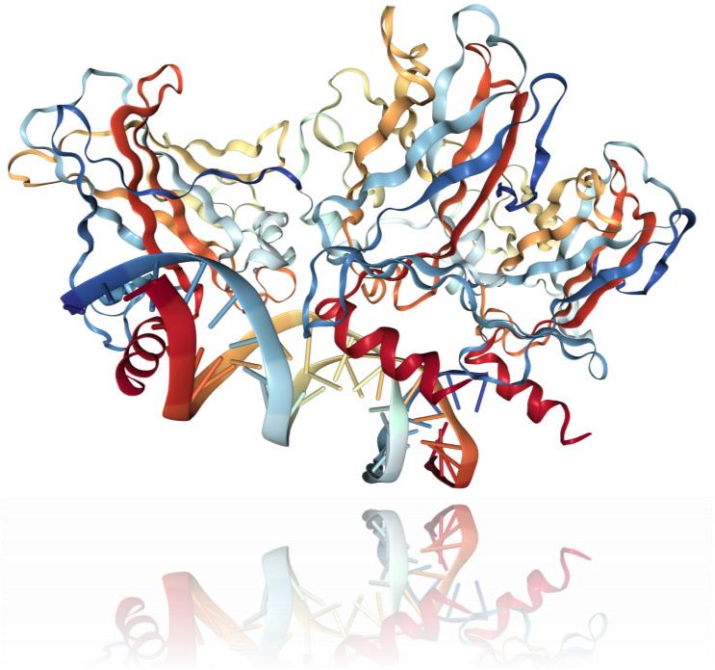
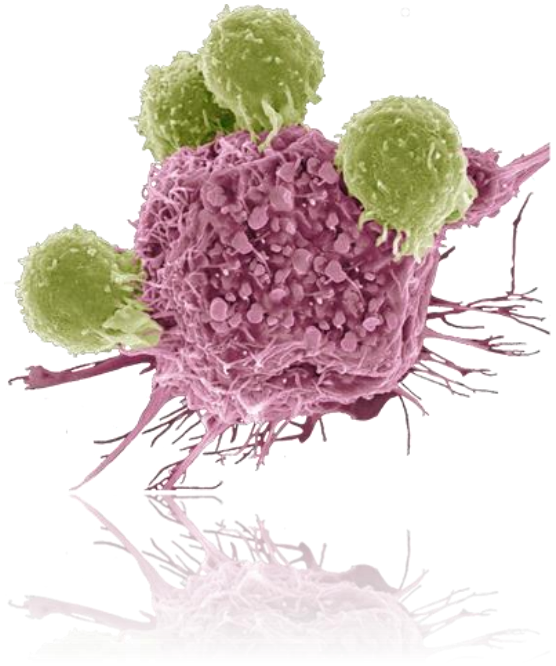
Klinik für Hämatologie und
Stammzelltransplantation
Universitätsmedizin Essen
Westdeutsches Tumorzentrum

# Das Beste aus der translationalen Forschung





## DGHO 2023, Hamburg

**Christian Reinhardt**
**Universitätsmedizin Essen**

# Interessenkonflikte

**Potentielle Interessenkonflikte Prof. Dr. Christian Reinhardt**

CR is an **advisor or consultant** for BMS/Celgene, Gilead Kite, Lilly, Miltenyi, Novartis, Noscendo, Roche, Amgen, Pfizer, Takeda, SinaBiomedics, and Merck Sharp & Dohme; has **received honoraria** from AbbVie, AstraZeneca, BMS, Novartis, Roche Pharma AG, Takeda, and Merck Sharp & Dohme; **reports research funding** from AstraZeneca and Gilead Kite; and **reports travel support** from AbbVie, AstraZeneca, Gilead Kite, Merck Sharp & Dohme, Roche, Takeda, and Novartis; is a **co-founder and stock holder** of CDL Therapeutics GmbH.

# Agenda

***Technology Development:***

- **A prime editor allele to facilitate precise *in vivo* modeling**

*Cancer neuroscience:*

- Glioblastoma networks display an actionable rhythmic activity
- Sympathetic catecholamine signaling drives T cell exhaustion

*Drug development:*

- Turning transcriptional repressors into activators

nature biotechnology

Article

https://doi.org/10.1038/s41587-023-01783-y

# A prime editor mouse to model a broad spectrum of somatic mutations in vivo

Received: 15 July 2022

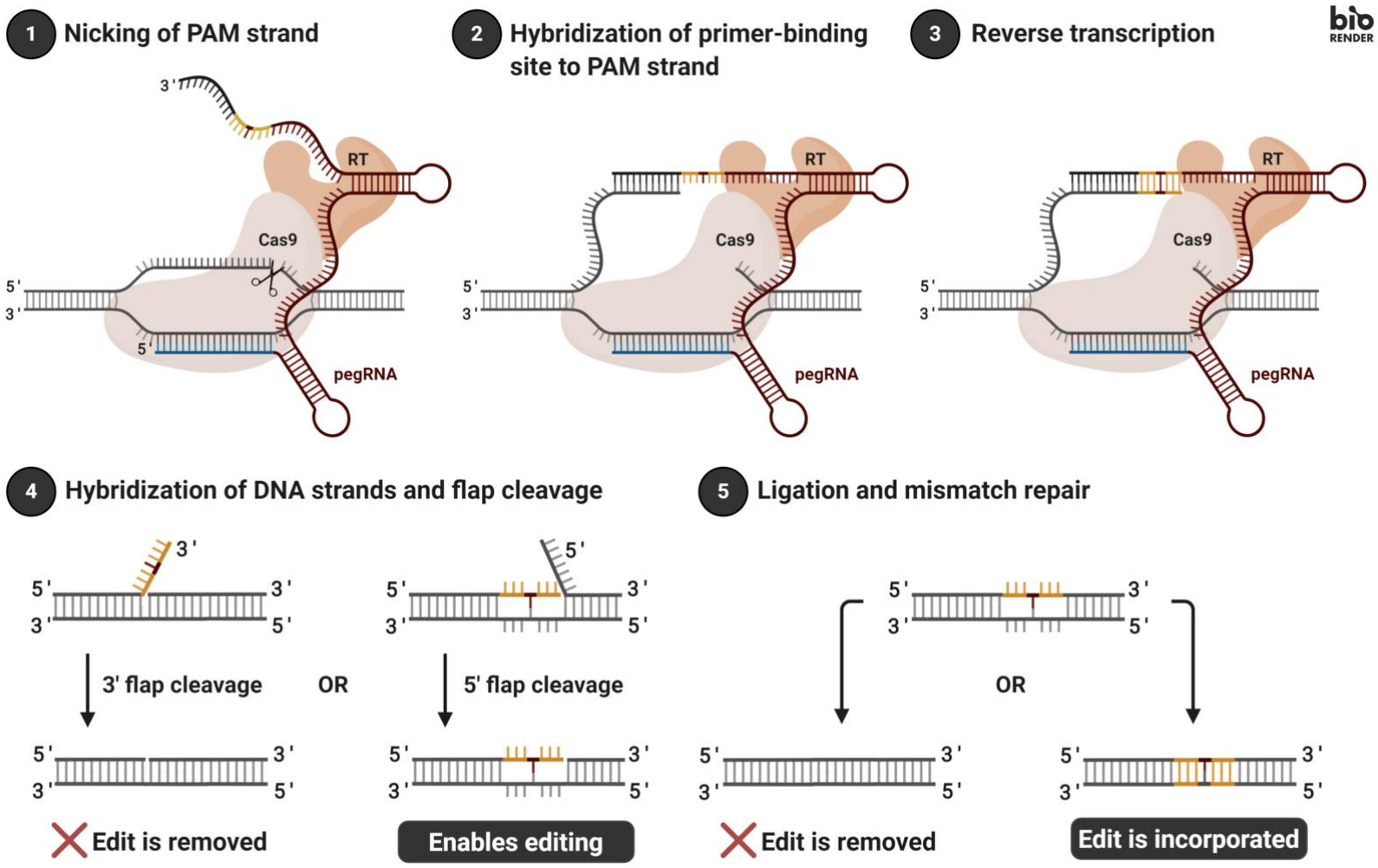
Accepted: 5 April 2023

Published online: 11 May 2023

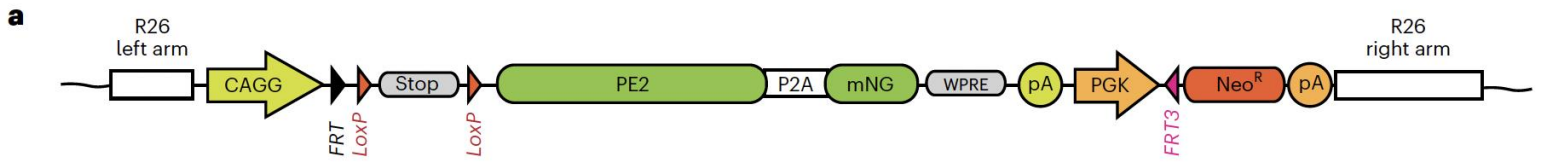
Check for updates

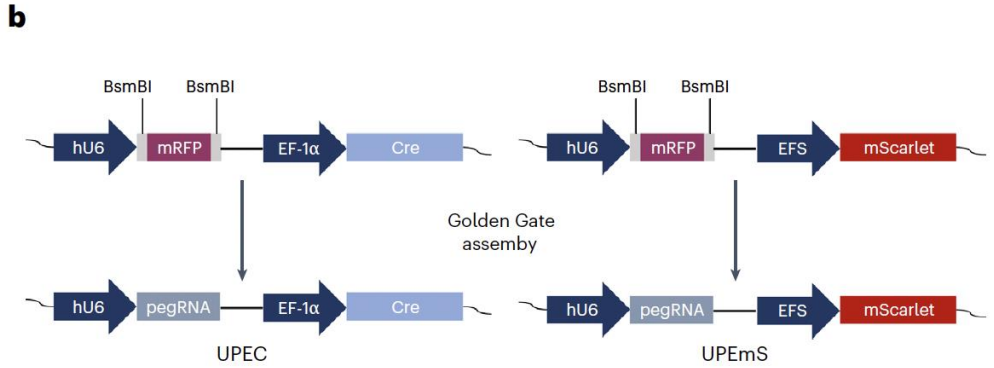
Zackery A. Ely[1,2,13], Nicolas Mathey-Andrews[1,2,3,13], Santiago Naranjo[1,2], Samuel I. Gould[1,2], Kim L. Mercer[1], Gregory A. Newby[4,5,6], Christina M. Cabana[1,2], William M. Rideout III[1], Grissel Cervantes Jaramillo[1,7], Jennifer M. Khirallah[8], Katie Holland[1,9], Peyton B. Randolph[4,5,6], William A. Freed-Pastor[1,3,10,11], Jessie R. Davis[4,5,6], Zachary Kulstad[1,10], Peter M. K. Westcott[1,12], Lin Lin[1], Andrew V. Anzalone[4,5,6], Brendan L. Horton[1], Nimisha B. Pattada[1], Sean-Luc Shanahan[1,2], Zhongfeng Ye[8], Stefani Spranger[1,2], Qiaobing Xu[8], Francisco J. Sánchez-Rivera[1,2], David R. Liu[4,5,6] & Tyler Jacks[1,2] ✉

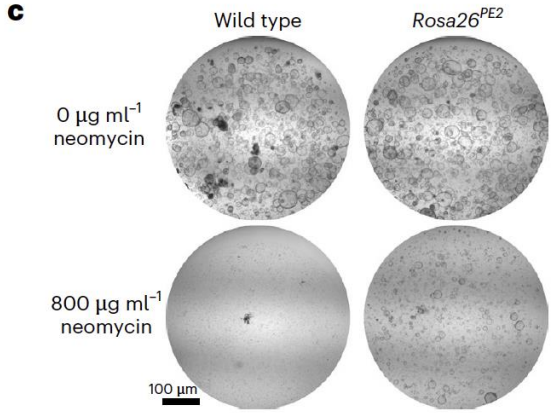
# Prime Editing

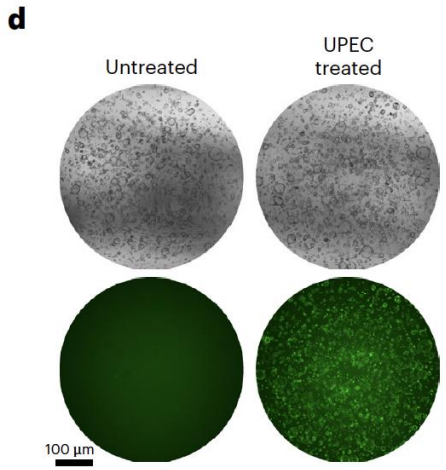


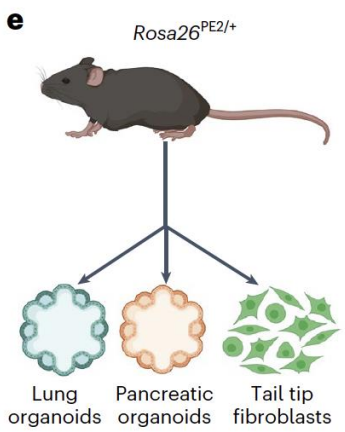
# Generation of a Prime Editor allele

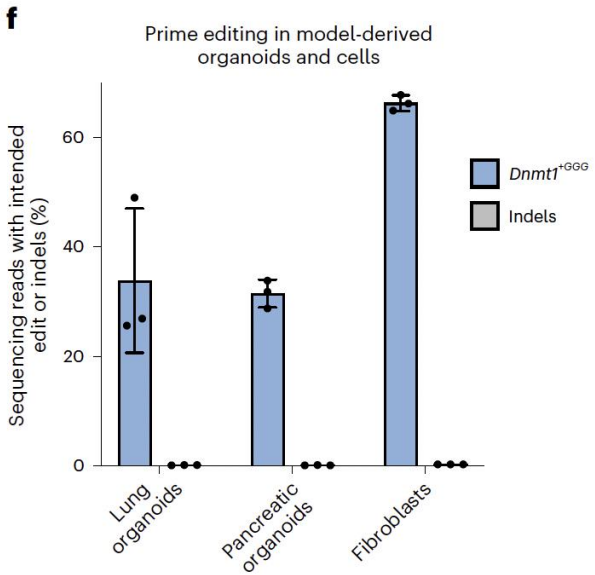


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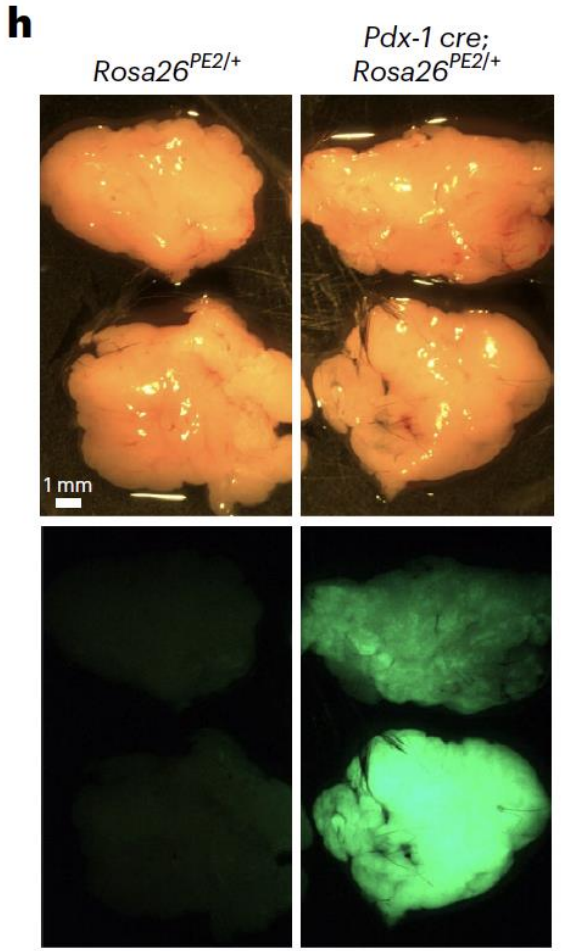
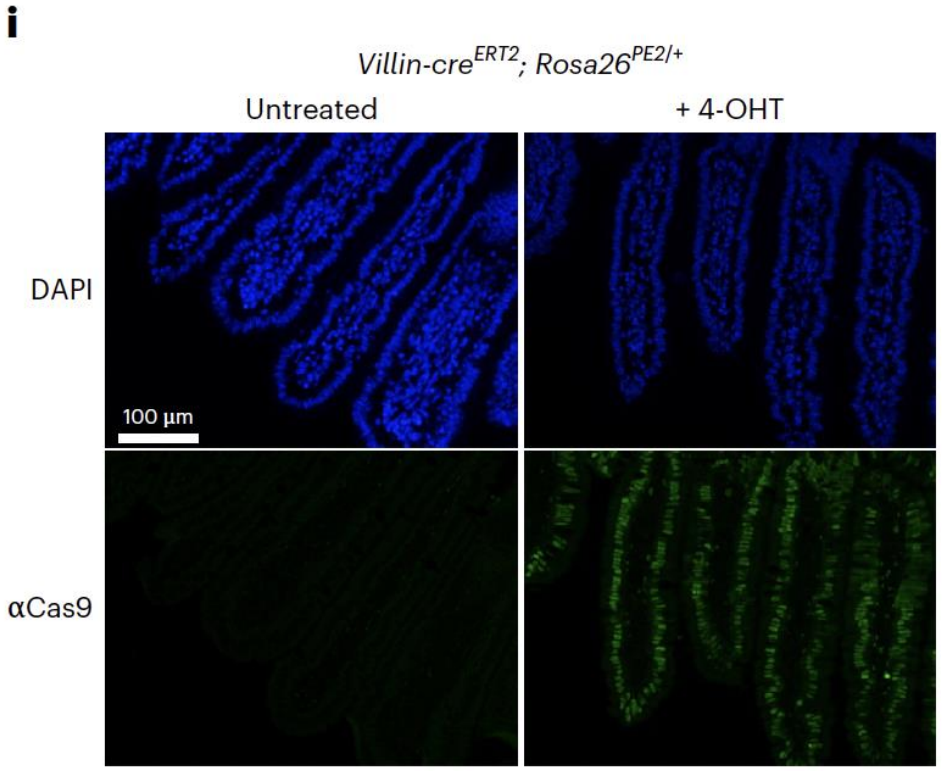
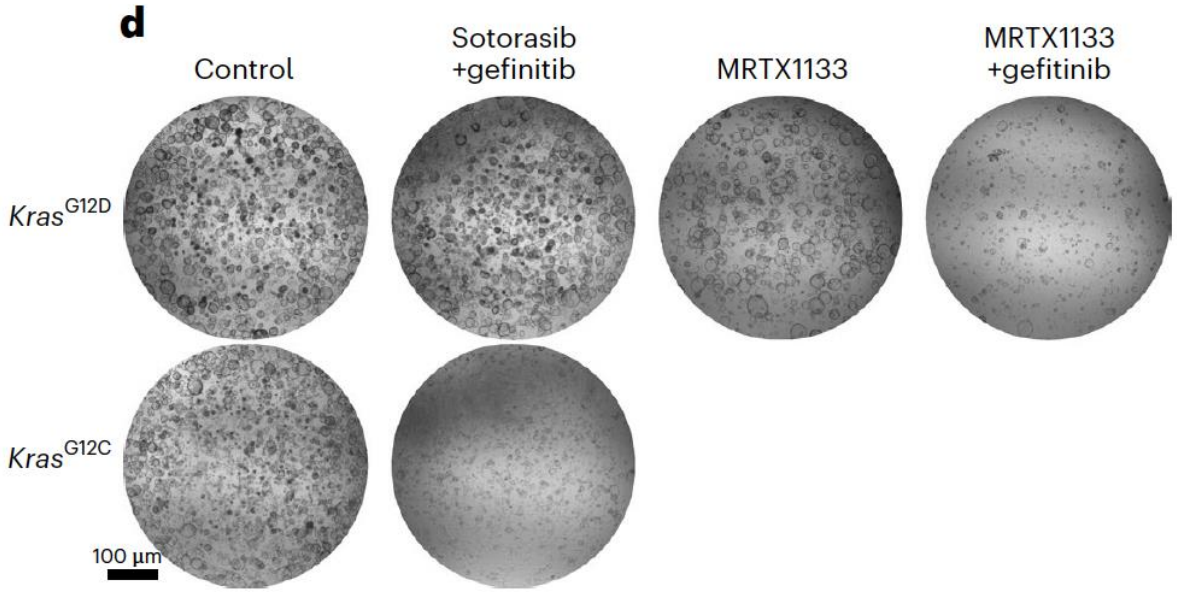


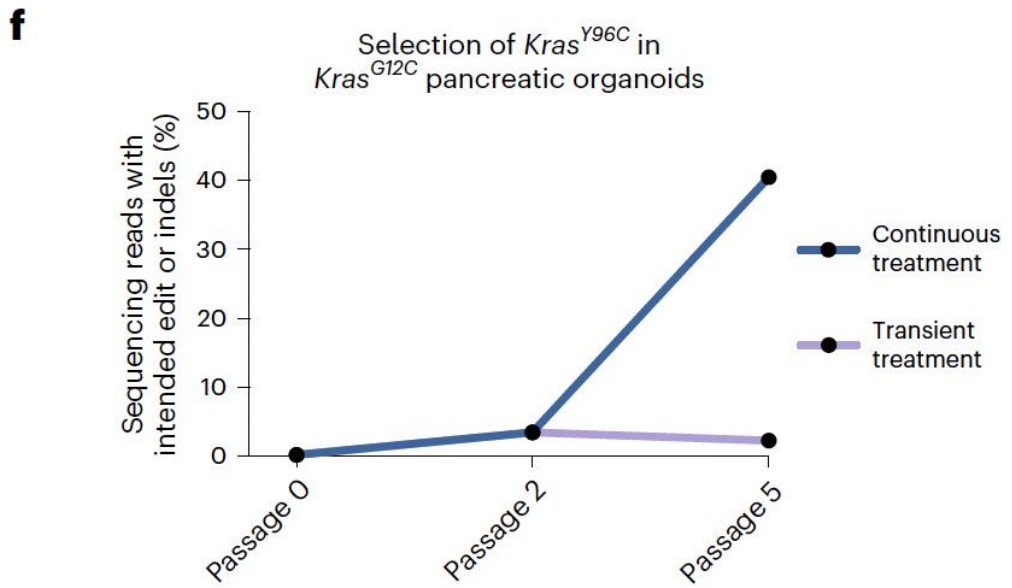

pancreas




colon

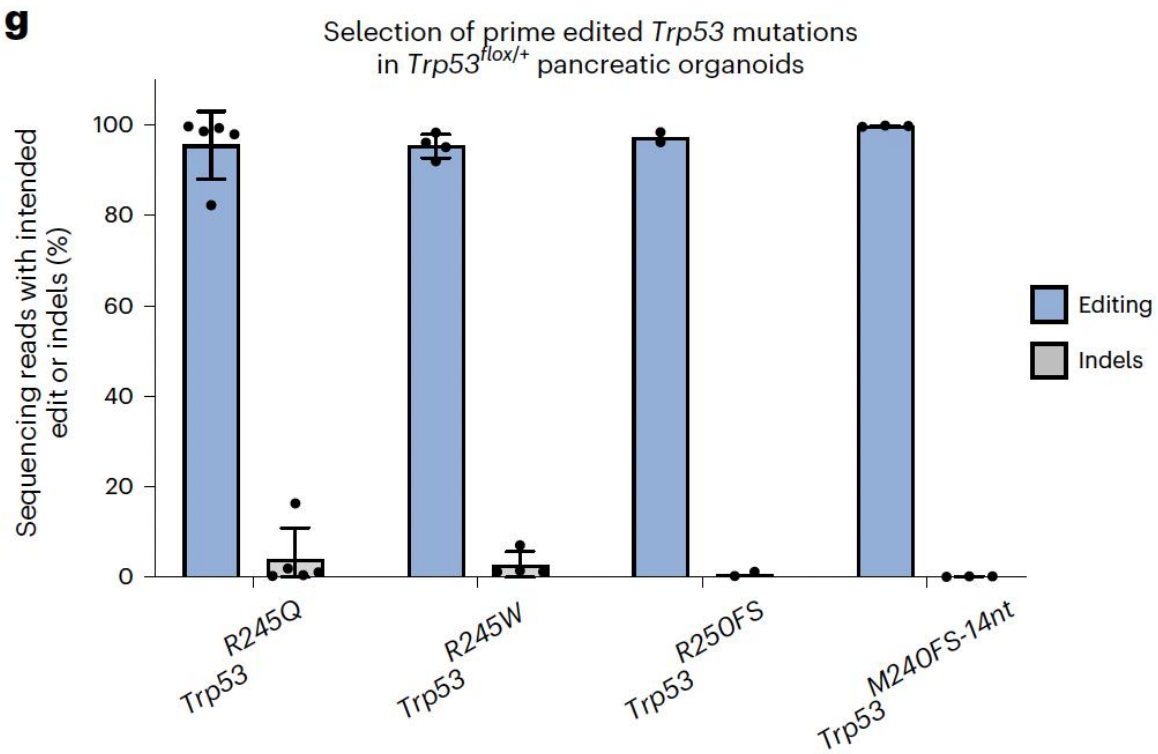
# Prime editing in organoids enables interrogation of selected mutations

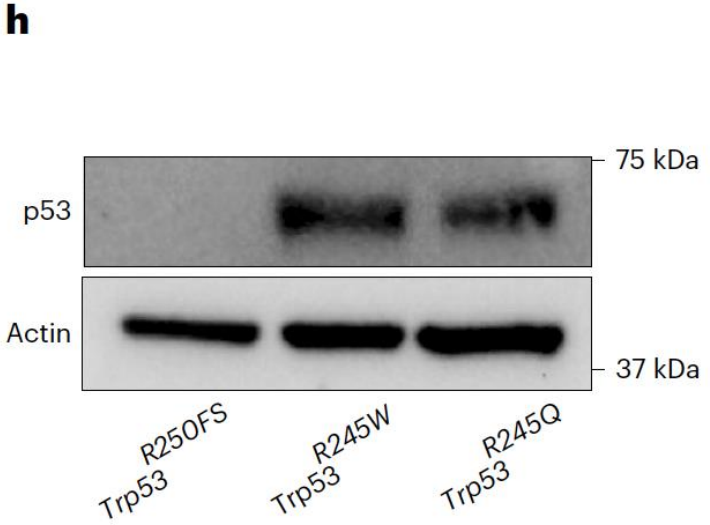


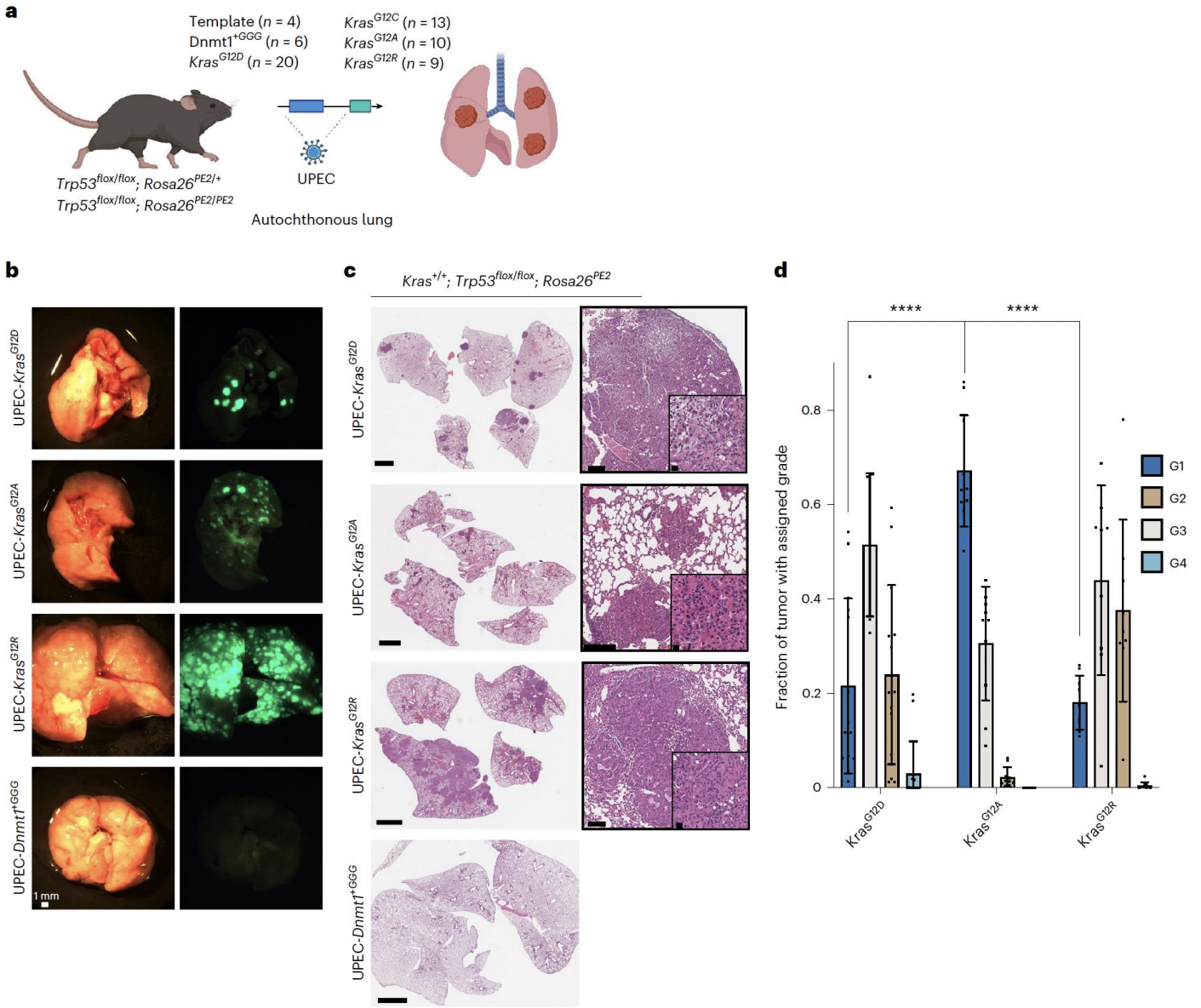

Sotorasib: KRAS$^{G12C}$ Inhibitor
MRTX1133: KRAS$^{G12D}$ Inhibitor
Gefitinib: EGFR Inhibitor

# Prime editing enables rapid generation of underexplored *Tp53* mutations



# Prime editing enables rapid generation of novel NSCLC models



# Persönliche Bewertung

- **Wichtiges neues experimentelles Tool, das rasche Interrogation bisher nicht ausreichend studierter genomischer Aberrationen erlaubt**
- **In Kombination mit tiefem genomischem Verständnis humaner Krebserkrankungen können mit diesem Tool präklinische *in vivo* Plattformen für Drug Discovery generiert werden**
- **Vor dem Hintergrund zunehmend restriktiver Wissenschaftspolitik im Hinblick auf *in vivo* Experimente bleibt der Nutzen für europäische Labore unklar**

# Agenda

*Technology Development:*

- A prime editor allele to facilitate precise *in vivo* modeling

***Cancer neuroscience:***

- **Glioblastoma networks display an actionable rhythmic activity**
- **Sympathetic catecholamine signaling drives T cell exhaustion**

*Drug development:*

- Turning transcriptional repressors into activators

Article

# Autonomous rhythmic activity in glioma networks drives brain tumour growth

https://doi.org/10.1038/s41586-022-05520-4

Received: 4 February 2021

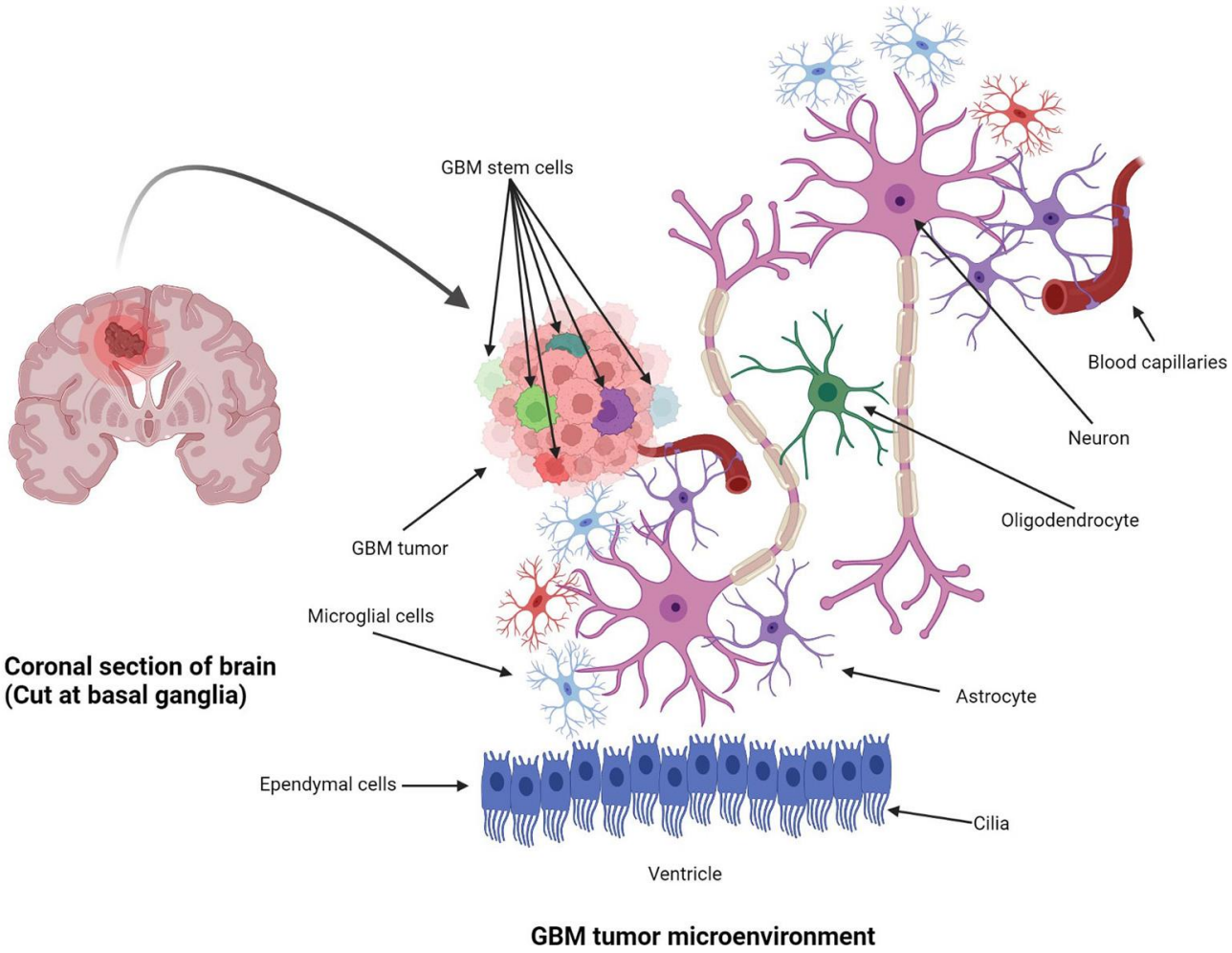
Accepted: 3 November 2022

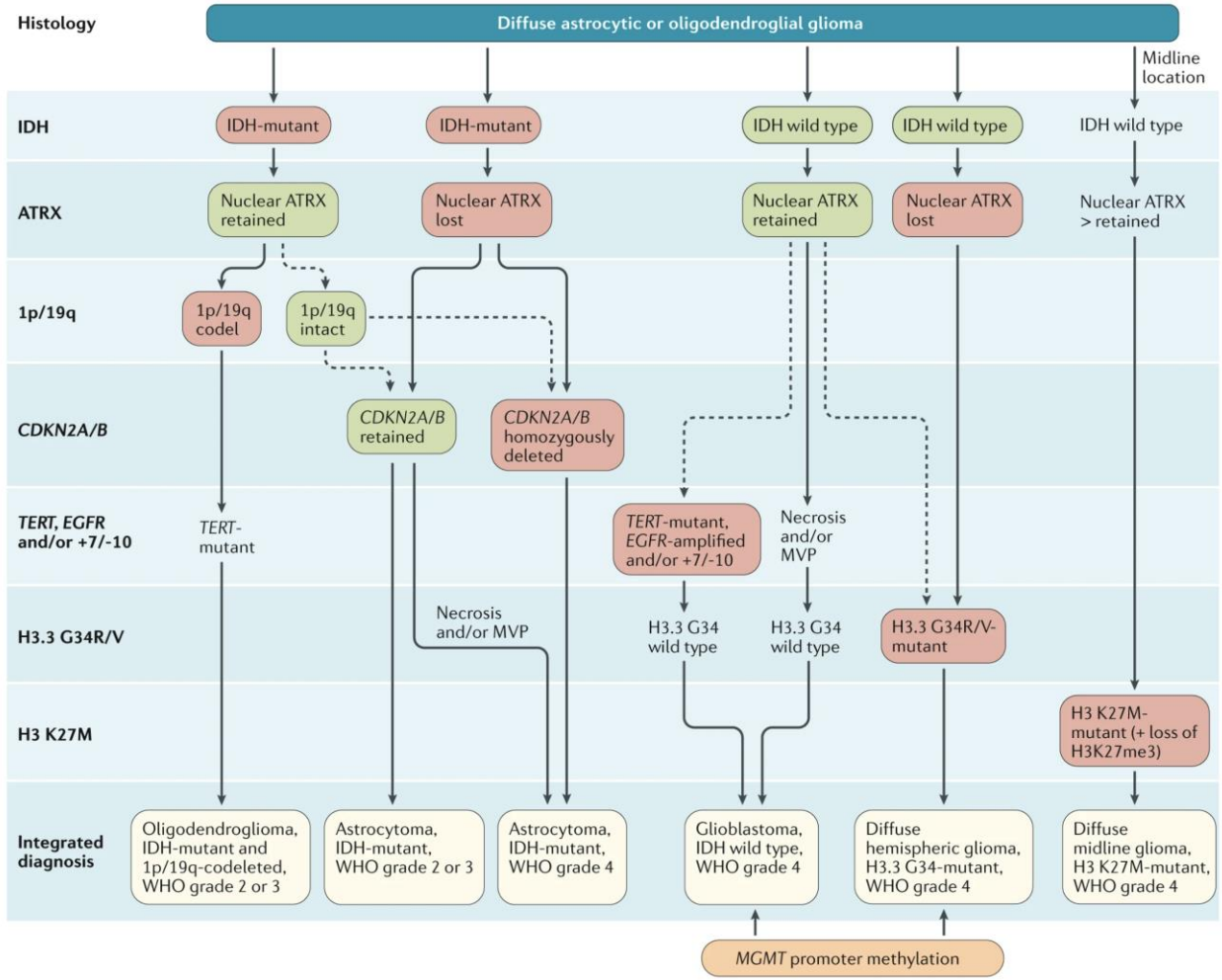
Published online: 14 December 2022

Check for updates

David Hausmann[1,2], Dirk C. Hoffmann[1,2,15], Varun Venkataramani[1,2,3,15], Erik Jung[1,2,15], Sandra Horschitz[4,5], Svenja K. Tetzlaff[3], Ammar Jabali[4,5], Ling Hai[1,2,6], Tobias Kessler[1,2], Daniel D. Azoŕin[1,2], Sophie Weil[1,2], Alexandros Kourtesakis[1,2], Philipp Sievers[7,8], Antje Habel[7,8], Michael O. Breckwoldt[9], Matthia A. Karreman[1,2], Miriam Ratliff[2,10], Julia M. Messmer[2,11], Yvonne Yang[1,2], Ekin Reyhan[1,2], Susann Wendler[1,2], Cathrin Löb[1,2], Chanté Mayer[1,2], Katherine Figarella[12], Matthias Osswald[1,2], Gergely Solecki[1,2,13], Felix Sahm[7,8], Olga Garaschuk[12], Thomas Kuner[3], Philipp Koch[4,5], Matthias Schlesner[6,14], Wolfgang Wick[1,2] & Frank Winkler[1,2]✉

# Glioblastoma

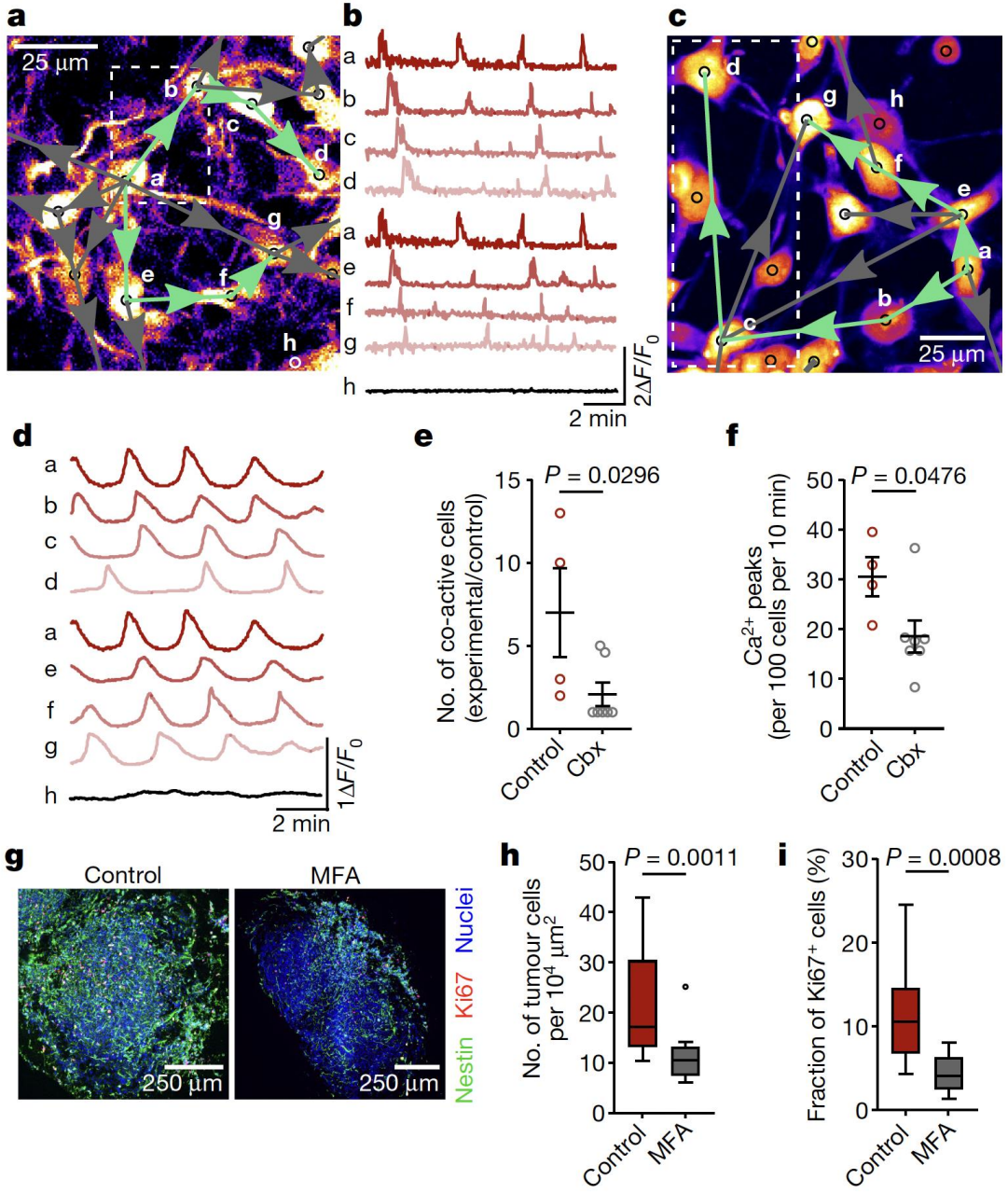



Teraiya *et al.*, Front Oncol, 2023

Weller *et al.*, Nature reviews Clinial Oncology, 2020

# $Ca^{++}$ communication in GBM networks



# **Patient-derived Human Glioblastoma Cells (S24 Line)** Xenograft in Mouse Brain

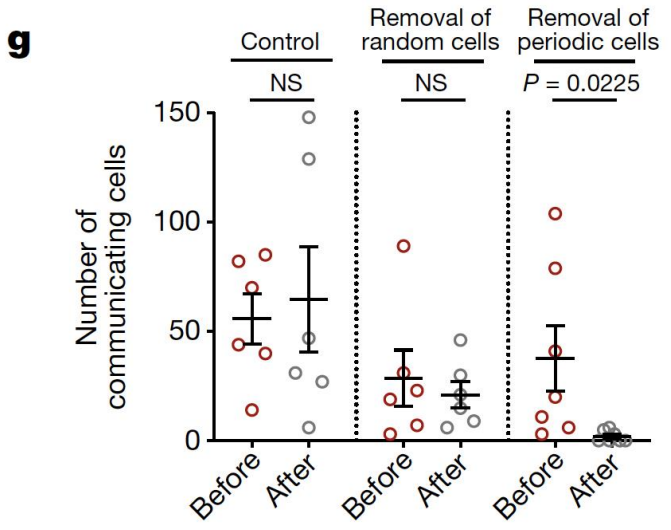
Calcium imaging with multiphoton microscopy in awake mouse demonstrating the autonomous calcium activity of periodic cells.

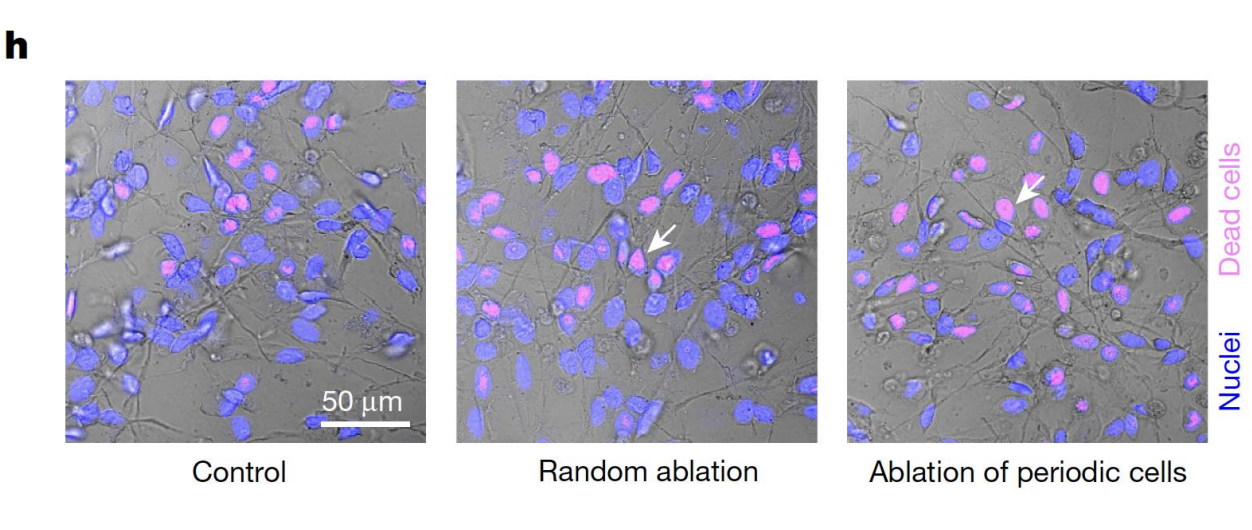
# **Patient-derived Human Glioblastoma Cells (S24 Line)** *In vitro* Monolayer Assay

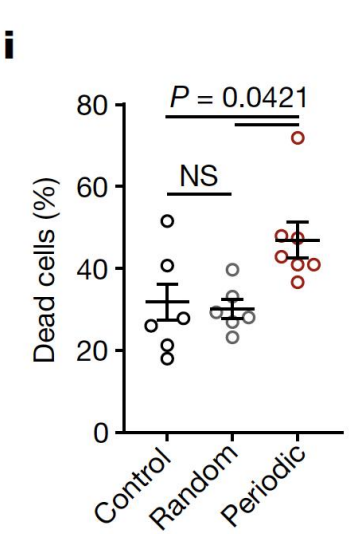
Calcium imaging with confocal microscopy demonstrating the autonomous calcium activity of periodic cells.

*Gap junction inhibition with meclofenamic acid (MFA) blocks the activation of connected cells but does not affect the periodic cell itself.*

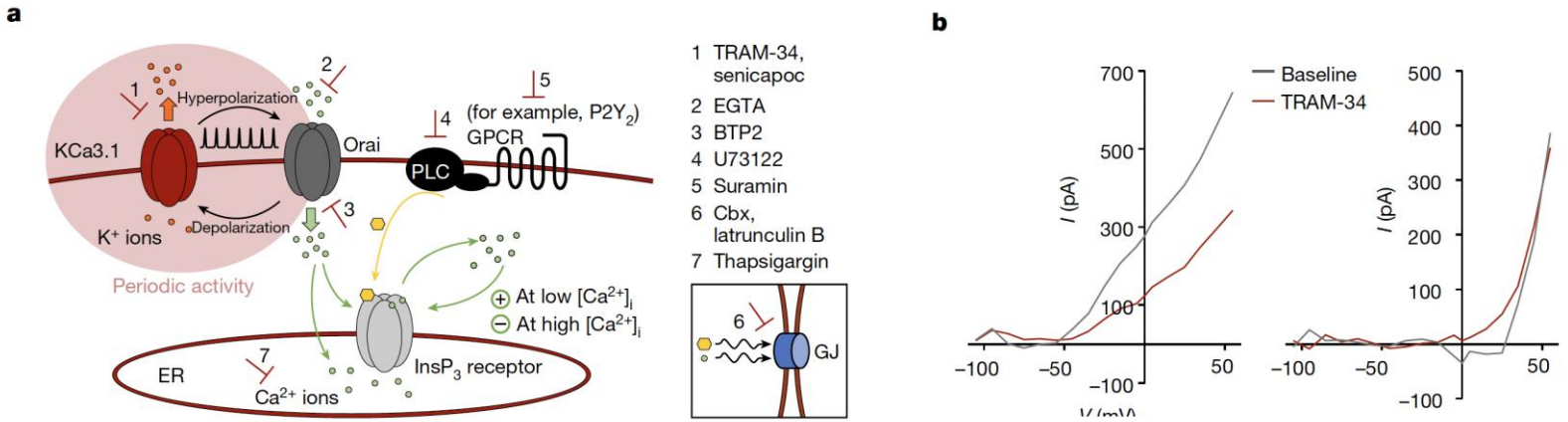
# Removal of periodic cells shrinks network size and leads to cell death



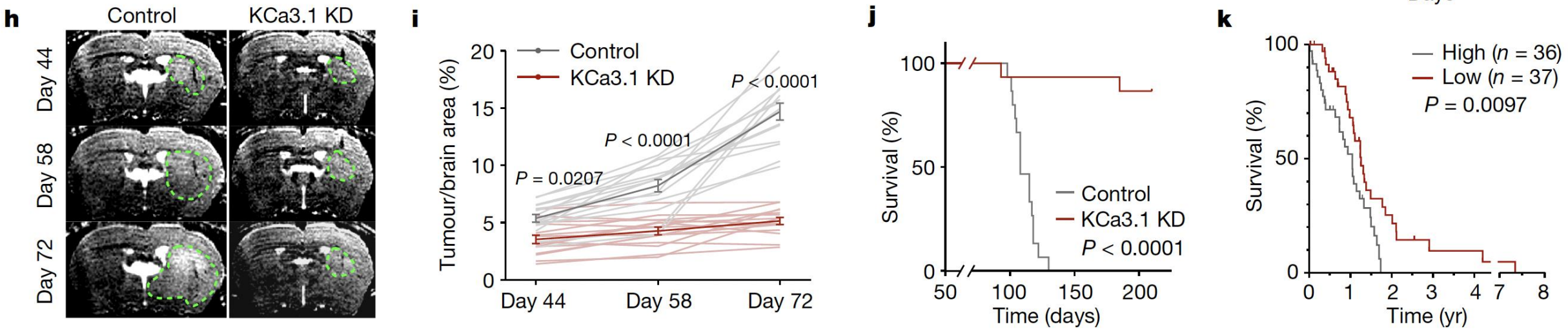



# KCa3.1 ($Ca^{++}$-activated K channel) mediates $Ca^{++}$ oscillations

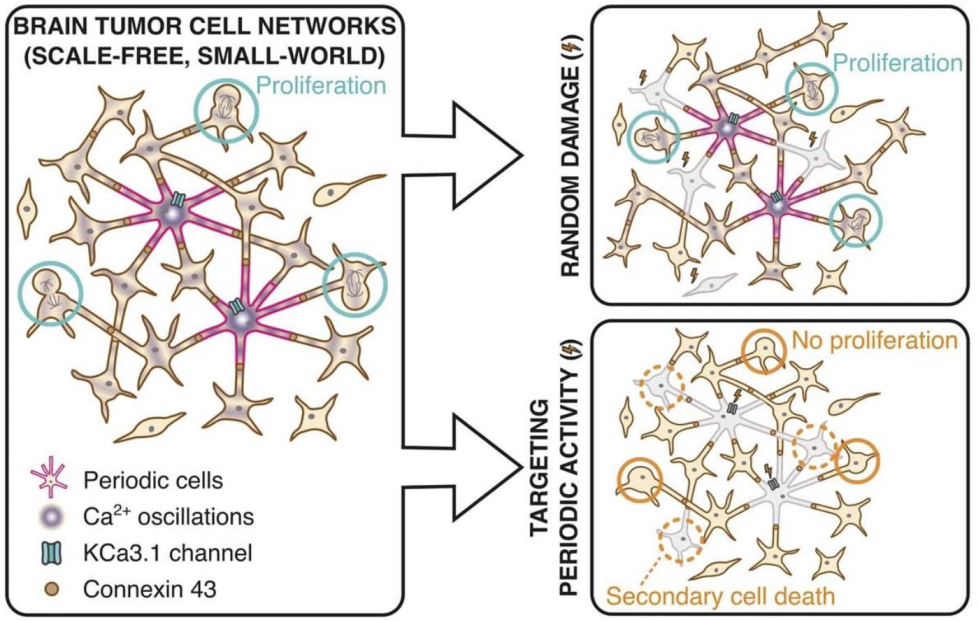


# KCa3.1 inhibition represses GBM growth *in vivo*



# Persönliche Bewertung

- **Wichtige Extension der vorherigen Beobachtung der Gruppe zu GBM Netzwerken**
- **Senicapoc Daten sind hochinteresant und bieten hohes translationales Potential**
- **Es sind keine Daten zu Kombinationen mit TMZ und/oder RT gezeigt worden, dies wäre als *in vivo* POC sicher wichtig vor klinischer Testung**



Article

# The $\beta_1$-adrenergic receptor links sympathetic nerves to T cell exhaustion

https://doi.org/10.1038/s41586-023-06568-6

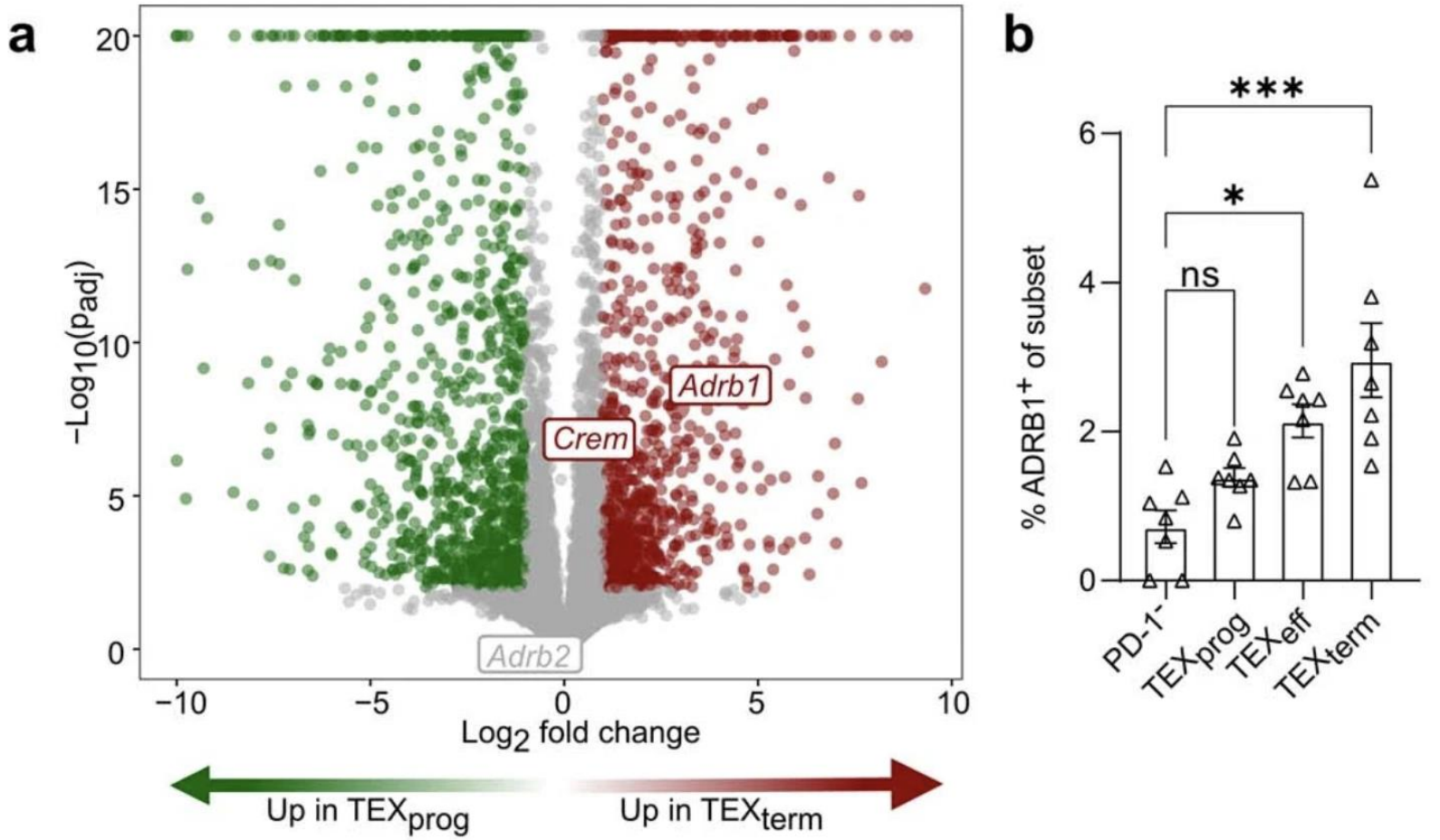
Received: 26 September 2022

Accepted: 24 August 2023

Published online: 20 September 2023

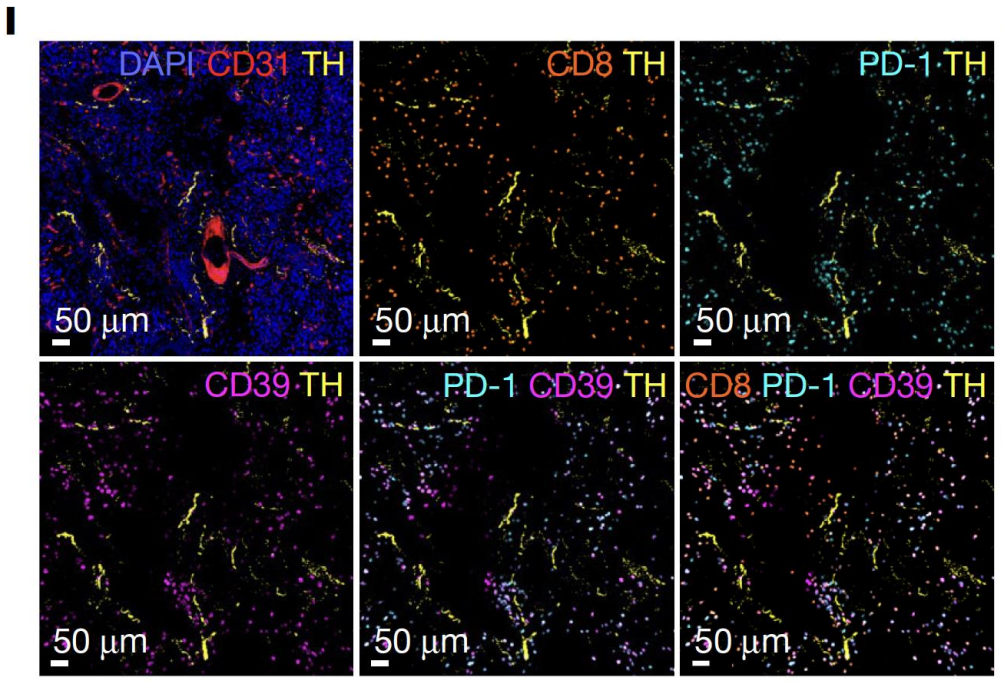
Anna-Maria Globig[1], Steven Zhao[1], Jessica Roginsky[1], Vivien I. Maltez[2], Juan Guiza[3], Natalia Avina-Ochoa[1], Maximilian Heeg[4], Filipe Araujo Hoffmann[1], Omkar Chaudhary[5], Jiawei Wang[6], Gokhan Senturk[7], Dan Chen[1], Carolyn O'Connor[1,8], Samuel Pfaff[7], Ronald N. Germain[2], Kurt A. Schalper[3], Brinda Emu[5] & Susan M. Kaech[1]✉

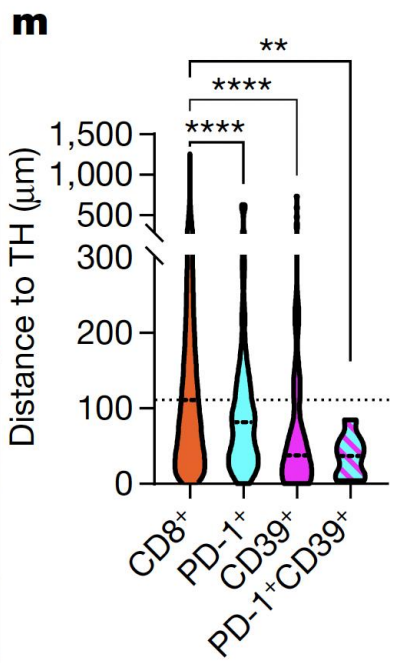
# The β1 adrenergic receptor gene *Adrb1* is upregulated in exhausted CD8 cells



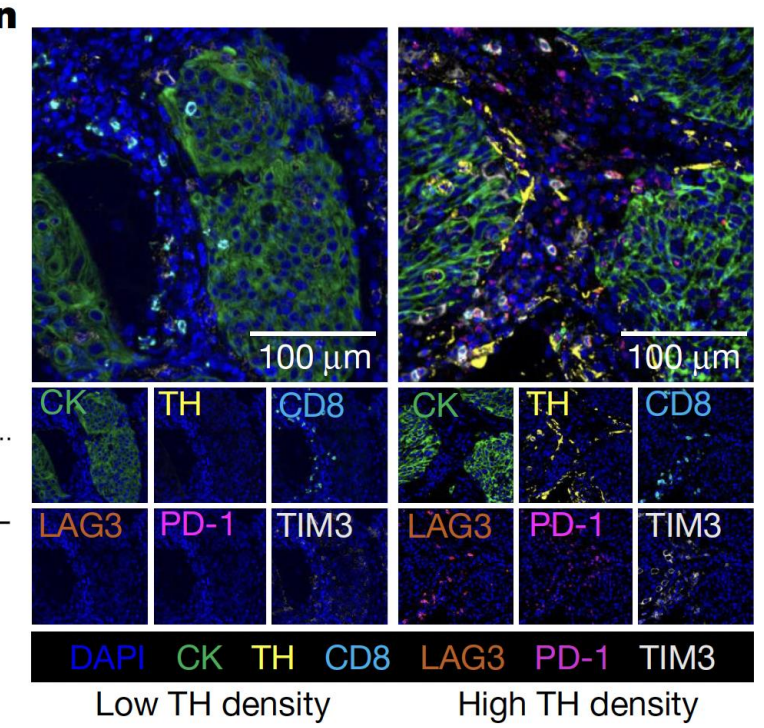

LCMV chronic viral infection model

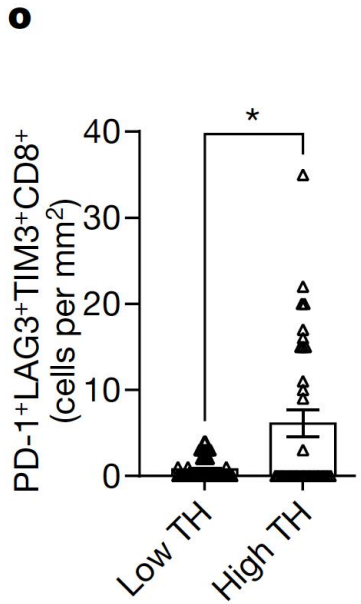
# Exhausted CD8 cells display close proximity to Tyrosine Hydroxylase (TH)-positive adrenergic nerve fibres in a murine PDAC model



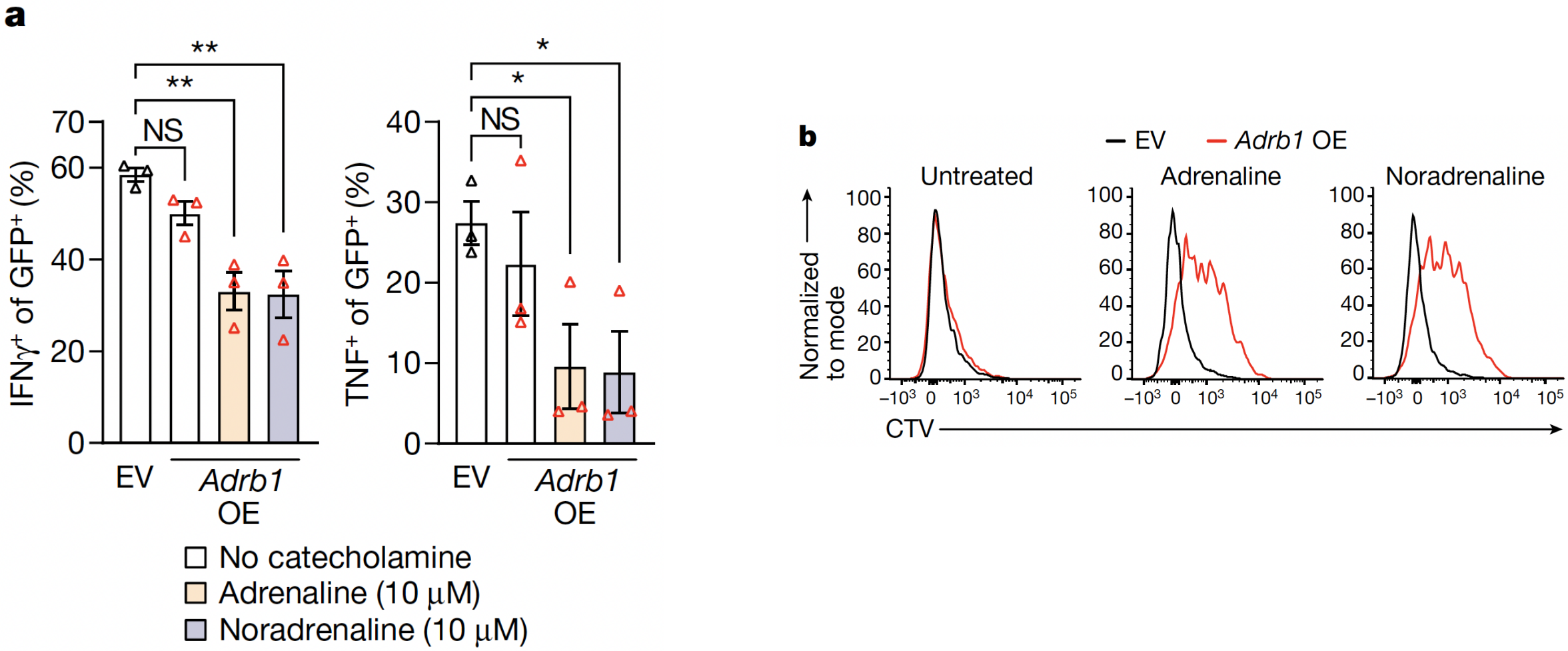




# TILs in TH$^{high}$ human NSCLC display an exhausted immune-phenotype

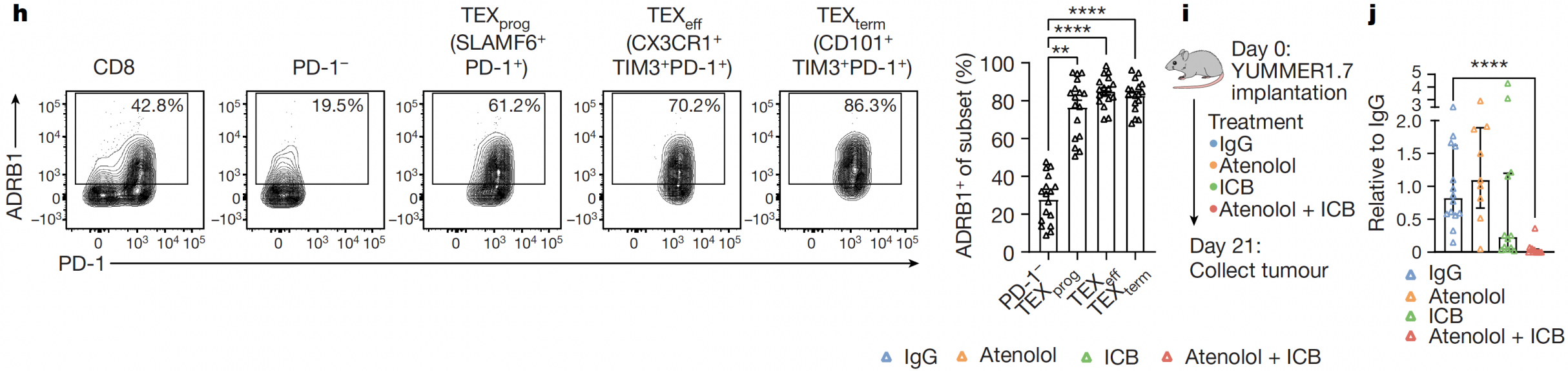


# *Adrb1* overexpression in CD8 cells impairs IFNγ production and proliferation



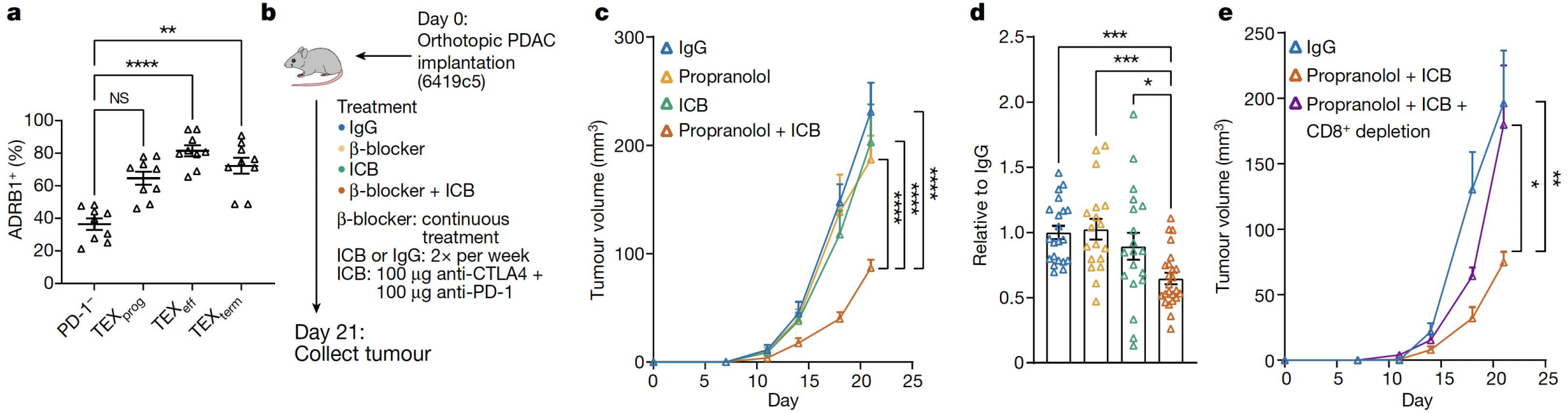
# In the YUMMER1.7 melanoma model, CD8 exhaustion correlates with *Adrb1* expression and combined β blockade and ICB display synergistic activity




CD8 cells isolated from YUMMER1.7 model

ICB: combined anti-PD1, anti-CTLA4

# In a orthotopic PDAC model, combined β blockade (β1 and 2) and ICB (aPD1/aCTLA4) display synergistic activity



# Persönliche Bewertung

- Sehr interessantes neues Konzept zum Neuro-Immun Cross-Talk
- Potentiell in einem translationalen Ansatz actionable
- Eine möglicherweise distinkte Rolle von β1, 2 und 3 Signaling ist nicht abschliessend geklärt
- Rolle von β1, 2 und 3 Signaling in anderen (Immun-)Subsets ist nicht vollständig geklärt

# Agenda

*Technology Development:*

- A prime editor allele to facilitate precise *in vivo* modeling

*Cancer neuroscience:*

- Glioblastoma networks display an actionable rhythmic activity
- Sympathetic catecholamine signaling drives T cell exhaustion

***Drug development:***

- **Turning transcriptional repressors into activators**

Article

# Rewiring cancer drivers to activate apoptosis

https://doi.org/10.1038/s41586-023-06348-2

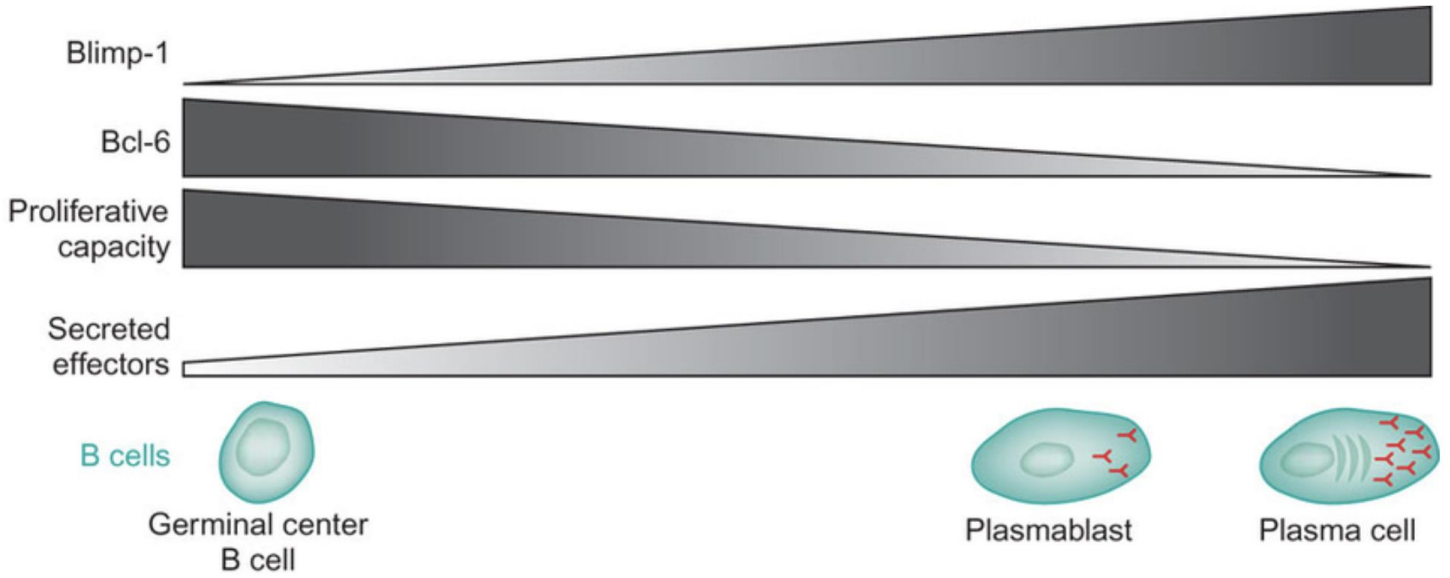
Received: 15 August 2022

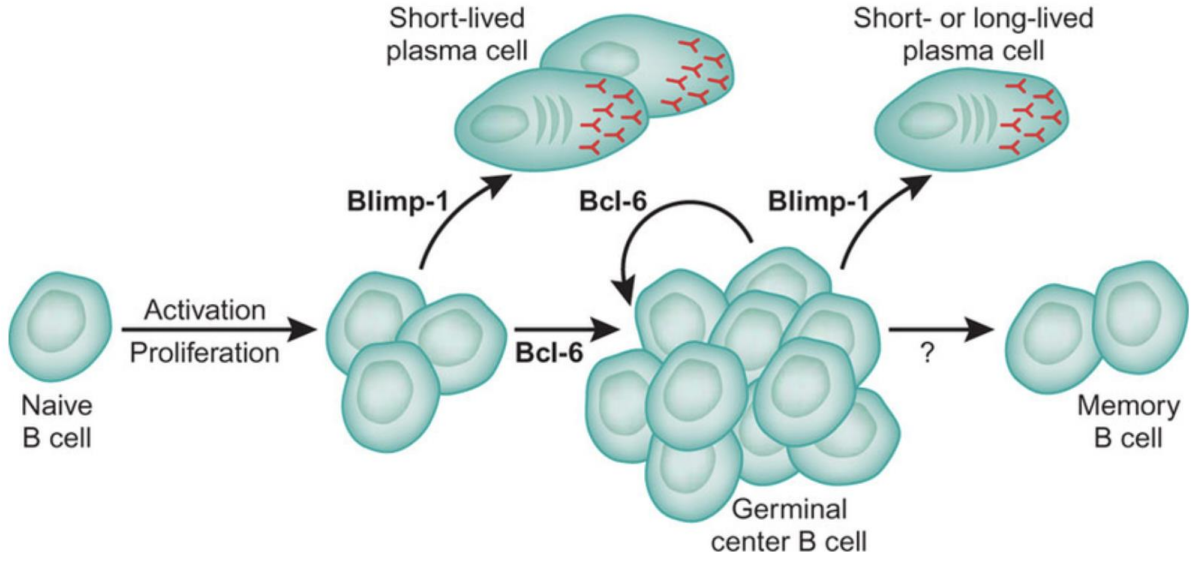
Accepted: 20 June 2023

Published online: 26 July 2023

Sai Gourisankar[1,2,6], Andrey Krokhotin[1,6], Wenzhi Ji[3,6], Xiaofan Liu[3], Chiung-Ying Chang[1], Samuel H. Kim[1], Zhengnian Li[3], Wendy Wenderski[1,4], Juste M. Simanauskaite[1], Haopeng Yang[5], Hannes Vogel[1], Tinghu Zhang[3], Michael R. Green[5], Nathanael S. Gray[3]✉ & Gerald R. Crabtree[1,4]✉

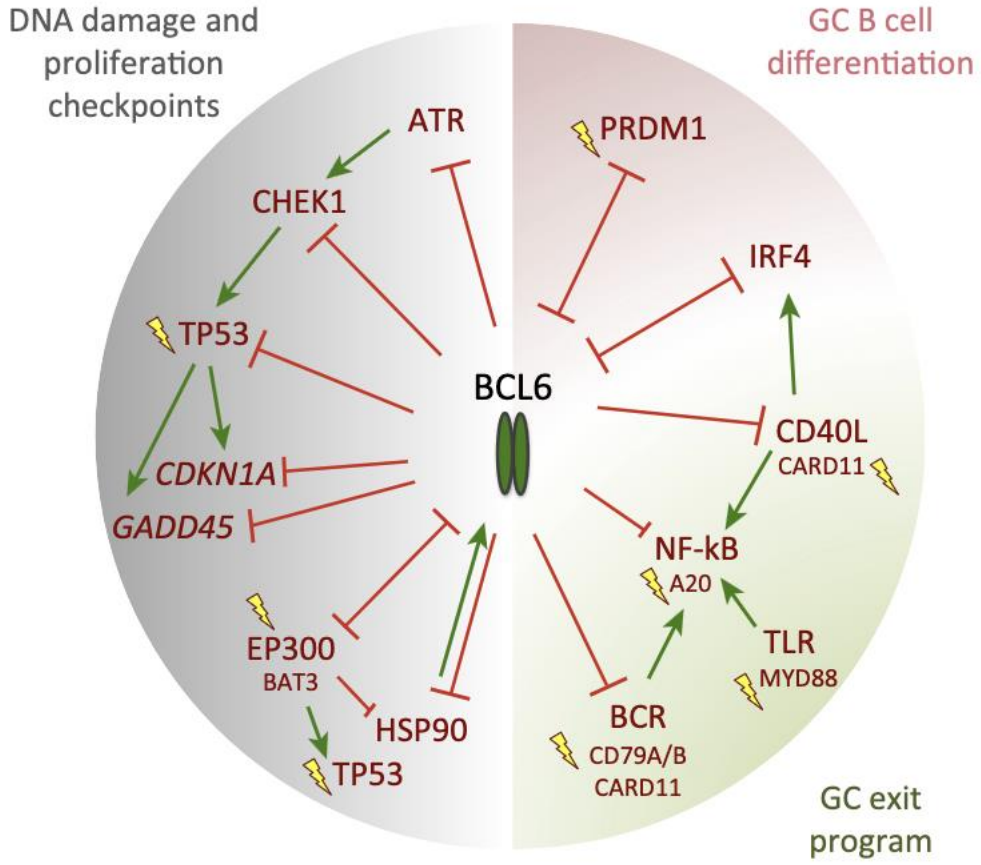
# BCL6 – Master Regulator of the GC Reaction

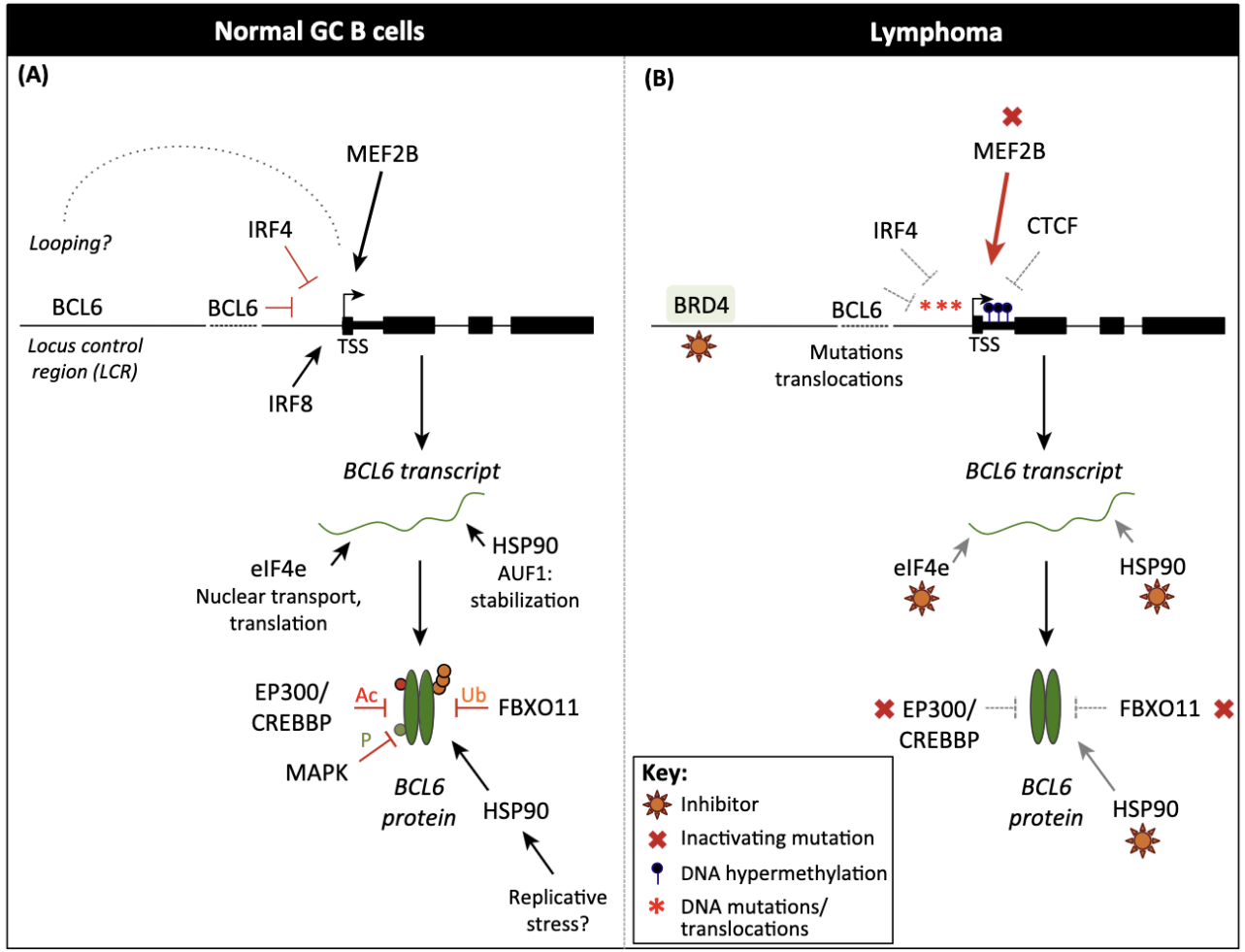


Klinik für Hämatologie und Stammzelltransplantation
Universitätsmedizin Essen
Westdeutsches Tumorzentrum

# BCL6 – Master Regulator of the GC Reaction

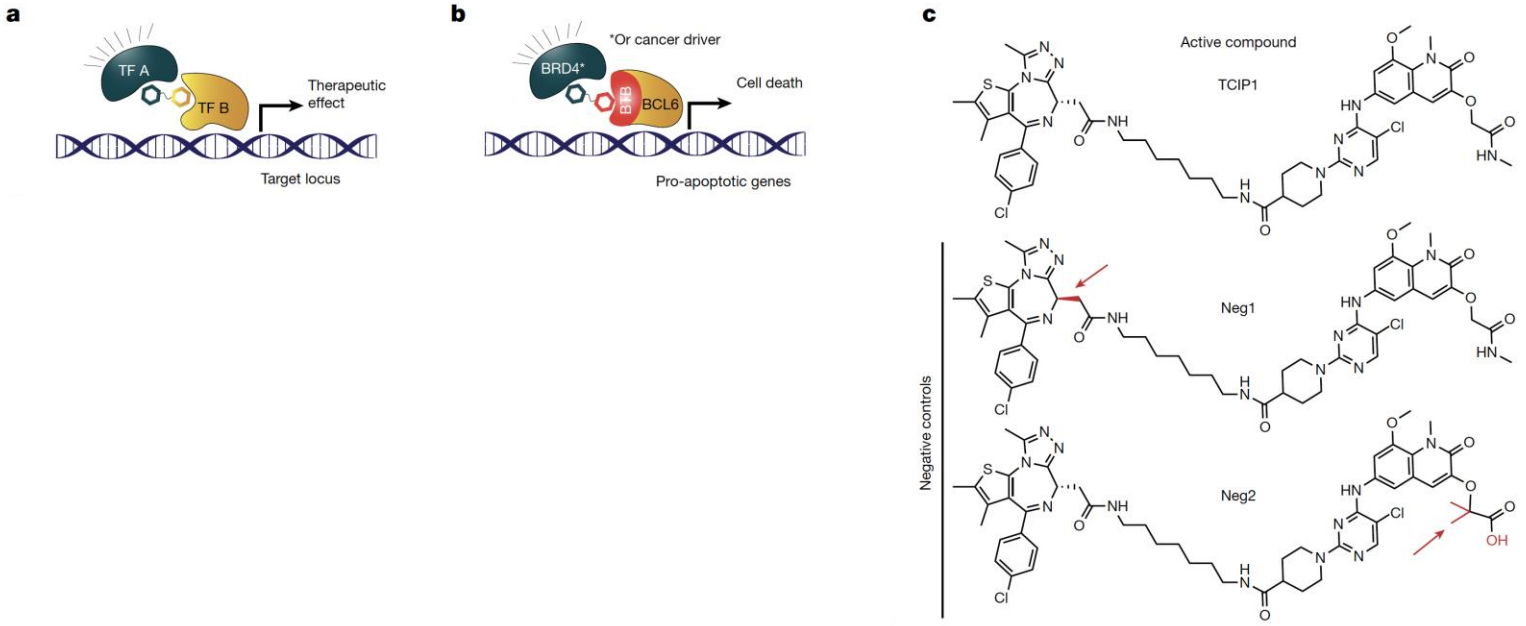



Hatzi and Melnick, TRENDS in Molecular Medicine, 2014

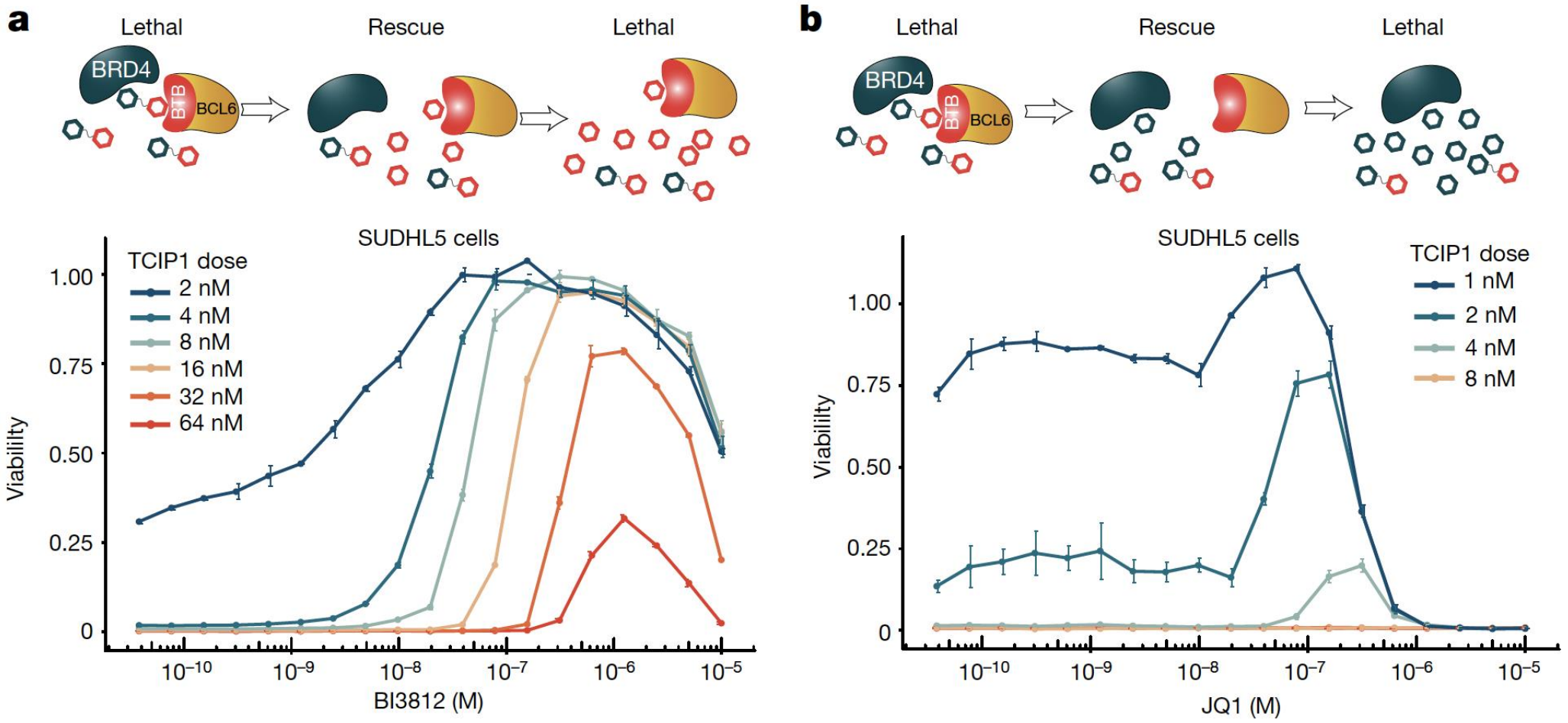
Klinik für Hämatologie und Stammzelltransplantation
Universitätsmedizin Essen
Westdeutsches Tumorzentrum

# Transcriptional chemical inducers of proximity (TCIPs)

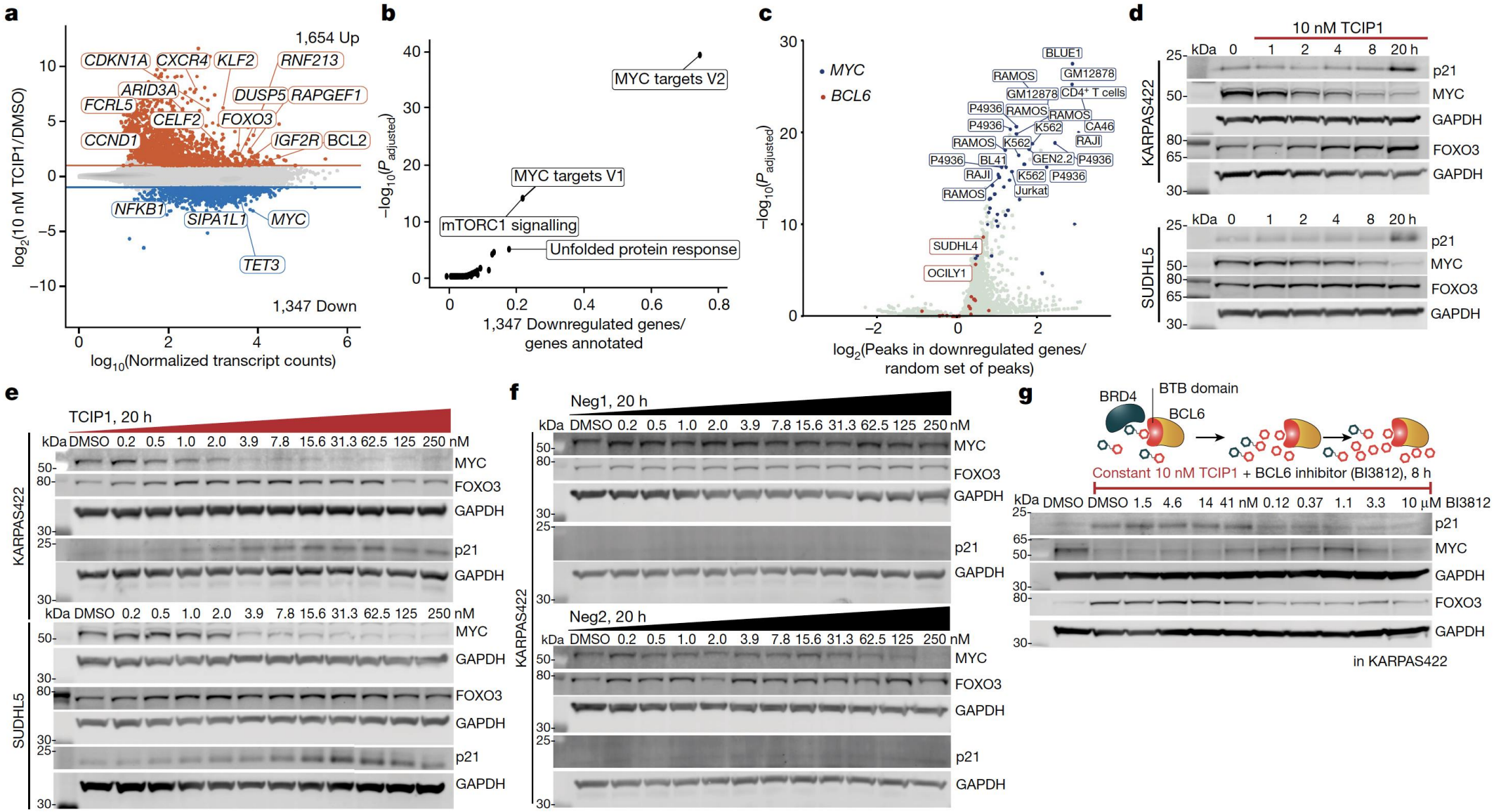



**TCIPs sind ein neues Wirkprinzip**

# TCIP1 induces a ternary complex

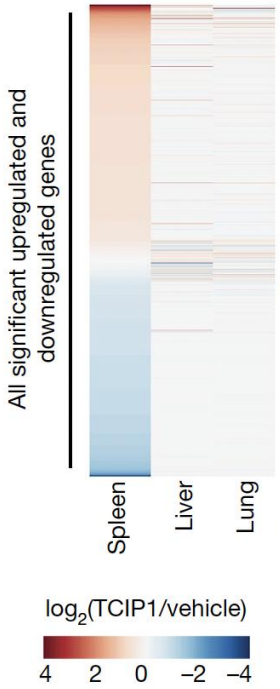


# TCIP1 represses MYC Target genes and induces pro-apoptotic transcripts



# TCIP1 displays activity *in vivo* at manageable toxicity

**a**

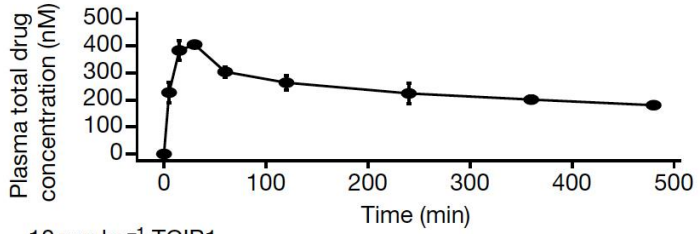



**b**

| | Concentration (μM ± s.d.) | Number of genes upregulated | Number of genes downregulated |
|---|---|---|---|
| Spleen | 48 ± 26 | 2,785 | 2,471 |
| Liver | 36 ± 18 | 301 | 204 |
| Lung | 12 ± 0.94 | 255 | 167 |

**c**

| | $t_{1/2}$ (h) | $t_{max}$ (h) | $C_{max}$ (μM) | $AUC_{0-last}$ (μM per h) |
|---|---|---|---|---|
| 10 mg kg$^{-1}$ i.p. | 9.7 ± 0.16 | 0.42 ± 0.14 | 0.41 ± 0.01 | 1.92 ± 0.07 |

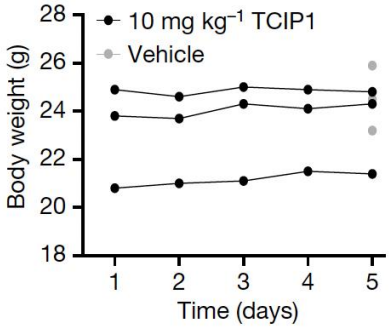



**d**

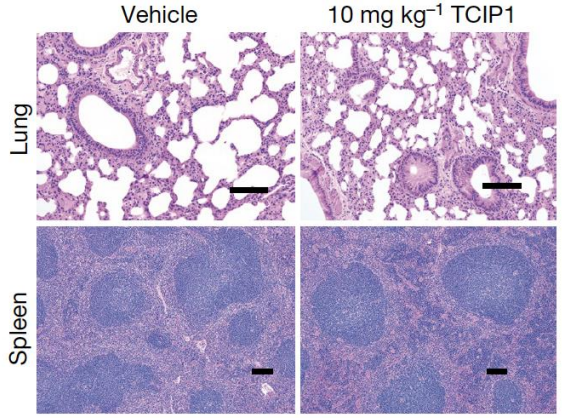
Fold change (10 mg kg$^{-1}$ or 10 nM TCIP1/vehicle)

| | | in KARPAS422 DLBCL cells | | | |
|---|---|---|---|---|---|
| Gene | Spleen | 1 h | 2 h | 4 h | 20 h |
| *Foxo3* | 1.7 | 1.0 | 2.6 | 3.0 | 4.3 |
| *Cdkn1a* | 2.4 | 1.0 | 1.2 | 2.2 | 69 |
| *Hexim1* | 1.6 | 1.9 | 3.4 | 5.8 | 4.6 |
| *Txnip* | 1.8 | 1.3 | 1.4 | 1.9 | 7.4 |

**e**




**f**



# Persönliche Bewertung

- **Sehr interessantes neues therapeutisches Konzept**
- **Basiert auf tiefem biologischen Verständnis der Lymphomagenese**

- **Generalisierbarkeit des Konzepts bleibt etwas unklar**
- **Keine Daten zu *in vivo* anti-Lymphom-Aktivität gezeigt**

# Persönliches Fazit:

**Fantastische Zeit, um in der Krebsforschung zu arbeiten!**

# Herzlichen Dank für Ihre Aufmerksamkeit!