Ulf Dietrich Kahlert, PhD

Tissue-specific progenitor cells derived from gene-engineered human induced pluripotent stem cells for early-stage drug development

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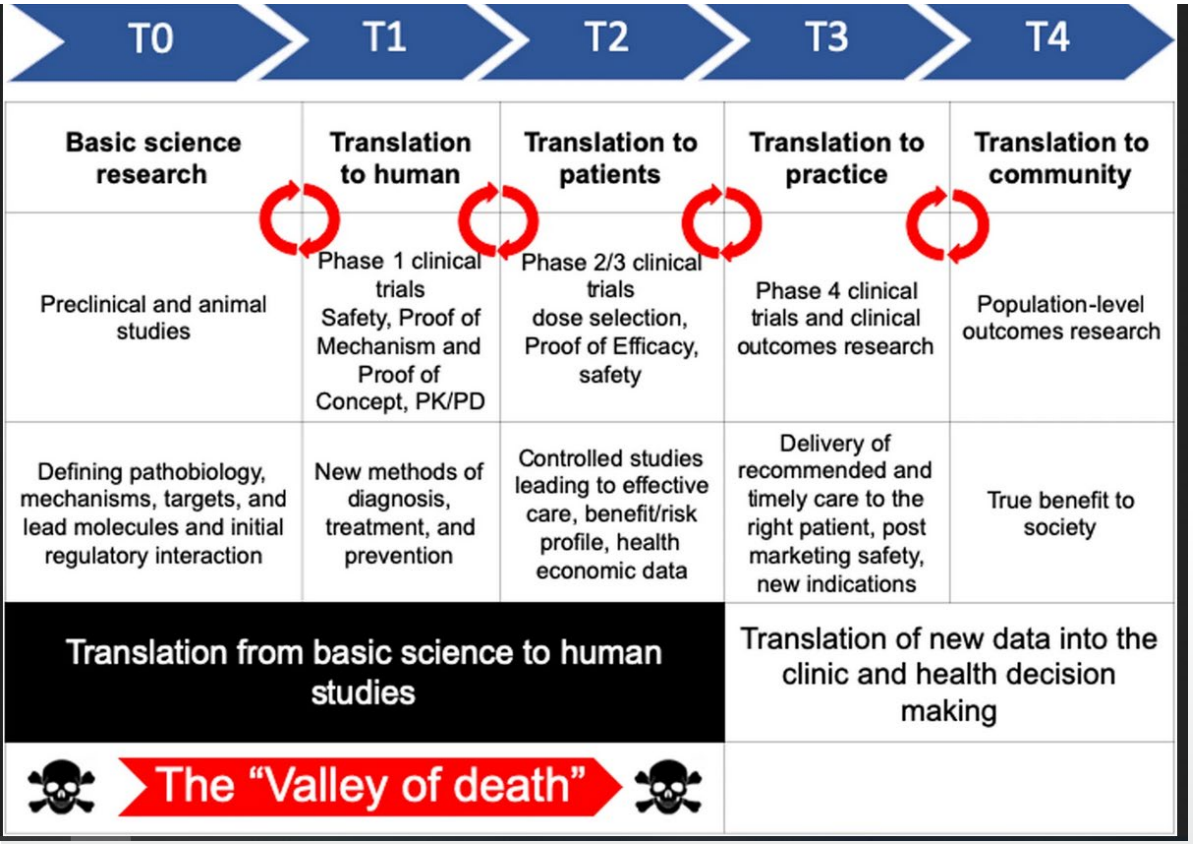
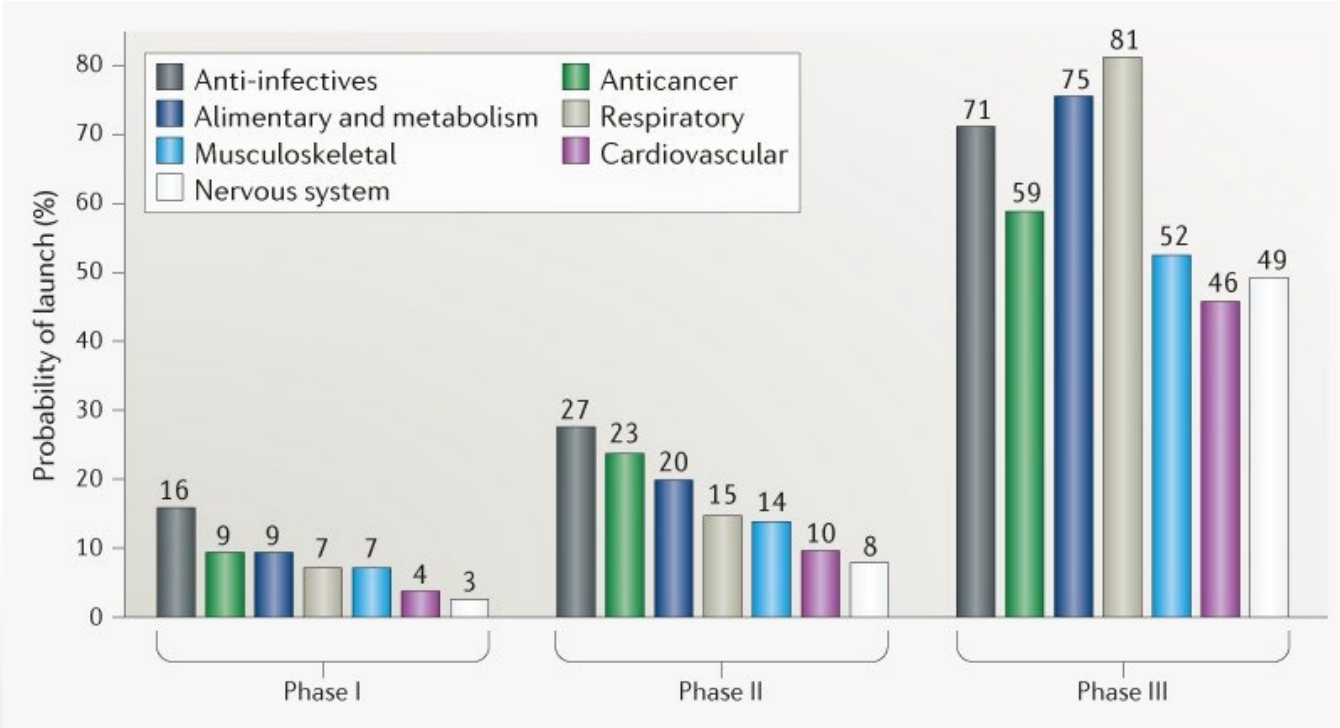
Lost in Translation

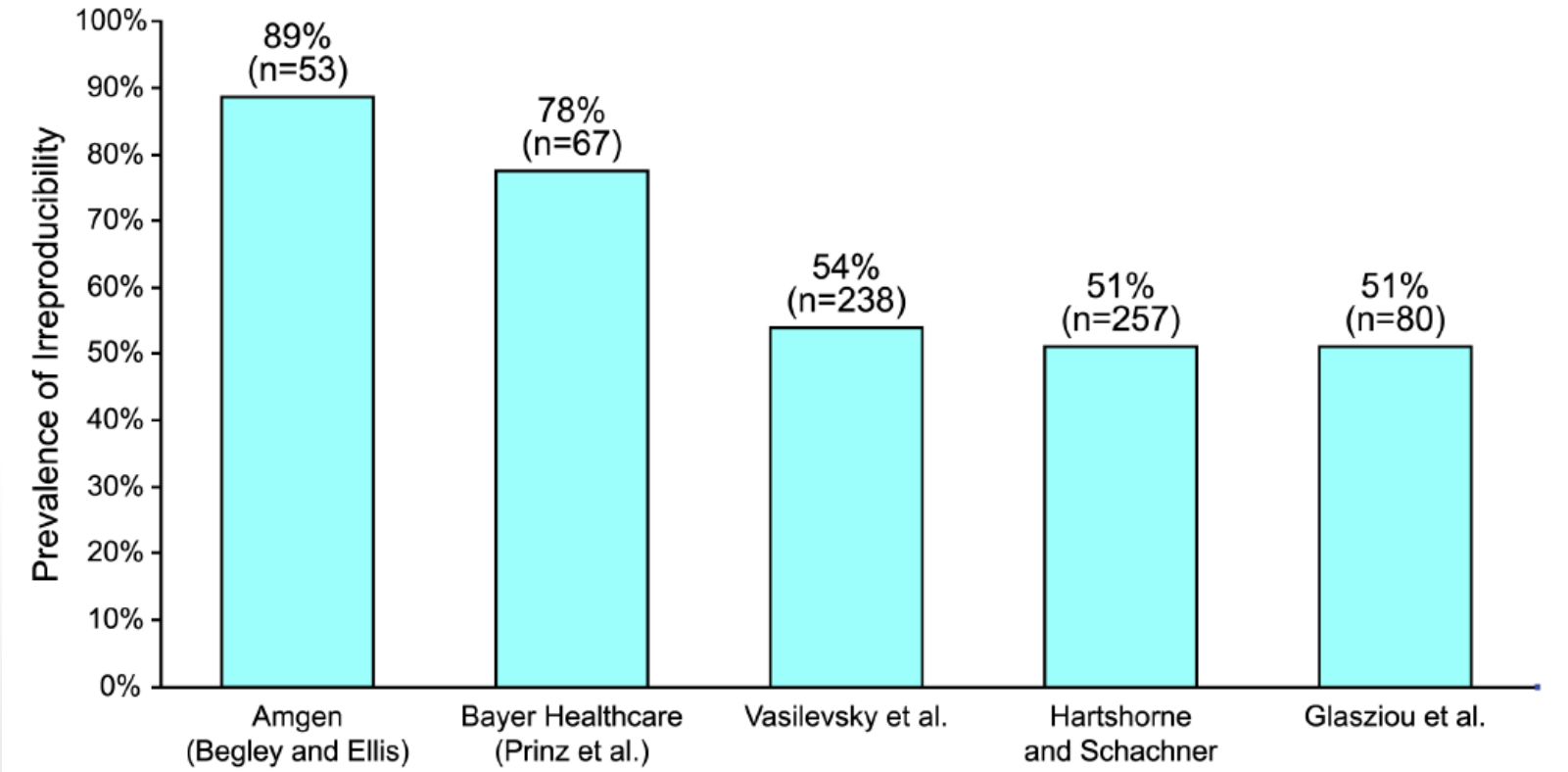




Therapeutic group		Phase 1 to Phase 2			Phase 2 to Phase 3			Phase 3 to approval			Overall	
		Total phase transitions	$POS_{1,2}$, %	(SE, %)	Total phase transitions	$POS_{2,3}$, %	SE, %	Total phase transitions	$POS_{3,APP}$, %	(SE, %)	POS, %	(SE, %)
Oncology	No biomarker	9349	28.0	(0.5)	4773	17.4	(0.5)	1159	33.6	(1.4)	1.6	(0.2)
	With biomarker	1136	43.5	(1.5)	742	38.8	(1.8)	77	63.6	(5.5)	10.7	(1.9)
	All	10485	29.7	(0.4)	5515	20.3	(0.5)	1236	35.5	(1.4)	2.1	(0.2)

Seyhan et al. **TMC**.
Dowden et al, **Nat. Rev. Drug Disc.**

The economic and ethical burden of cancer research

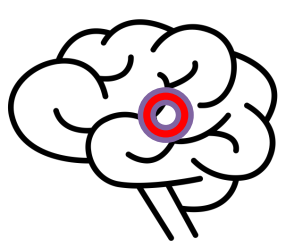


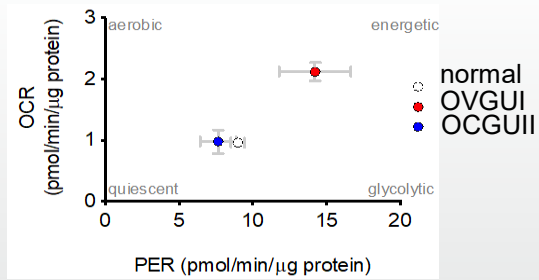
"Inconsistency in study material is main contributor to irreproducibility." (46%)

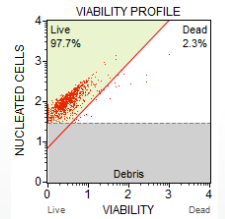
Freedmann et al., **Plos Biol**.

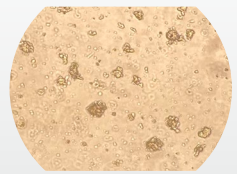
The economic and ethical burden of cancer research

Patient-derived cell line as fundamental study tool in early stage projects









Patient data
(therapy, follow up. etc.)

Enzymatic/mechano tissue separation, erythrocyte wash out

Optimized culture assays

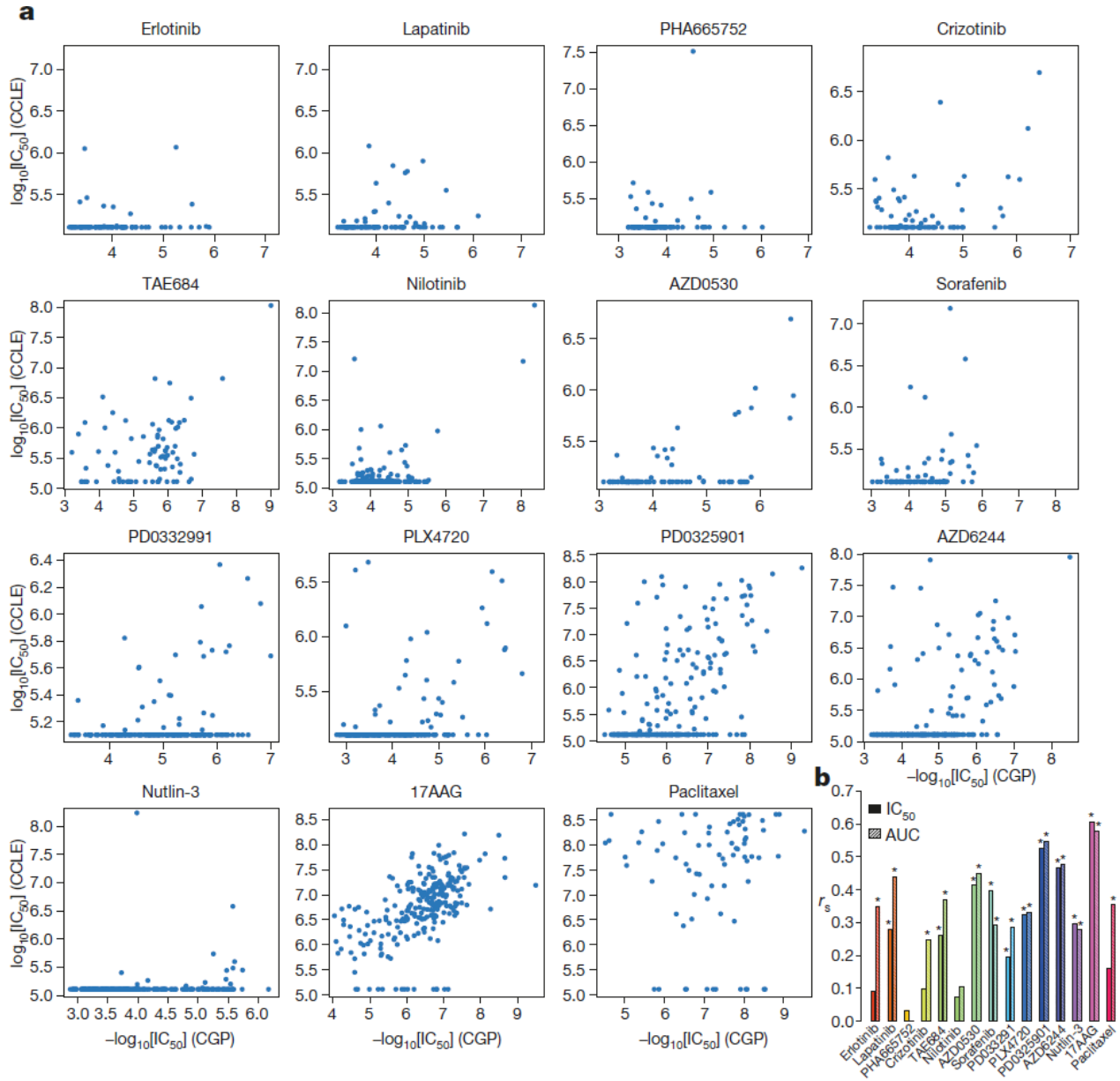
Primary models

The economic and ethical burden of cancer research

Inconsistency in large pharmacogenomic studies

Benjamin Haibe-Kains[1,2], Nehme El-Hachem[1], Nicolai Juul Birkbak[3], Andrew C. Jin[4], Andrew H. Beck[4]*, Hugo J. W. L. Aerts[5,6,7]* & John Quackenbush[5,8]*

CCLE (Broad, USA) vs CGP (Wellcome, UK)



Haibe-Kains et al., **Nature**

The economic and ethical burden of cancer research

Genetic and transcriptional evolution alters cancer cell line drug response

Uri Ben-David[1], Benjamin Siranosian[1], Gavin Ha[1,2], Helen Tang[1], Yaara Oren[1,3], Kunihiko Hinohara[1,2], Craig A. Strathdee[1], Joshua Dempster[1], Nicholas J. Lyons[1], Robert Burns[2], Anwesha Nag[2], Guillaume Kugener[1], Beth Cimini[1], Peter Tsvetkov[1], Yosef E. Maruvka[1], Ryan O'Rourke[1,2], Anthony Garrity[1], Andrew A. Tubelli[1], Pratiti Bandopadhayay[1,2,3], Aviad Tsherniak[1], Francisca Vazquez[1], Bang Wong[1], Chet Birger[1], Mahmoud Ghandi[1], Aaron R. Thorner[2], Joshua A. Bittker[1], Matthew Meyerson[1,2,3], Gad Getz[1,4], Rameen Beroukhim[1,2,3,5,7]* & Todd R. Golub[1,2,3,6,7]*

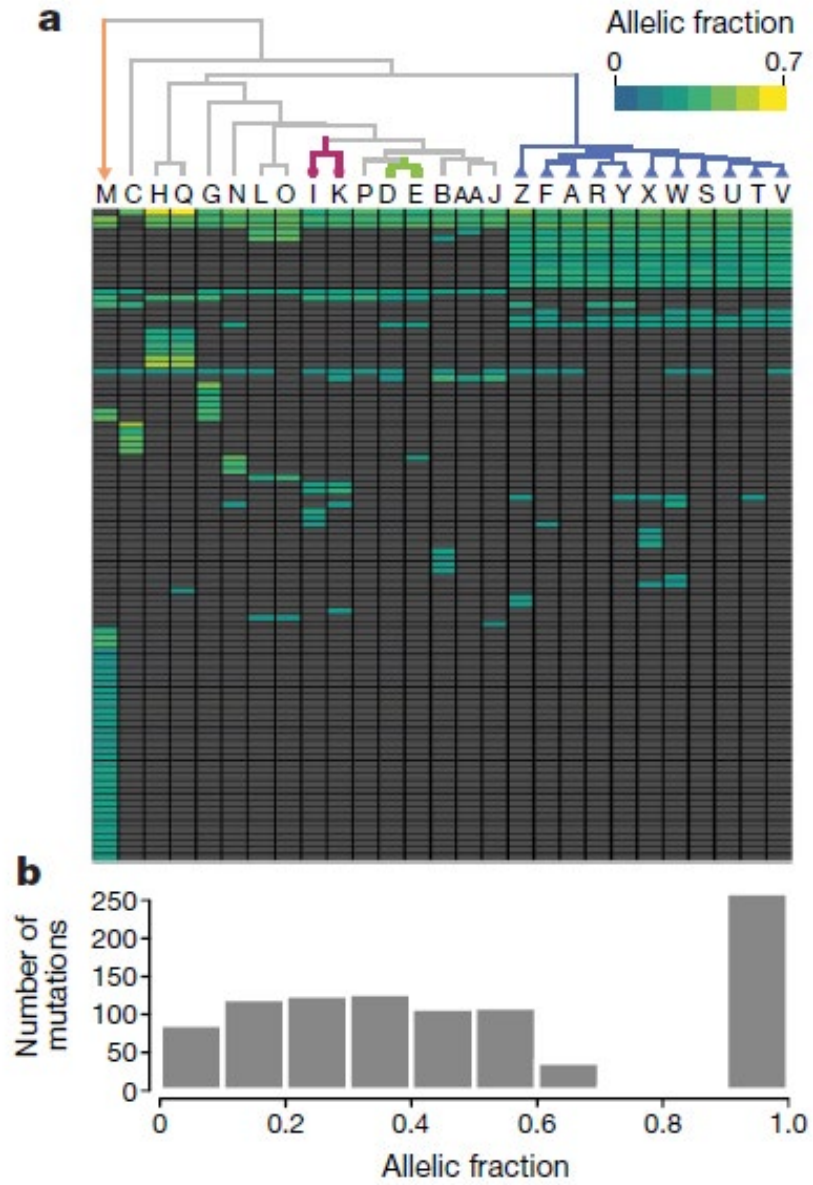
Lab-to lab validation

106 cell lines

- 27% CNV could not redetected
- 22% of genome altered by subclonal events

MCF-7-M (27 strains)

- Ten chromosome arms (25% of the genome) were differentially gained or lost
- 283 genes with copy number gains and 405 genes with copy number losses in at least one strain. Only a small minority of these changes (13% of gains and 21% of losses) were detected in all strains.



Ben-David et al., **Nature**

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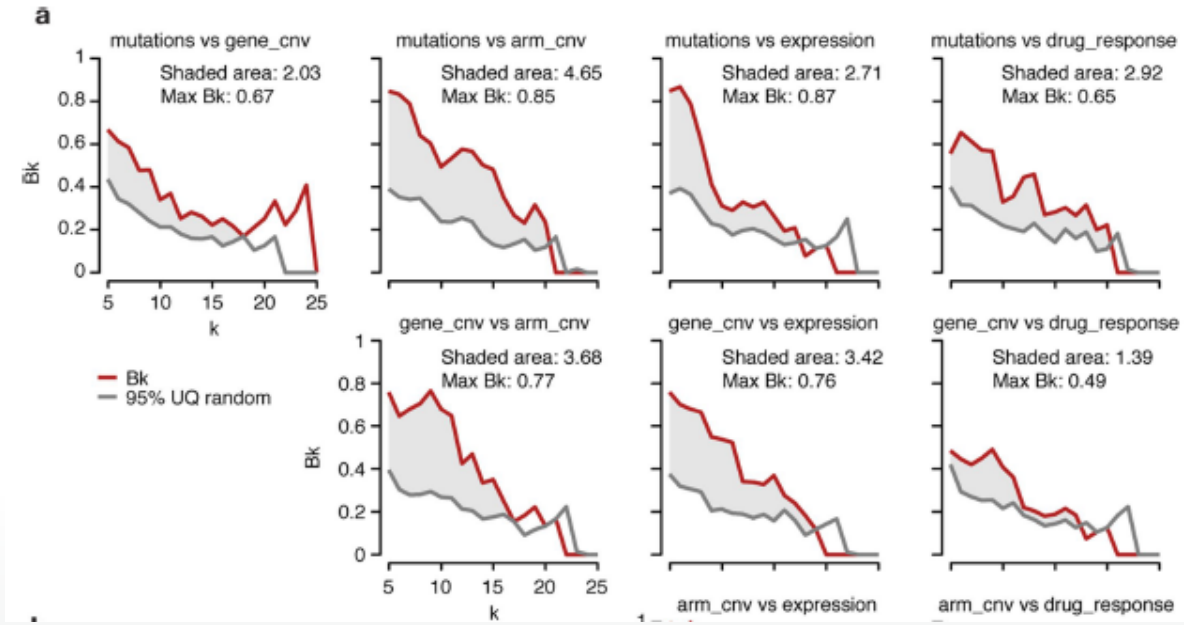
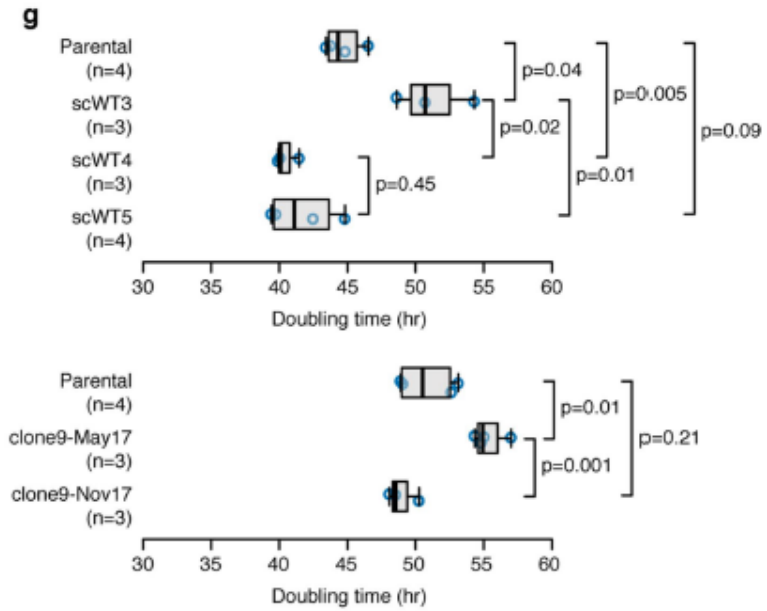
The economic and ethical burden of cancer research



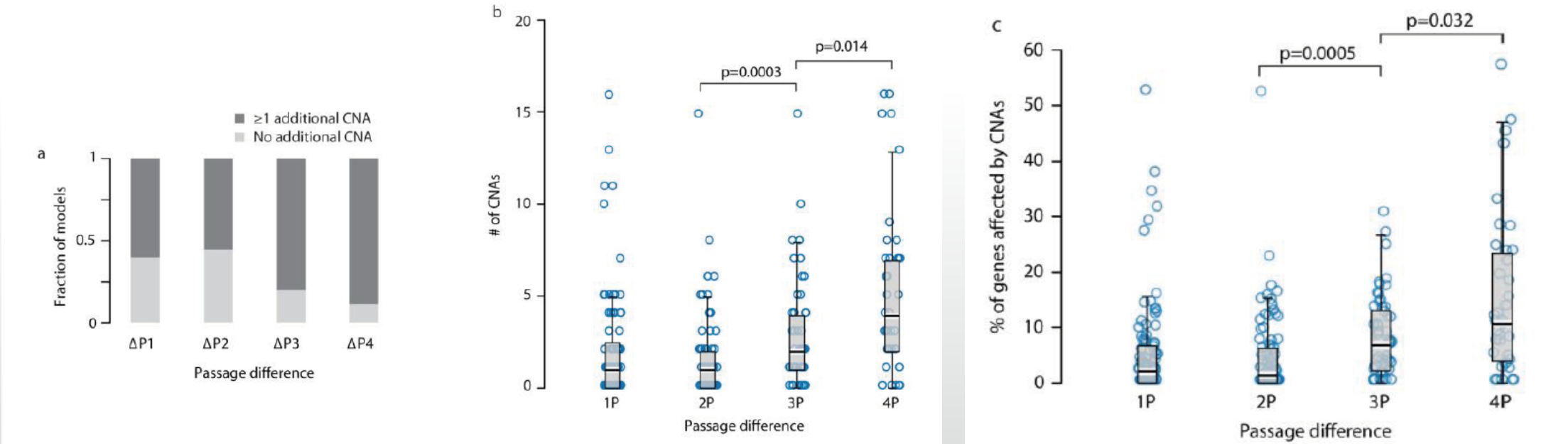


Ben-David et al., **Nature**

The economic and ethical burden of cancer research

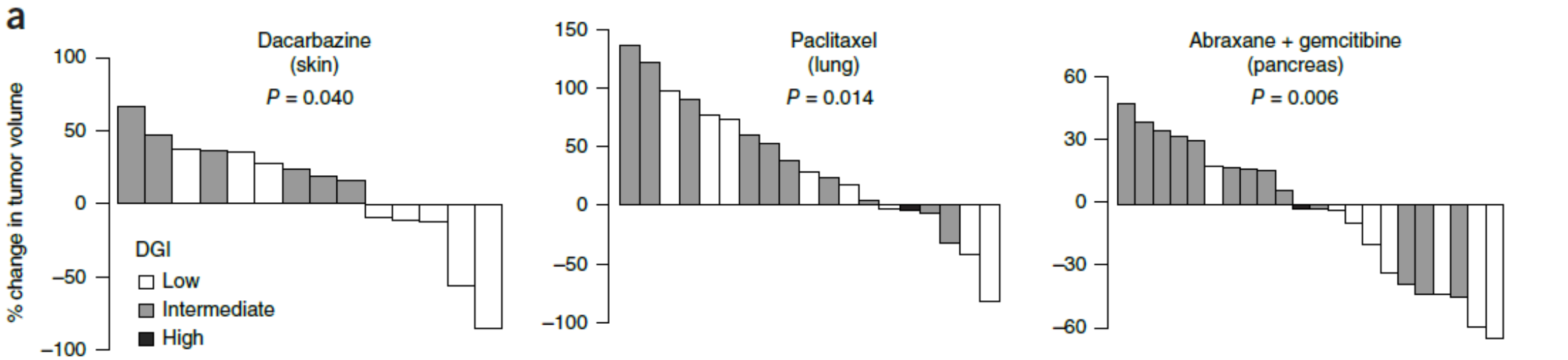
1100 PDX samples across 24 cancer types, compared to parental cell model (incl. primary model)

We found that large (>5-Mb) CNAs arose rapidly in PDXs: 60% of the PDX models acquired at least one large chromosomal aberration within a single *in vivo* passage, and 88% acquired at least one large aberration within four passages



Ben-David et al., **Nature Genetics**

The economic and ethical burden of cancer research

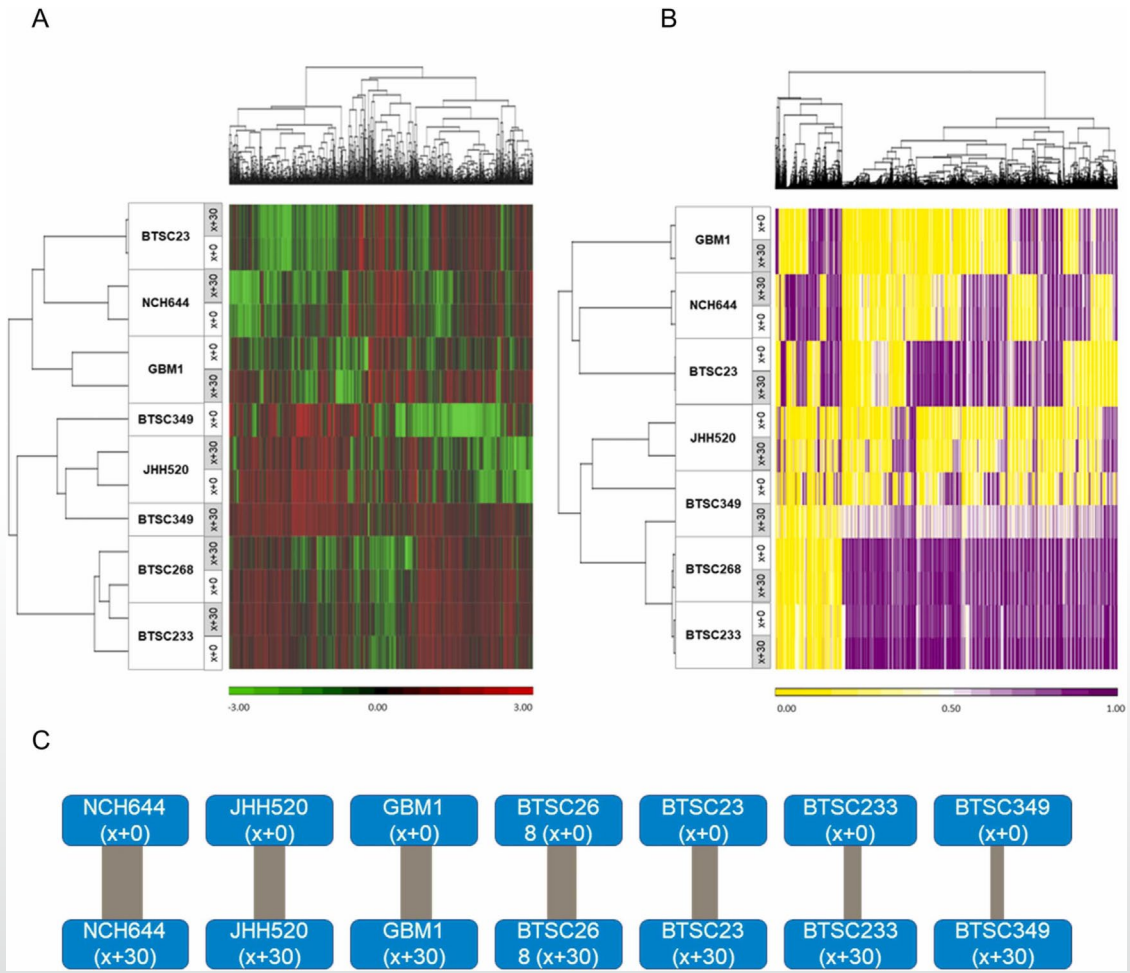


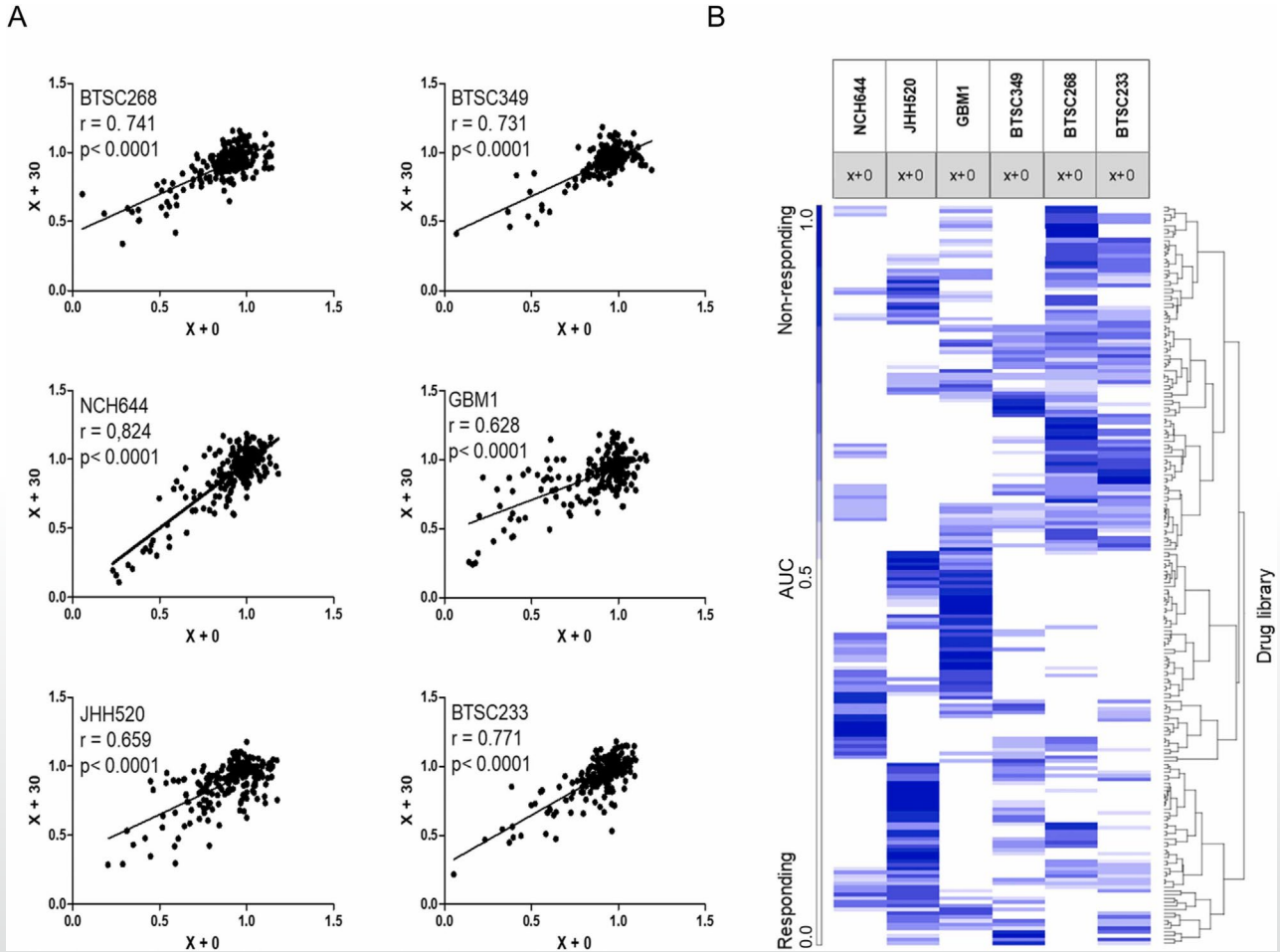
➢Alternative preclinical modeling strategies are warranted:

1. **to overcome the issue of heterogeneity of results**
2. **aiming to increase frequency of clinical translationability**

Ben-David et al., **Nature Genetics**

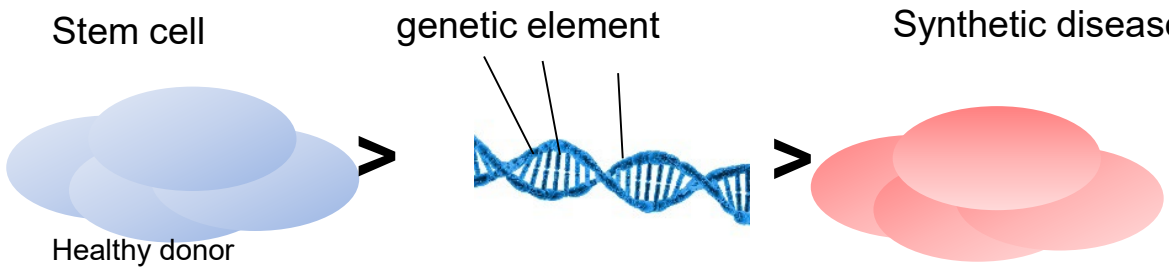
Patient-derived stem cell models of cancer as reliable source



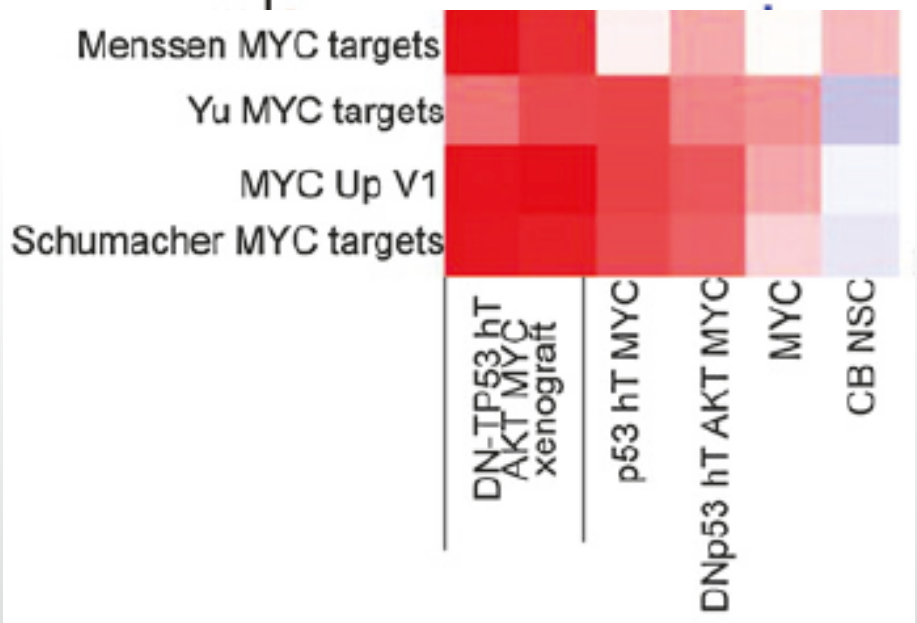


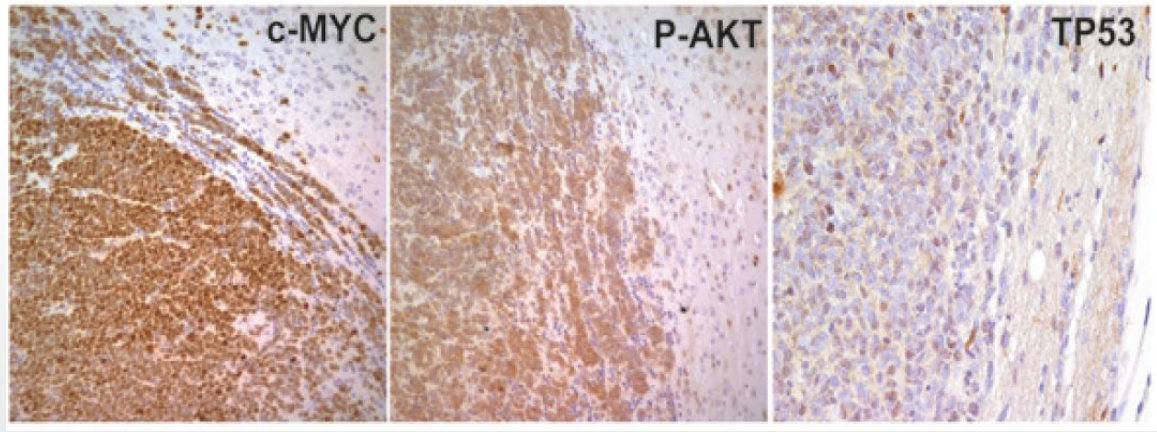
Ben-David et al., **Nature Genetics**

Synthetic alternatives of cancer stem cells



- human fetal stem cell-derived cancer models





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Hanaford et al., **CCR**

Synthetic alternatives of cancer stem cells

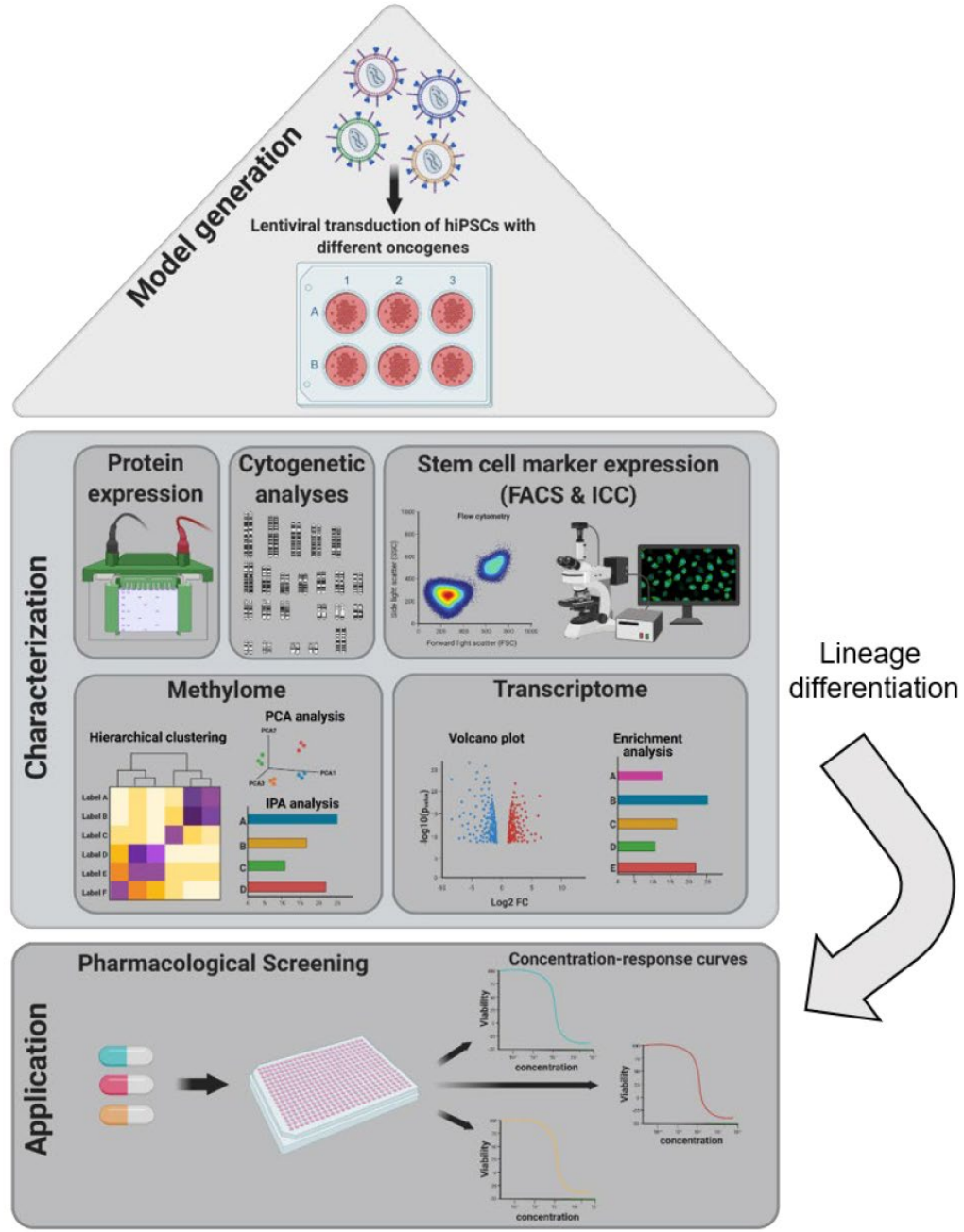
Biotechnology Journal
Systems & Synthetic Biology · Nanobiotech · Medicine

RESEARCH ARTICLE | Open Access

Progenitor cells derived from gene-engineered human induced pluripotent stem cells as synthetic cancer cell alternatives for in vitro pharmacology

Constanze Uhlmann, Ann-Christin Nickel, Daniel Picard, Andrea Rossi, Guanzhang Li, Barbara Hildebrandt, Gabriele Brockerhoff, Farina Bendt, Ulrike Hübenthal, Michael Hewera, Hans-Jakob Steiger, Dagmar Wieczorek, Aristoteles Perrakis, Wei Zhang, Marc Remke, Katharina Koch, Julia Tigges, Roland S. Croner, Ellen Fritsche, Ulf D. Kahlert ... See fewer authors

First published: 25 March 2022 | https://doi.org/10.1002/biot.202100693



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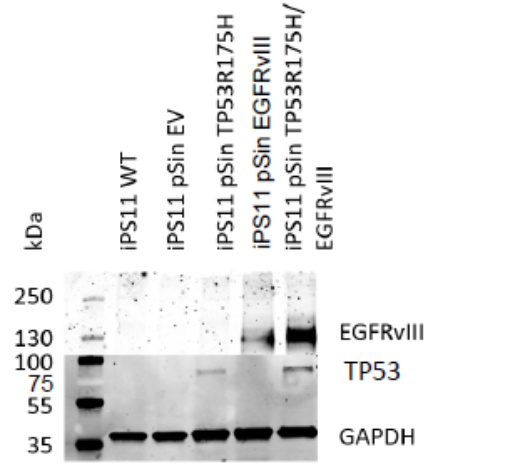
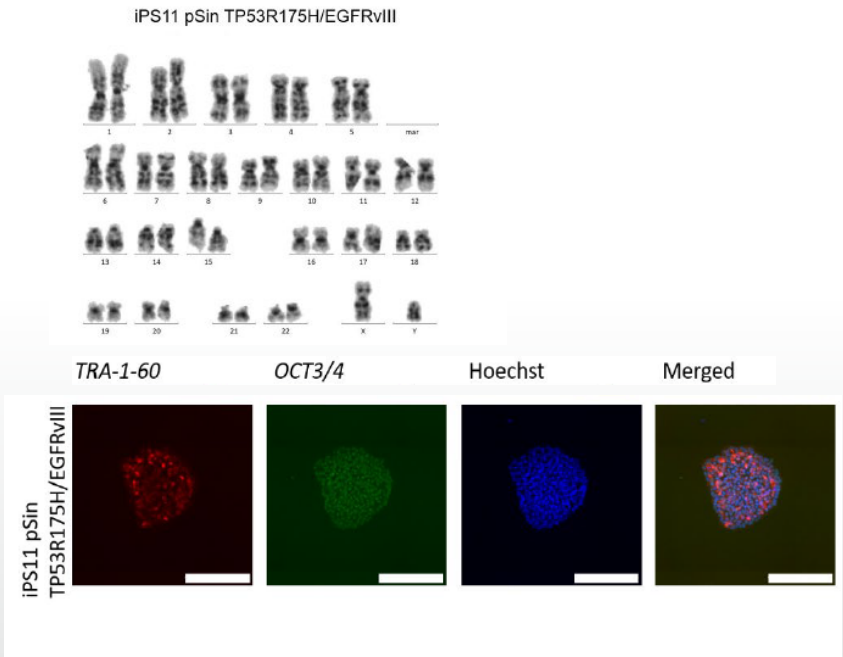
Synthetic alternatives of cancer stem cells

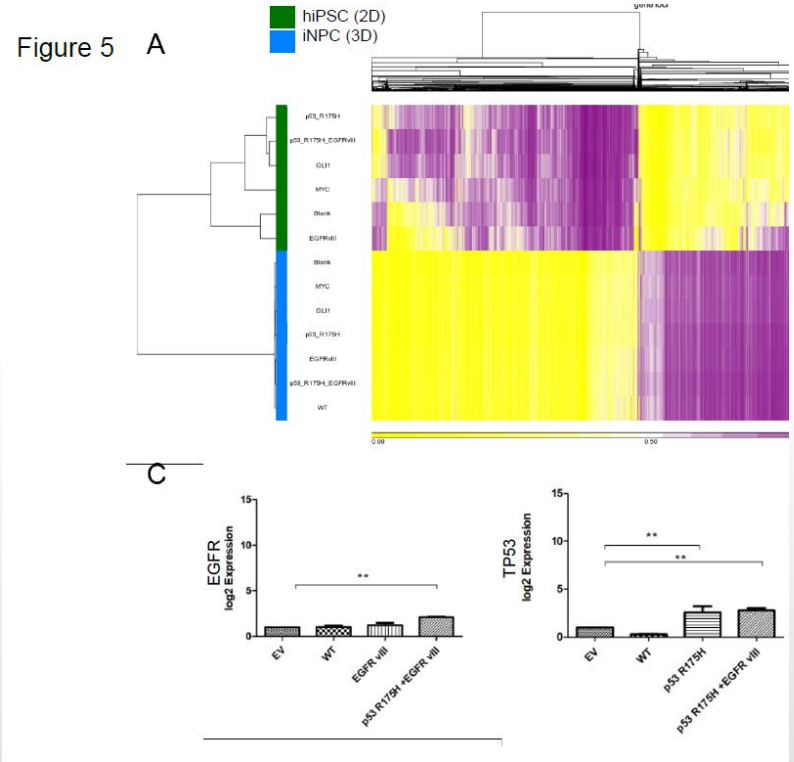
Engineering



QC



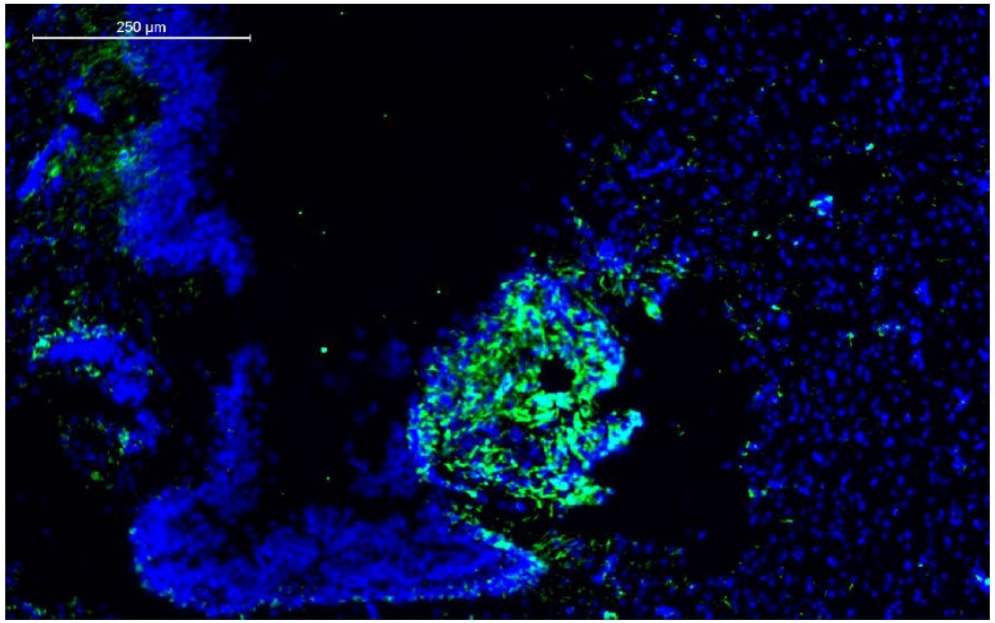
Lineage differentiation

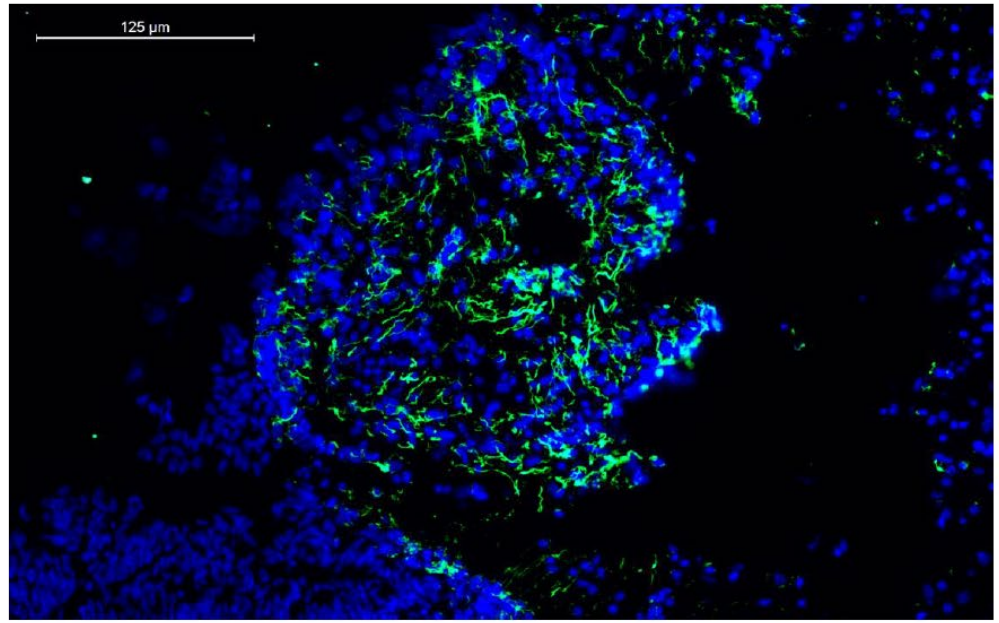


Uhlmann et al., **BTJ**

Synthetic alternatives of cancer stem cells

In vivo tumorgenicity potential ?

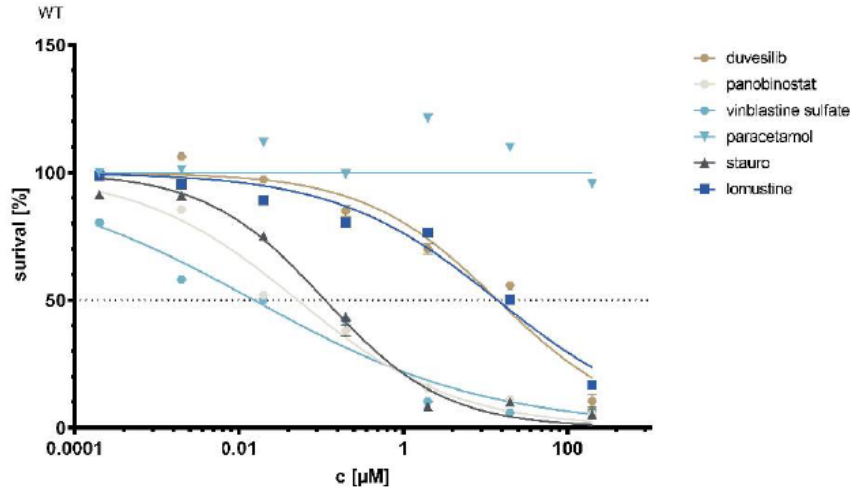


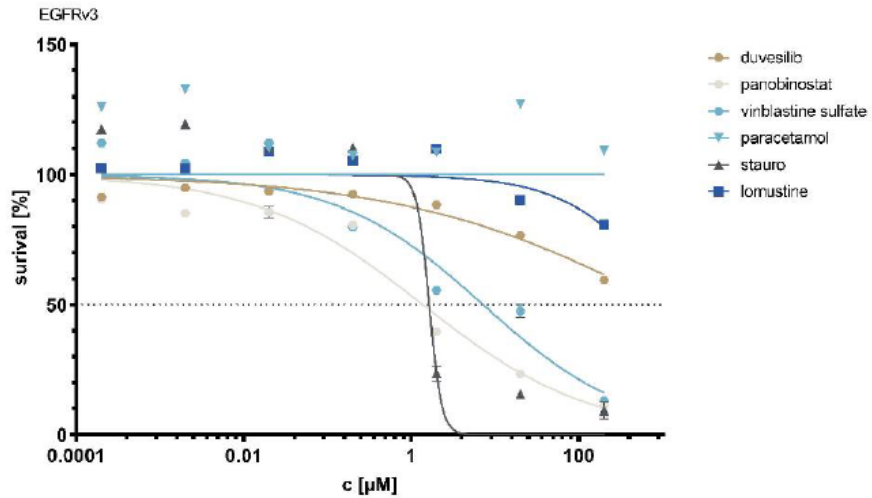


Krause et al., **in prep.**

Synthetic alternatives of cancer stem cells

substance	NPC WT	NPC -EV	NPC -GLI1	NPC -c-MYC	NPC - TP53R175H	NPC - EGFRvIII	NPC– EGFRvIII/ TP53R175H
Panobinostat	0.05164	0.2940	0.4568	0.1237	0.01986	1.367	0.2856
Vinblastine sulfate	0.01518	0.003848	0.4806	0.01955	0.02161	7.166	3.291
Lomustine	13.96	188.8	2410	217.10	191.30	1364	270
Duvelisib	14.04	75.29	53.4	48.68	732.90	1062	322.50
Paracetamol	X	X	X	X	X	X	X
Staurosporine	0.1118	0.5545	0.1986	0.2675	1.657	1.639	0.1599





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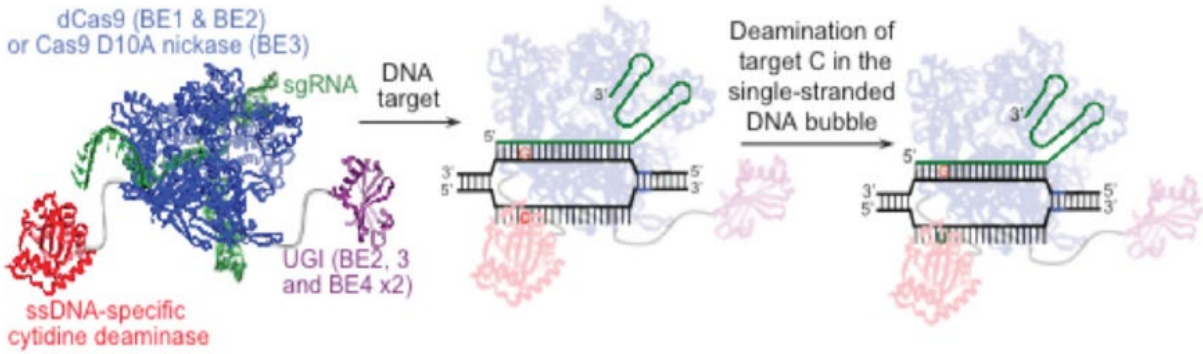
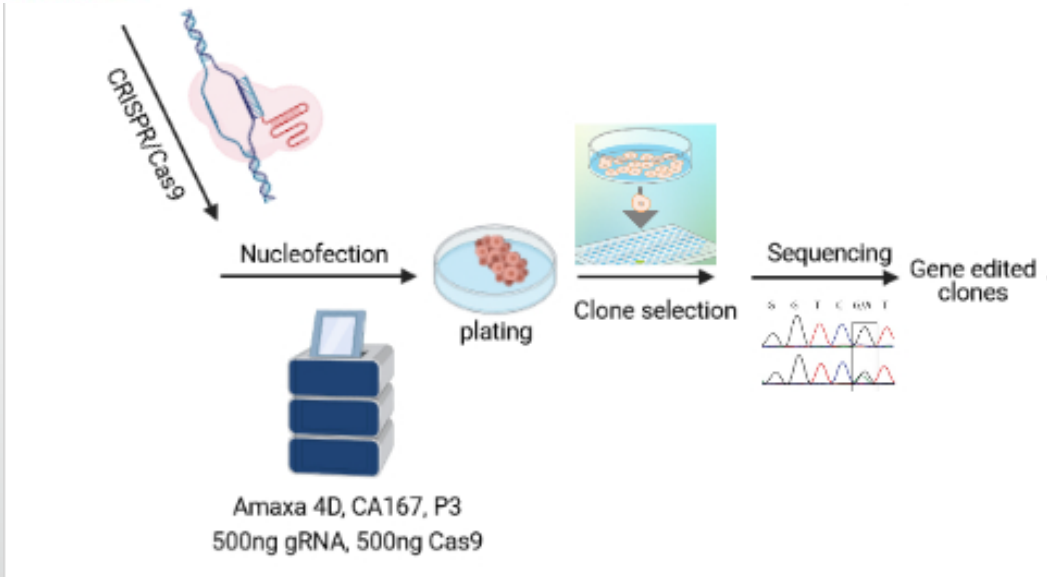
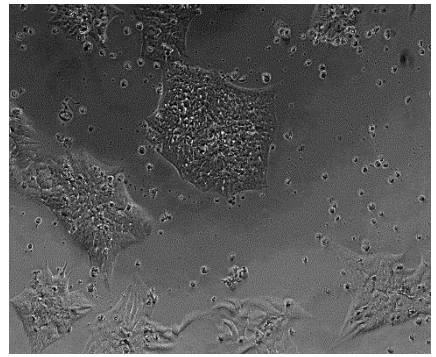
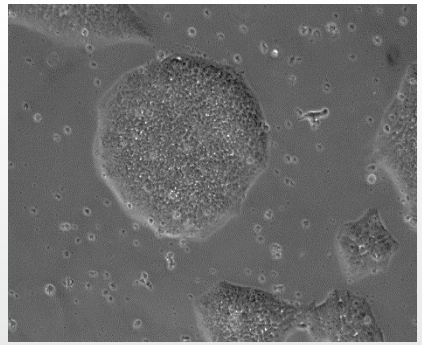
Uhlmann et al., **BTJ**

Synthetic alternatives of cancer stem cells 2.0







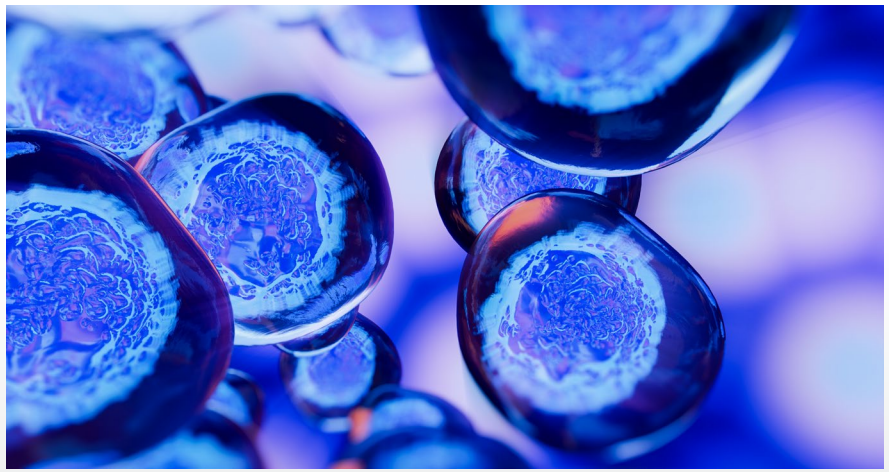


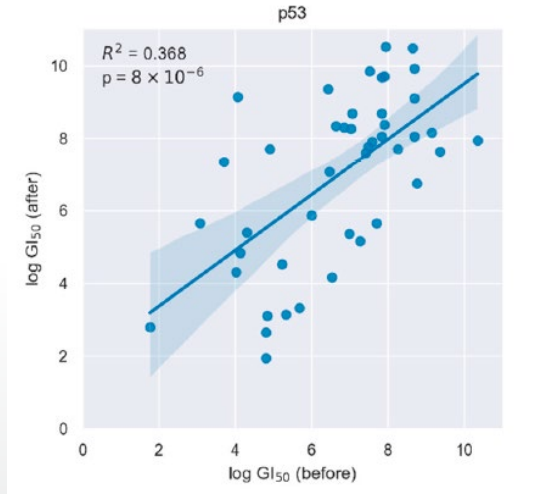
Rees & Liu, **Nature Methods**

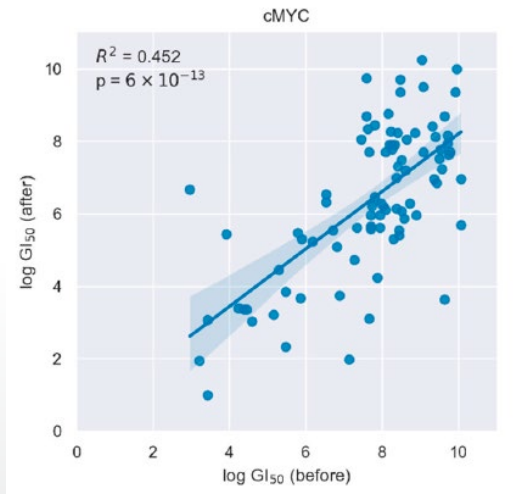
Synthetic alternatives of cancer stem cells – Why?

- Single cell of origin
- Genetic reduction

→ Reduction of heterogeneity?





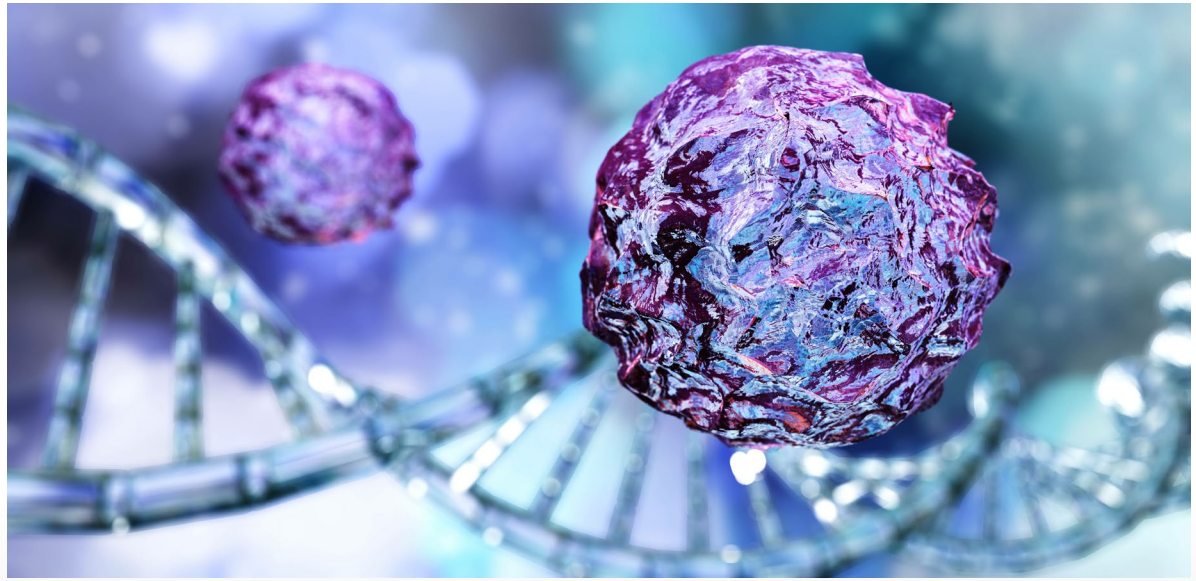


- Biomarker specific
- stem cell/ progenitor cell specific

→ Better molecular targeted /anti- cancer stem cell specific test system ?

Khan et al., **Pharmaceuticals**

Synthetic alternatives of cancer stem cells – Why?

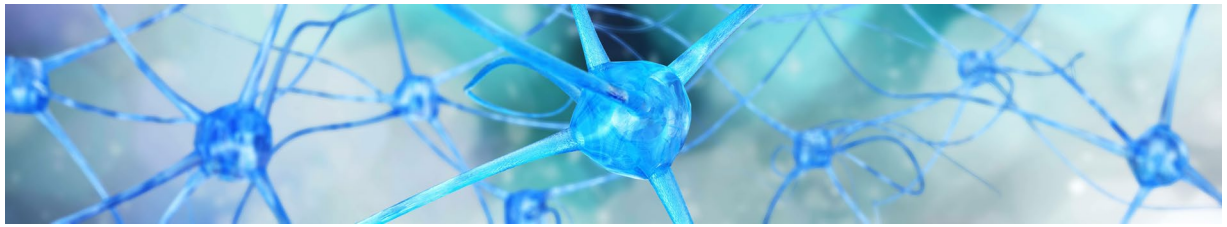


isogenic controlled conditions amendable for multi-lineage differentiation comparisons

oncogenic potential of onco-proteins, early vs. late stage cancer progression models, Targeting cancer stem cell niche…

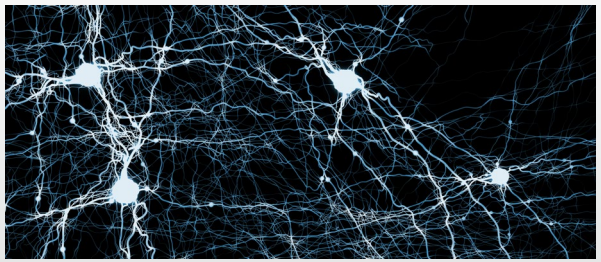
Preclinical testing matrix

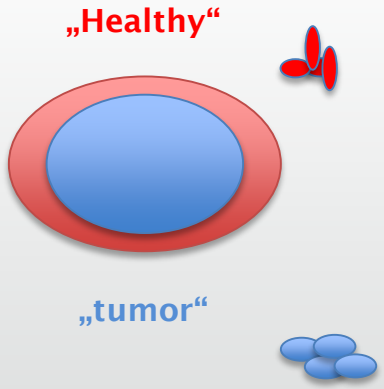
Synthetic alternatives



Diversity (gender, immune, ethnic…)
- Patient-specific iPS generation
  (episomal transformation, via electroporation, NEPA)
- multi-factor and adjustable

Patient-derived systems





Off-target assessment

Pre-analytic issue:

patient recruitment, consent, OR surveillance and reminder

biomaterial logistics

Cooperation pathologist

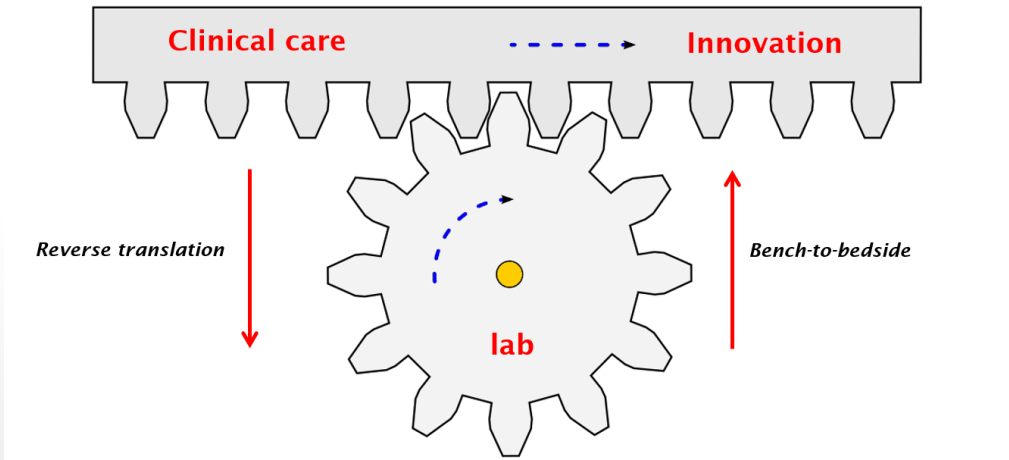
Translational MES biobank (since 01/22)

- Cooperation with surgical partners Roland Croner and Aris Perrakis & surgical team of the clinic for surgery OVGU
- Inspired by German Institute for Normalization (D.I.N.) standards
  (Prof. Kahlert is a permanent member „Biobanks/ Bioresources" - NA 063-09-02-02 AK)
- Comprised high quality tissue and blood acquisition (minimal pre-analytical time window)
- Association of clinical data at time point of operation and follow-up
- Development of functional models of healthy and tumor tissue to present comprehensive, patient-matched in vitro banking to conduct
  off-target assays of drug candidates in immunological and genetically matched background associated to tissue
- Pancreas, Colon, Rectum, Liver, hepatic metastasis

Thank you

Repeatable & predictive

rapid



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COST WG Workshop
16/17 June Magdeburg

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