eha Sf(PM)

Single cell mass-based biomarkers for functional precision medicine

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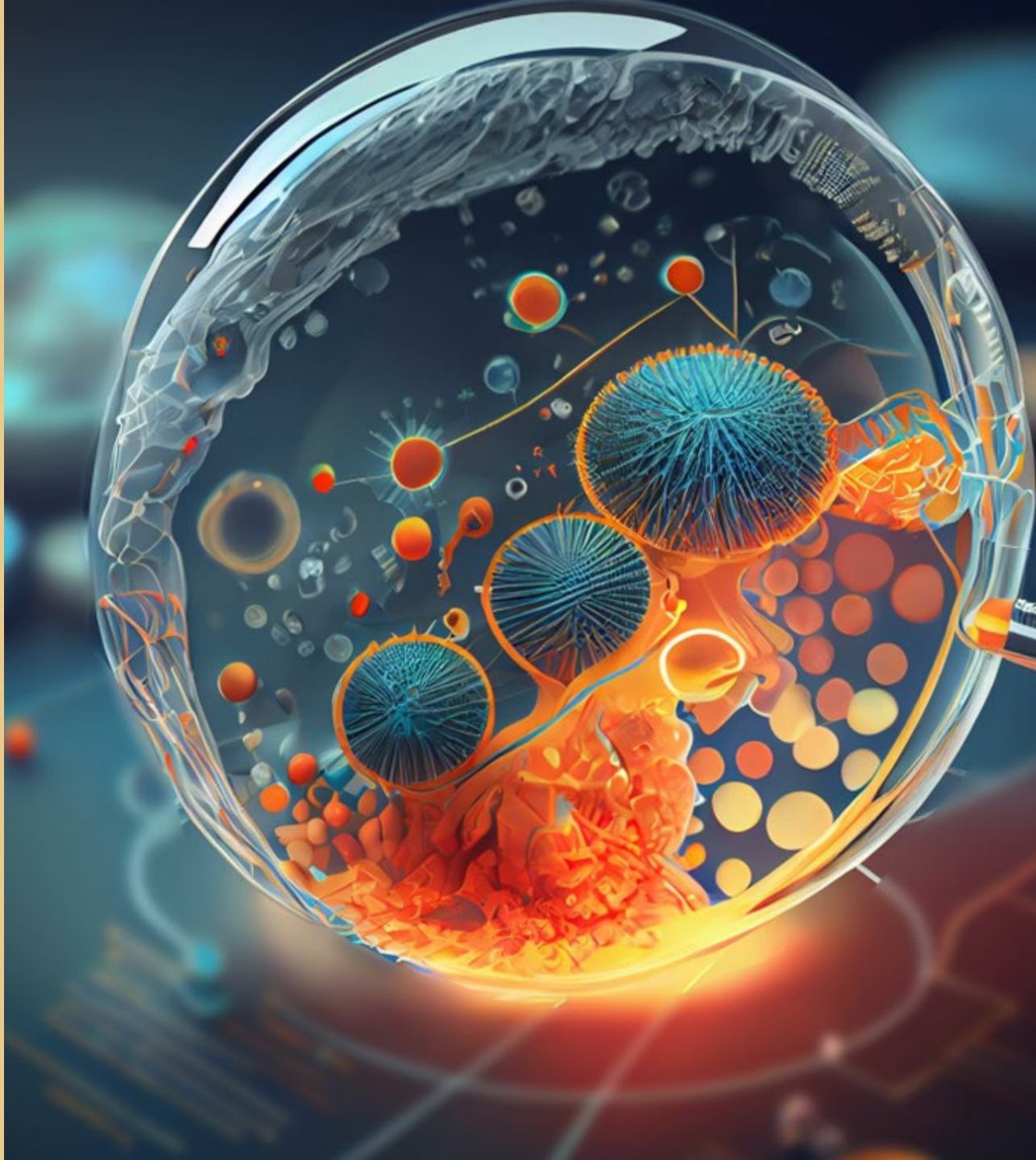
26 September 2024 Technologies Session

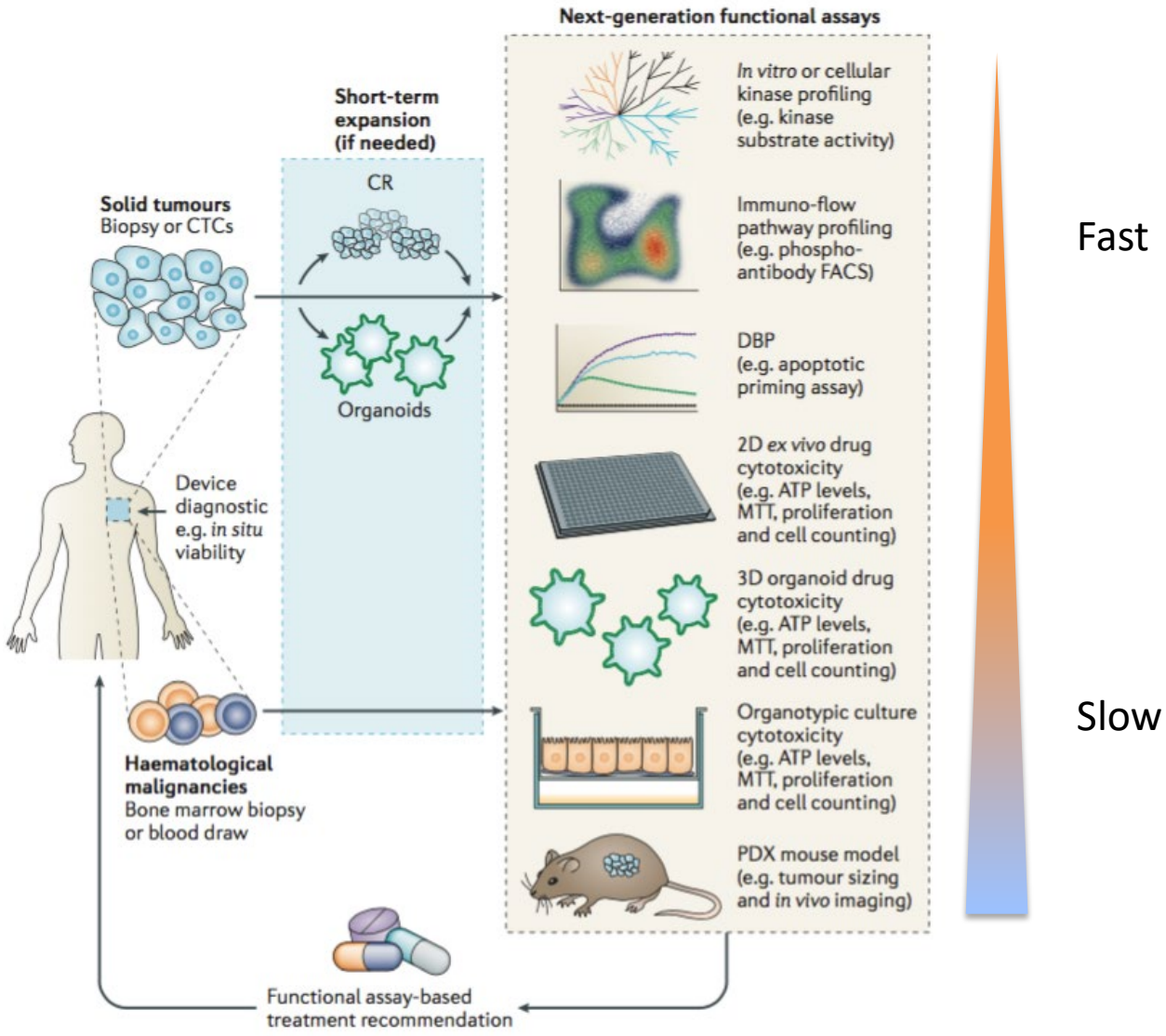


Disclosures

- Travera Inc. — founder, consultant, equity holder
- BMS — consultant, research support
- Servier — consultant
- Blaze Bioscience — consultant
- LEK — consultant
- Integragen — consultant

Functional precision medicine technologies in cancer

Next-generation functional diagnostics



Friedman et al., Nat Rev Cancer (Dec 2015)

Diverse FPM Technologies with wide ranging pros and cons – many may not be easy to clinically scale

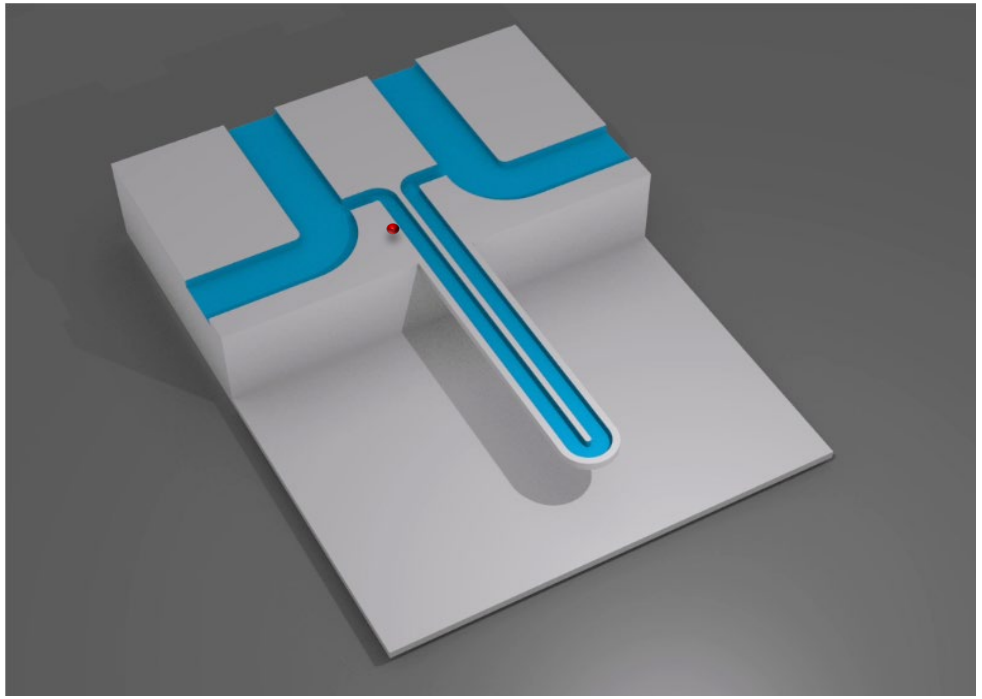
Can we develop new technologies with potential for easier FDA approval and pathology lab implementation?

Wish list

- Low cell budget
- Rapid results
- High content data
- Scalable and low-touch

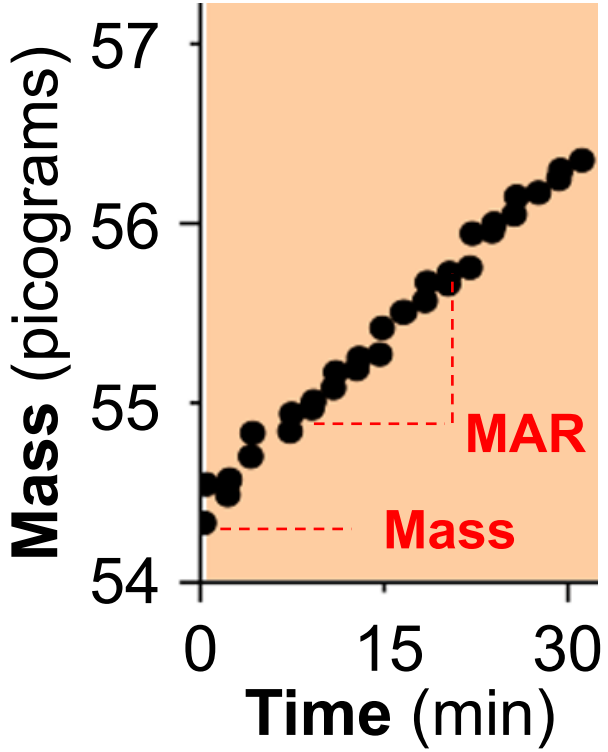
Suspended Microchannel Resonator (SMR) Technology

SMR – Culture Conditions of
Media/Temp/Gas Controlled within Device



Burg et al. Nature 2007

Mouse lymphoblast cell



Manalis Koch/ MIT

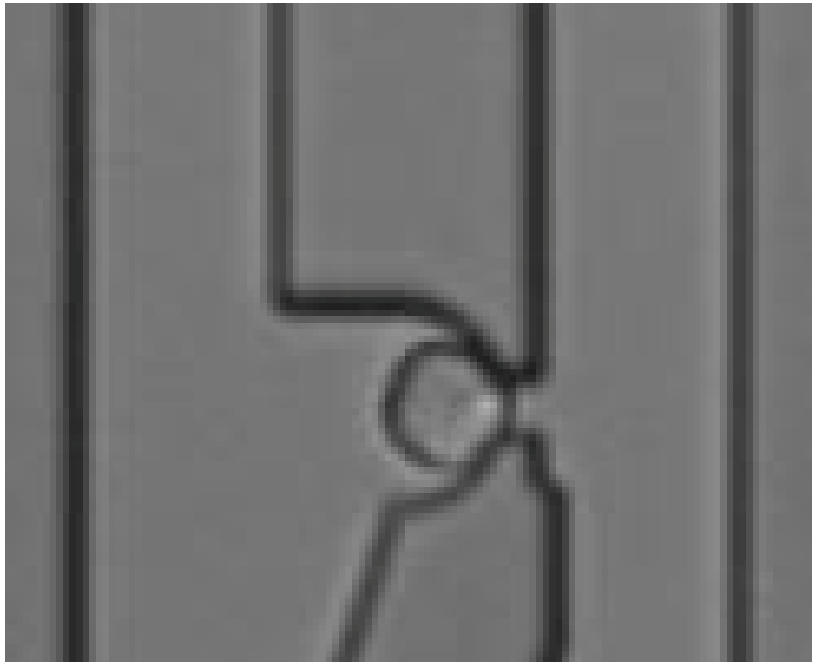
The SMR can weigh floating **live** cells with a precision near 0.01% of the cell mass

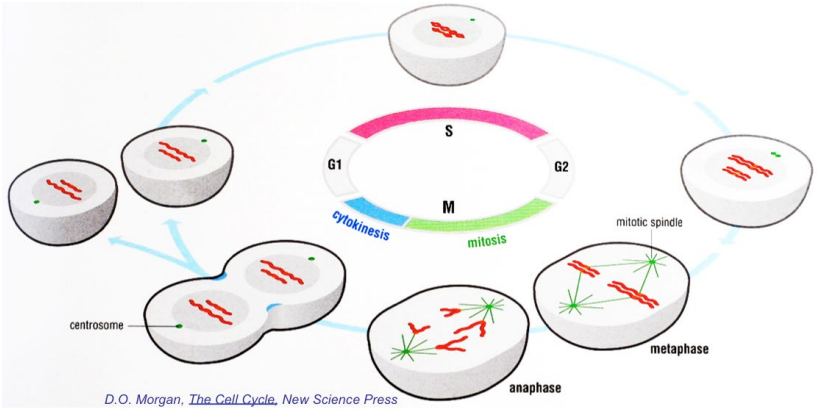
Cancer is….

Two separate processes often viewed as one…

Cell growth
Accumulation of mass

Cell division cycle
Genome duplication



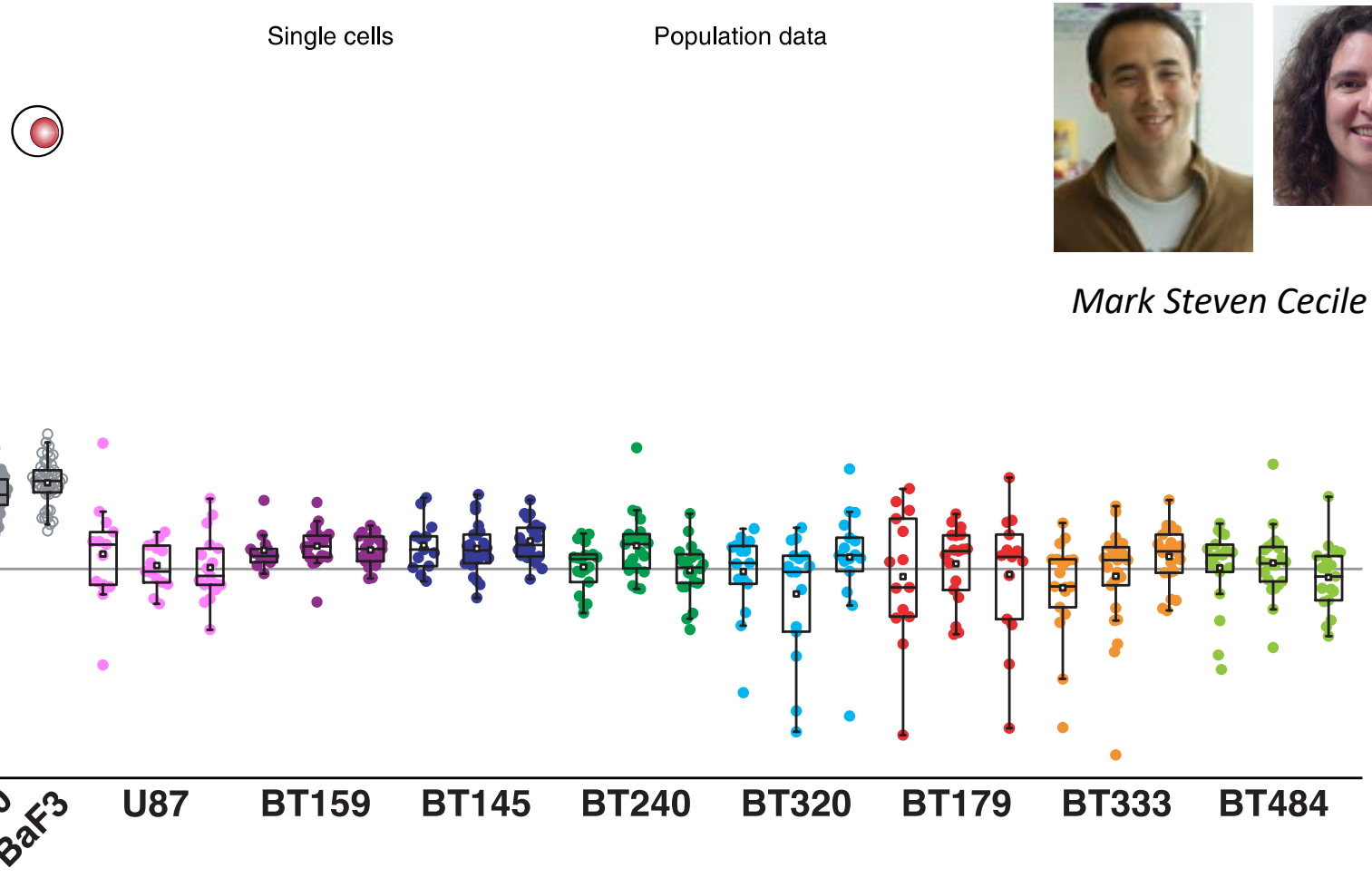


Fundamental to growth and division is that a cell MUST accumulate nutrients (e.g. glucose) to prepare for division

Courtesy of Scott Manalis MIT

Single cell mass accumulation rate reveals growth heterogeneity within and across patient derived models

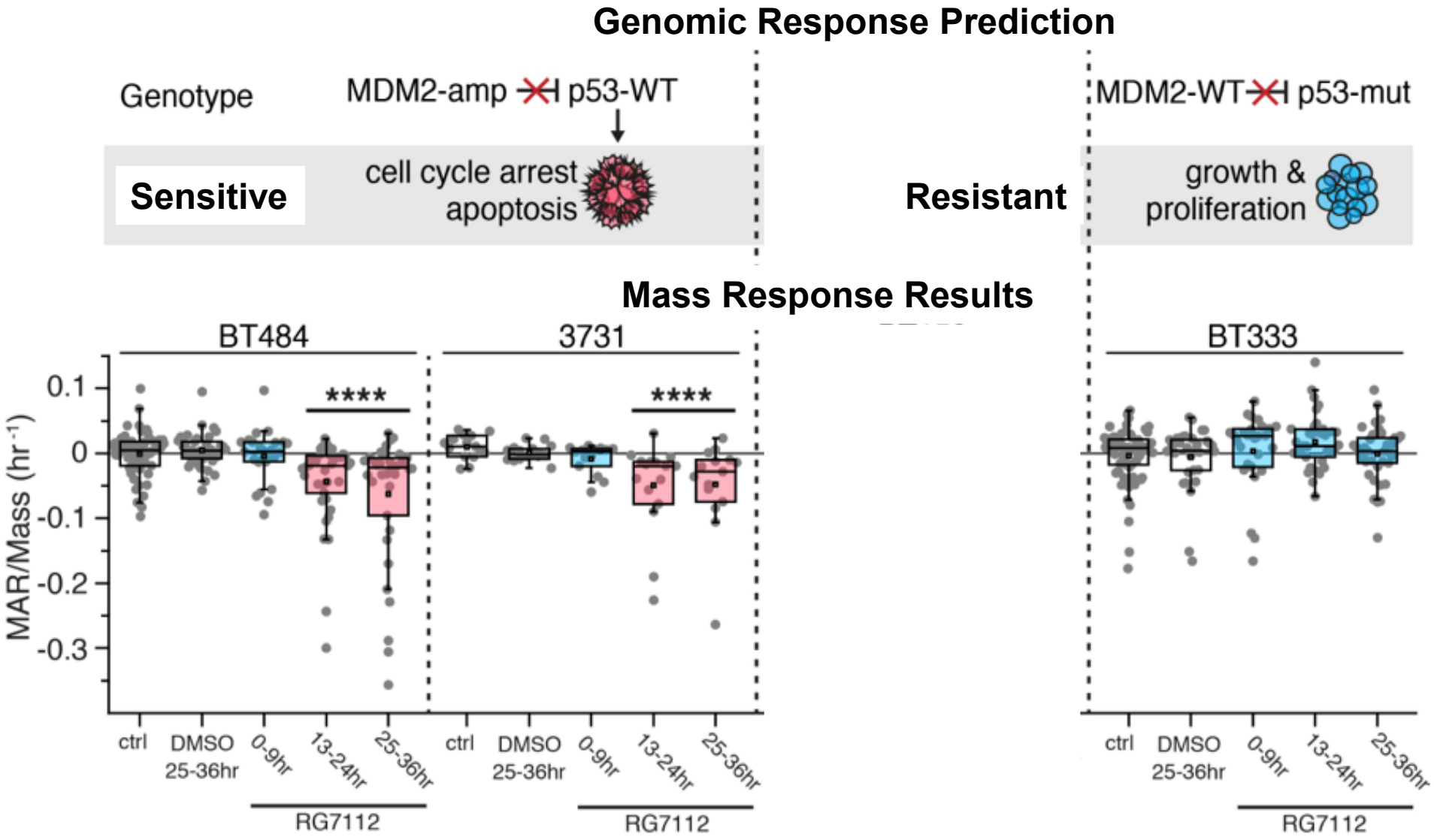
Ligon Lab Collection of GBM 3D Neurospheres/Organoids)



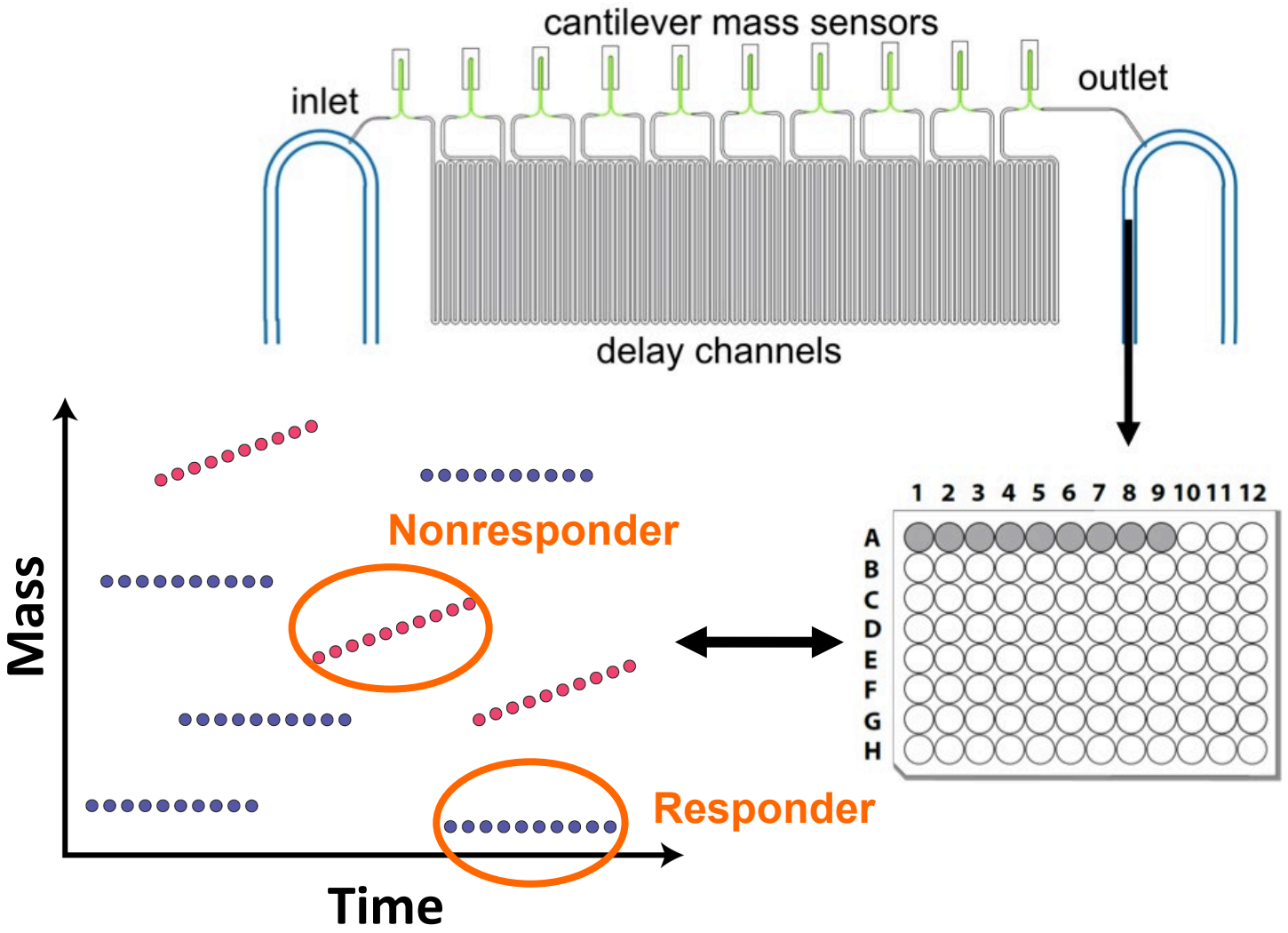
Mark Steven Cecile Maire and Nigel Chou

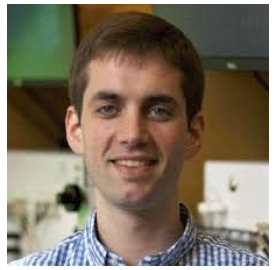
Nature Biotechnology 2016

Single cell mass biomarker aids prediction of MDM2i targeted therapy drug response in GBM models



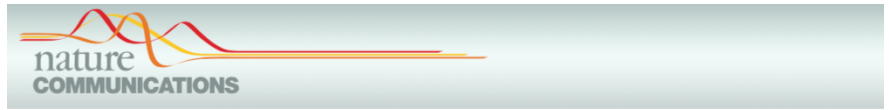
Serial SMR design allows sorting and linking scRNA-seq to MAR following *ex vivo* drug treatment





Rob Kimmerling

Compare gene expression in responding and non-responding cells linked to their functional response



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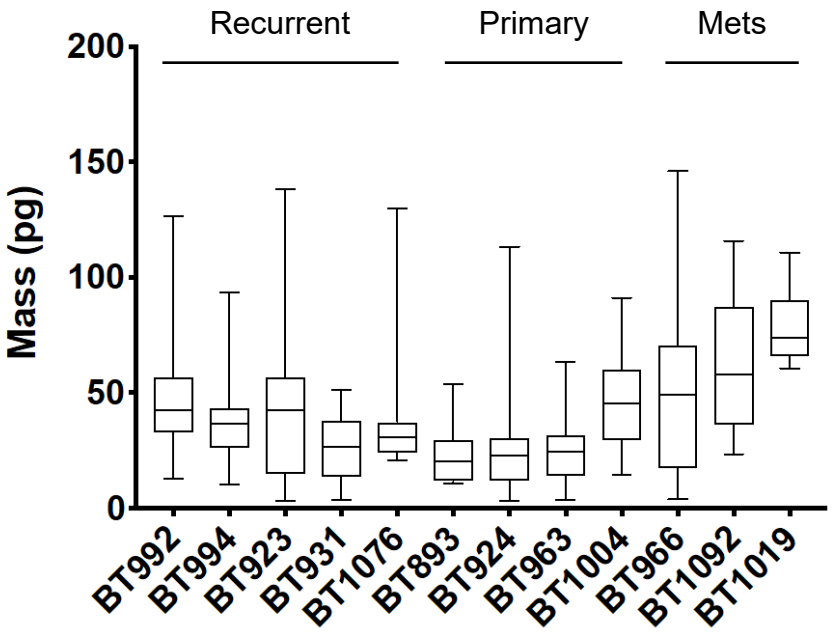
A microfluidic platform enabling single-cell RNA-seq of multigenerational lineages

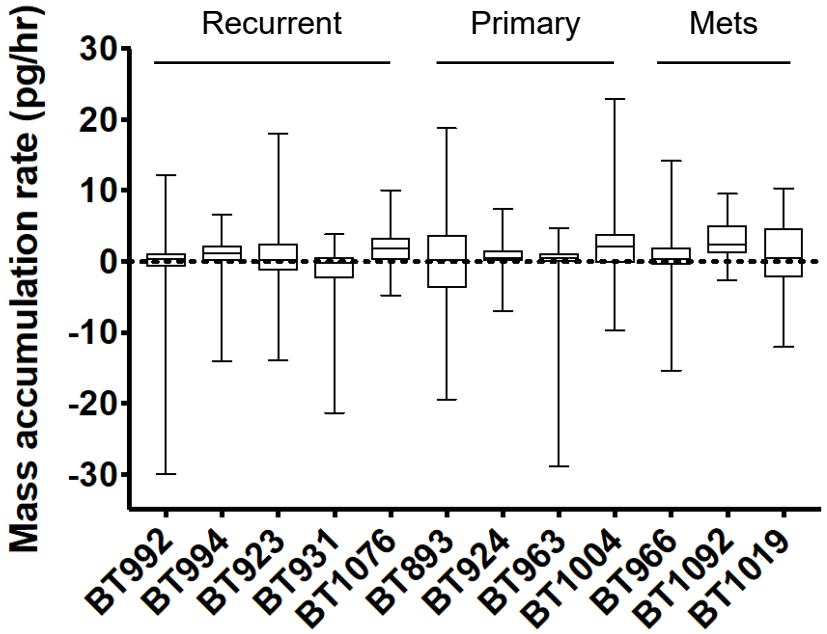
Robert J. Kimmerling[1,2], Gregory Lee Szeto[1,2,3,4,†], Jennifer W. Li[2], Alex S. Genshaft[4,5,6,7], Samuel W. Kazer[4,5,6,7], Kristofor R. Payer[8], Jacob de Riba Borrajo[2,7], Paul C. Blainey[2,7], Darrell J. Irvine[1,2,3,4,9], Alex K. Shalek[4,5,6,7,10,11] & Scott R. Manalis[1,2,12]

Single-cell Mass/MAR in Freshly Isolated CNS Tumor Samples

- *IDH*-mutant high-grade glioma
- *IDH*-wild type glioblastoma
- NSCLC
- Breast

Measurements at 18-36 hours after surgery





Real world lesson learned:
Serial assays feasible but clinical samples inherently challenging to implement due to physical clogs and debris

Seth Malinowski, Mehdi Touat, Kristine Pelton, Mark Stevens

Parallel SMR Array approach enables retrospective clinical-scale mass biomarker testing of patient models


Max Stockslager


Seth Malinowski


Mehdi Touat

Single mass snap-shot on multiple cells

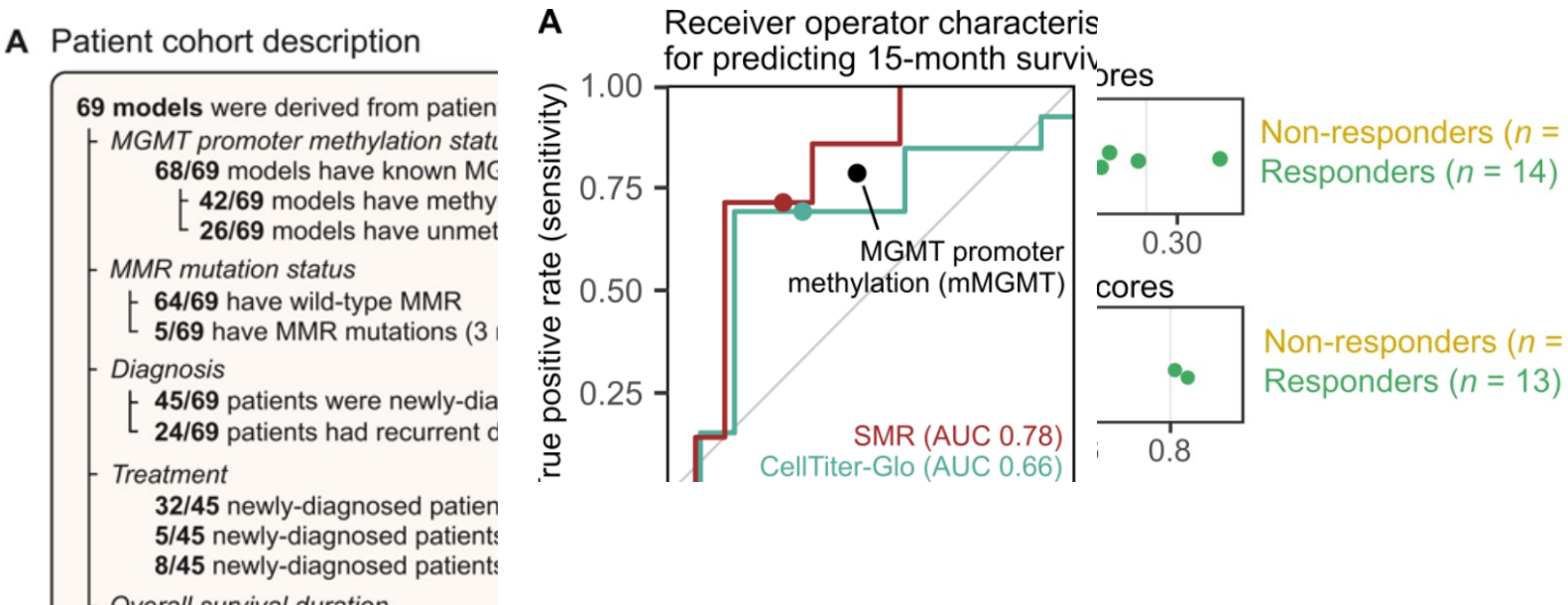
AKA - Mass Blaster!

Question: Can single cell mass biomarker predict response to relevant SOC and trial drugs in GBM patient derived spheroids/organoids?

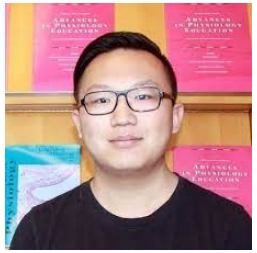
Ex vivo cell mass response predicts longer overall survival in GBM patients

Patient 1
Response

Patient 2
No Response



Capturing scDensity+Mass is achievable using in-line fluorescent imaging



Richard Wu
MIT

Teemu Miettinen
MIT

Kin Hoe Chow
DFCI

Wu et al *in review*

scDensity is a highly sensitive functional biomarker of lymphocyte state

Evaluation for potential I/O biomarker of response to PD1i and others agents

scDensity response in absence of detectable scMass response predicts in vivo response to chemotherapy in PDAC PDX

PDAC PDX

PDAC PDX
In vivo Response

PD

PR

Future validation of screening in PDX ex vivo as “replacement” for expensive in vivo preclinical studies

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SU2C
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NCI
3000 Miles to the Cure Foundation

Patient donors and their families!