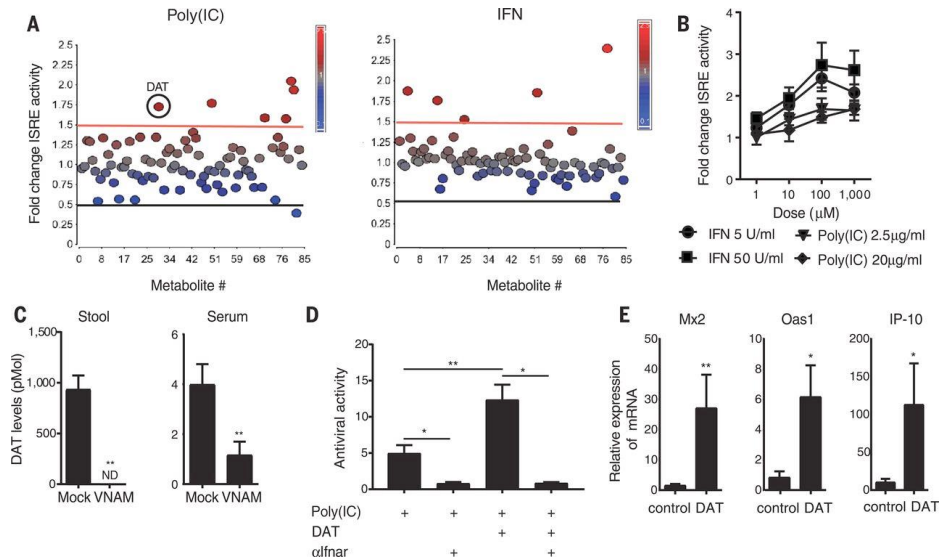
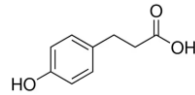


Microbial-derived metabolites induzieren IFN-I signaling

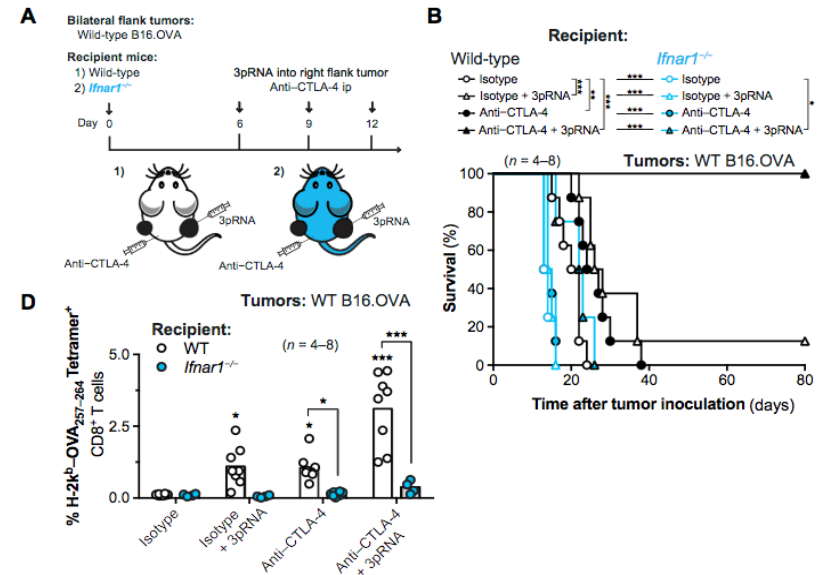
Desaminotyrosine in the literature



Host IFN-I is important for anti-CTLA-4 efficacy

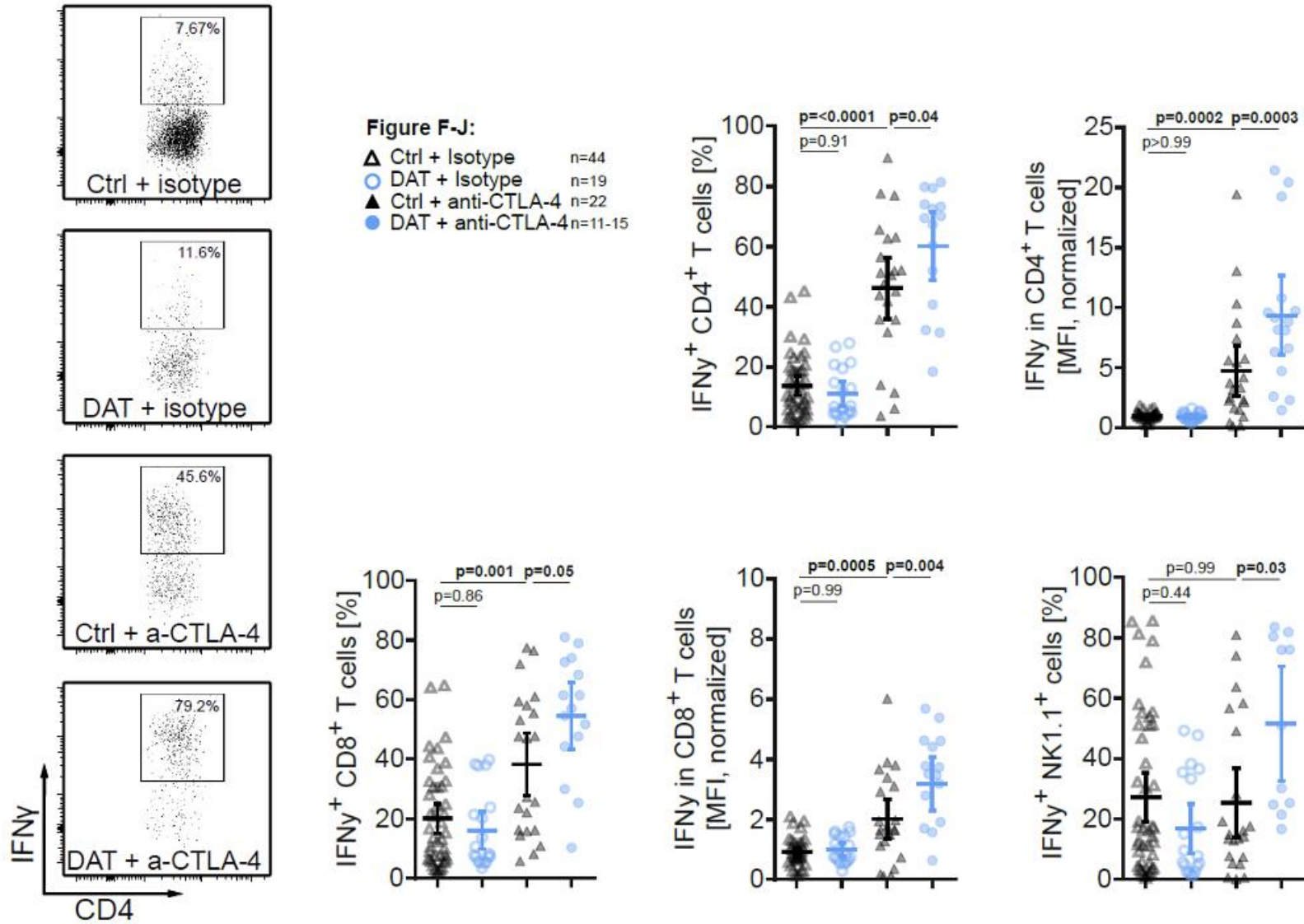


Steed et al., *Science* (2017)

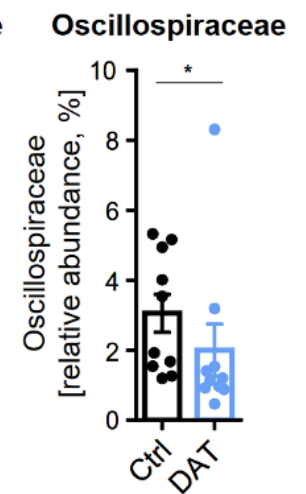
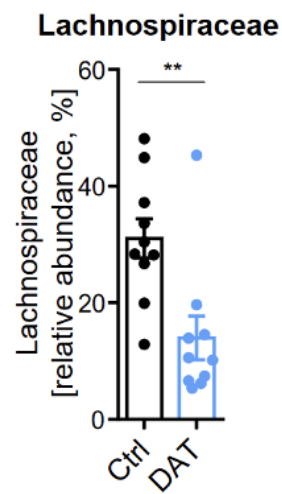
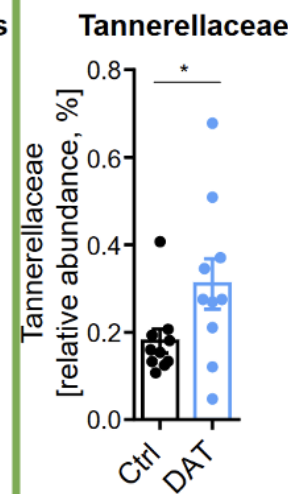
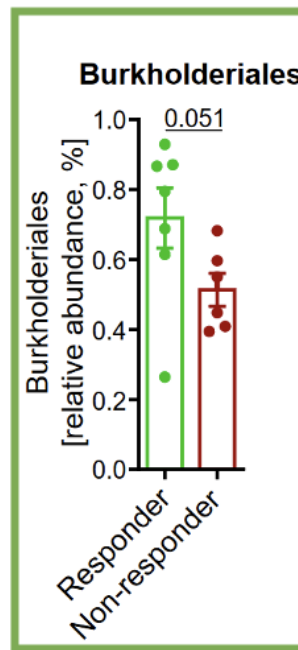
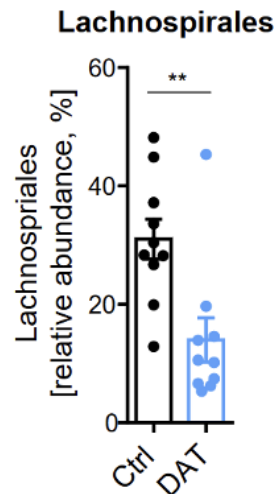
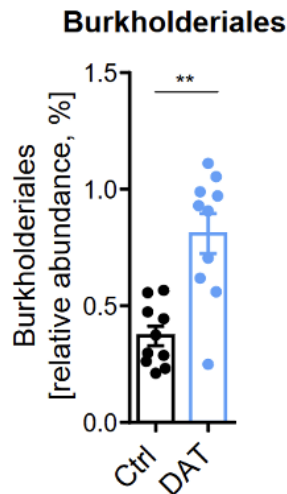
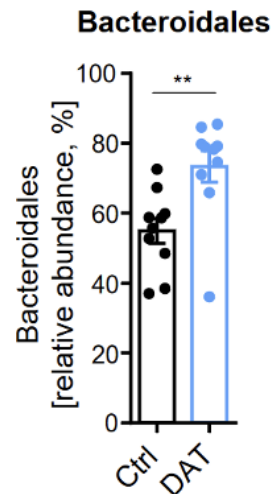
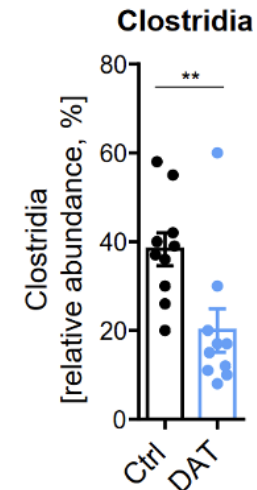
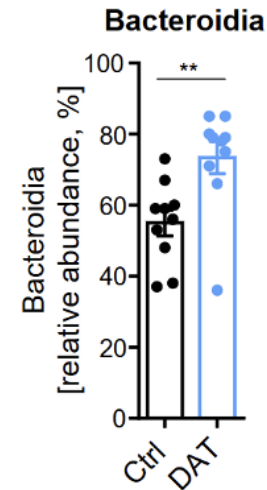
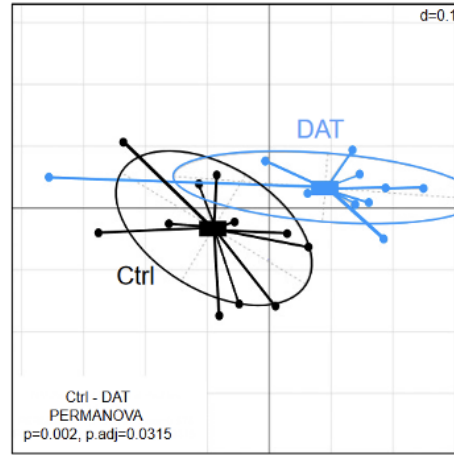
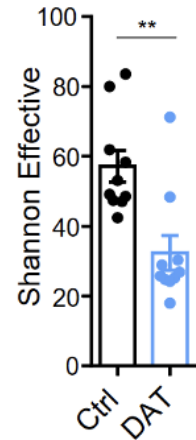
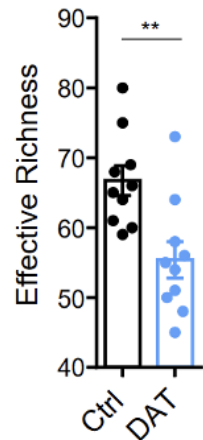


Heidegger et al., *Sci Immunol* (2019)

DAT verbessert die Wirkung von Anti-CTLA-4 und verändert das TME

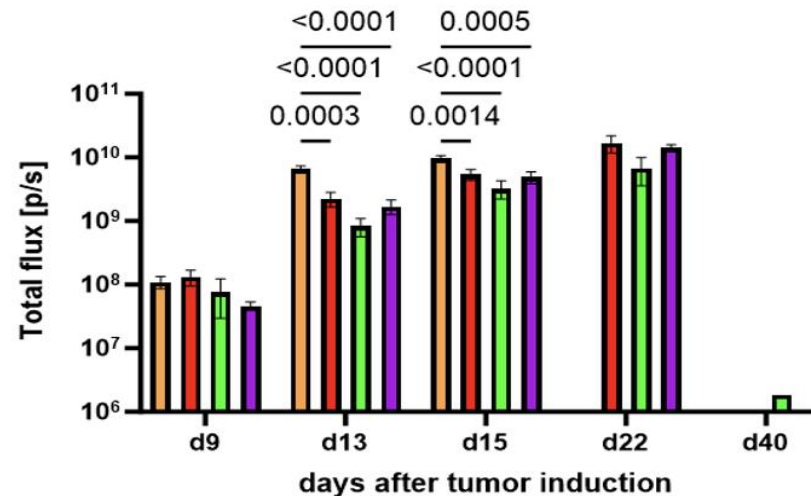
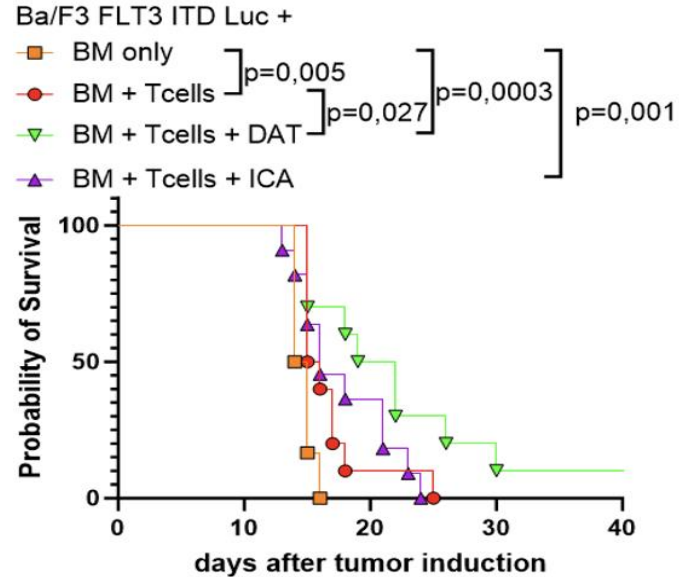
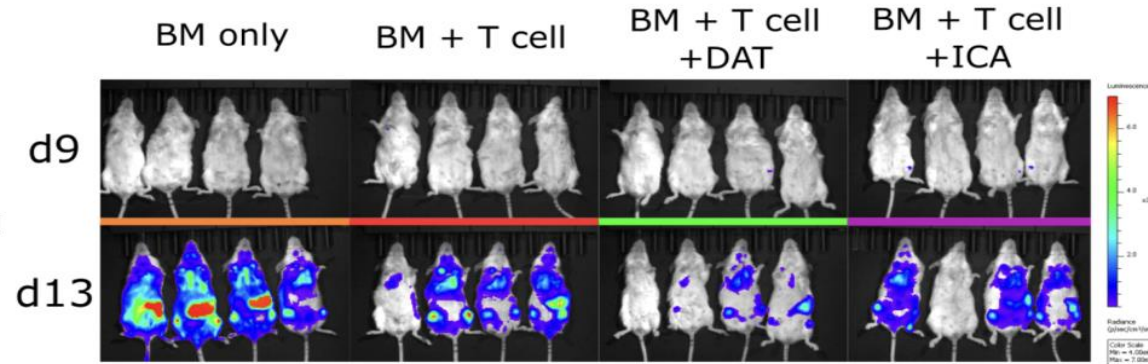
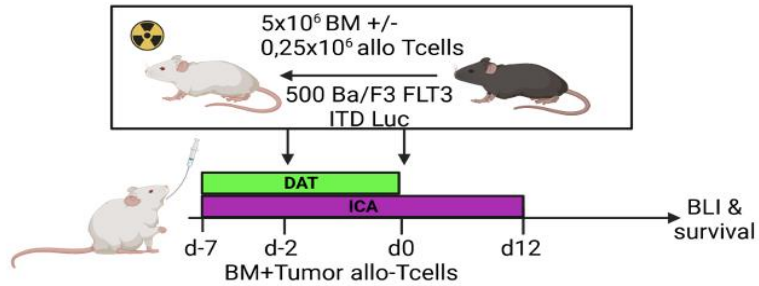


DAT kompensiert die negativen Effekte von Antibiotika auf ICI und verändert das intestinale microbiome



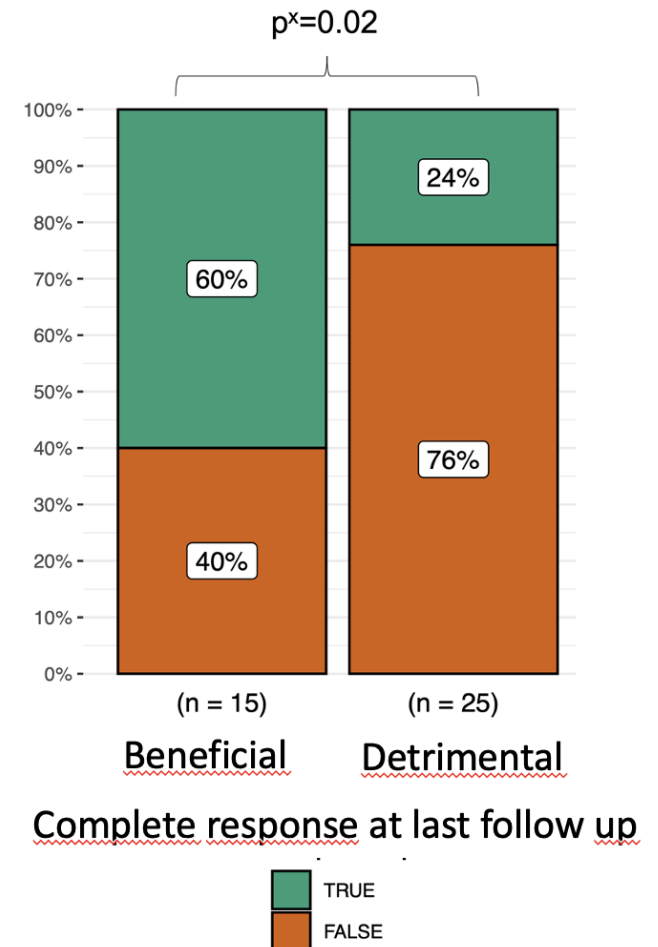
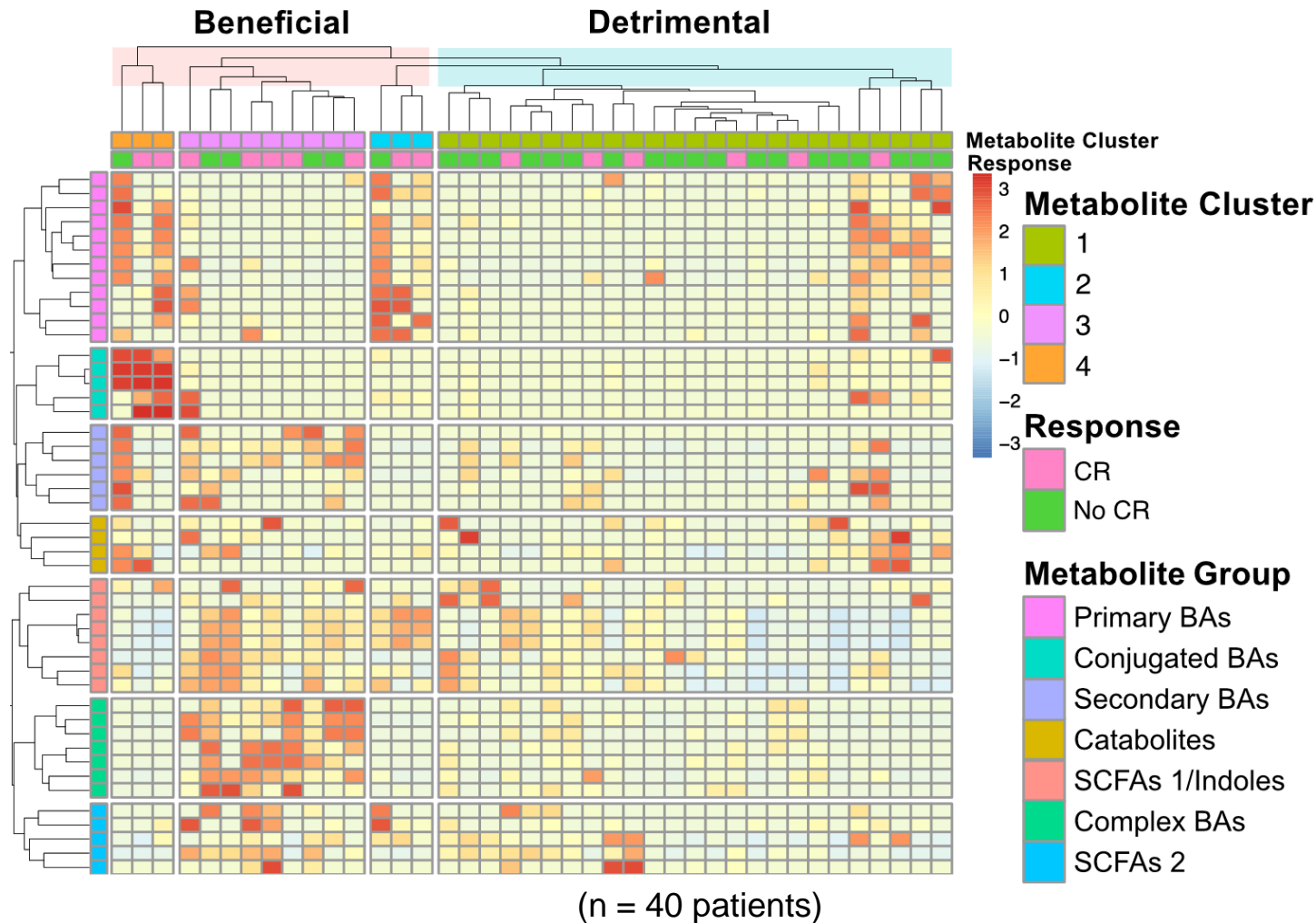
Microbial-derived metabolites korrelieren mit klinischem Ansprechen bei cancer immunotherapies

Allo-SCT

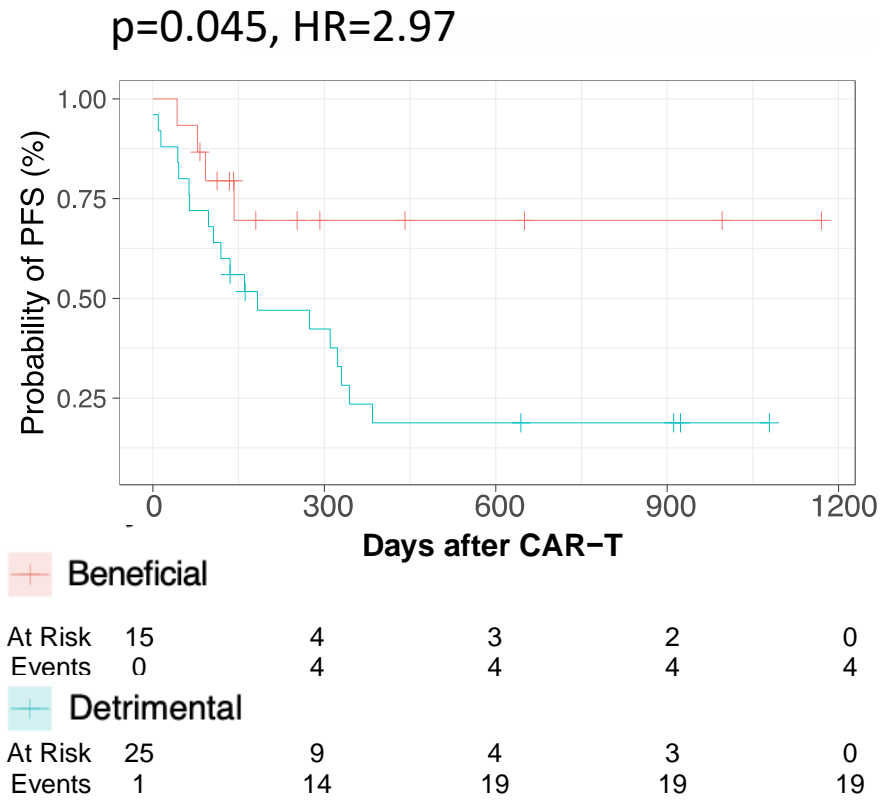


Microbial-derived metabolites korrelieren mit klinischem Ansprechen bei cancer immunotherapies

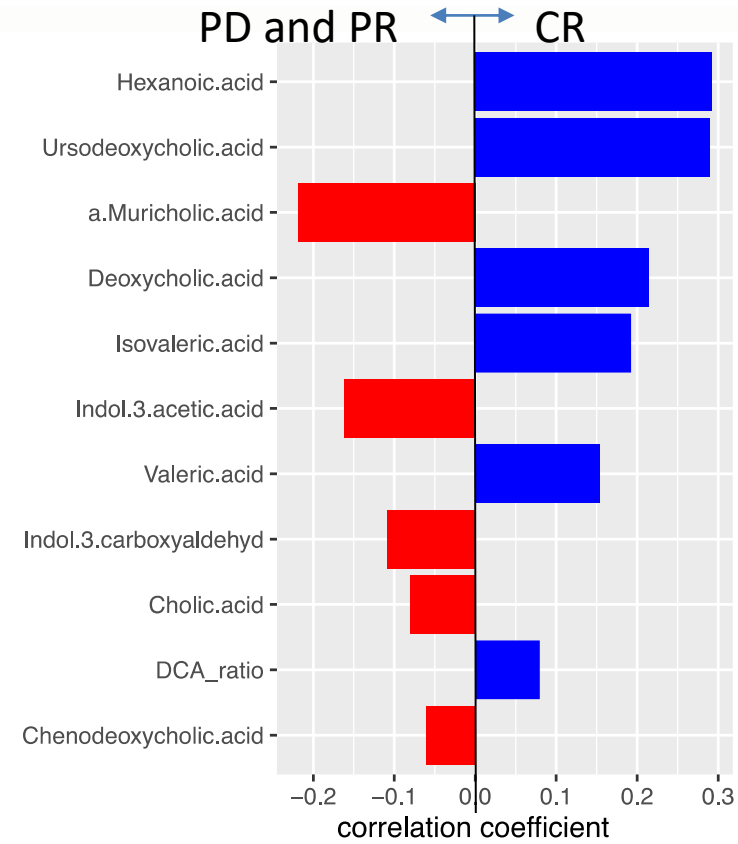
CAR T cells



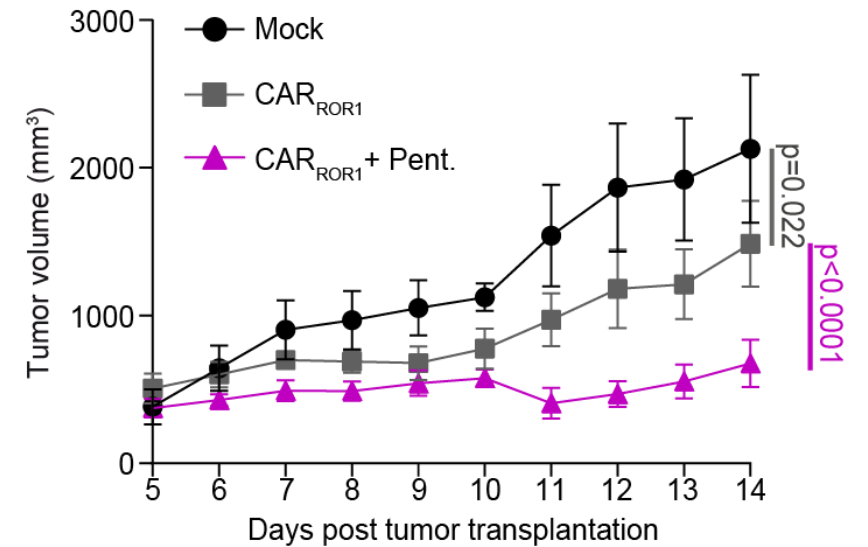
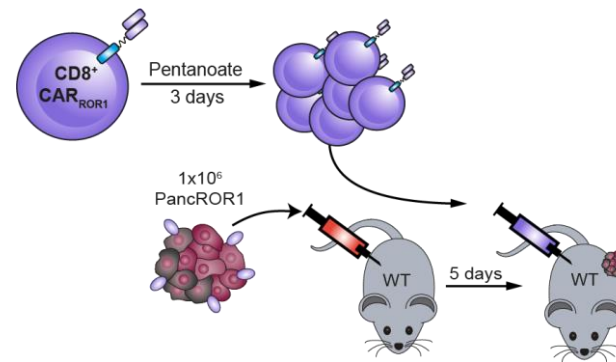
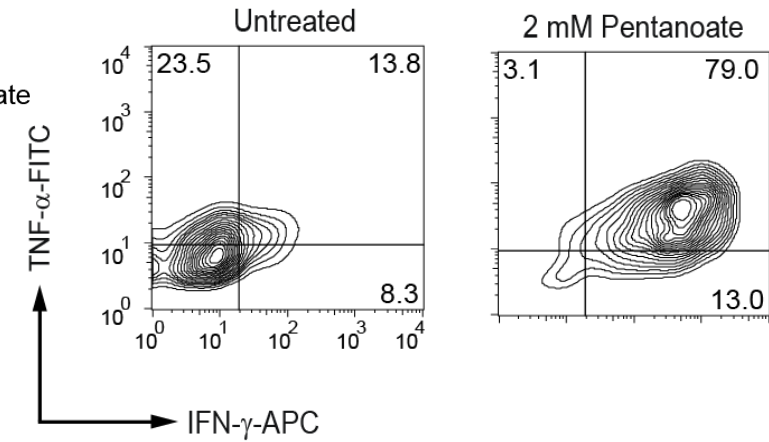
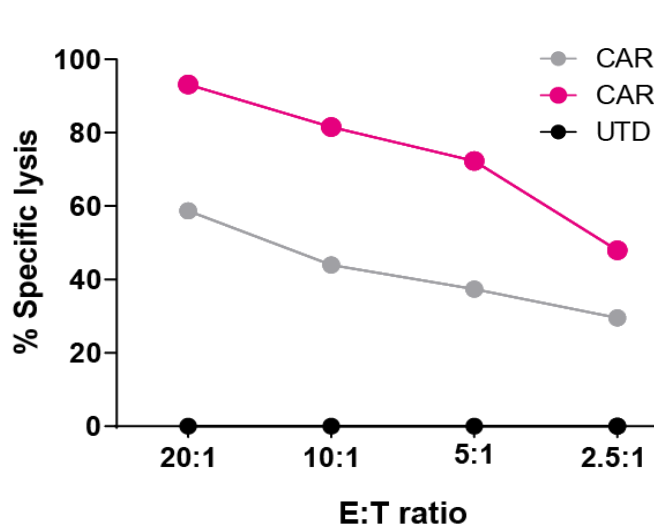
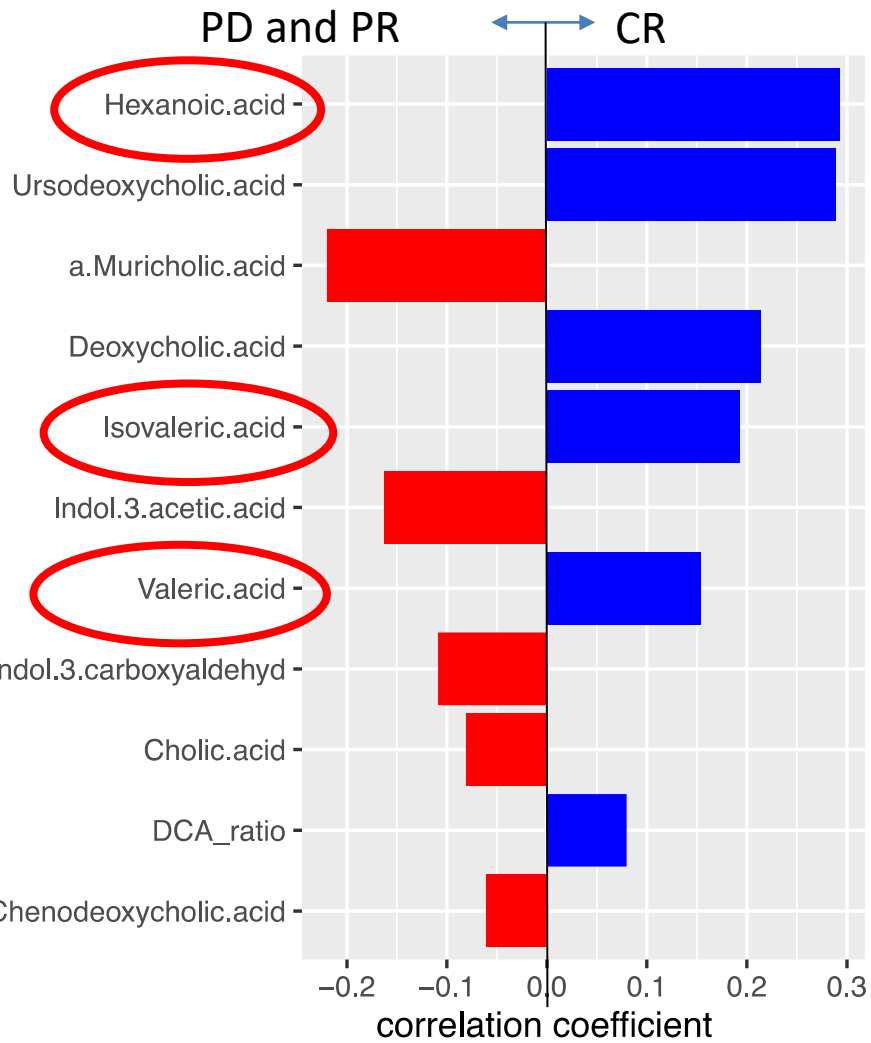
Microbial-derived metabolites korrelieren mit klinischem Ansprechen bei cancer immunotherapies



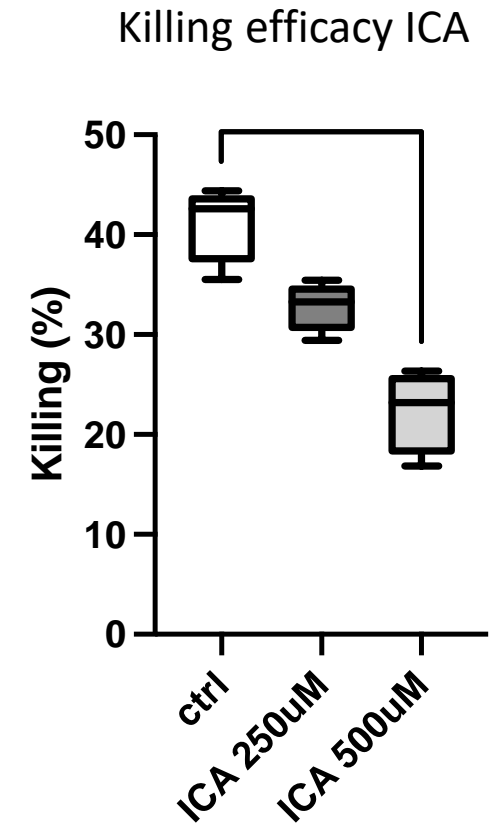
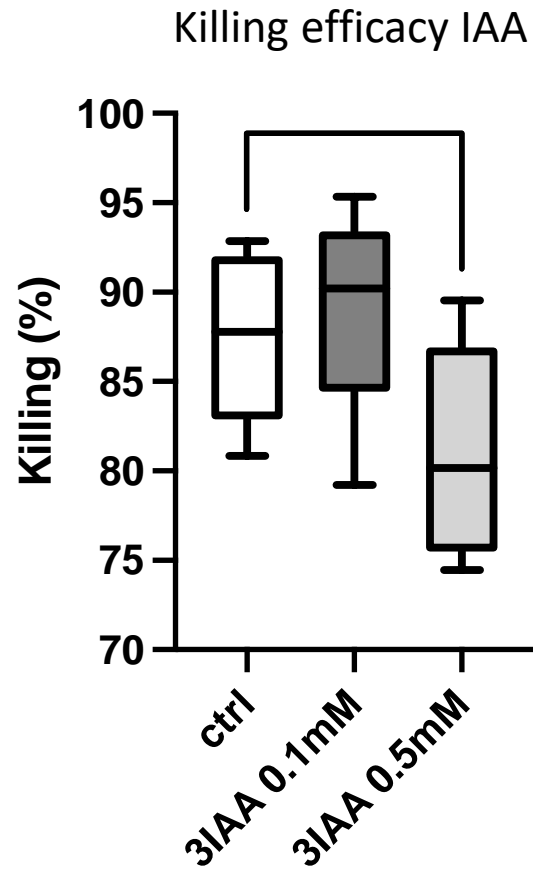
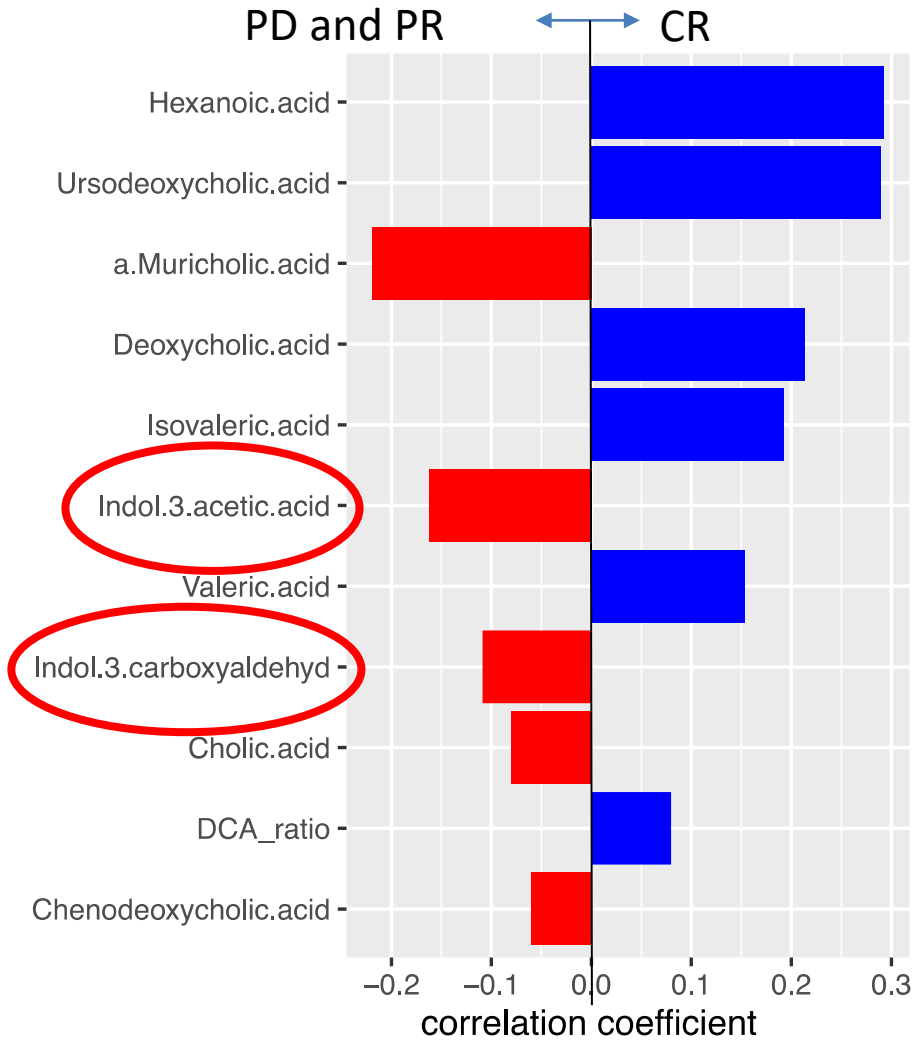
n=40 CAR T patients



Short-chain fatty acid Pentanoate (=Valeric acid erhöhen die Wirksamkeit von CAR-T-Zellen



Indole verschlechtern CAR-T-Zell Wirksamkeit



Zusammenfassung

- Tumor-intrinsische und extrinsische Faktoren modulieren die Wirksamkeit von Cancer immunotherapies
- Mögliche neue (Kombinations-) Strategien zur Überwindung von Resistenzen sind nucleic acid therapeutics, EVs und Mikrobiom-basierte Therapien (z.B. FMT, Postbiotics etc.)
 - Besseres mechanistisches Verständnis erforderlich

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