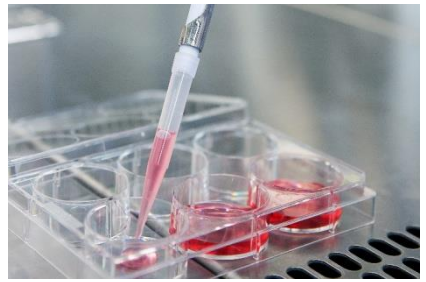
19.09.2023

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

Hendrik Poeck



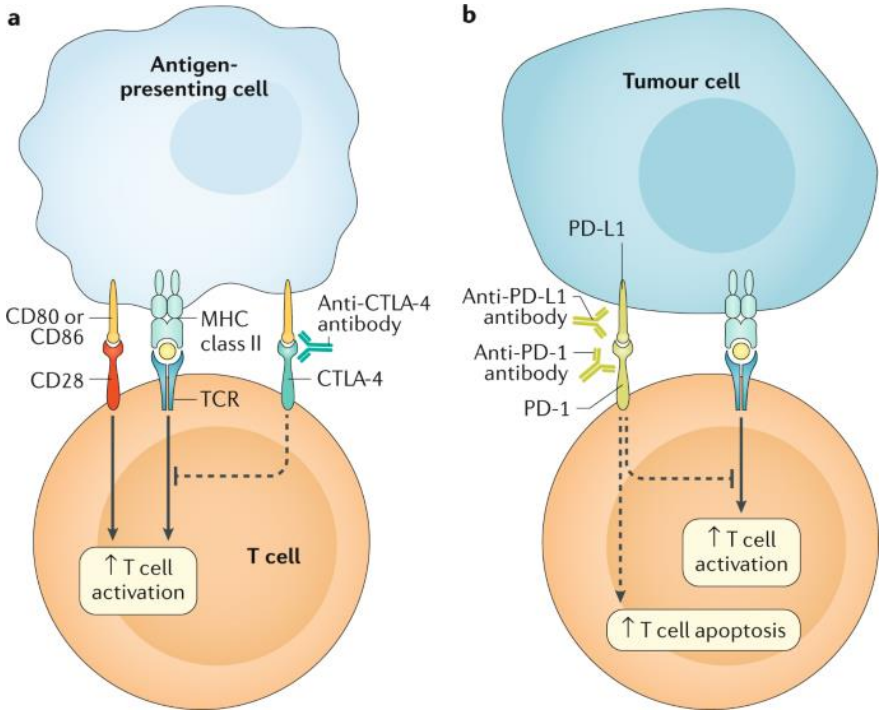
Offenlegung Interessenskonflikte

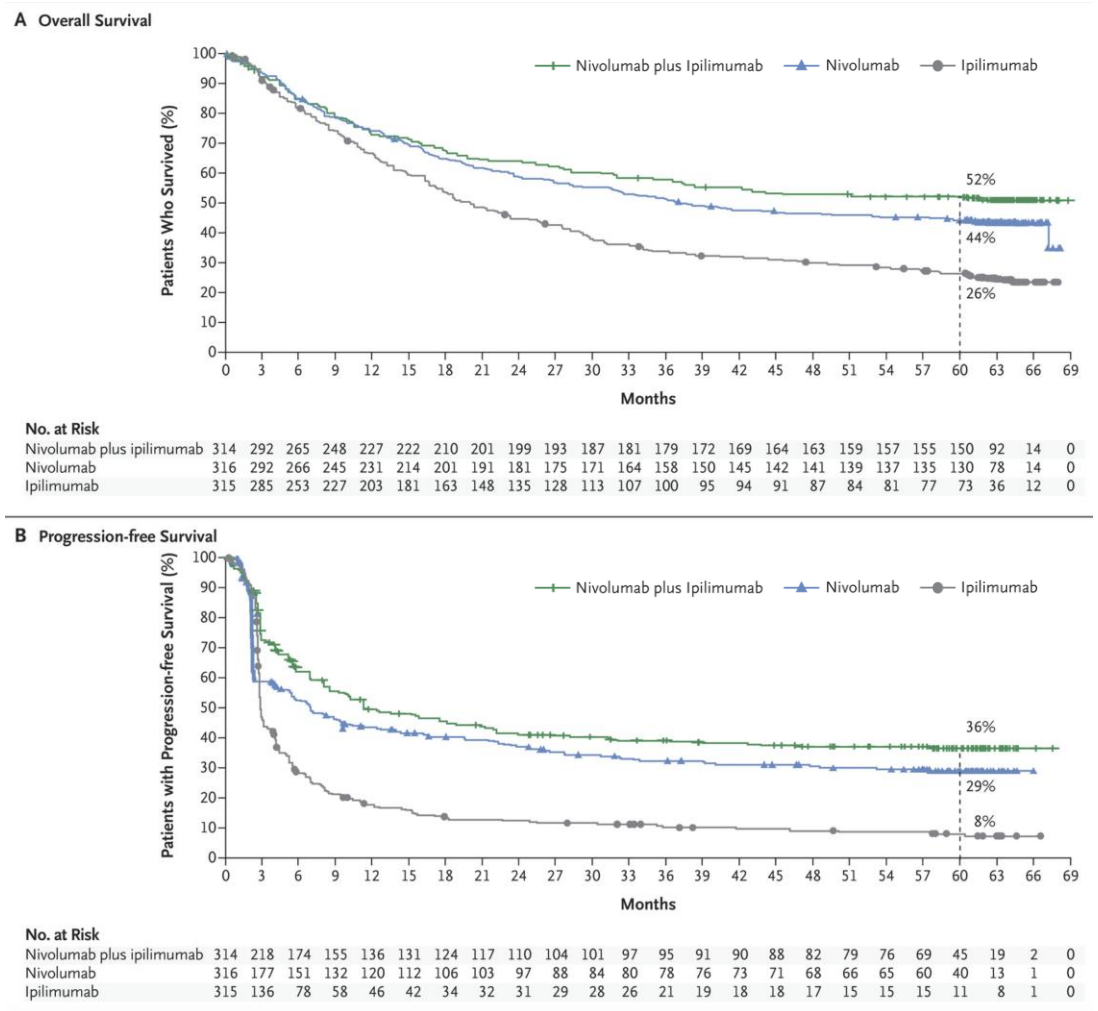
Beratungs-, Gutachtertätigkeit	Gilead/Kite; AbbVie; Pfizer; Bristol Myers-Squibb/Celgene, Servier
Honorare	Abbvie, Gilead/Kite, Novartis, Servier, Bristol Myers-Squibb/Celgene, Pfizer; Astellas, MSD, Janssen-Cilag
Finanzierung wissenschaftlicher Untersuchungen	Bristol Myers-Squibb/Celgene
Andere finanzielle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

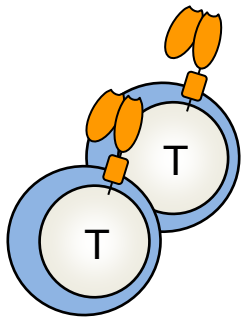
→ ORR 57 %, mPFS 11.5 months, mOS > 36 months

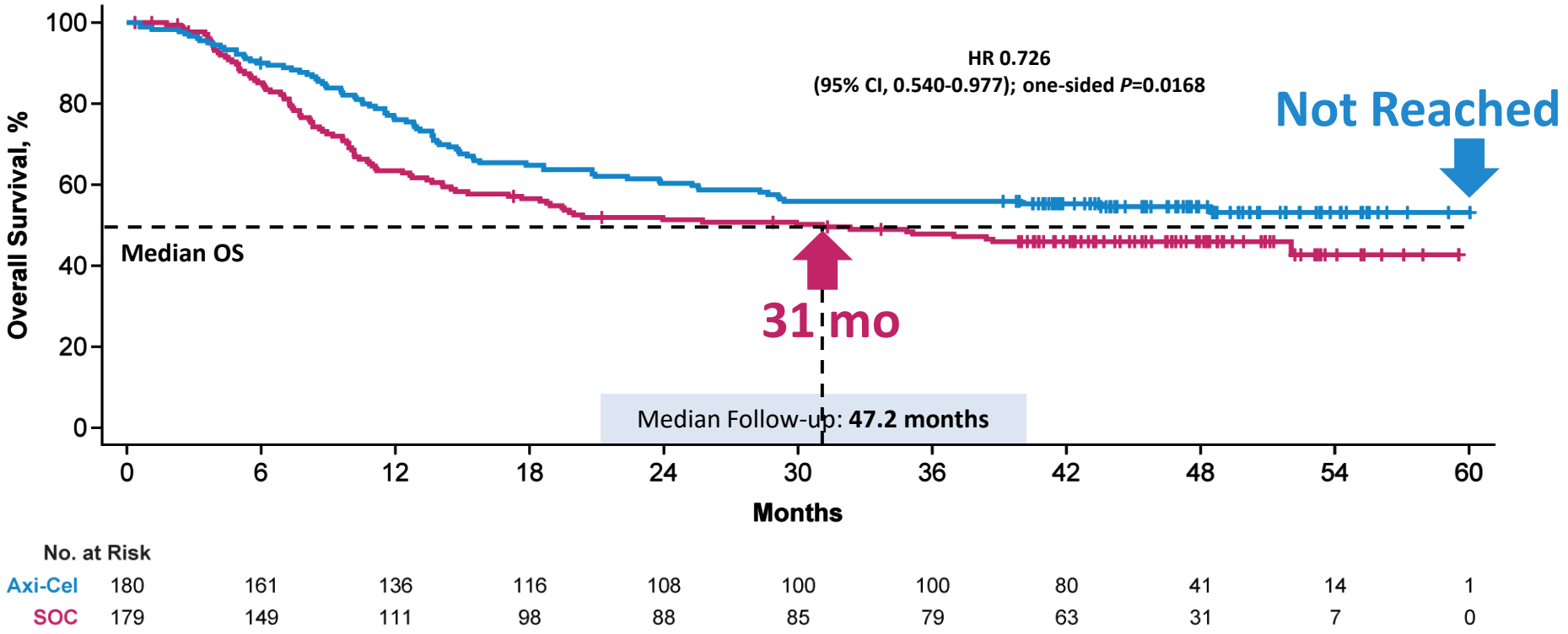
Larkin et al., *N Engl J Med* (2019)

Cancer Immunotherapies: Nicht alle sprechen an

CAR T cells

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

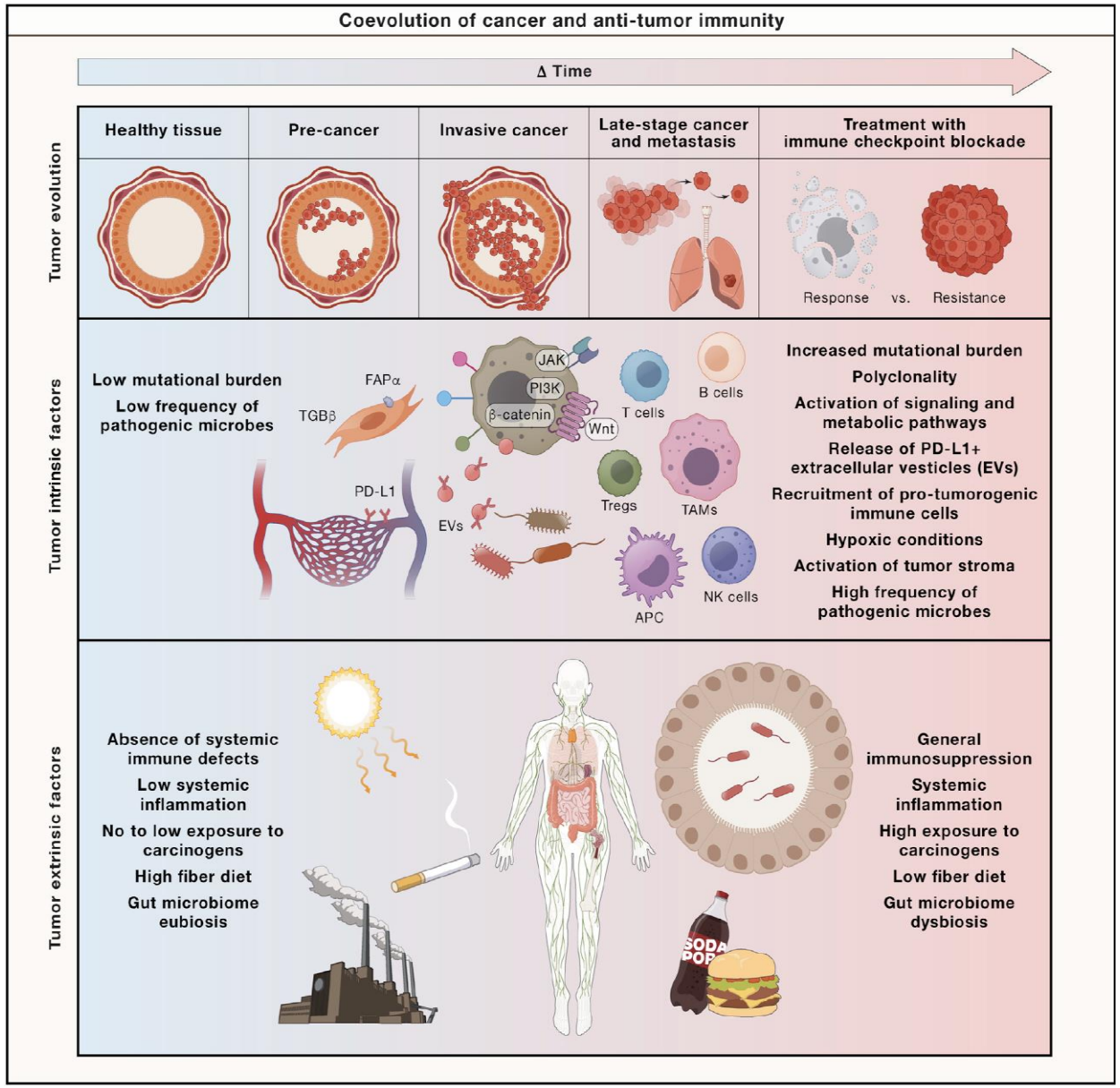




Westin et al., *N Engl J Med* (2023)

Resistenzmechanismen

ICI



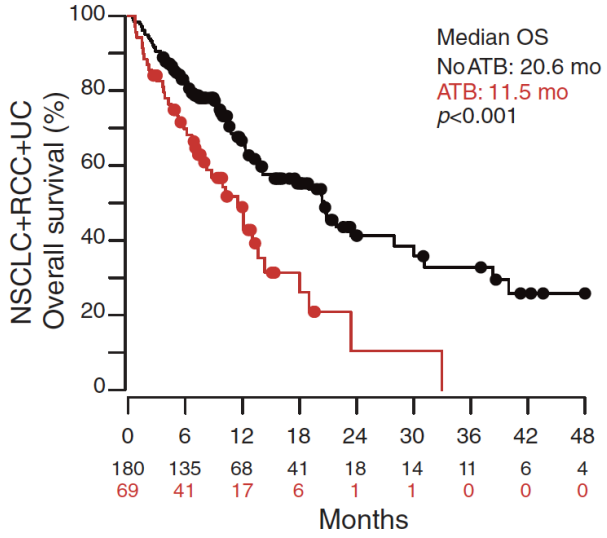
Adapted from Morad et al., *Cell* (2021)

Mikrobiom als Masterregulator für Cancer Immunotherapies

ICI

Routy et al., Science (2018)

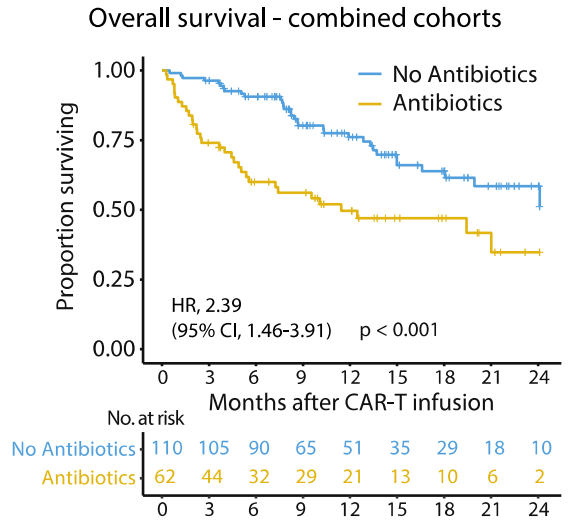
Derosa et al. *Cancer Discovery* (2021)



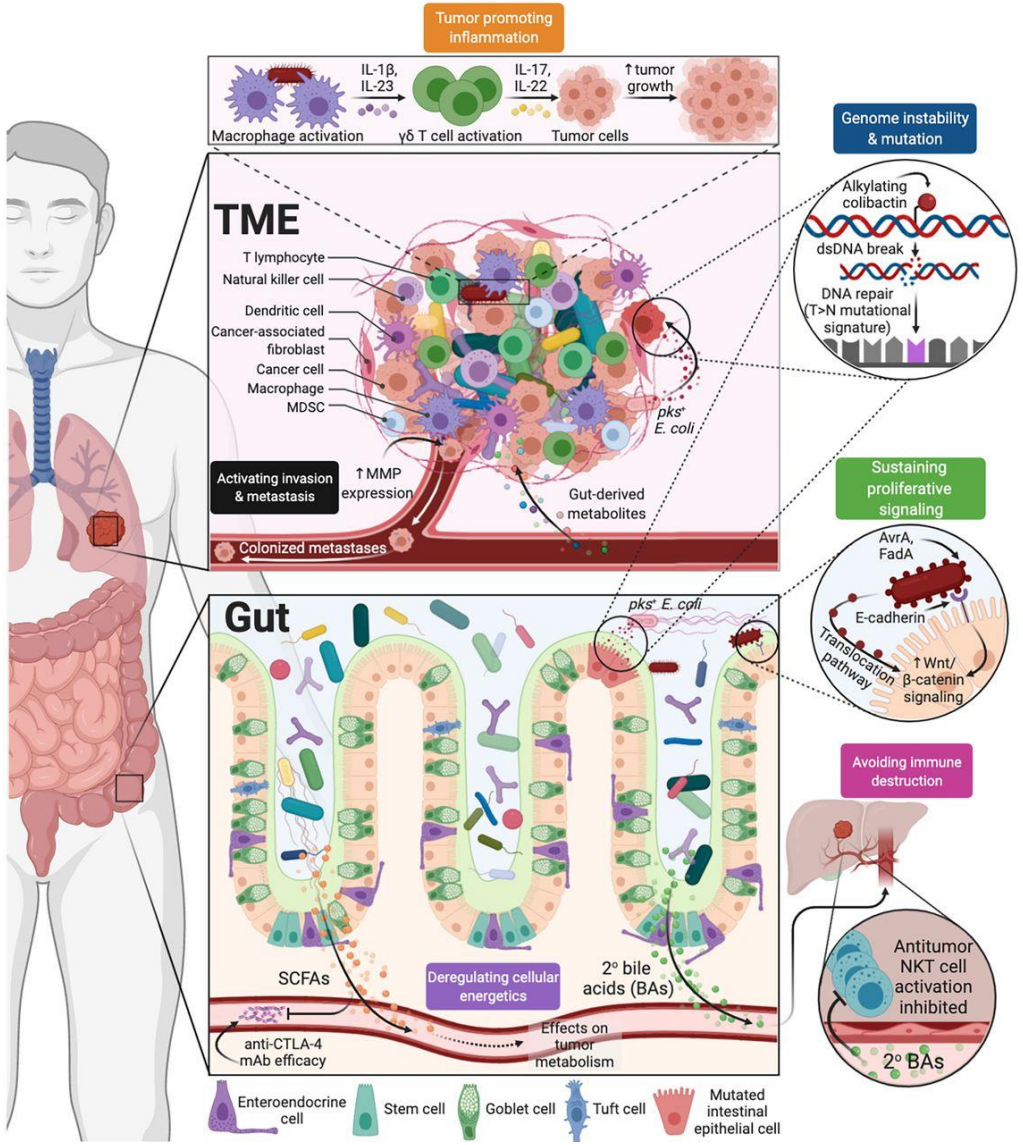
CAR T cells

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

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

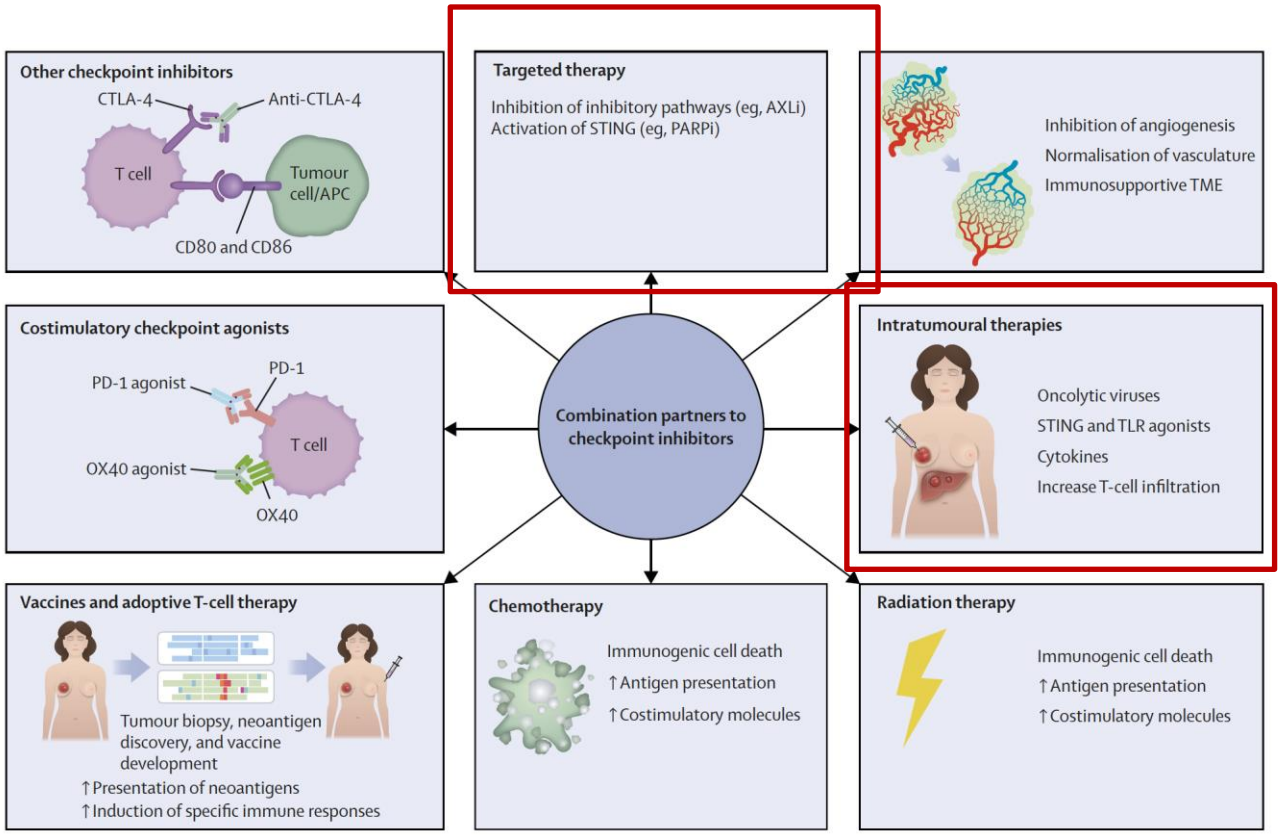


Wie beeinflusst das Mikrobiom Cancer Immunotherapies ?



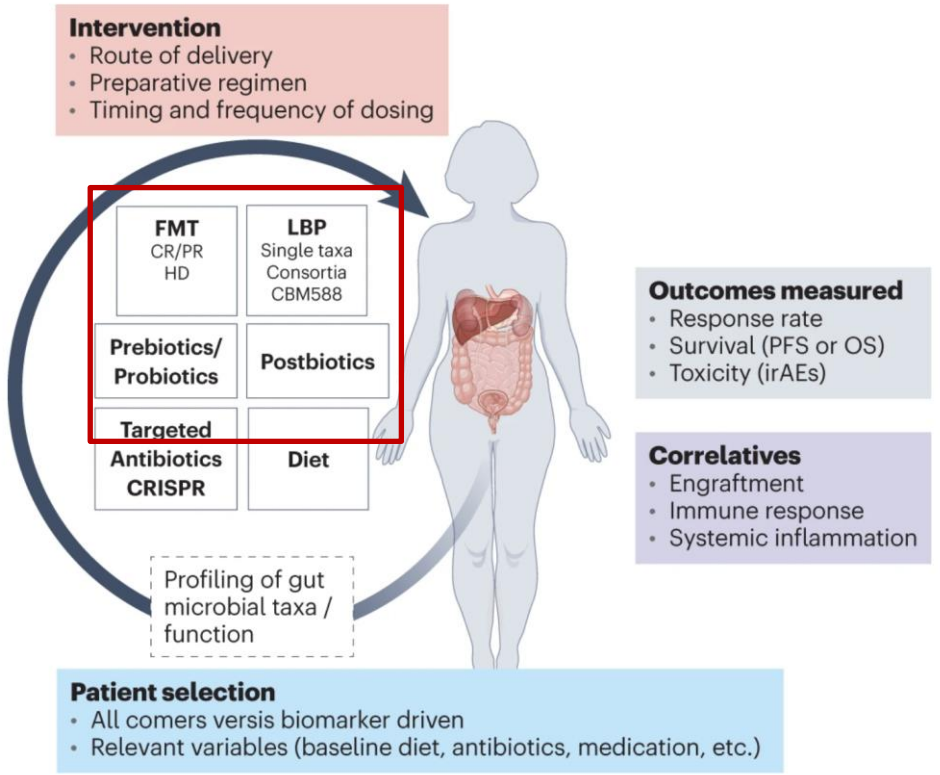
Adapted from Sepich-Poore et al., *Science* (2021)

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**

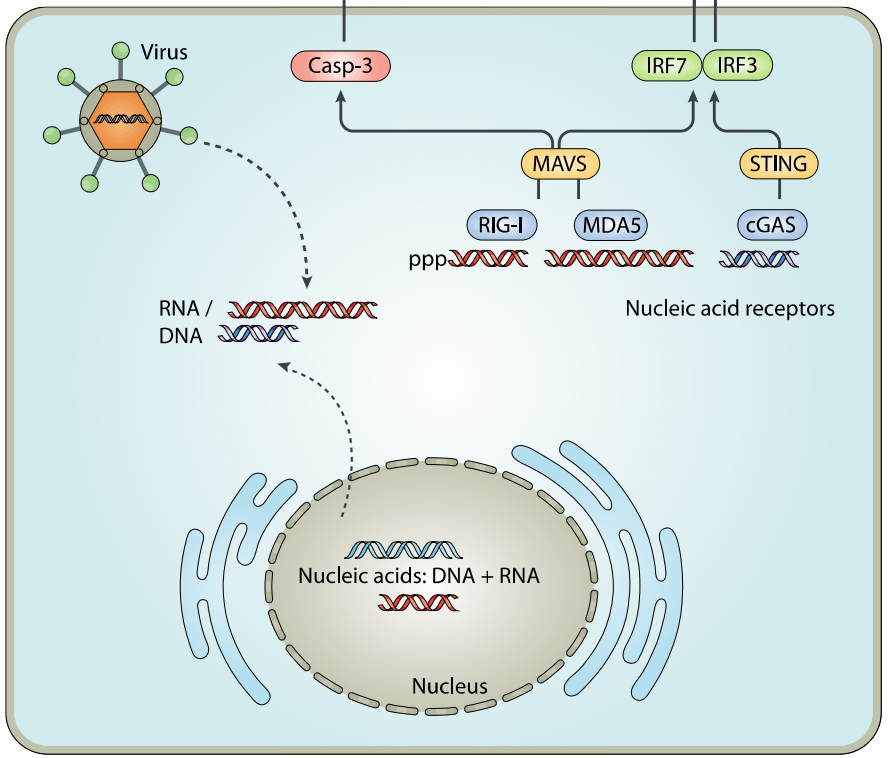
Nucleid acid therapeutics für cancer immunotherapies

Tumor cells

Immunogenic cell death

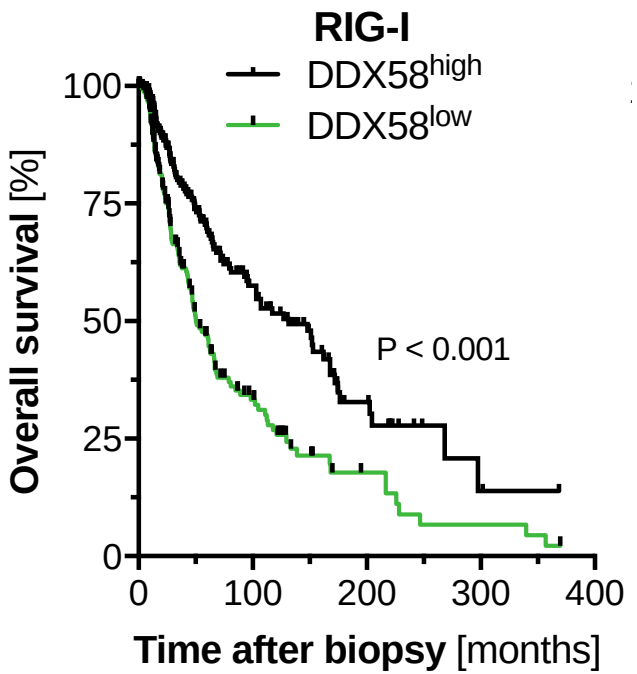
Type I Interferon + Inflammatory cytokines

Anti-tumor T-cell response



Immune cells

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

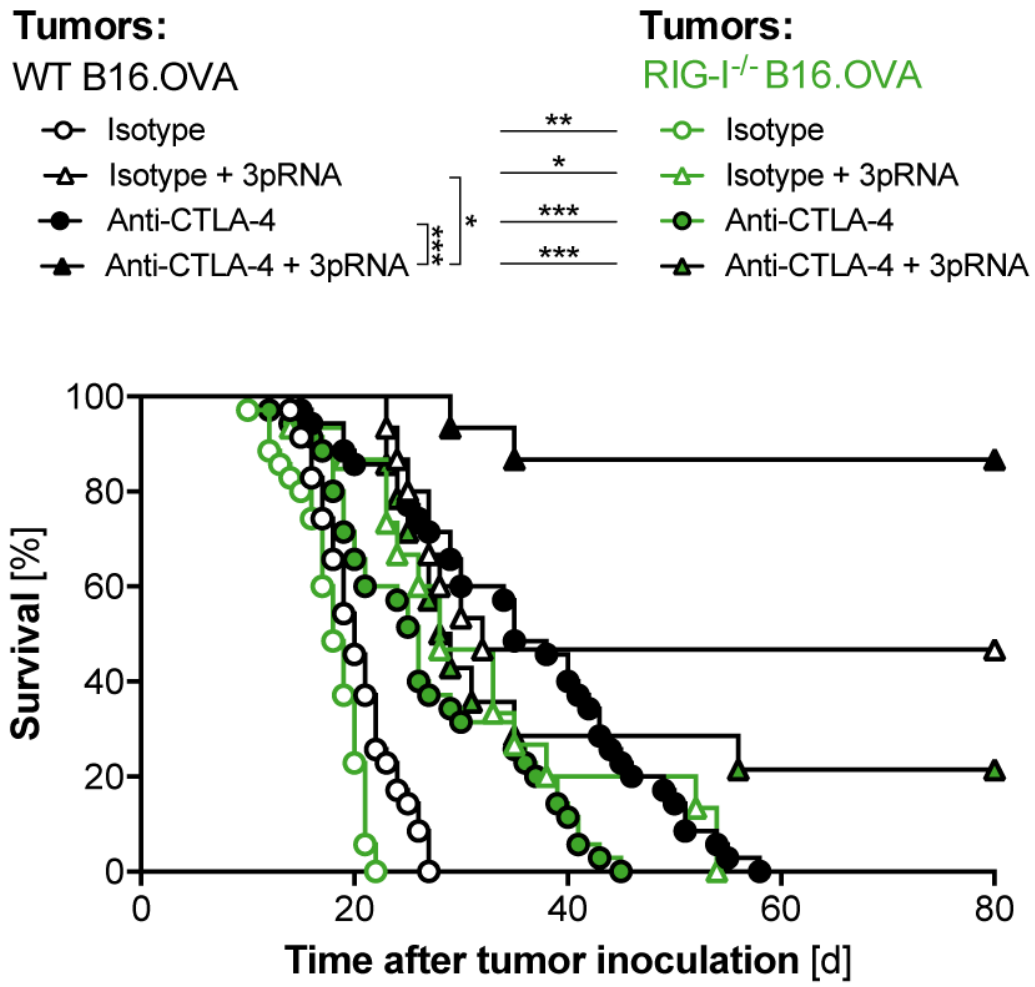


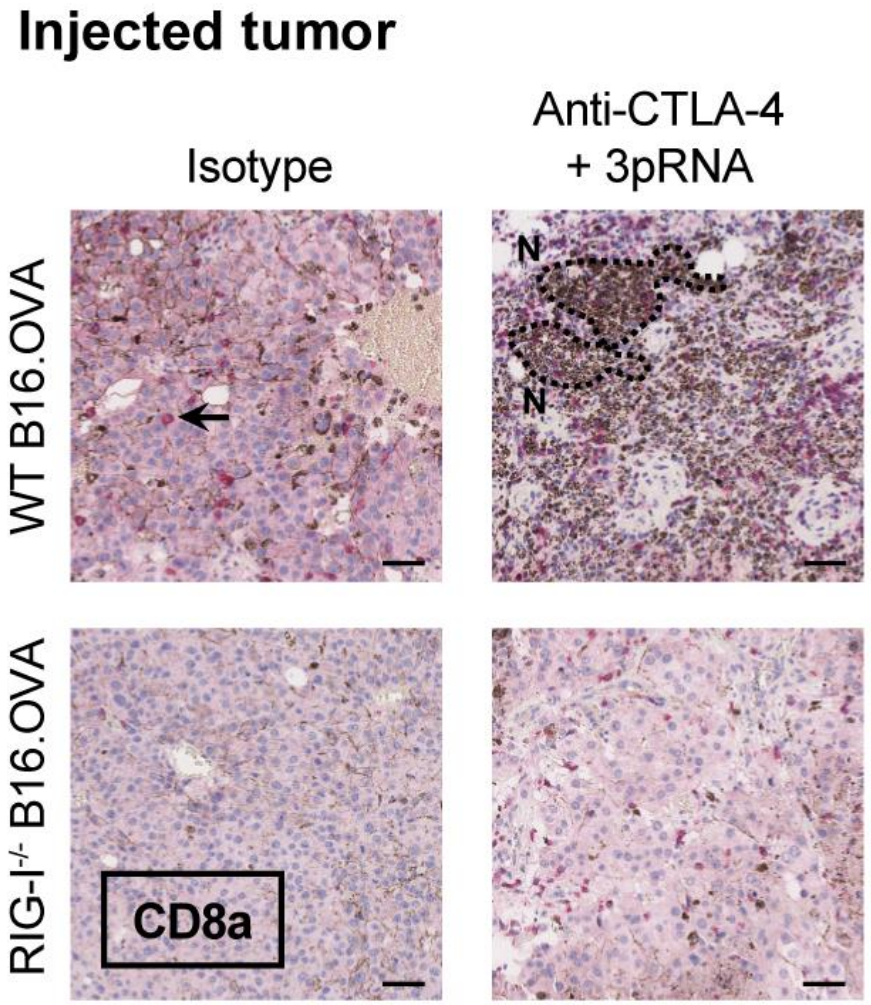
No. at risk								
High	228	113	60	32	14	4	2	1
Low	228	71	33	14	8	3	3	2

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

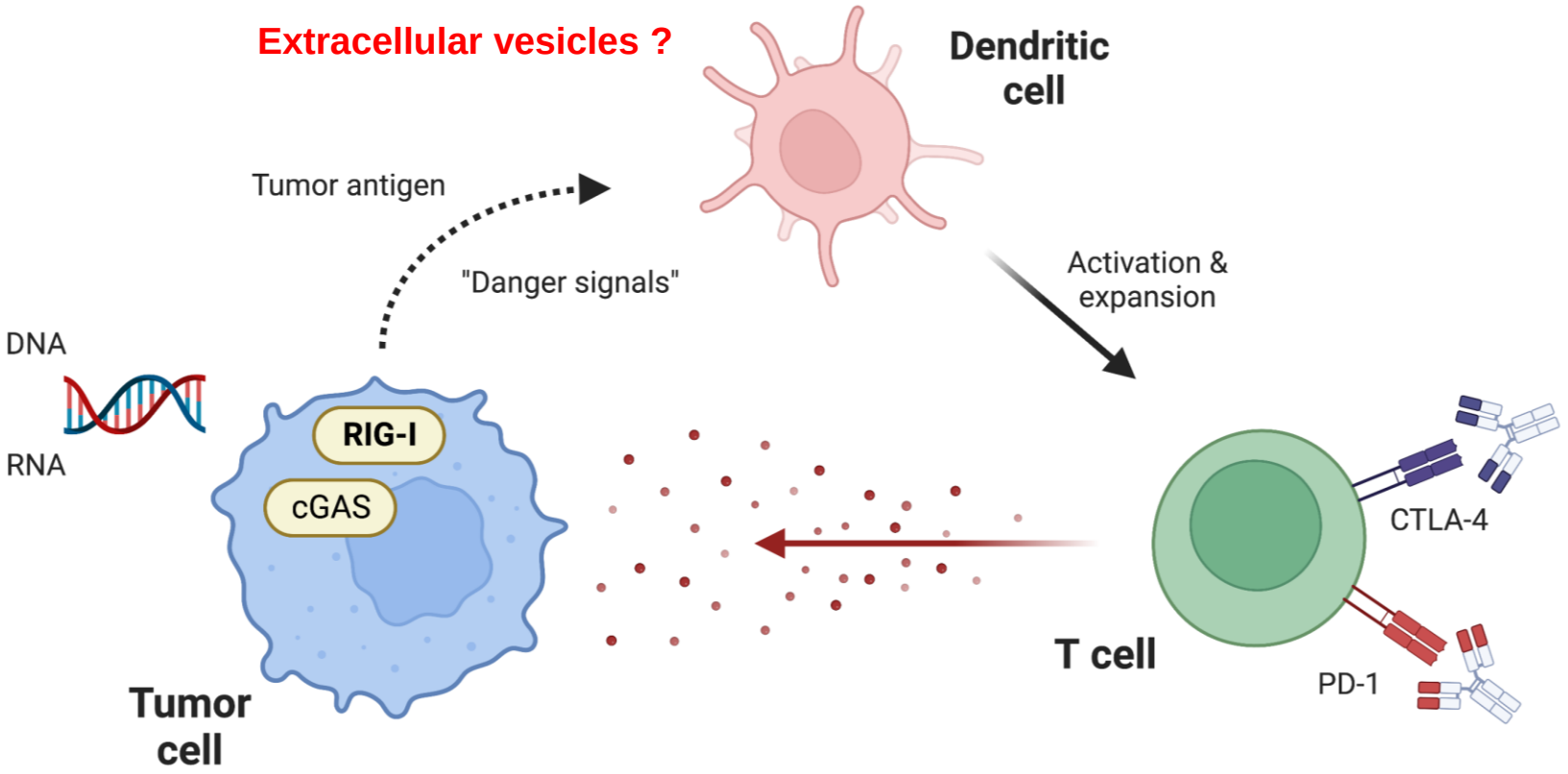
Heidegger et al., *Sci Immunol* (2019)

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



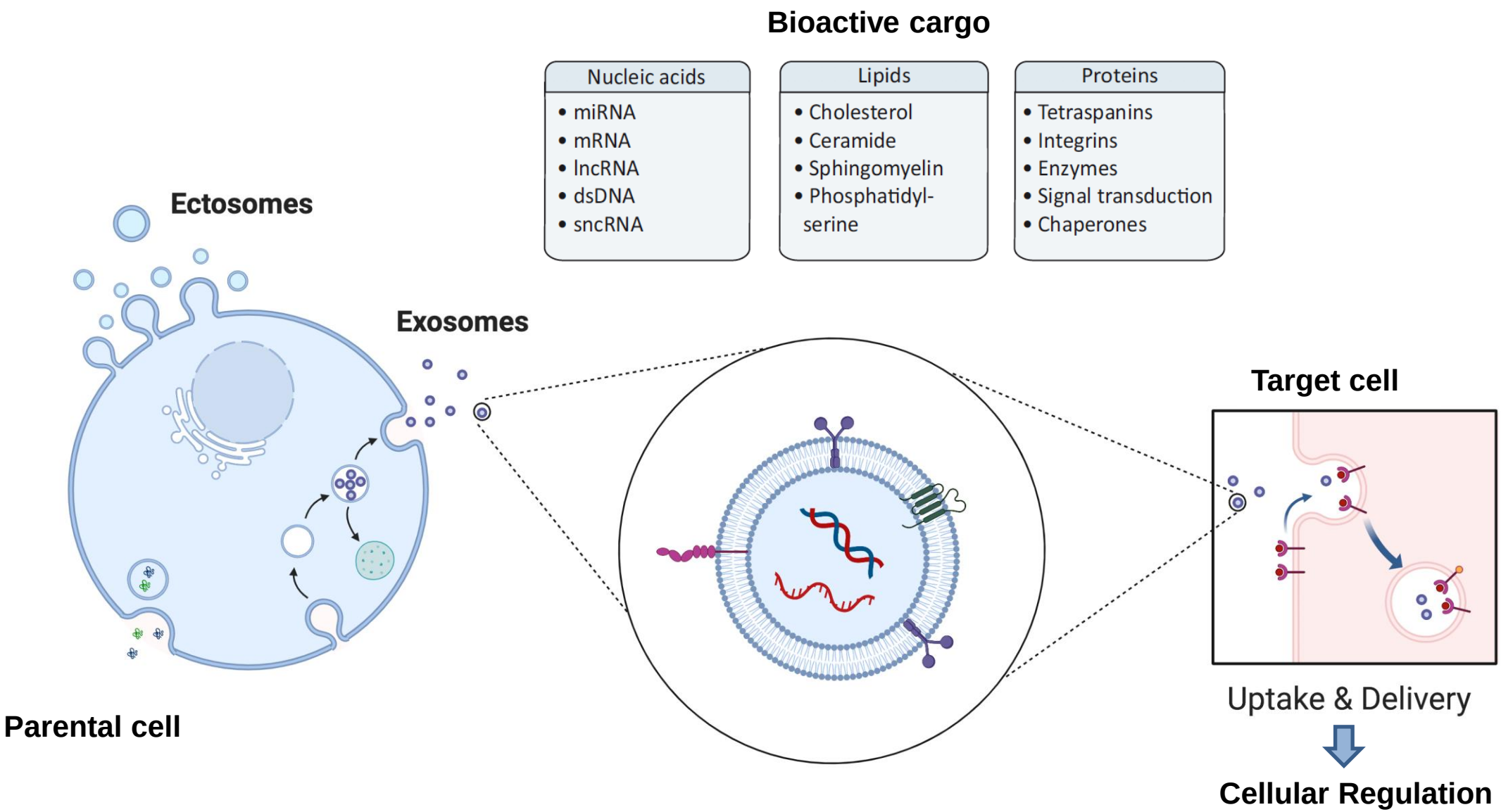


Heidegger et al., Sci Immunol (2019)

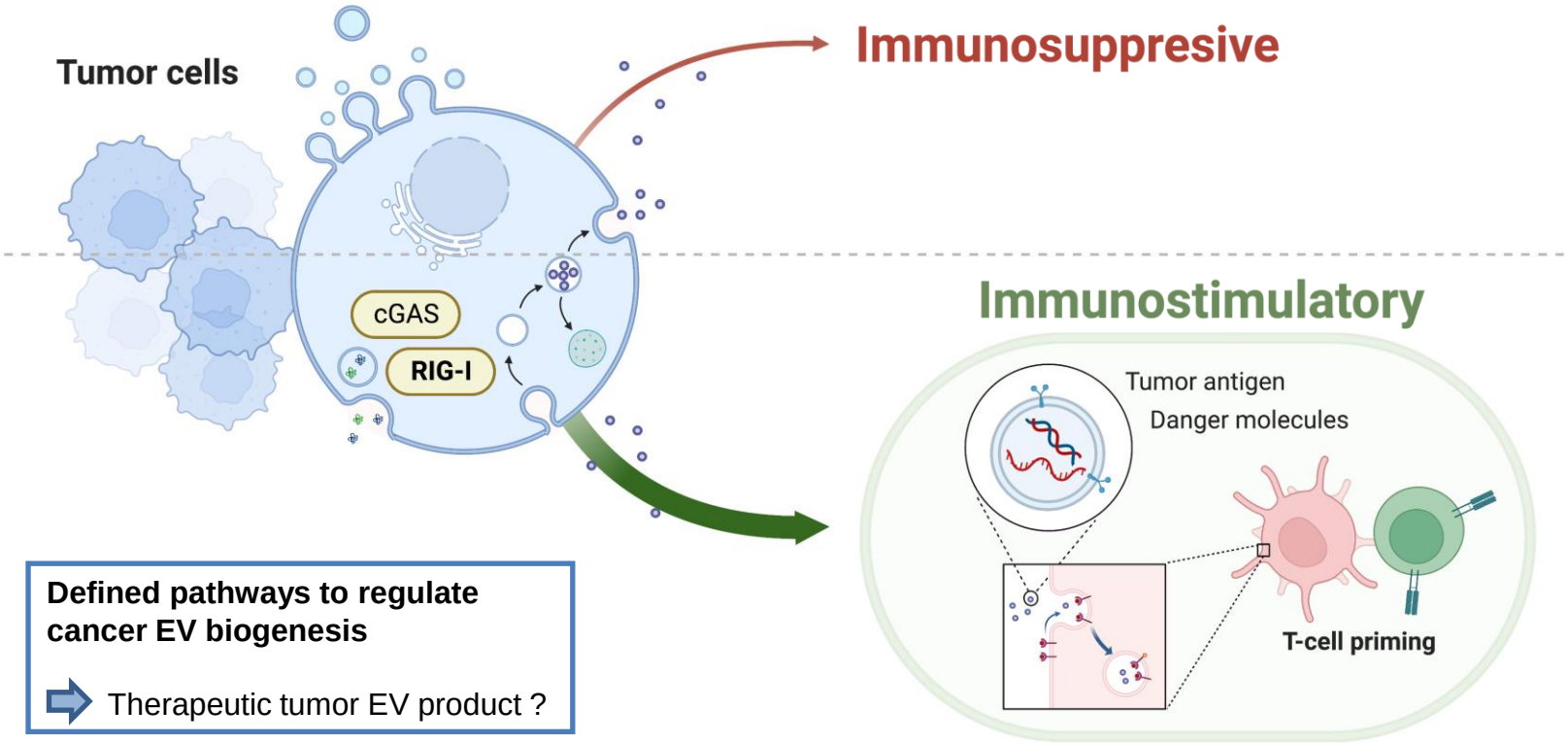


Heidegger et al., *Sci Immunol* (2019); Heidegger et al., *EBioMedicine* (2019);
Bek et al., *OncoImmunology (2019); Poeck et al., Eur J Immunol (2021)*

Extracellular vesicles (EVs): intercellular communication devices



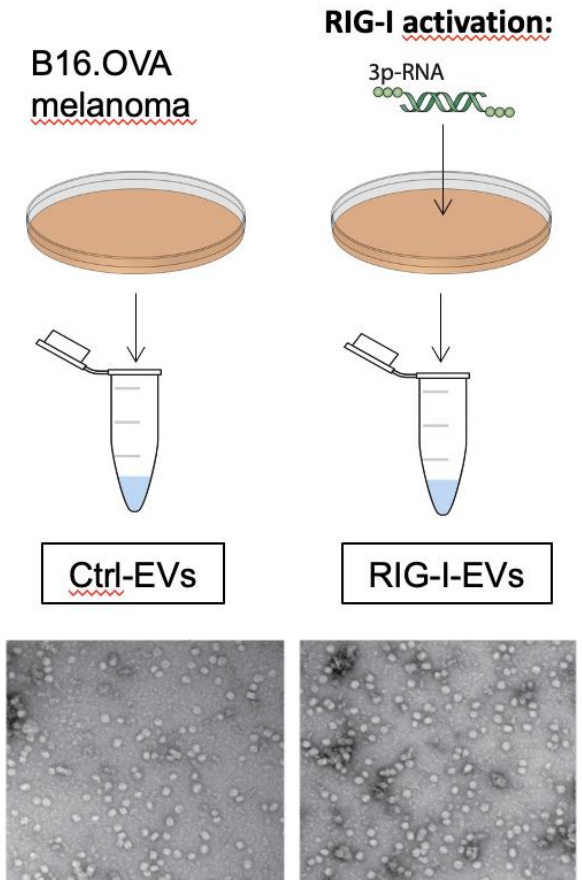
Dichotome Rolle von EVs in cancer



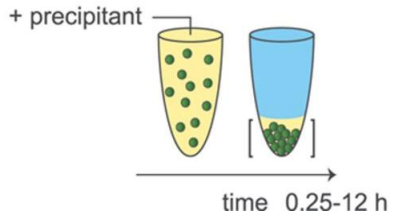
Defined pathways to regulate cancer EV biogenesis

➡ Therapeutic tumor EV product ?

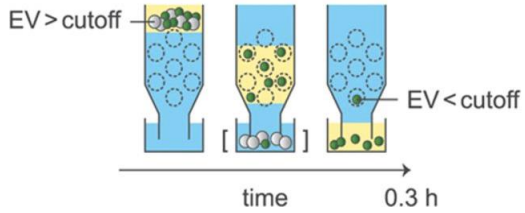
EVs aus Tumorzellen mit aktivem RIG-I signaling induzieren Interferone



Conventional isolation method:
Precipitation-based

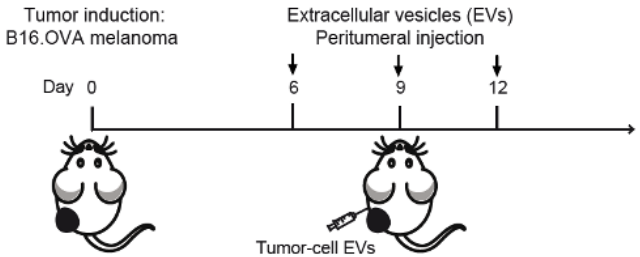


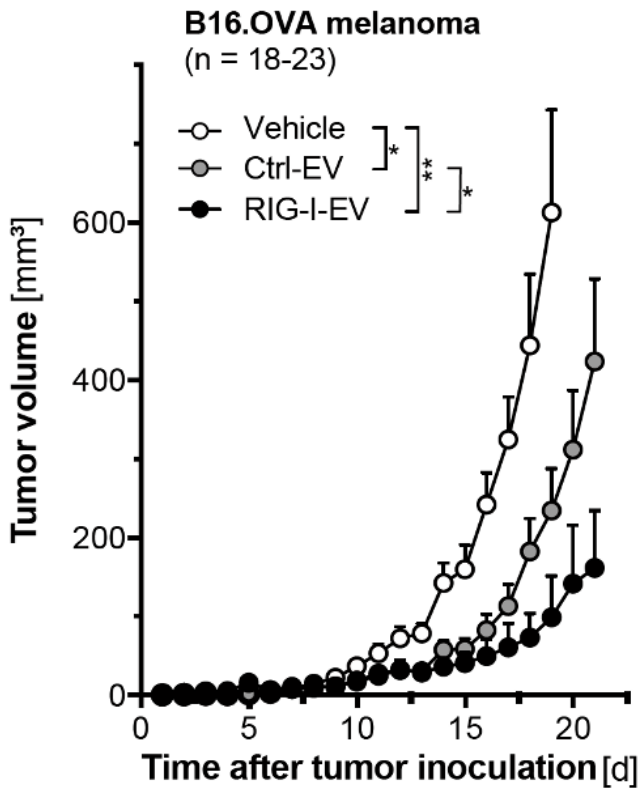
Complementary isolation method:
Size-exclusion chromatography

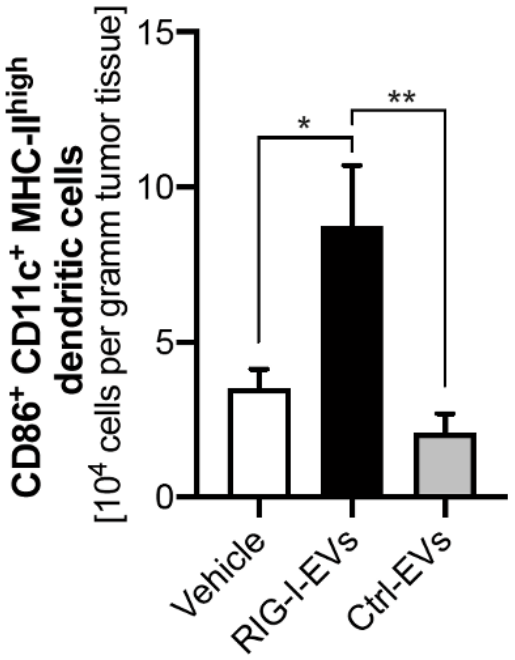


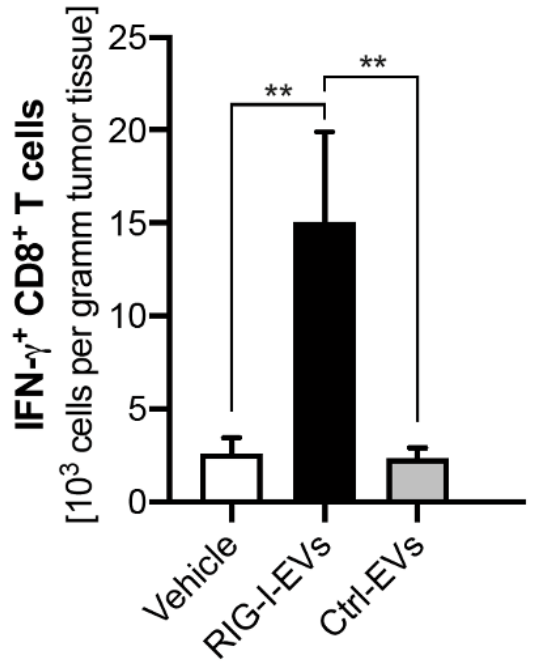
Heidegger et al., *Cell Rep Med* (2023)

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



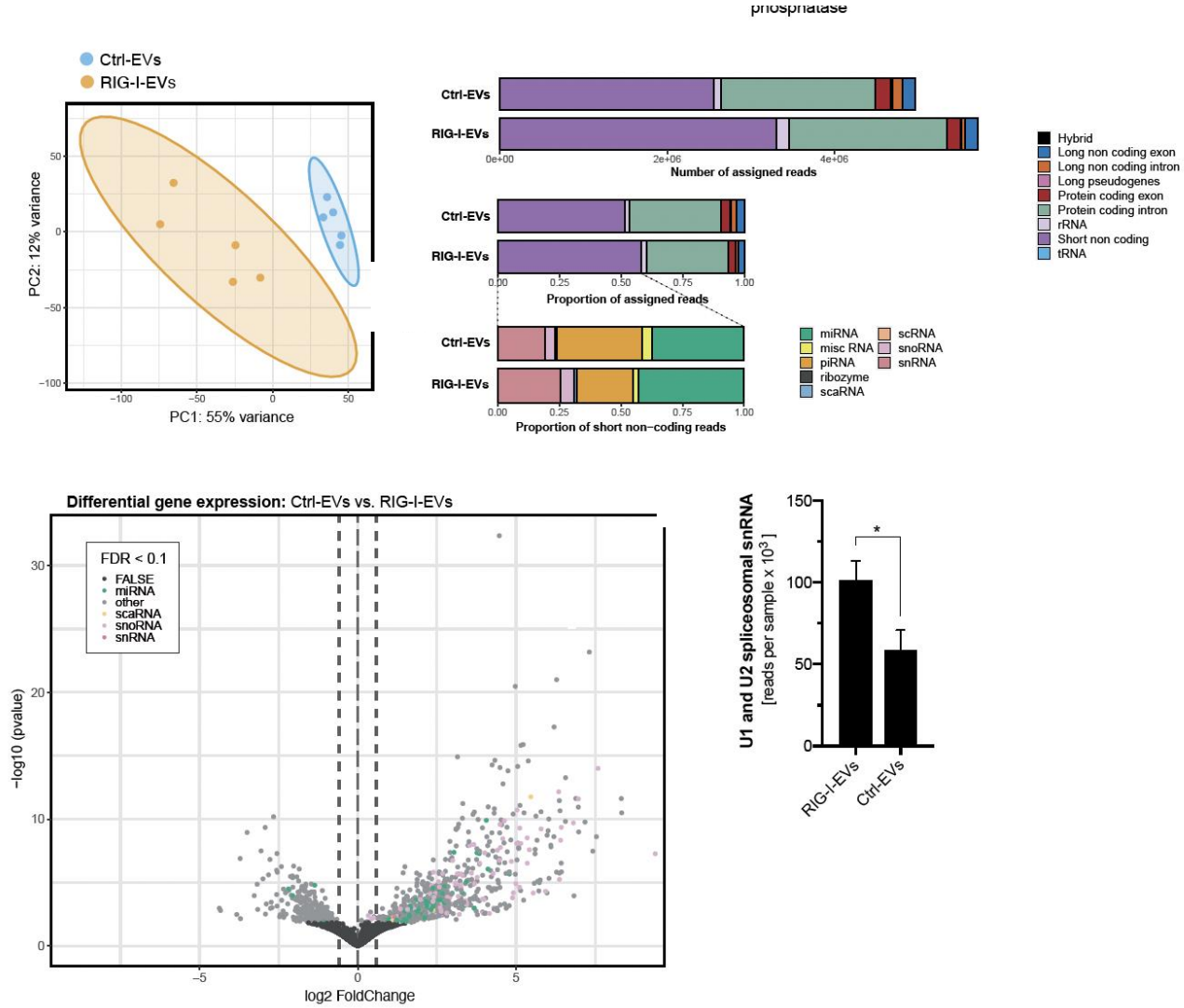






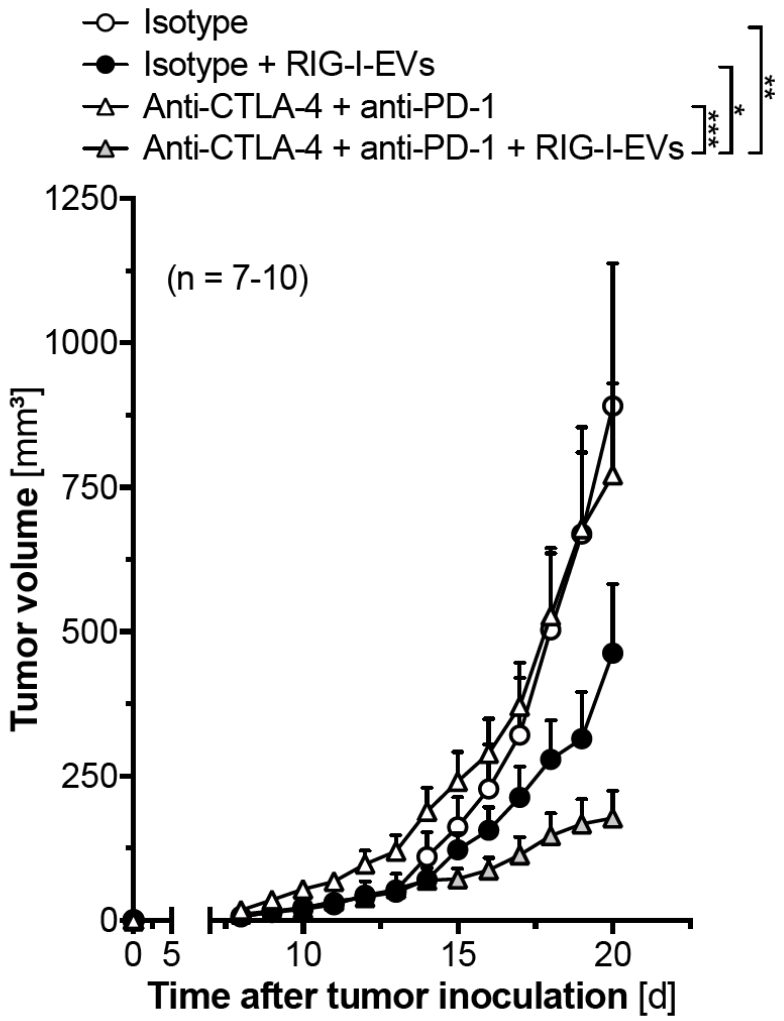
Heidegger et al., *Cell Rep Med* (2023)

RIG-I Aktivierung in Tumorzellen reguliert das EV RNA cargo



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

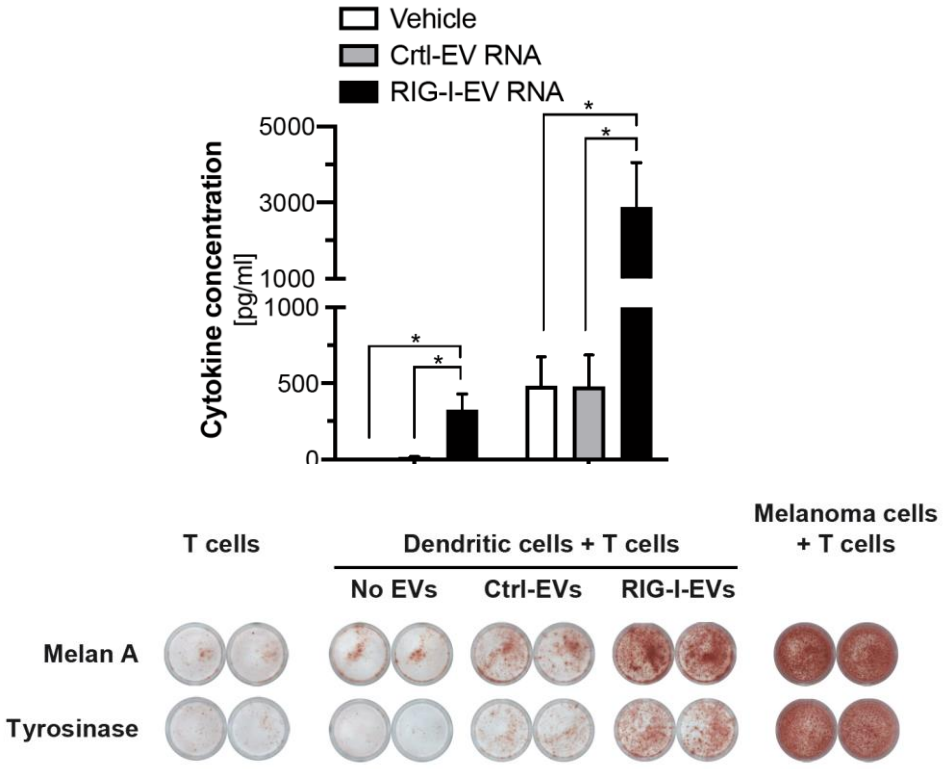
RIG-I EVs verstärken die Wirkung von Immun-Checkpoint-Inhibitoren in Mäusen und aktivieren menschliche T-Zellen



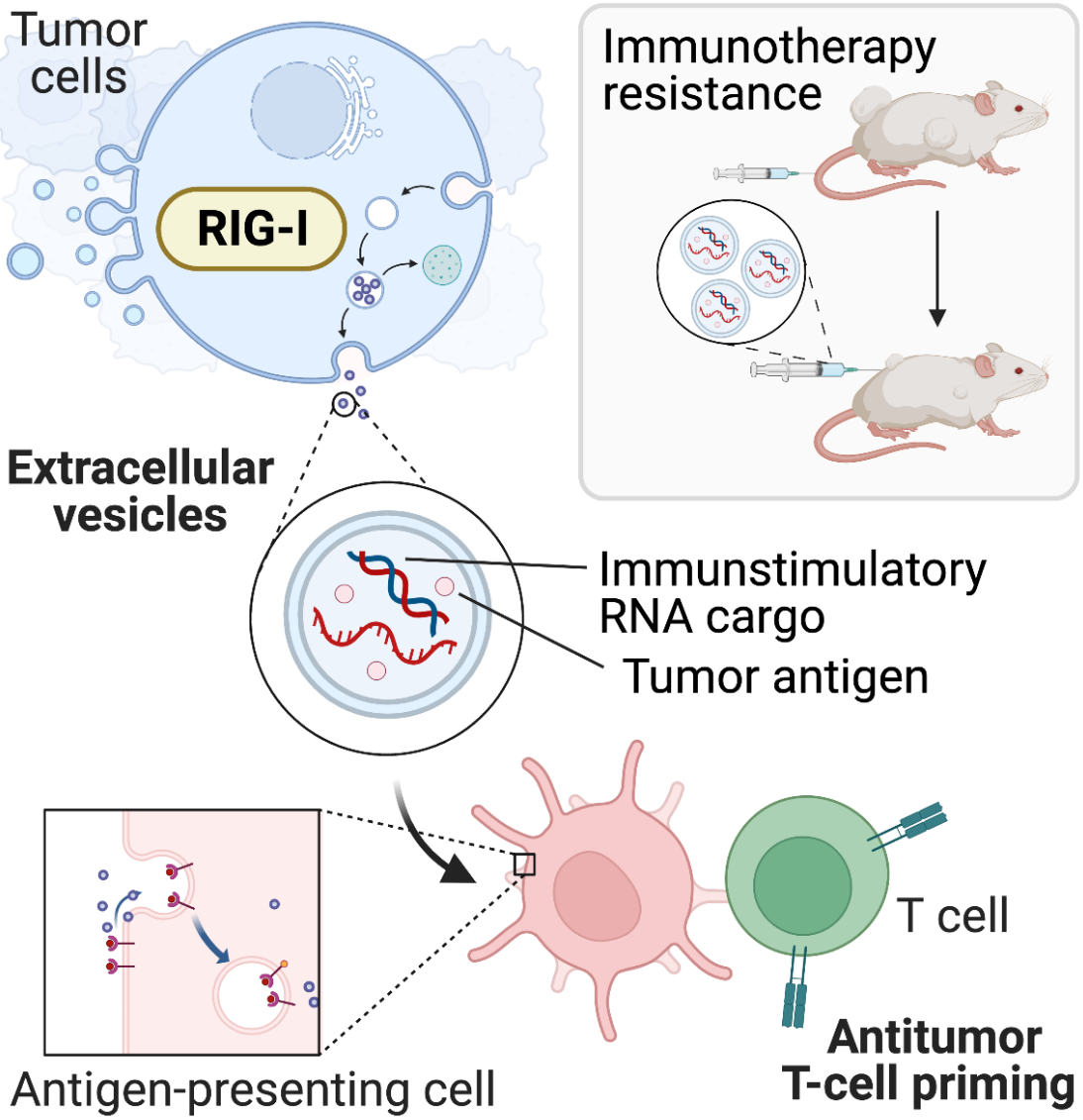
Heidegger et al., *Cell Rep Med* (2023)

EV source: Human melanoma cells (D04mel)

Target cells: PBMCs

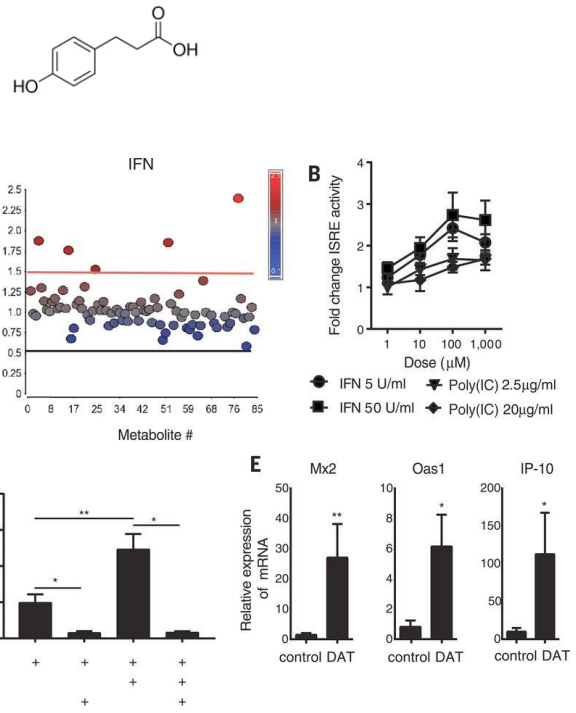


Umprogrammierung von Tumor-EVs zur Modulation von T-Zell-Immunität

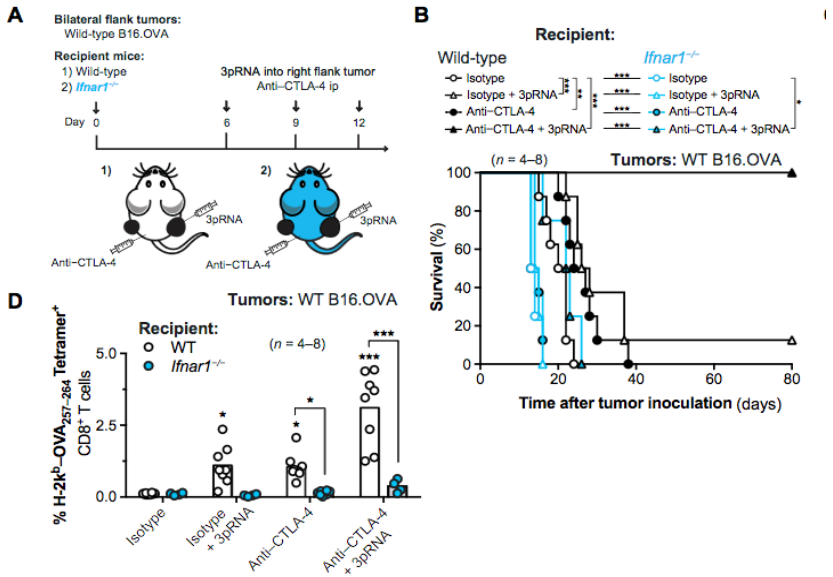


Microbial-derived metabolites induzieren IFN-I signaling

Desaminotyrosine in the literature → Host IFN-Is are important for anti-CTLA-4 efficacy

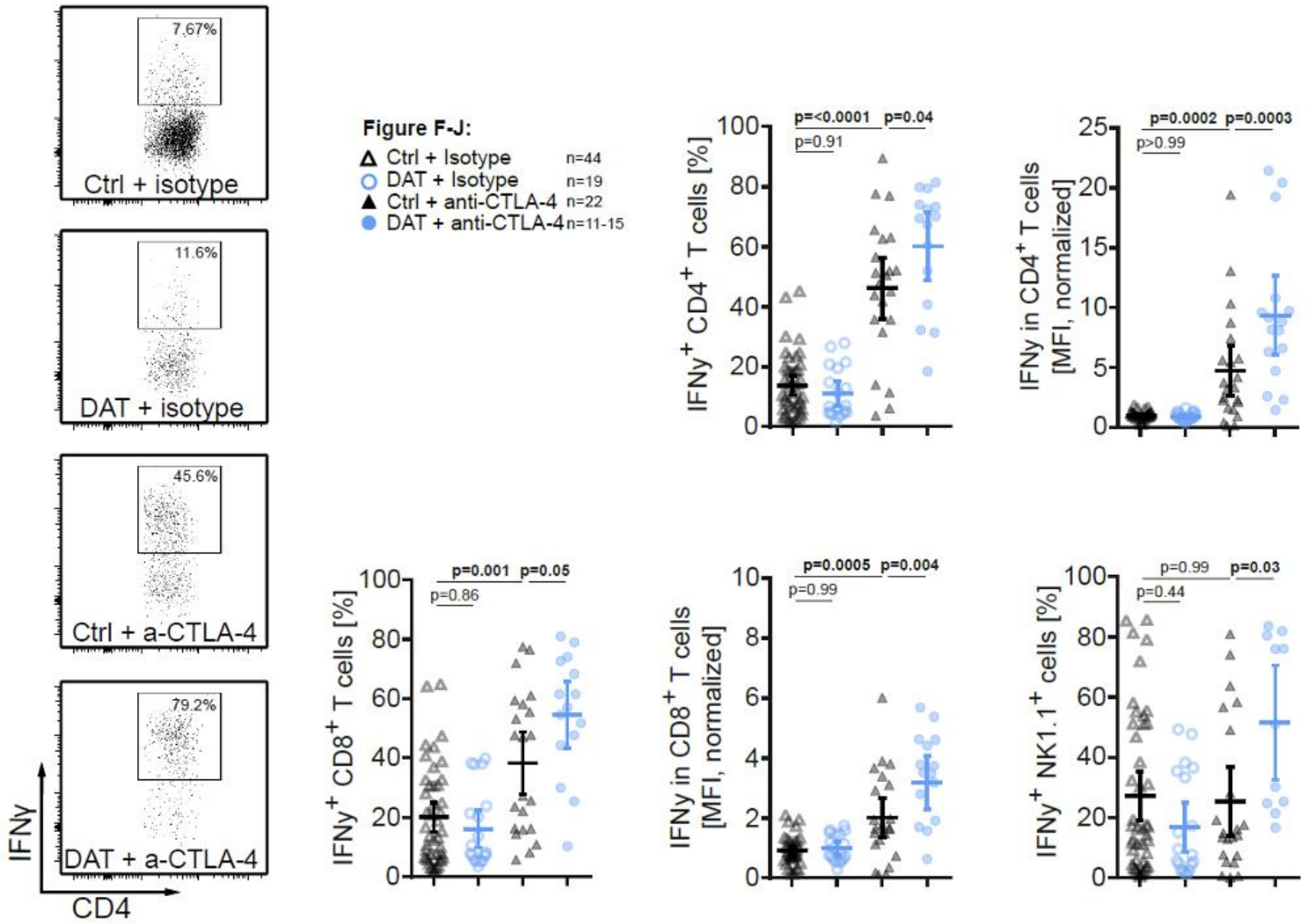


Steed et al., *Science* (2017)



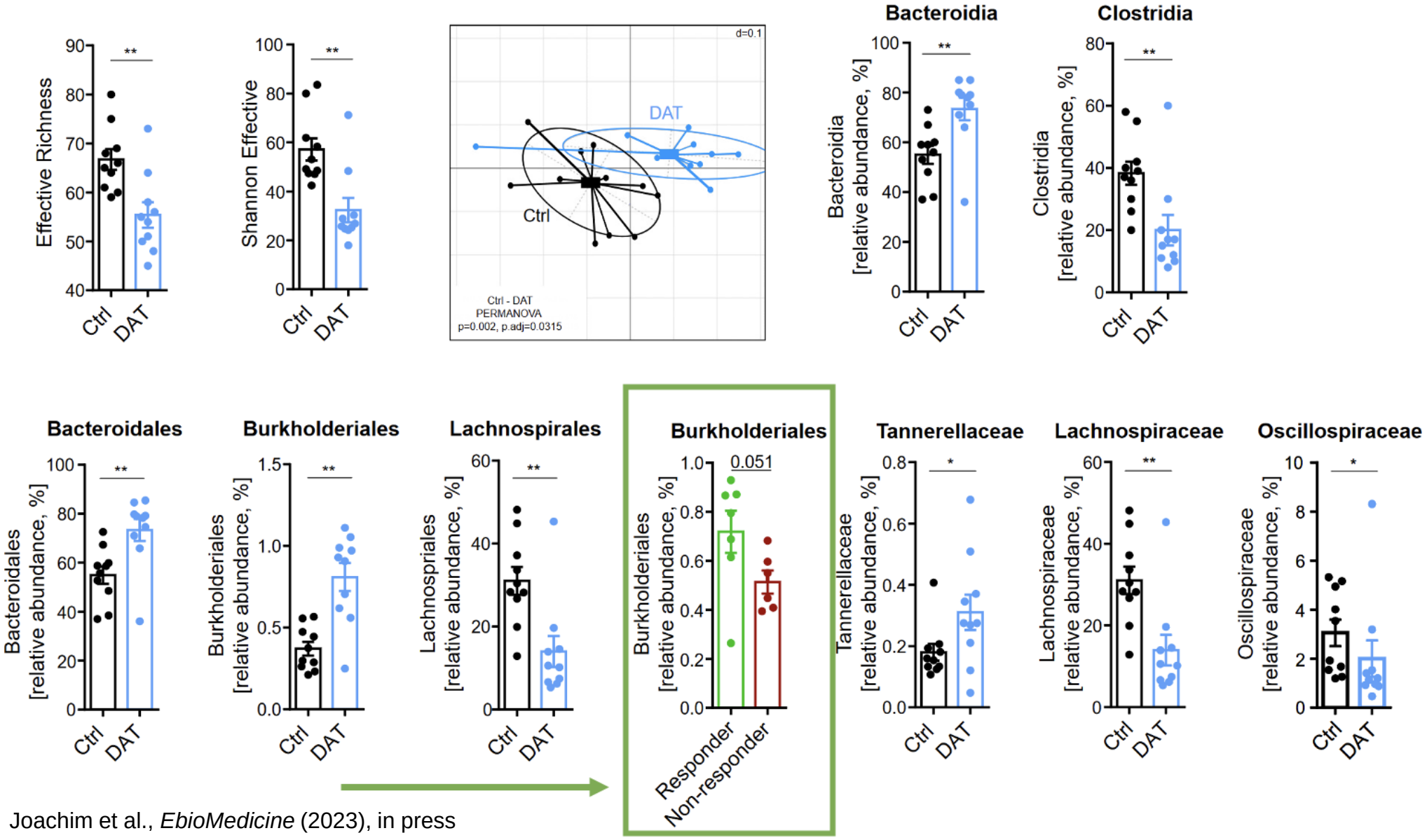
Heidegger et al., *Sci Immunol* (2019)

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



Joachim et al., *EbioMedicine* (2023), in press

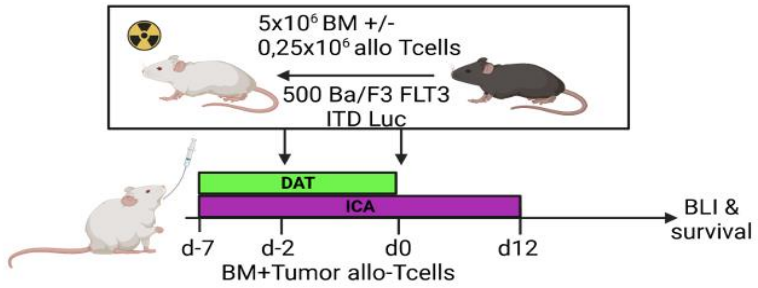
DAT kompensiert die negativen Effekte von Antibiotika auf ICI und verändert das intestinale microbiome

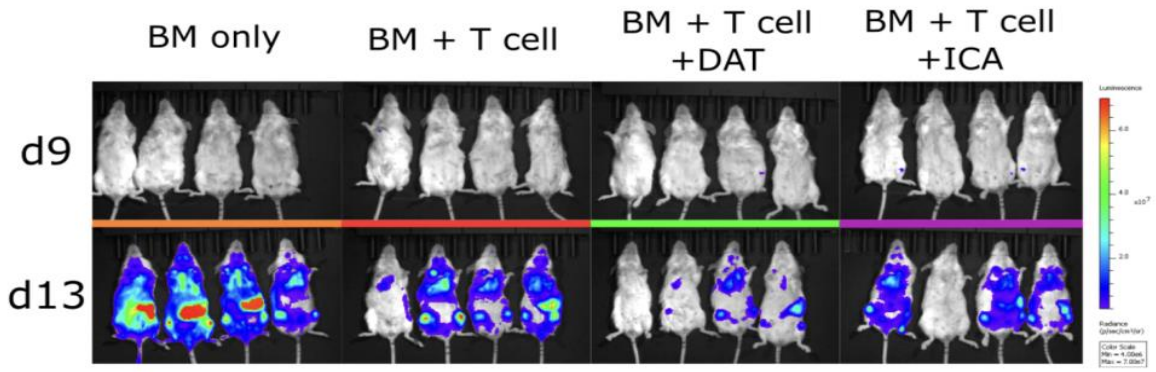


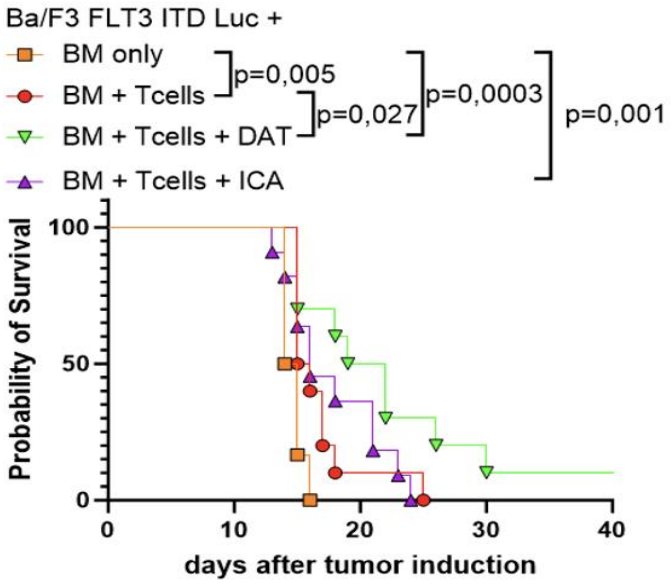
Joachim et al., *EbioMedicine* (2023), in press

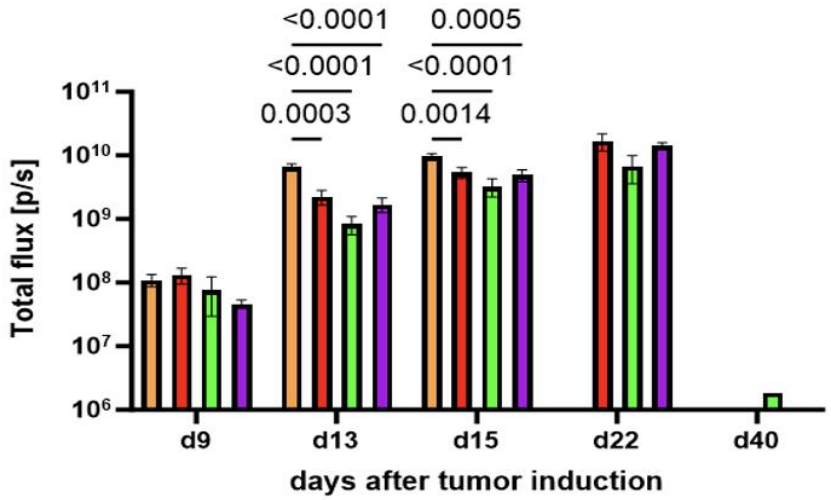
Microbial-derived metabolites korrelieren mit klinischem Ansprechen bei cancer immunotherapies

Allo-SCT







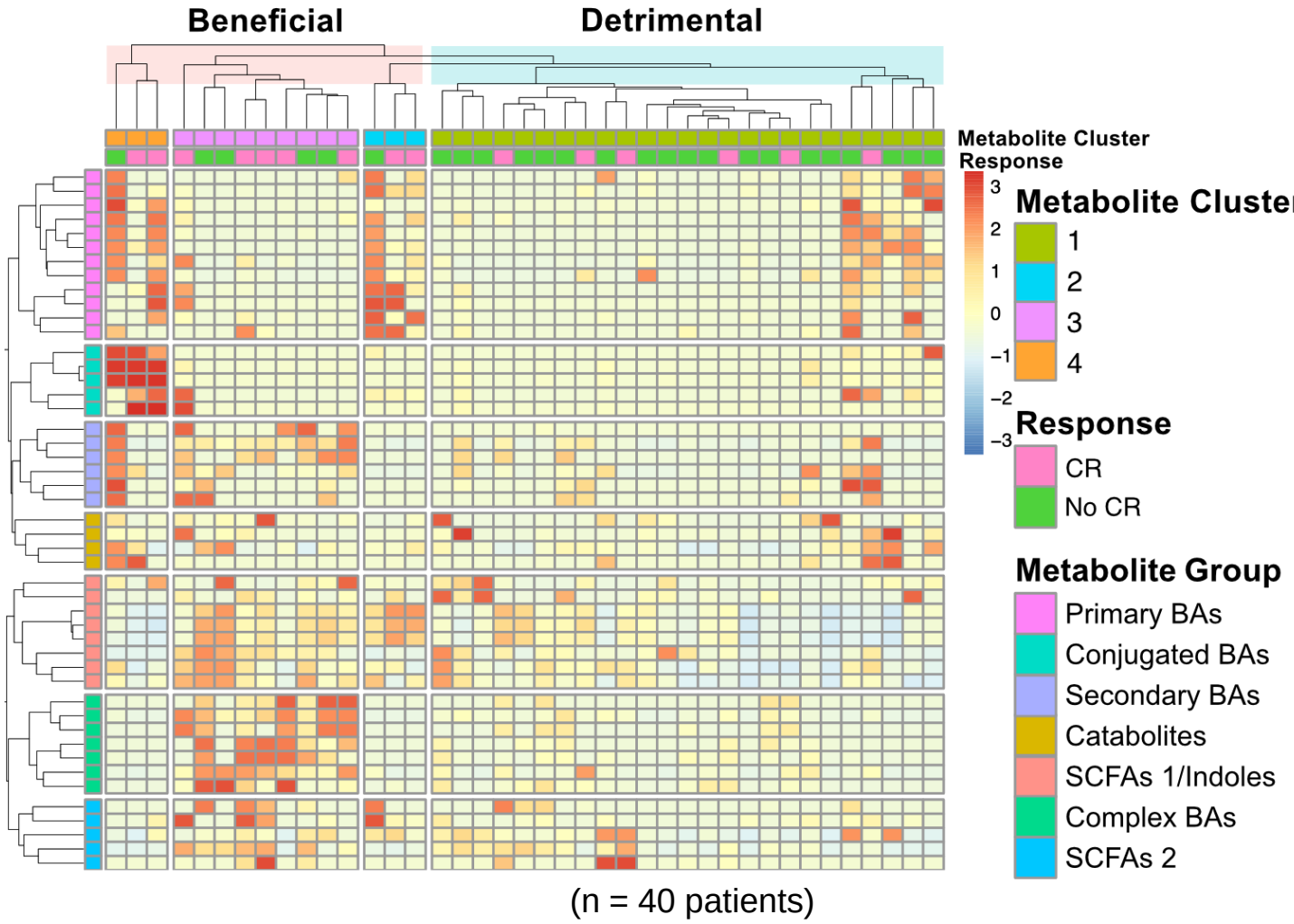


Orberg, Meedt et al., *Nat Cancer* (2023), in press

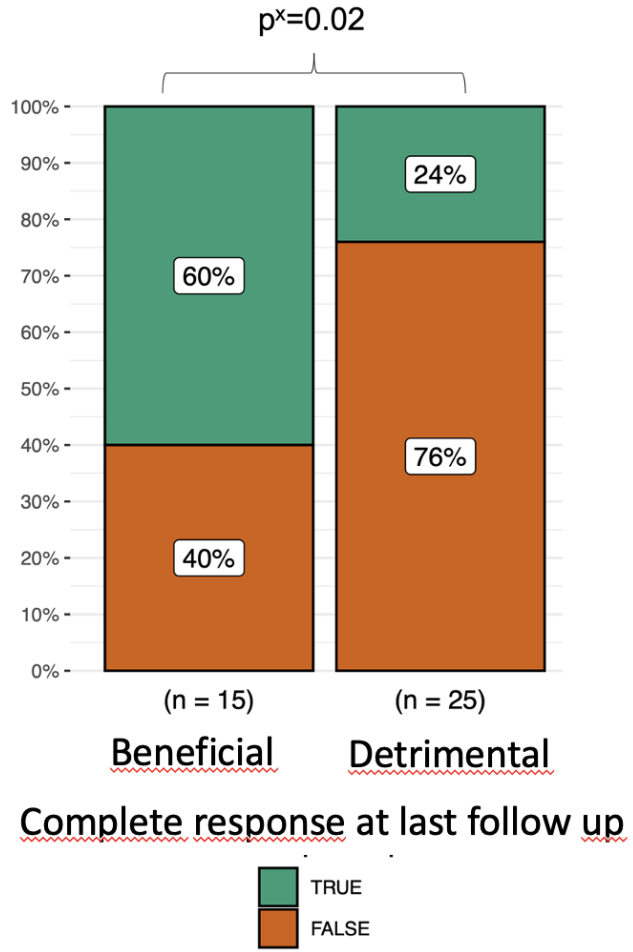
Göttert et al., *unpublished*

Microbial-derived metabolites korrelieren mit klinischem Ansprechen bei cancer immunotherapies

CAR T cells

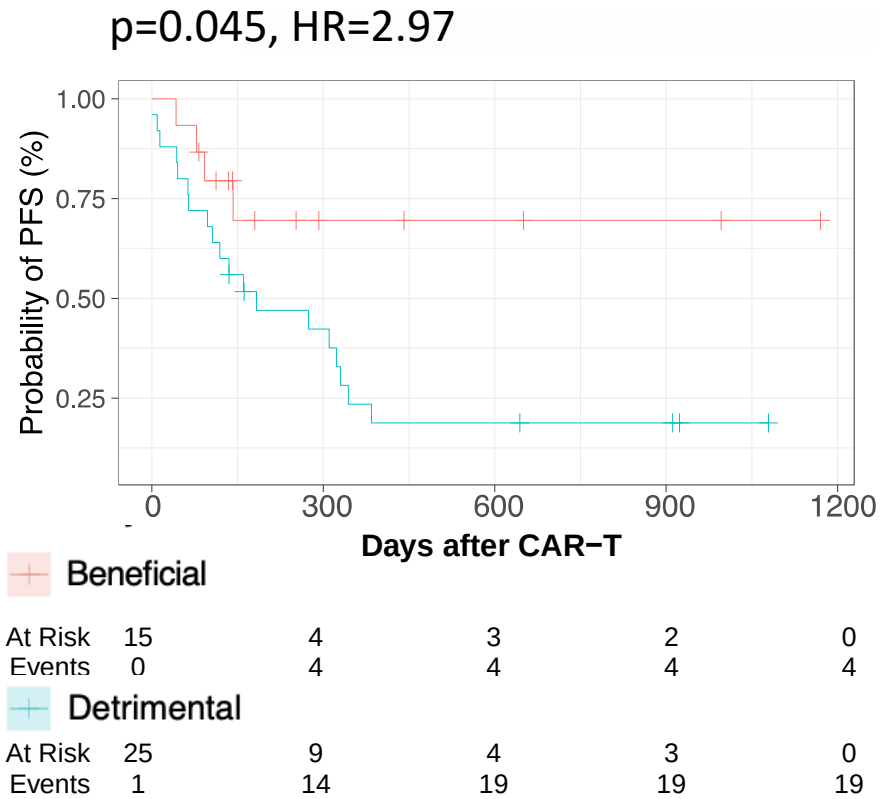


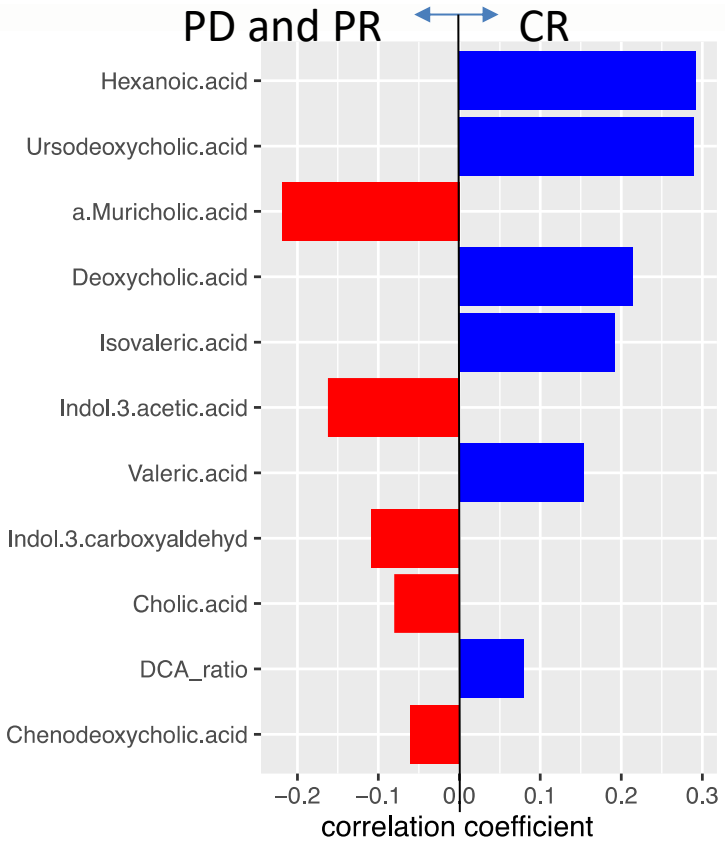
(n = 40 patients)



Perl, Fante et al, *unpublished*

Microbial-derived metabolites korrelieren mit klinischem Ansprechen bei cancer immunotherapies

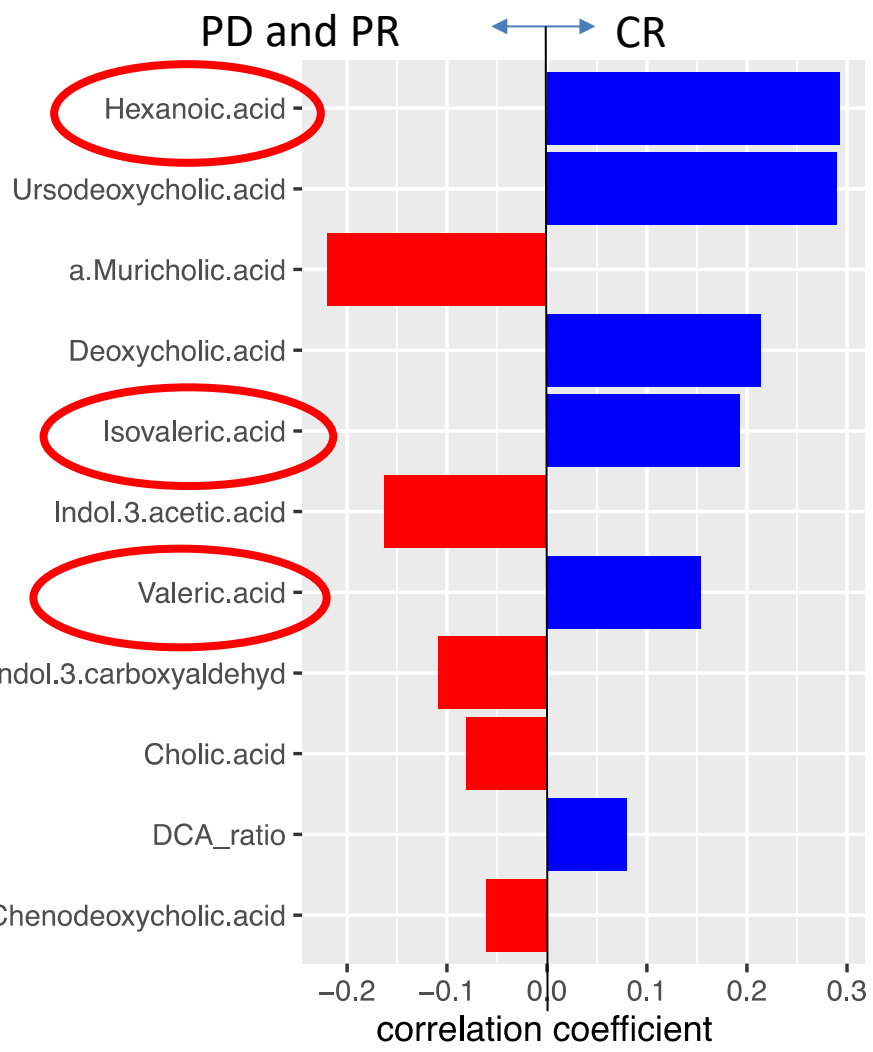


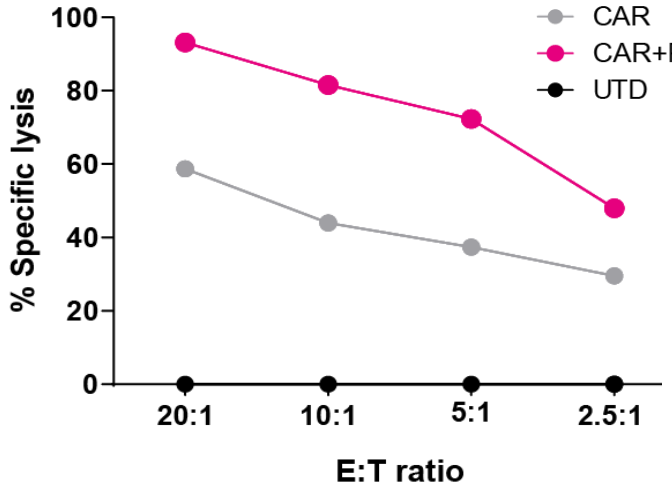


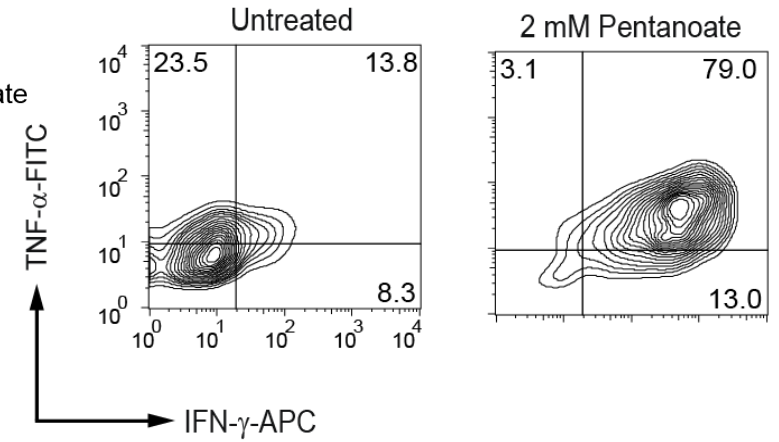
n=40 CAR T patients

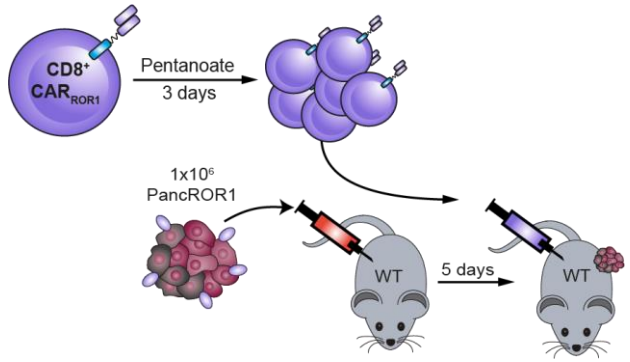
Perl, Fante et al, *unpublished*

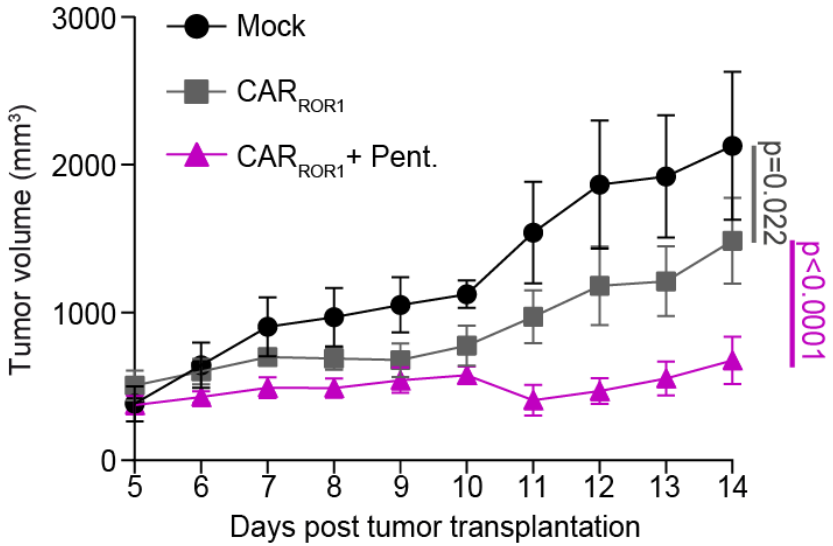
Short-chain fatty acid Pentanoate (=Valeric acid erhöhen die Wirksamkeit von CAR-T-Zellen





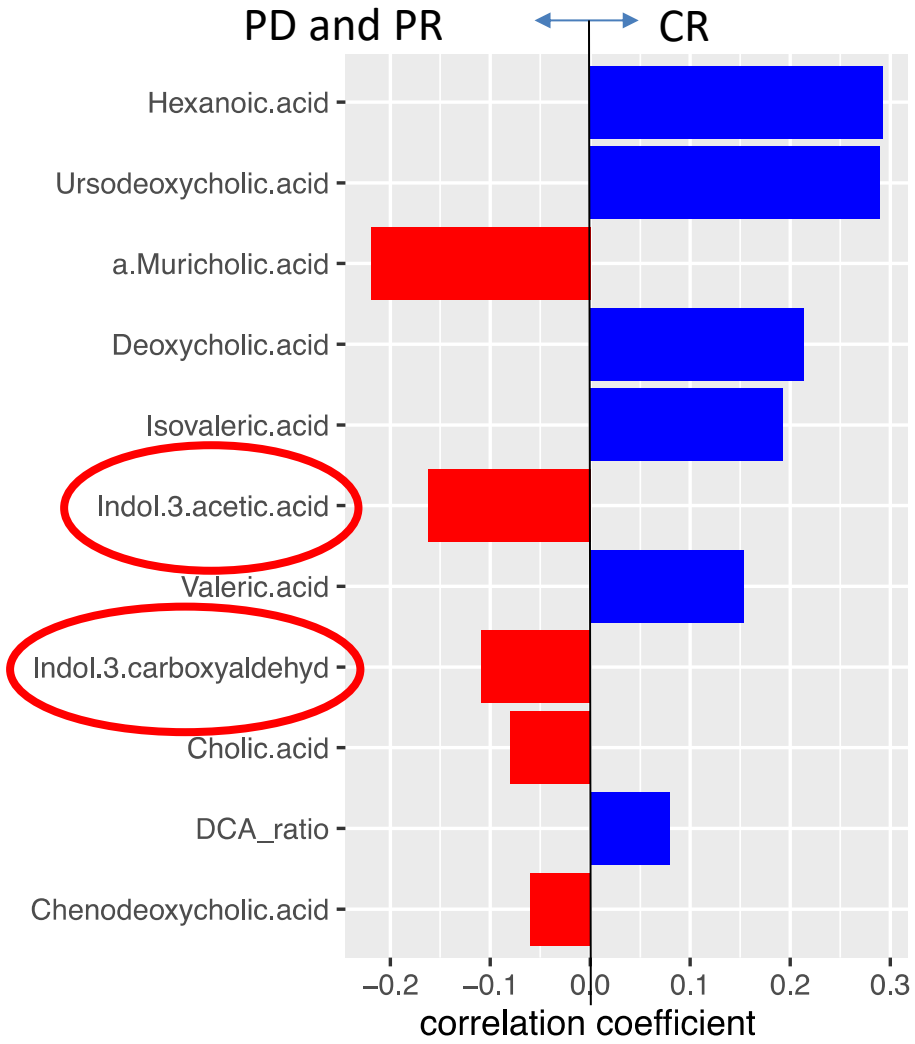


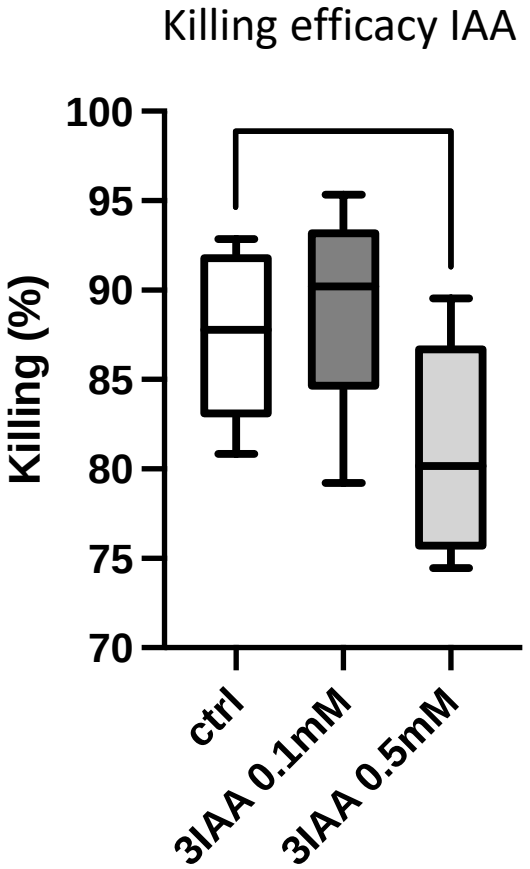


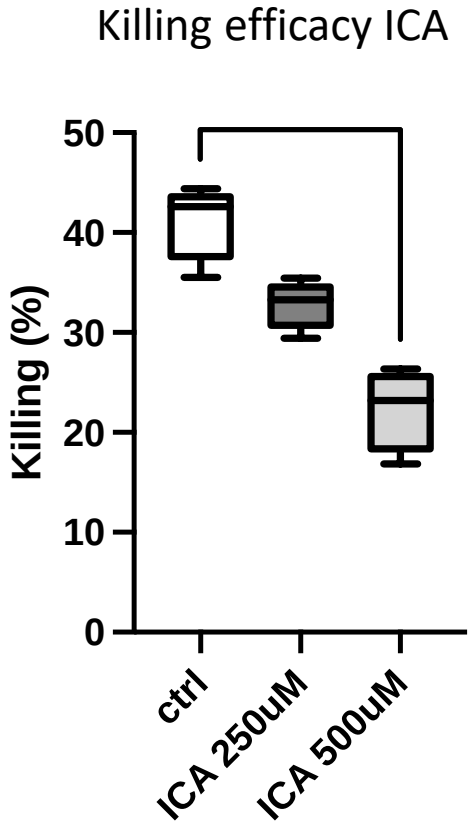


Perl, Fante et al., *unpublished* & Luu et al., *Nat Commun. (2021)*

Indole verschlechtern CAR-T-Zell Wirksamkeit







Perl, Fante et al., *unpublished* & Luu et al., *Nat Commun. (2021)*

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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Suqi Li
Misbah Tariq
Sascha Göttert
Leonard Knödler
Luisa Becker
Paul Heinrich
Maria Krieger
Christine Fooks-Kölbl
Eva Herschberger
Konstantin Herfeld
Alexander Denk
Matthias Fante

Medizinische Klinik III (TUM)
Simon Heidegger
Erik Thiele Orberg
Peter Herhaus
Mareike Verbeek
Florian Bassermann

Medizinische Klinik 3 (UKR)
Ernst Holler
Sakhila Ghmirie
Matthias Fante
Elisabeth Meedt
Wolfgang Herr
Matthias Edinger
Daniel Wolff
Daniela Weber
Michael Rehli

Bavarian Center for Biomolecular Mass Spectrometry (TUM)
Karin Kleigrewe

Uniklinikum Würzburg
Michael Hudecek
Maik Luu

MSKCC
Marcel van den Brink
Sarah Lindner
Oriana Miltiadous

UPenn
Marco Ruella

Klinische Chemie (TUM)
Jürgen Ruland

LIT
Christian Schmidl
Luca Gattinoni

Mikrobiologie und Hygiene (UKR)
Andre Gessner
Andreas Hiergeist

Chirurgie (TUM)
Klaus-Peter Janssen

Universität Tübingen/ DKFZ
Christoph Stein-Thoeringer

Mikrobiologie und Hygiene (TUM)
Dirk Busch
Sebastian Jarrosch

LMU München
Sebastian Kobold

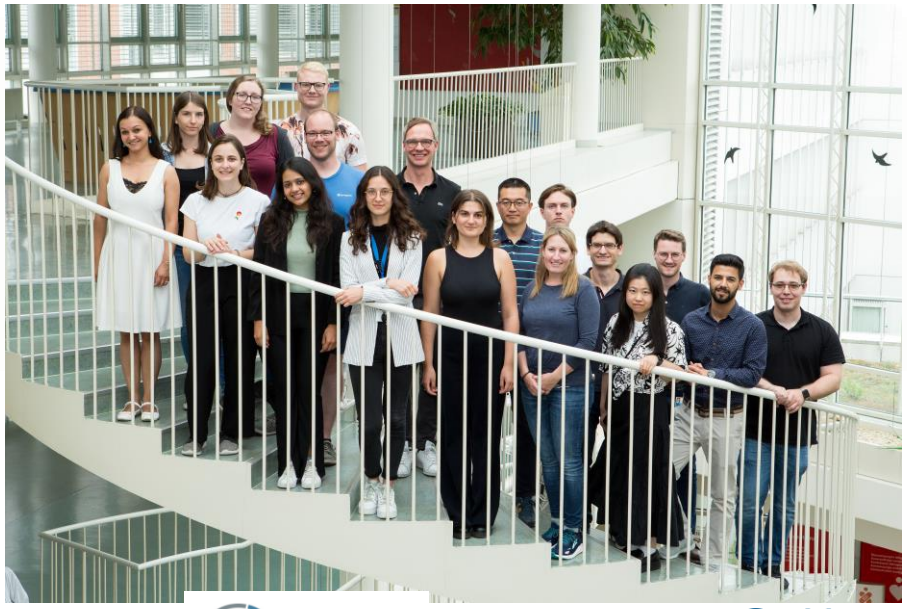
Helmholtz Zentrum München/TUM
Li Deng
Jinling Xue

Uniklinikum Erlangen
Fabian Müller
Andreas Mackensen

MD Anderson Cancer Center
Robert Jenq

Universität Bonn
Felix Meissner
Gunther Hartmann

Neurologie, UKR
Peter Hau



NCT
BZKF Bayerisches Zentrum für Krebsforschung
MAGIC
G>H G>L sfb transregio 221
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
Melanoma Research Alliance
UKR Universitätsklinikum Regensburg
CCC WERA
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DFG Deutsche Forschungsgemeinschaft
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Leibniz Institute for Immunotherapy Cells built to Cure