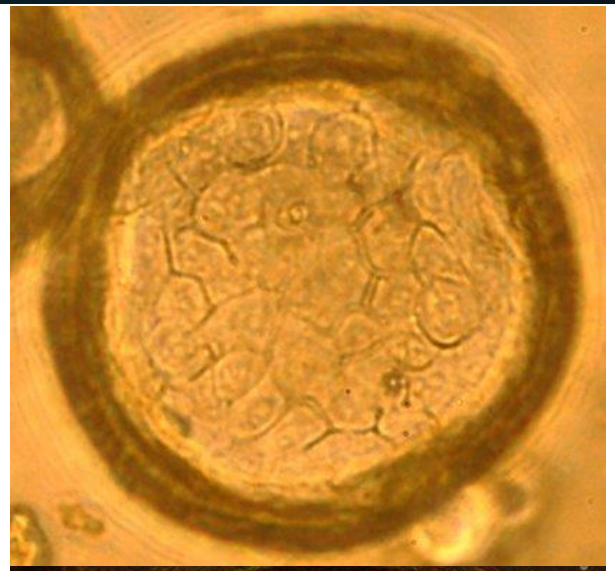
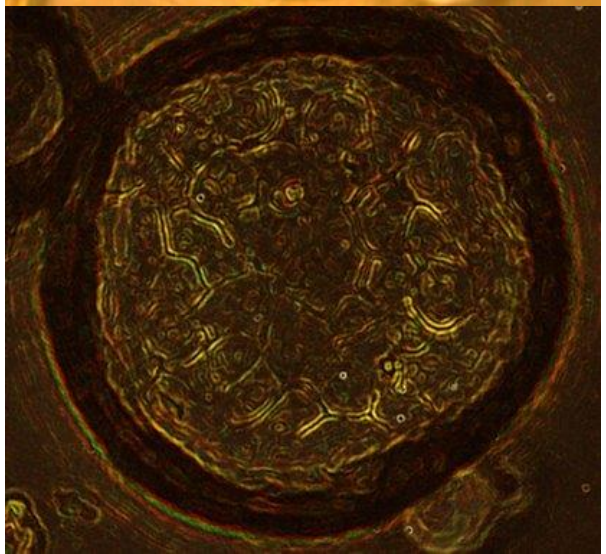
Introducing a ‘Phase 0’ in clinical trials with precise organoid-based disease models

Presented by:
Courtney Tindle, M.S.
Director of HUMANIOD™

UC San Diego





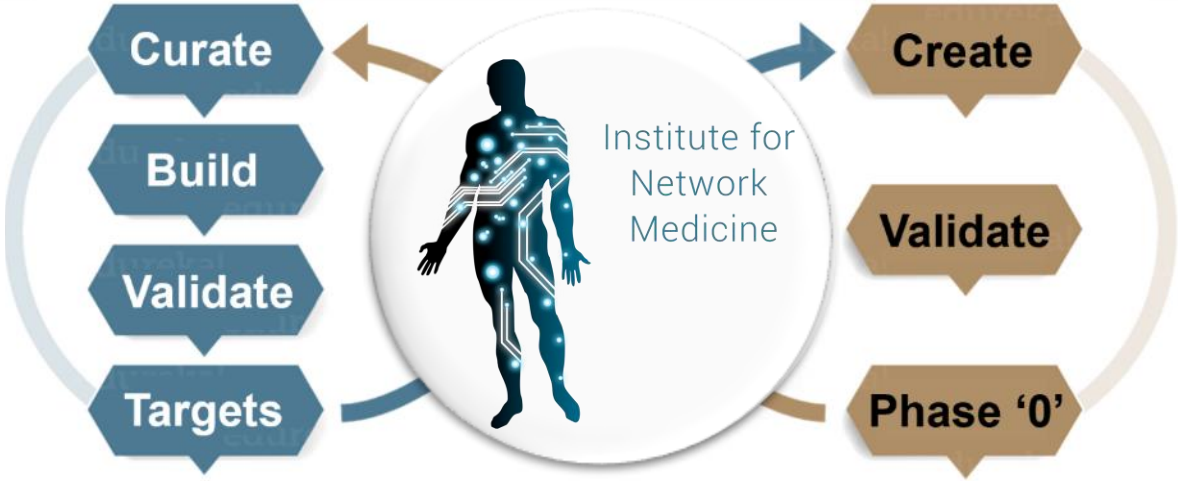
This work features cancer PDOs that were commercially obtained from The ATCC®.

PRECSN AND HUMANOID ENABLE PHASE 'ZERO'

Precision Computational Systems Network

PreCSN

USING BOOLEAN NETWORK EXPLORER [BoNE]



Center of Research Excellence

HUMANOID™

USING HUMAN ORGANOID-BASED MODELS OF DISEASES

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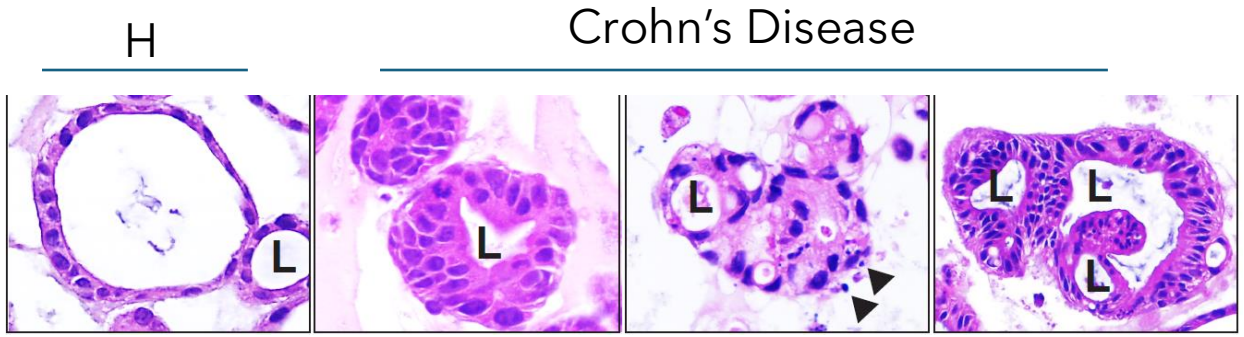
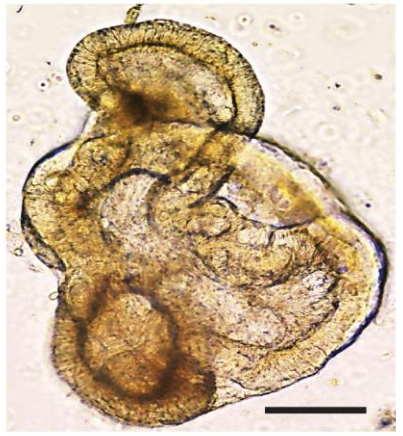
HOW DO WE CHOOSE WHICH MODELS

It's an equation: Passion + Public Need + Funding

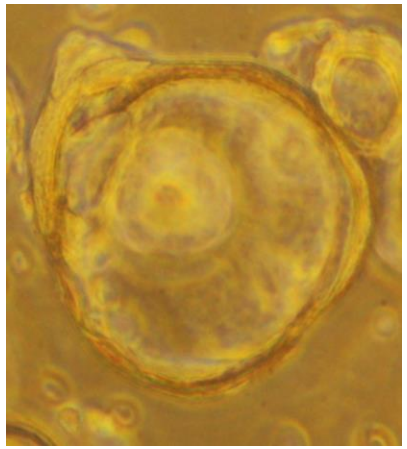
Gastrointestinal:



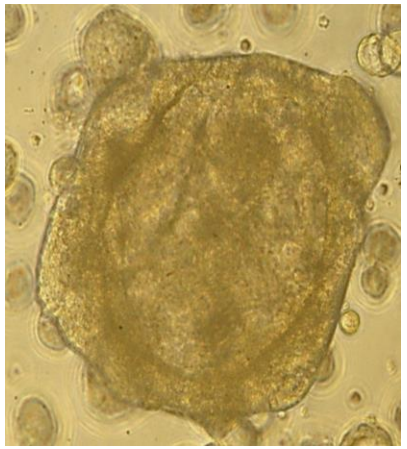
FAP Organoid



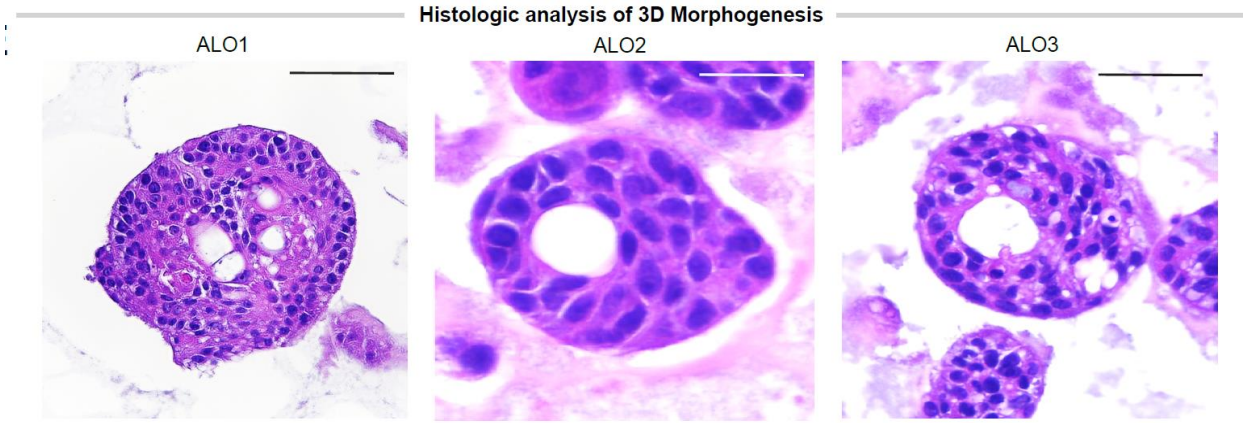
Ulcerative Colitis



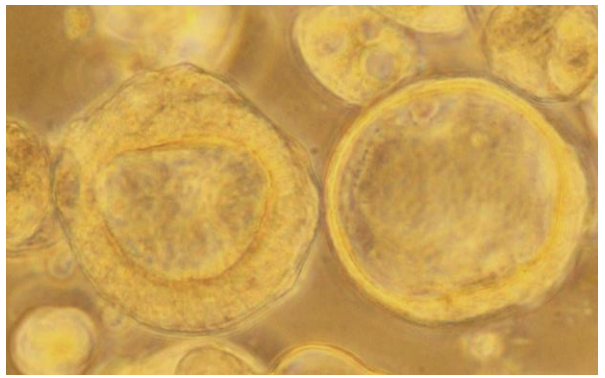
GEJ of BE

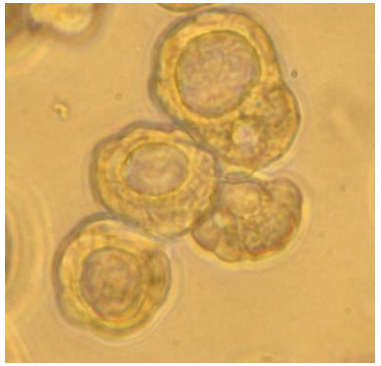


Respiratory:



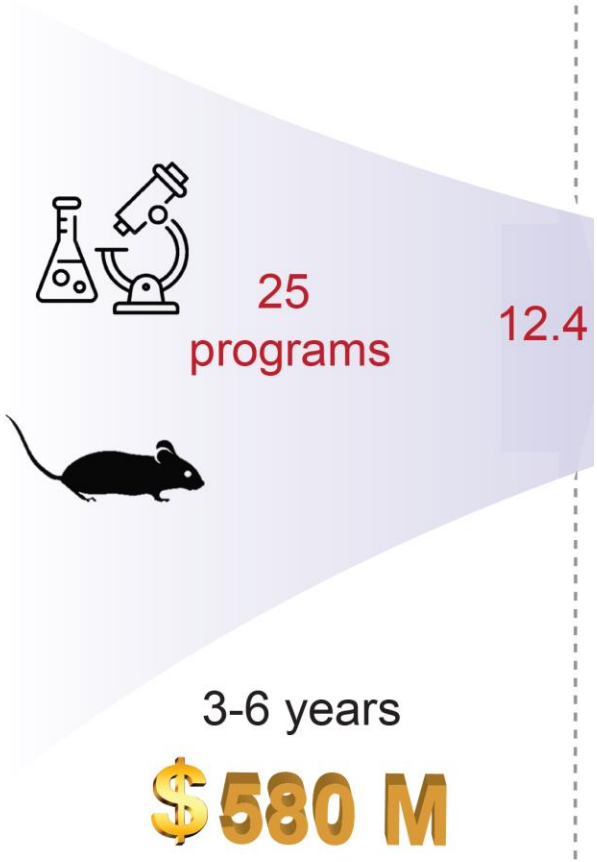
Multiple adenocarcinomas (ATCC's Resource)





THE DRUG DISCOVERY PROCESS IS FLAWED

THE PROBLEM



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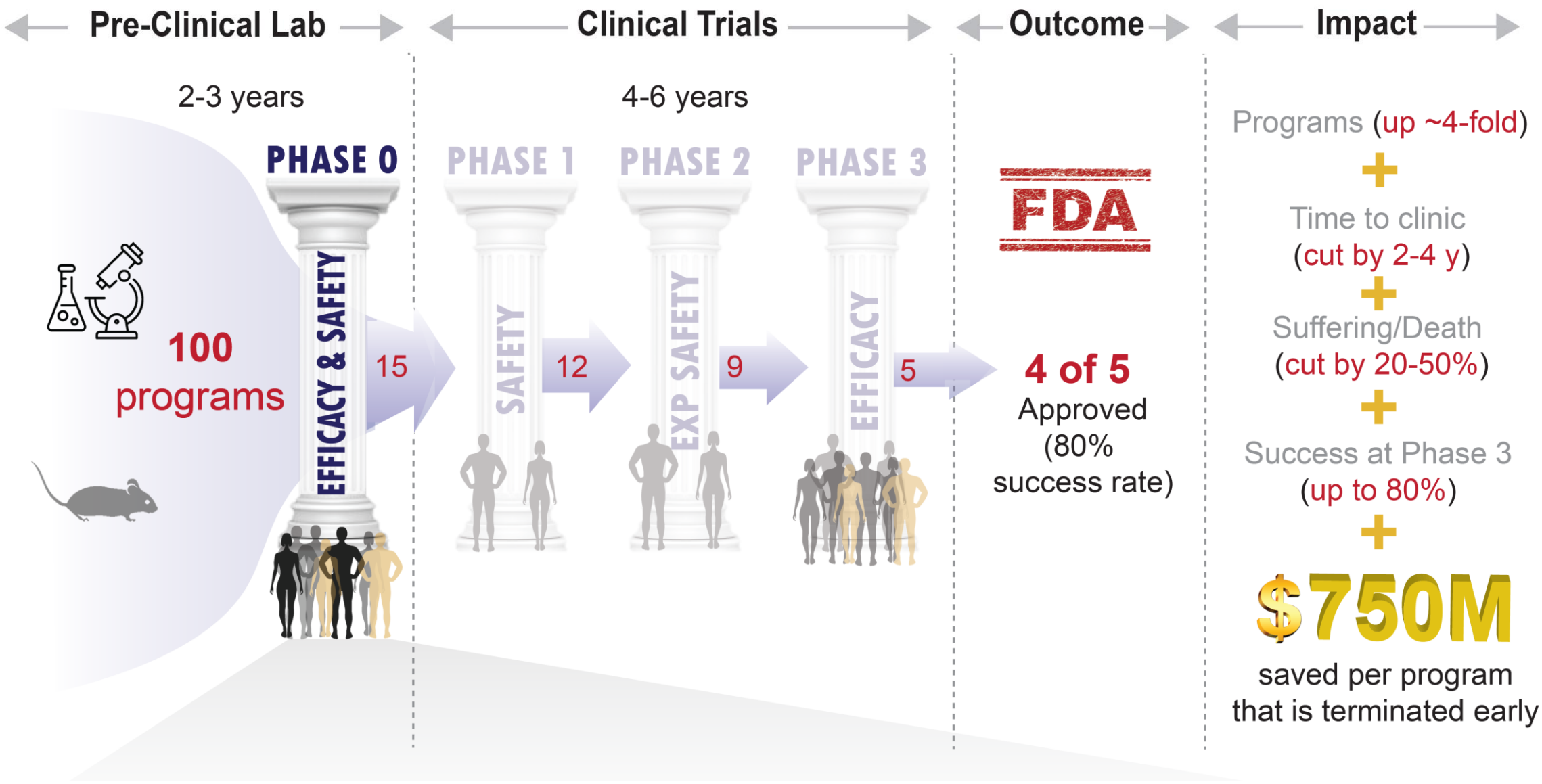
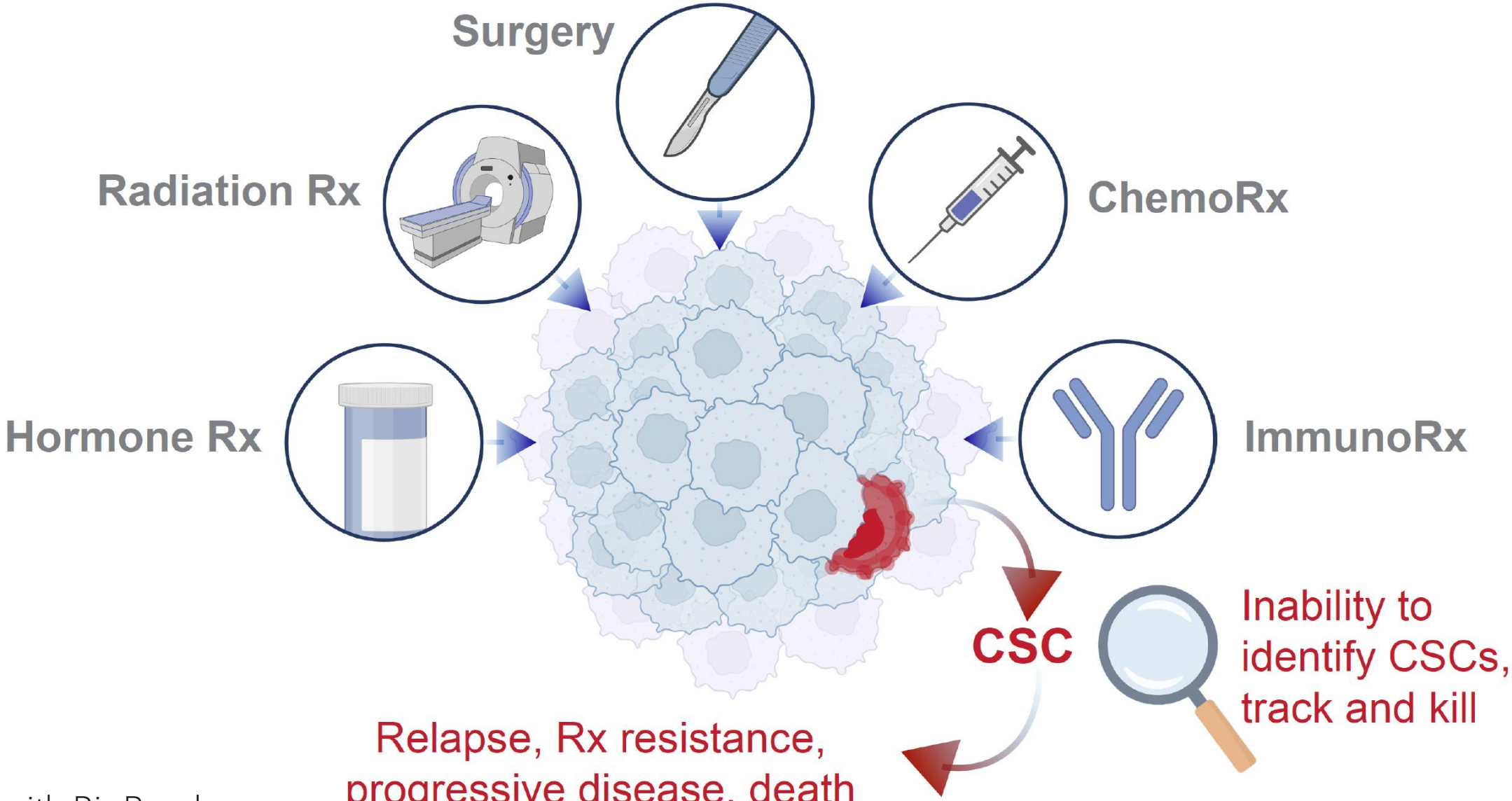
TESTING EFFICACY EARLY ON CAN FIX IT



The Problem: Cancer Stem Cells escape Rx



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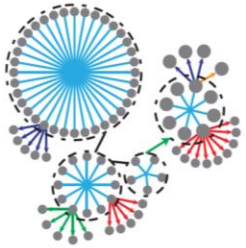
The Solution: Targeted CSC Differentiation

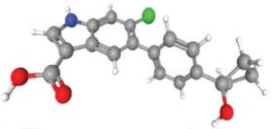
Network-guided identification of a first-in-class agent

Network-prioritized Target



Network transcriptomics

Machine learning

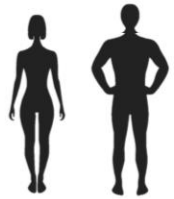


Druggable Target

Network-prioritized Models

Cancer cell lines

Xenografts

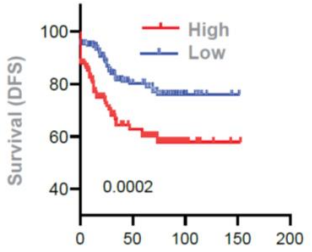


Patient-Derived Organoids-PDOs

Network-based Metrics of Success & Impact

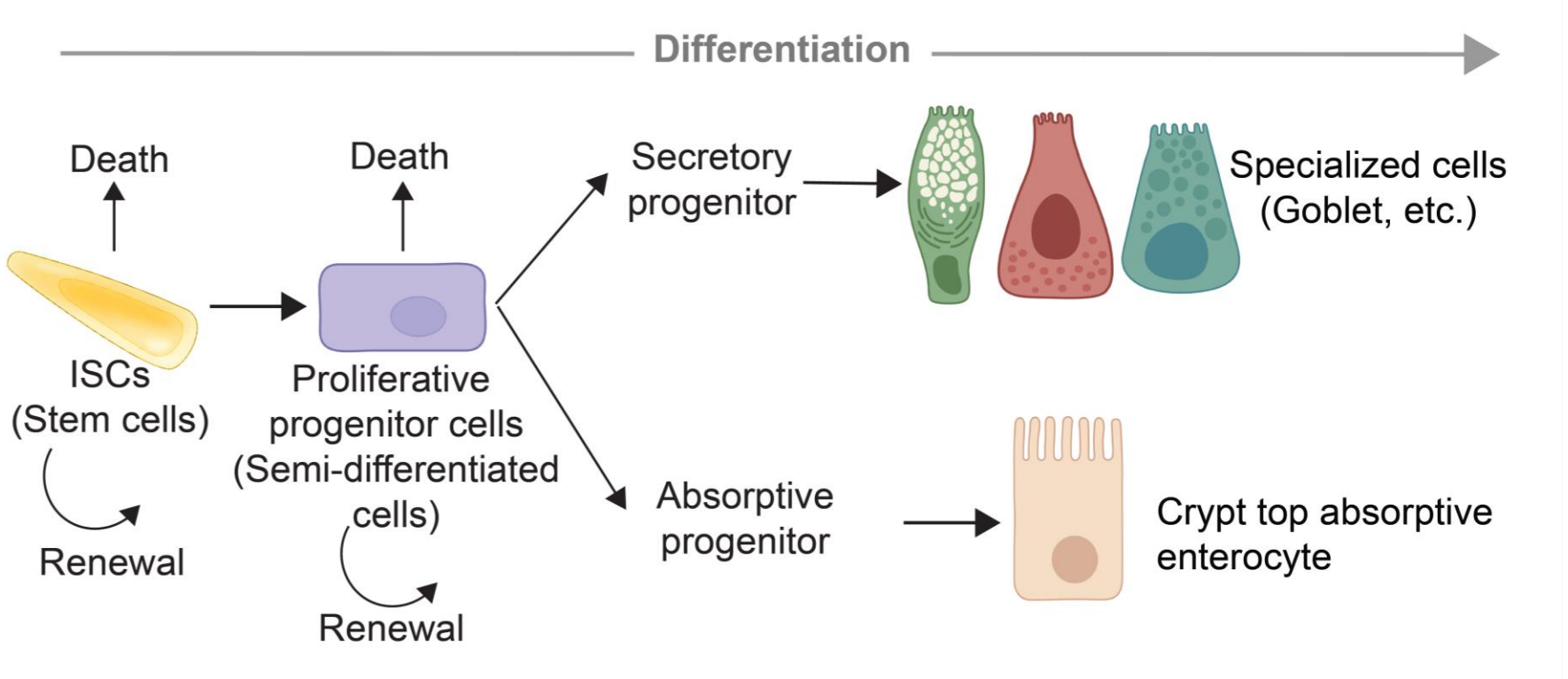
Predictable network perturbation

Rx specificity, Synergy with other Rx modalities



Relapse-free survival

WHAT ARE KEY 'EVENTS' THAT PUSH THE STEMNESS-DIFFERENTIATION AXIS?



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MATHEMATICAL APPROACH: ABSENCE OF CDX2 EQUALS STEMNESS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 21, 2016 VOL. 374 NO. 3

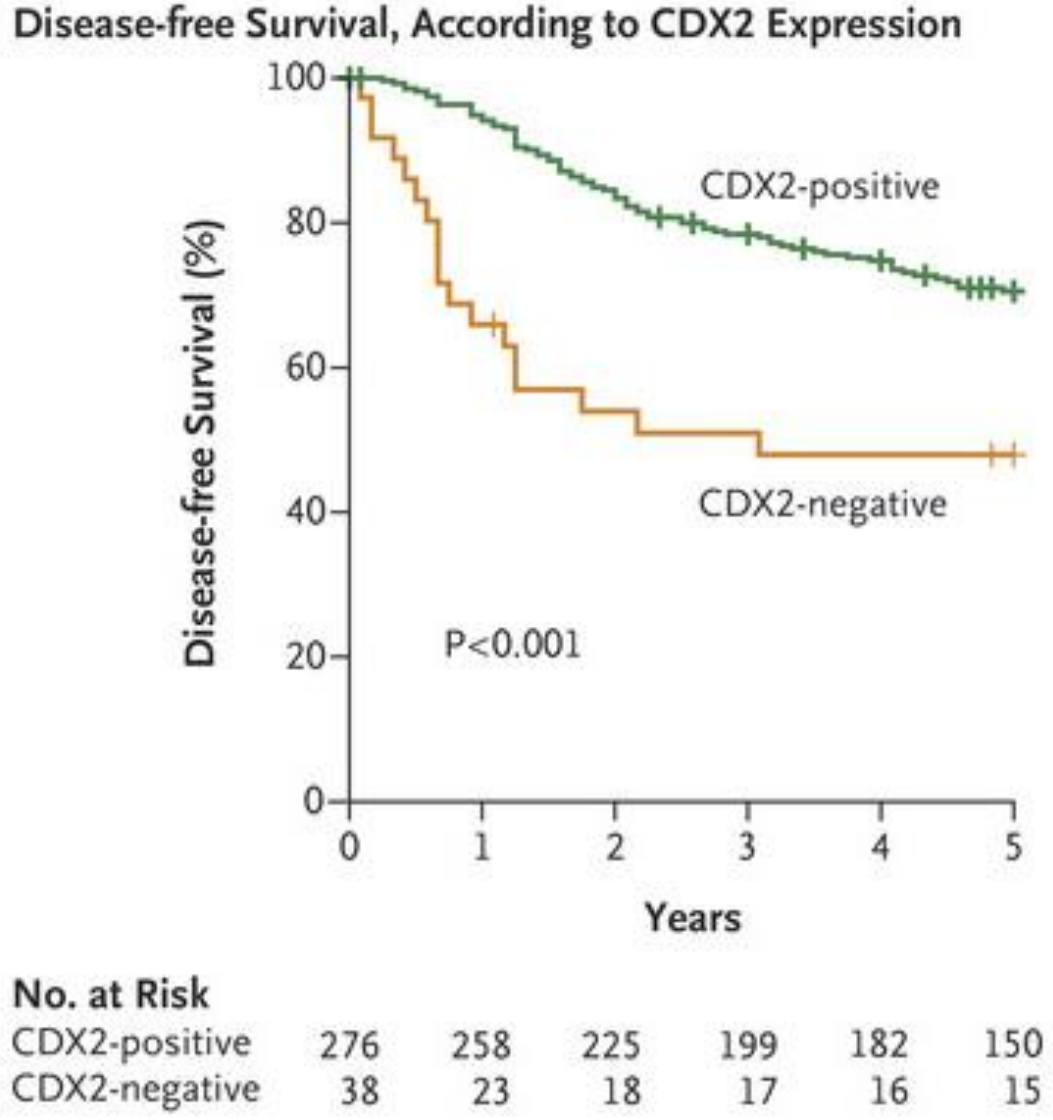
CDX2 as a Prognostic Biomarker in Stage II and Stage III Colon Cancer

Piero Dalerba, M.D., Debashis Sahoo, Ph.D., Soonmyung Paik, M.D., Xiangqian Guo, Ph.D., Greg Yothers, Ph.D., Nan Song, Ph.D., Nate Wilcox-Fogel, M.S., Erna Forgó, M.D., Pradeep S. Rajendran, B.S., Stephen P. Miranda, B.A., Shigeo Hisamori, M.D., Ph.D., Jacqueline Hutchison, Tomer Kalisky, Ph.D., Dalong Qian, M.D., Norman Wolmark, M.D., George A. Fisher, M.D., Ph.D., Matt van de Rijn, M.D., Ph.D., and Michael F. Clarke, M.D.

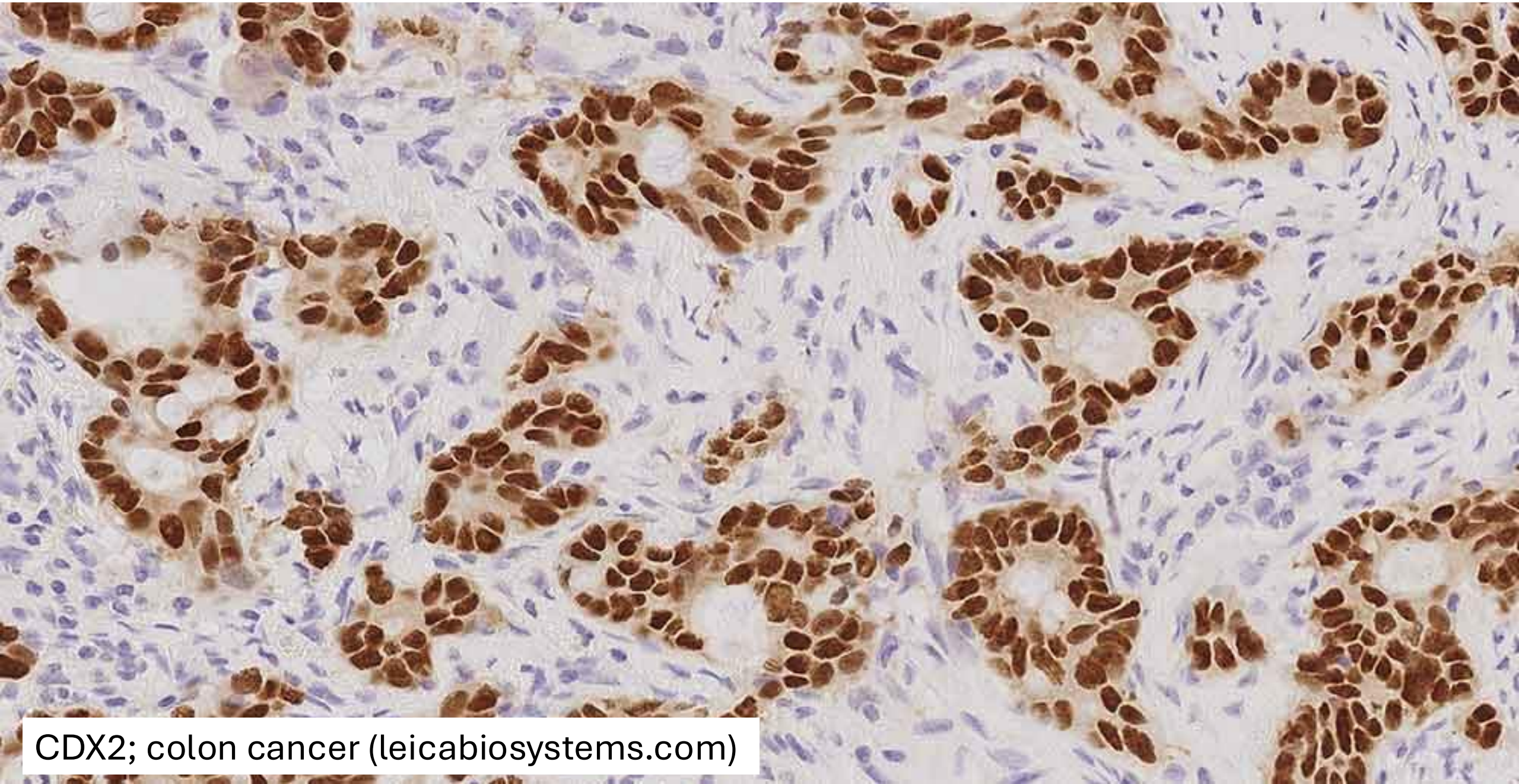
Cell Stem Cell
In Translation

CDX2: Linking Cell and Patient Fates in Colon Cancer

Eric R. Fearon[1,2,3] and Emina H. Huang[4,5,*]
[1]Division of Molecular Medicine and Genetics, Department of Internal Medicine
[2]Department of Pathology
[3]Department of Human Genetics
University of Michigan, Ann Arbor, MI 48109, USA
[4]Department of Stem Cell Biology and Regenerative Medicine
[5]Department of Colorectal Surgery
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH 44195, USA
*Correspondence: huange2@ccf.org
http://dx.doi.org/10.1016/j.stem.2016.01.011



CDX2 (CAUDAL HOMEOBOX 2) IS A TF



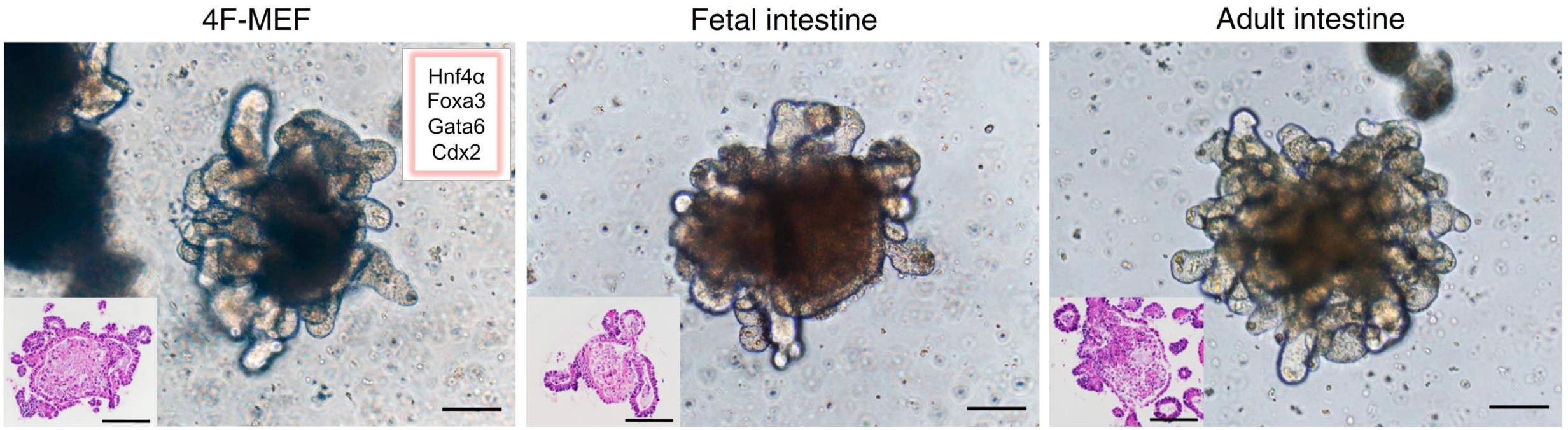
CDX2; colon cancer (leicabiosystems.com)

CDX2 IS ESSENTIAL FOR COMMITTED DIFFERENTIATION INTO INTESTINE

Article

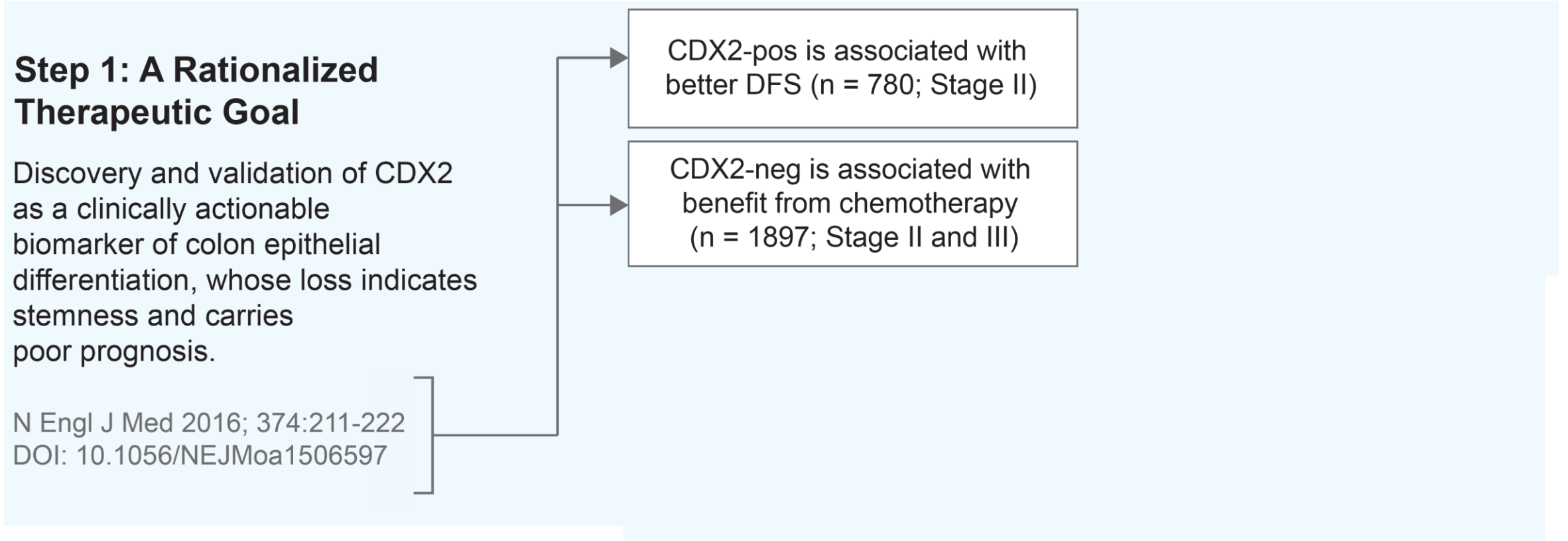
Cell Stem Cell

Generation of Mouse and Human Organoid-Forming Intestinal Progenitor Cells by Direct Lineage Reprogramming



Miura, Shizuka et al. Cell Stem Cell, Volume 21, Issue 4, 456 - 471.e5

PREMISE AND STUDY RATIONALE



MULTIPLE PRIOR ATTEMPTS AT PHARMACOLOGICAL REINSTATEMENT OF CDX2 HAVE FAILED

NETWORK MODEL TO IDENTIFY TARGETS FOR DIFFERENTIATION RX

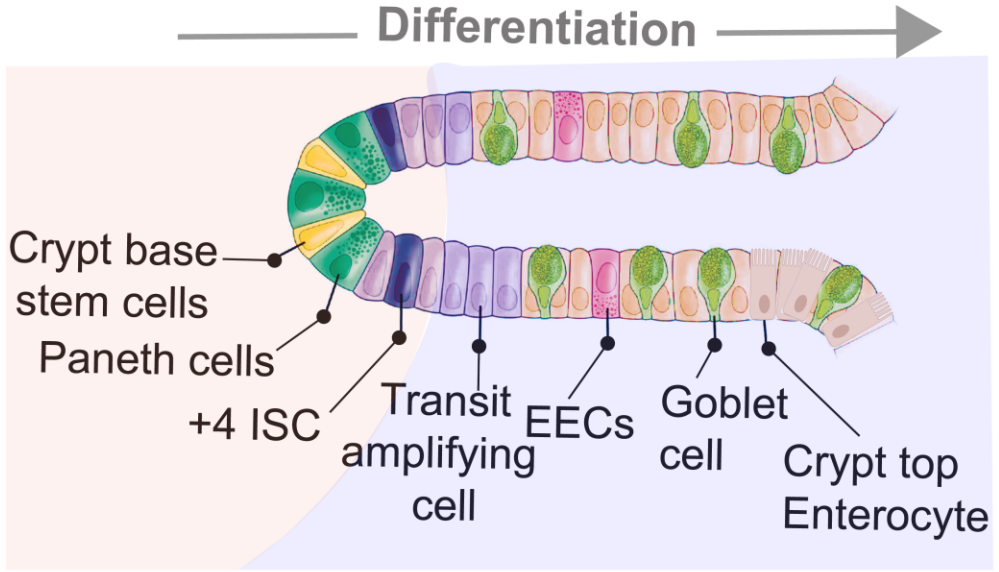
Step 2: Target Identification

Discovery of a clinically actionable therapeutic target to reinstate CDX2

Bioinformatics search for markers of CRC differentiation, using *CDX2* as a 'seed' gene, and based on the fulfilment of the "*CDX2*-neg implies *X*-neg" Boolean relationship identifies 42 putative target genes.

(**Model training**: n=1969 samples; normal =183; adenomas = 85; CRCs =1690).

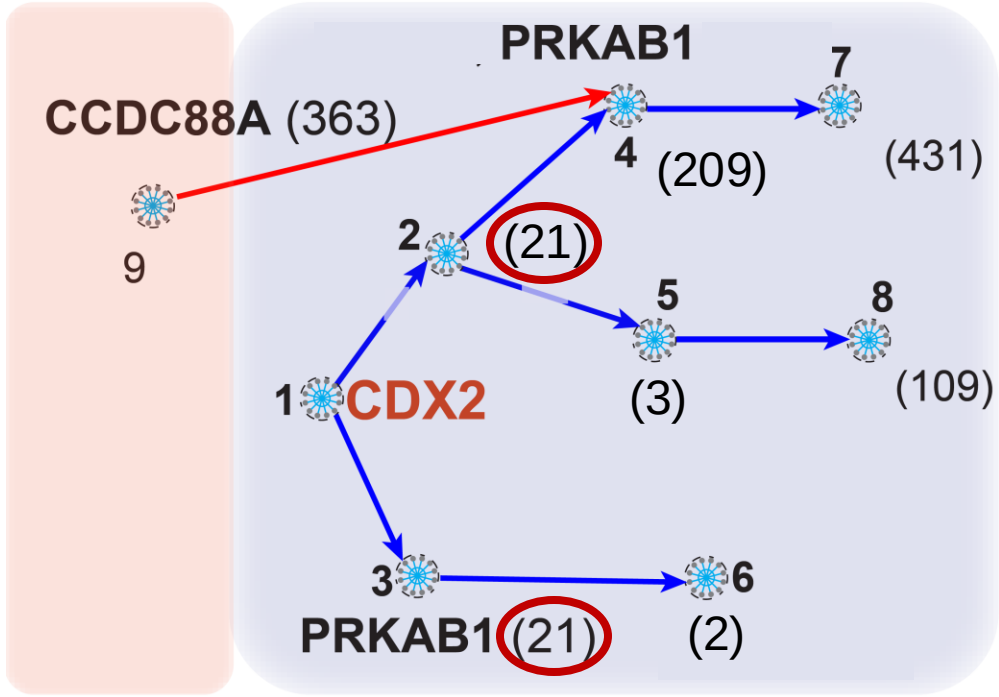
AN ACTIONABLE NETWORK MODEL FOR DIFFERENTIATION THERAPY



Boolean Implication Formula

CDX2 neg => ***"X"*** neg

Numbers in () indicate no. of genes in clusters



BOOLEAN LOGIC: If one of the 42 genes in clusters #2 and #3 are upregulated, ***CDX2*** must be upregulated; ***CCDC88A*** must be downregulated

NETWORK MODEL TO IDENTIFY TARGETS FOR DIFFERENTIATION RX

PreCSN

Step 2: Target Identification

Discovery of a clinically actionable therapeutic target to reinstate CDX2

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(**Model training**: n=1969 samples; normal =183; adenomas = 85; CRCs =1690).

(**Model validation**: 1911 human; 107 mouse)

NETWORK-GUIDED TARGET VALIDATION

Institute for Network Medicine

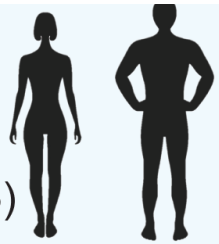
Step 3: Target Validation

Models

Hu CRC cell lines
(n = 4)

CRC
Xenograft

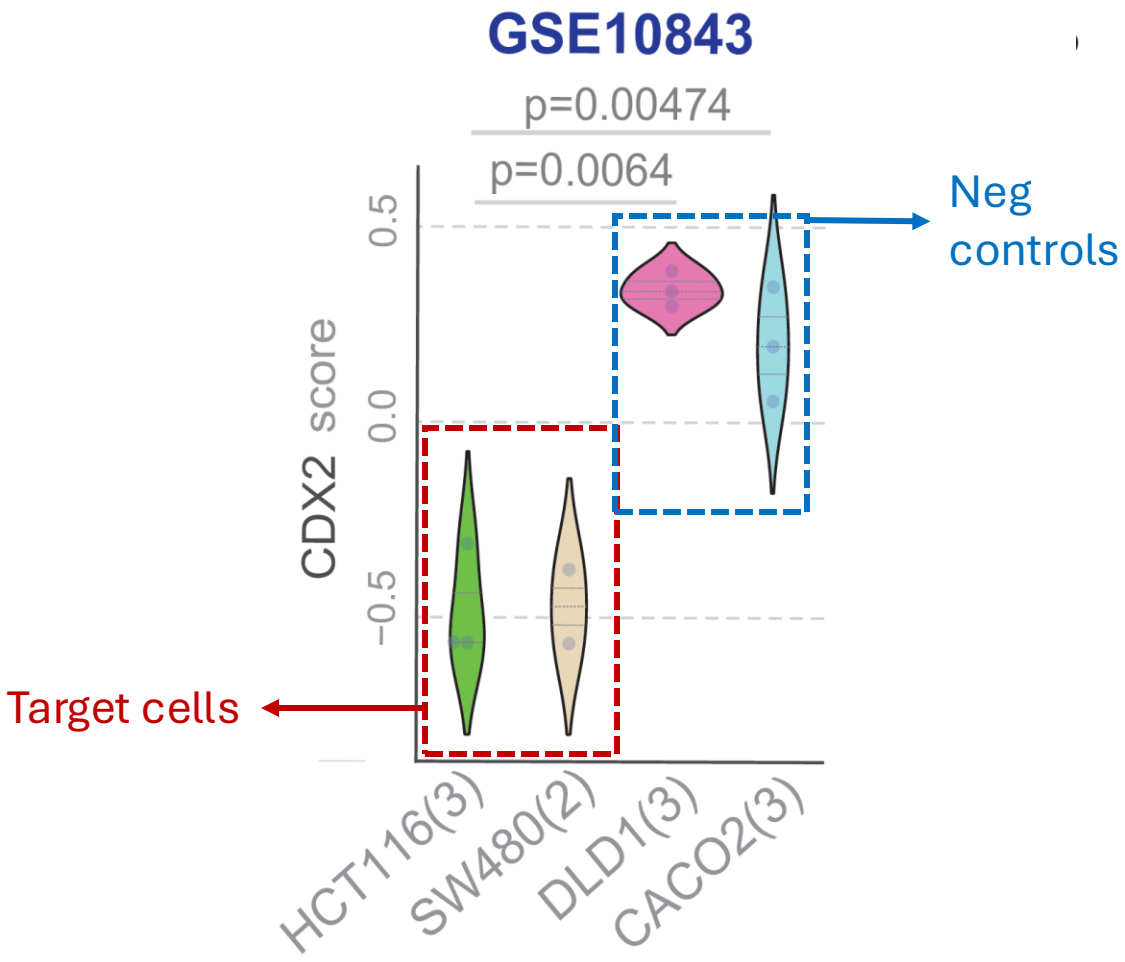
Patient-Derived
Organoids-PDOs
(healthy 3, CRC 23)



We Leveraged The ATCC® Catalog to Acquire Established CRC Lines

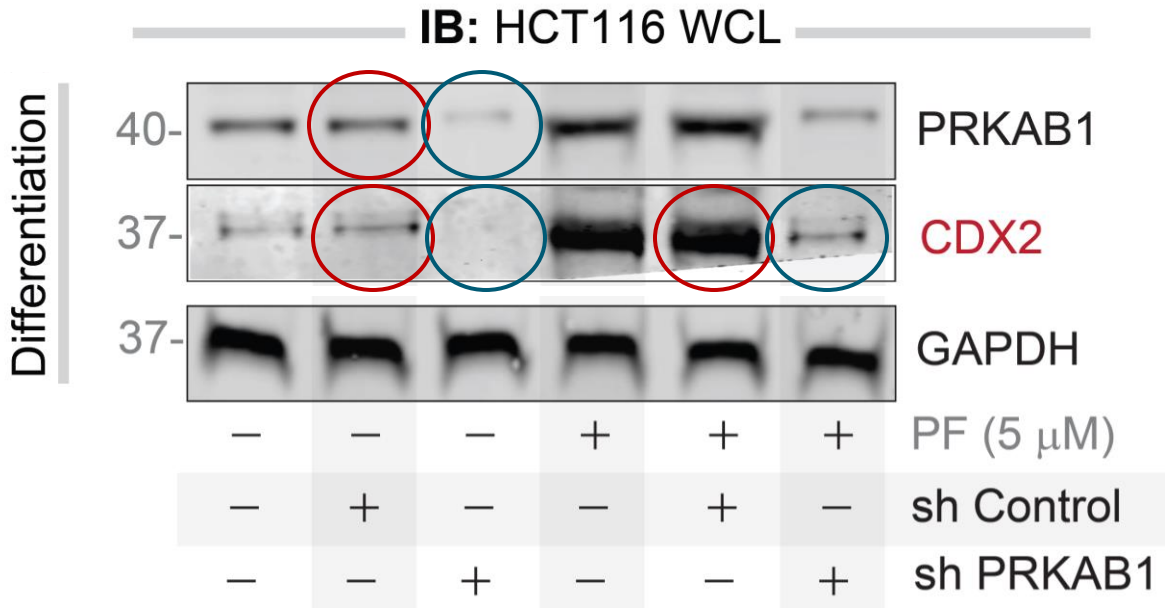
ATCC® Cat No.	Cell Line
CCL-247	HCT116
CCL-228	SW480 [SW-480]
CCL-221	DLD1
HTB-37	Caco-2

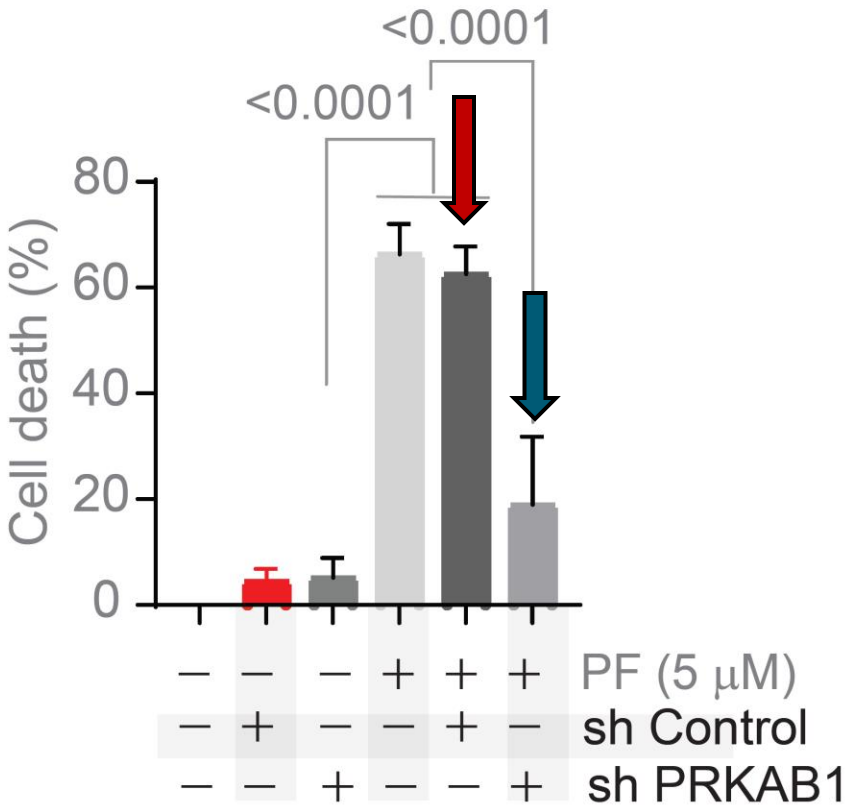
NETWORK-GUIDED MODEL SELECTION



- ✓ Impact of Rx was dose dependent
- ✓ No impact on DLD1 and Caco2 cells
- ✓ Induction of protein (CDX2 and other markers) by immunoblotting
- ✓ Late apoptosis as Mechanism of Death (FACS)

TARGET SPECIFIC ACTION





NETWORK-GUIDED MODEL SELECTION

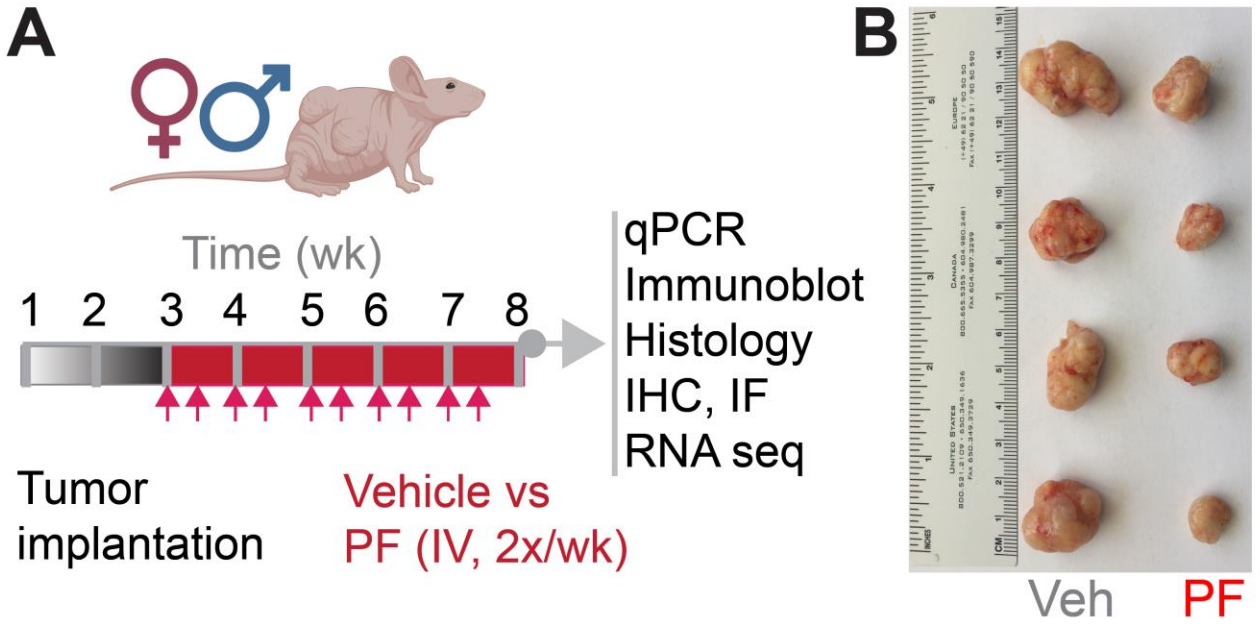
Michael Bouvet

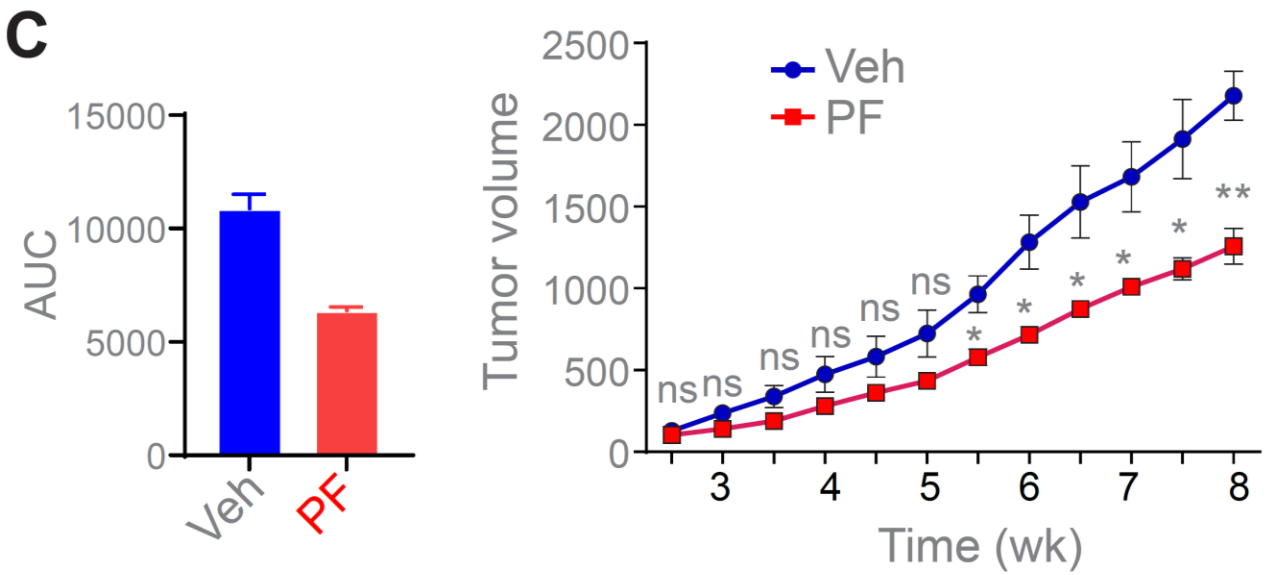
Siamak Amirfakhri

Saptarshi Sinha

Joshua Alcantara

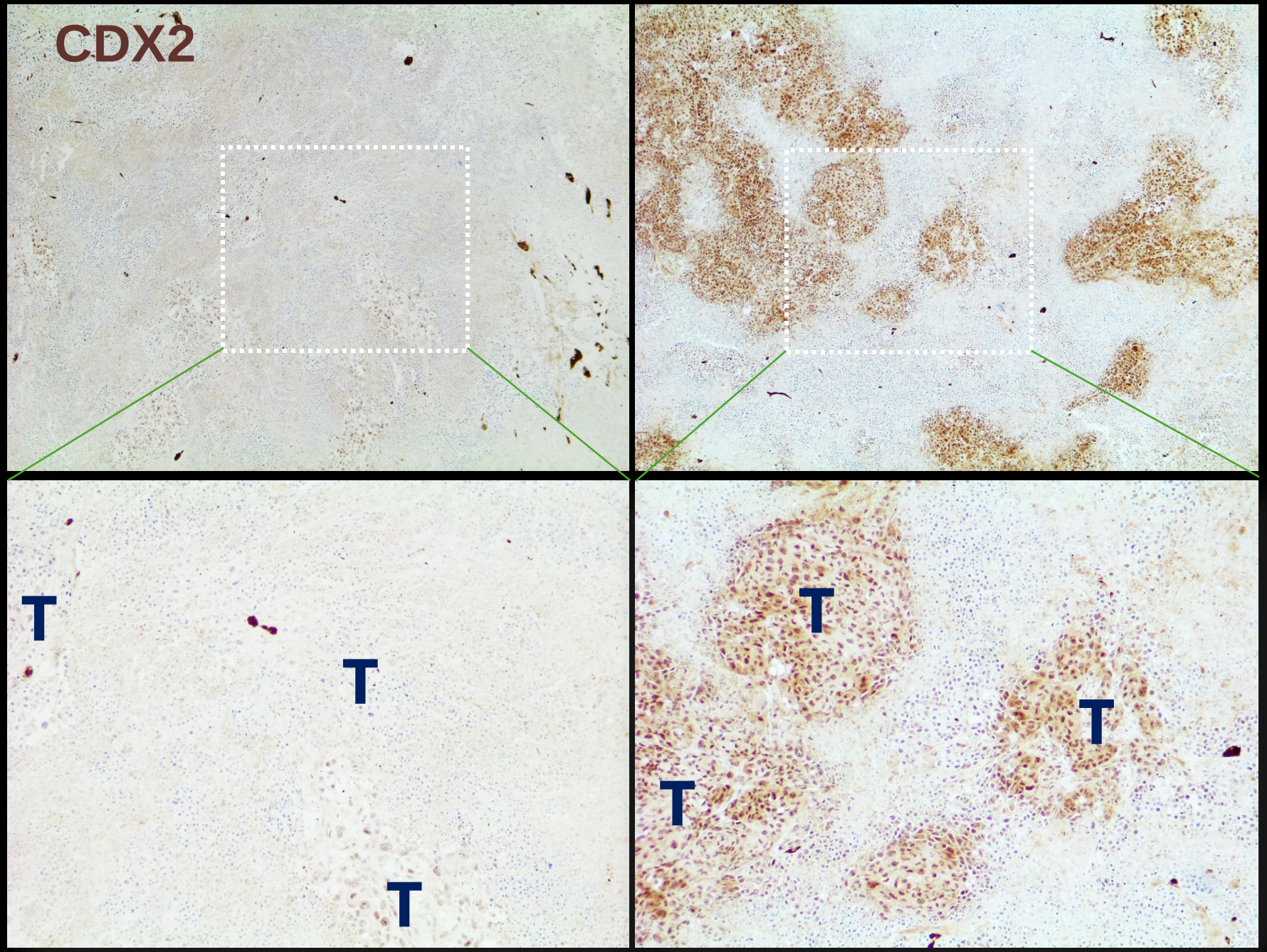
Vanessa Castillo-LFL





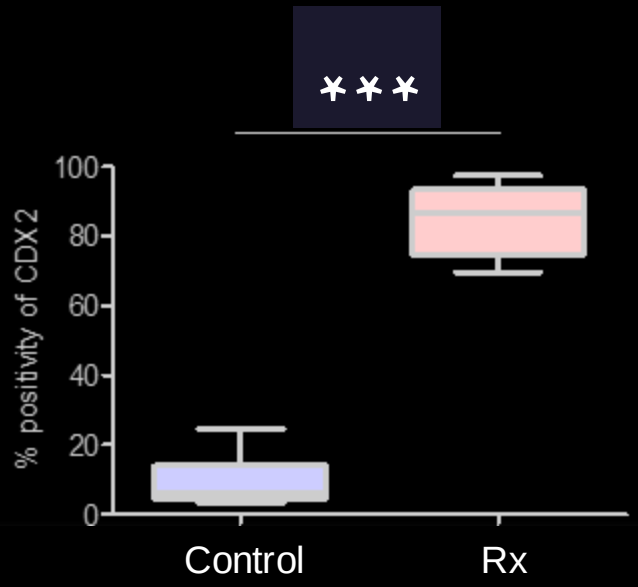
Vehicle

PF



CDX2 is successfully induced in HCT116 cell xenotransplants

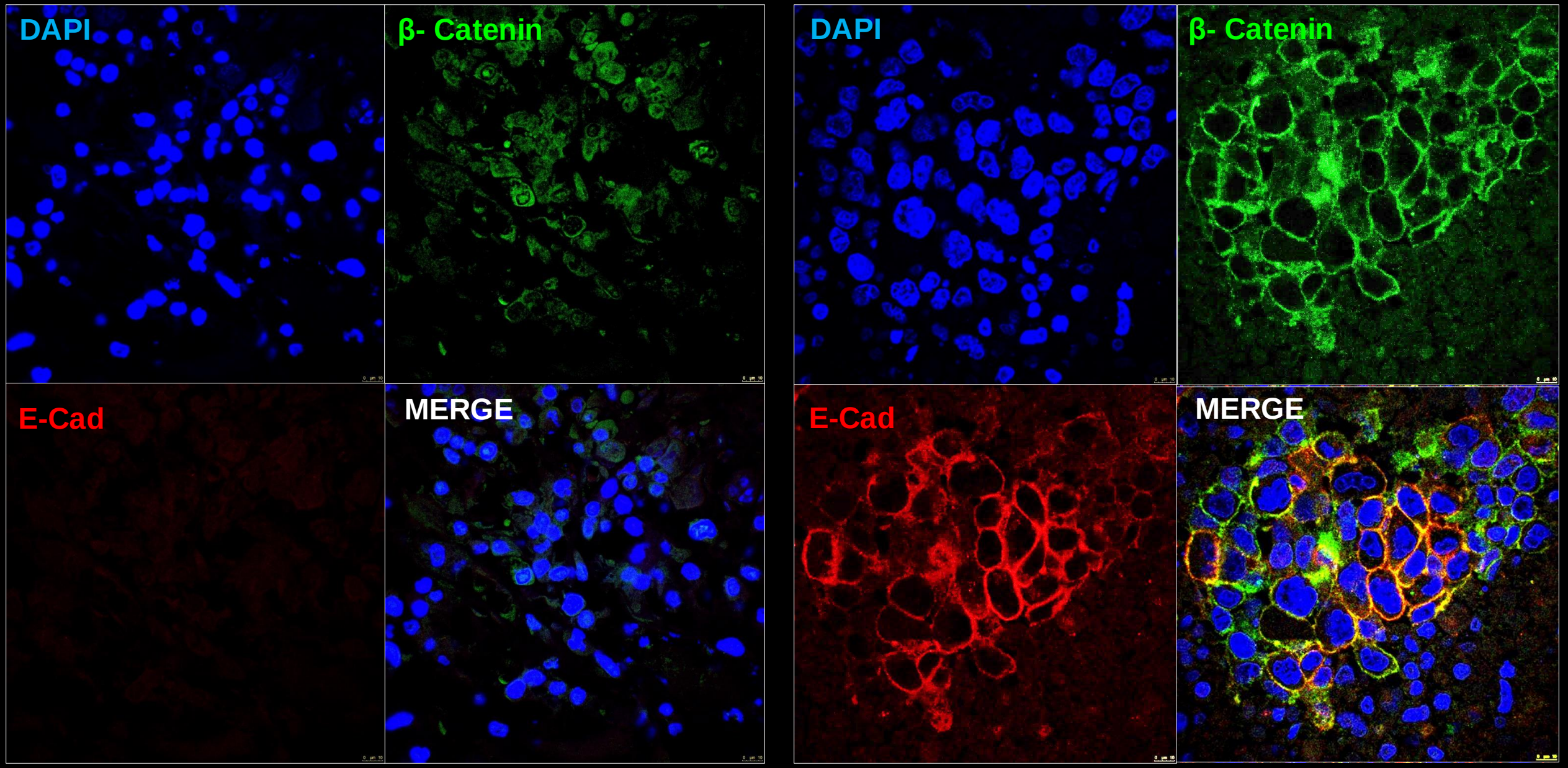
T = viable tumor



CDX2 induction promotes βCat/E-Cadh localization at junctions

Veh-treated Xenografts

PF-Treated Xenografts



DOES IT WORK IN HUMAN PHASE 'ZERO' TRIAL?

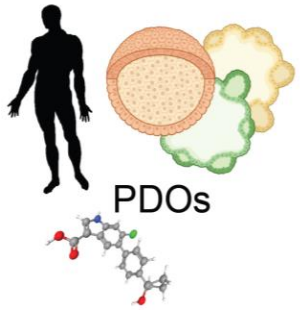
We Leveraged The ATCC® Catalog to Build a Cohort

ATCC® Cat No.	Cohort #	Age	Sex	Race	Primary Site
PDM-255™	1	73	F	White	Colon
PDM-356™	2	58	M	Unk	Colon
PDM-8™	2	75	M	Asian	Colon
PDM-191™	1	56	M	White	Rectum
PDM-264™	2	67	F	White	Rectosigmoid junction
PDM-5™	2	60	F	White	Colon
PDM-275™	1	73	F	White	Colon
PDM-4™	1	50	M	White	Colon
PDM-95™	2	61	M	Black	Colon
PDM-279™	1	51	M	Black	Colon
PDM-2™	1	68	M	White	Colon
PDM-50™	1	78	M	White	Colon

ATCC® Cat No.	Cohort #	Age	Sex	Race	Primary Site
PDM-9™	1	63	M	Asian	Colon
PDM-276™	2	54	M	Black	Colon
PDM-1™	1	75	M	White	Colon
PDM-185™	1	71	M	White	Colon
PDM-94™	2	67	M	White	Colon
PDM-7™	2	75	M	Black	Colon
PDM-257™	2	53	F	Unk	Rectosigmoid junction
PDM-363™	2	72	M	Unk	Colon
PDM-277™	2	76	F	White	Colon
PDM-359™	2	64	F	Unk	Colon
PDM-103™	2	51	F	Black	Colon

ONLY LOW CDX2 PDOs ARE SENSITIVE TO RX

ATCC®



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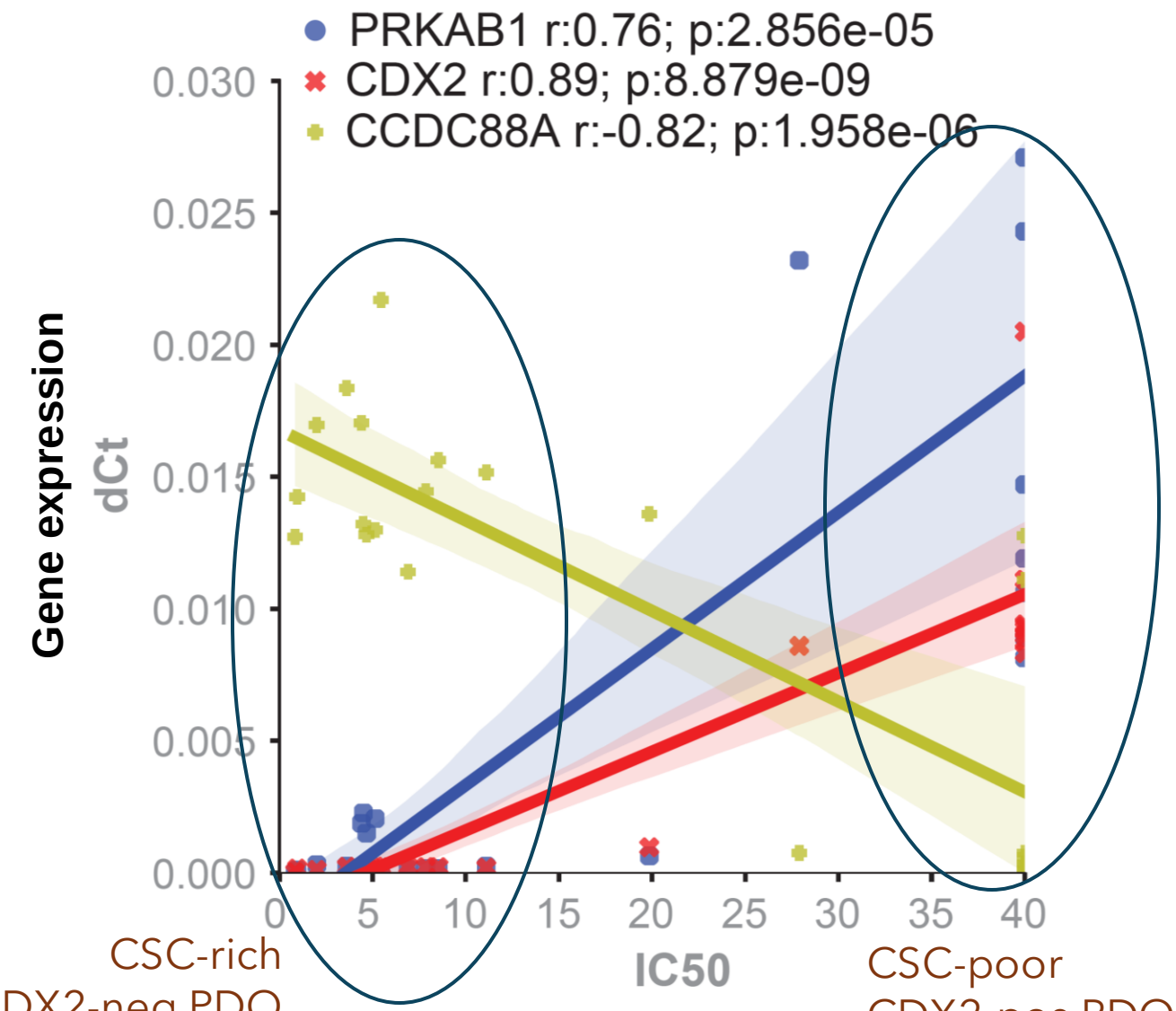
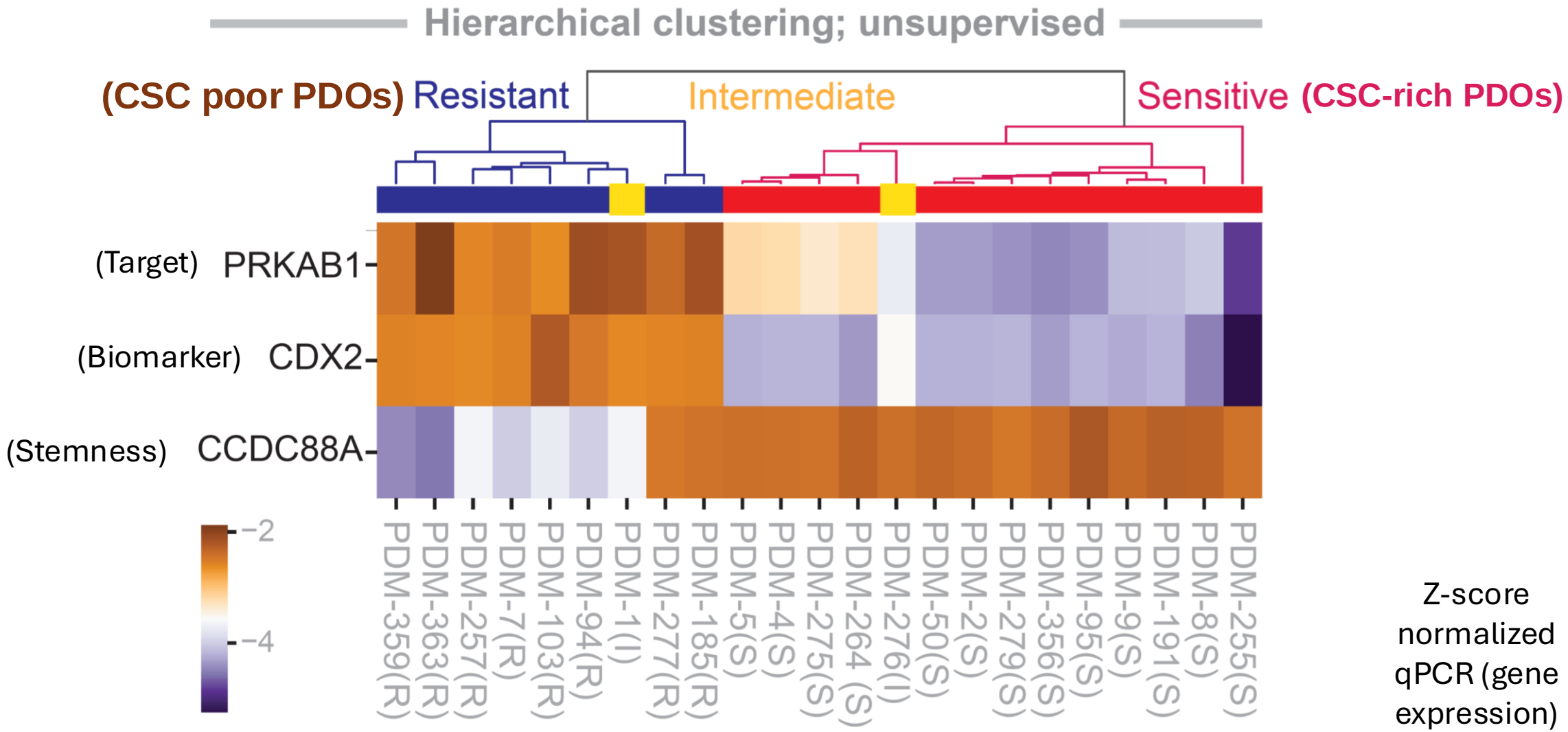
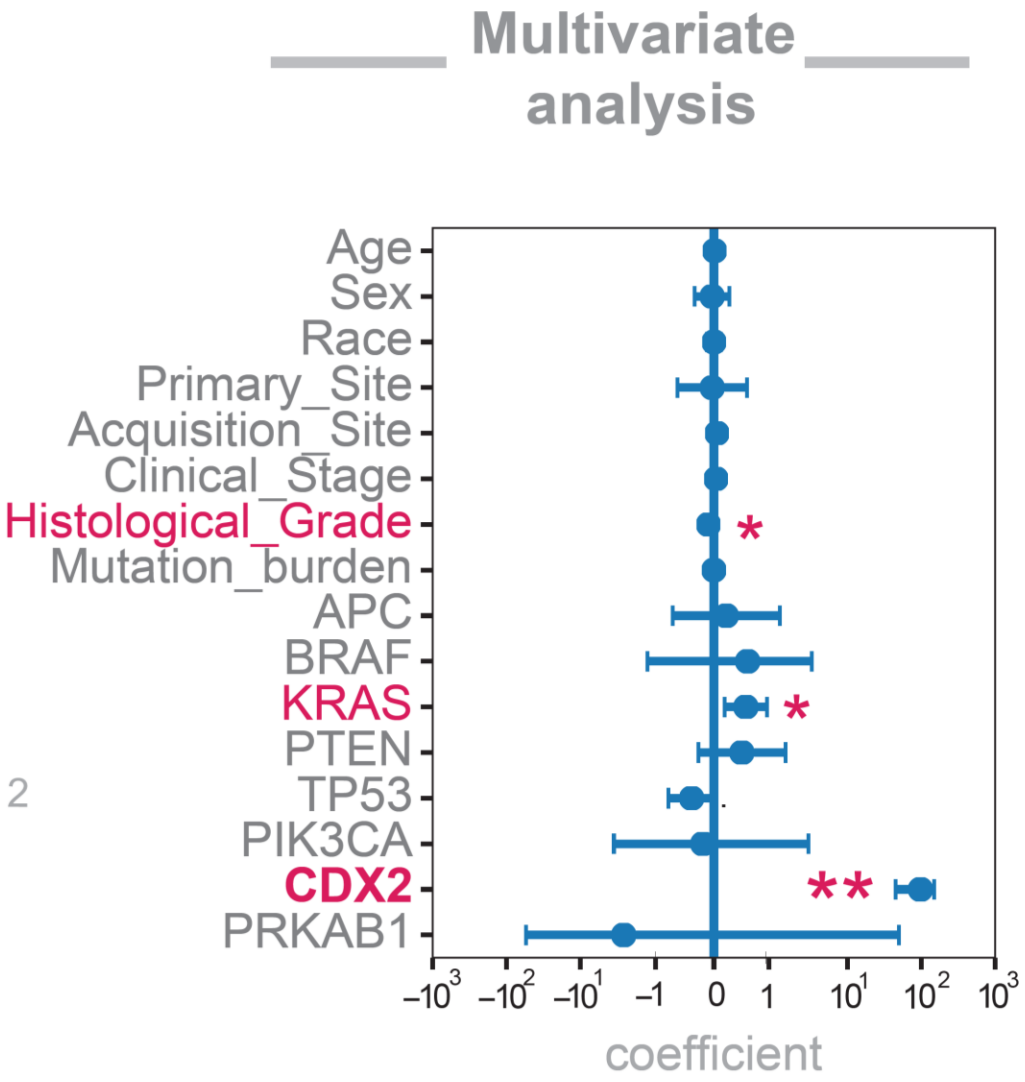


ONLY LOW CDX2 PDOs ARE SENSITIVE TO RX



Z-score normalized qPCR (gene expression)

CDX2, GRADE AND KRAS STATUS ARE CO-VARIATES



Saptarshi Sinha

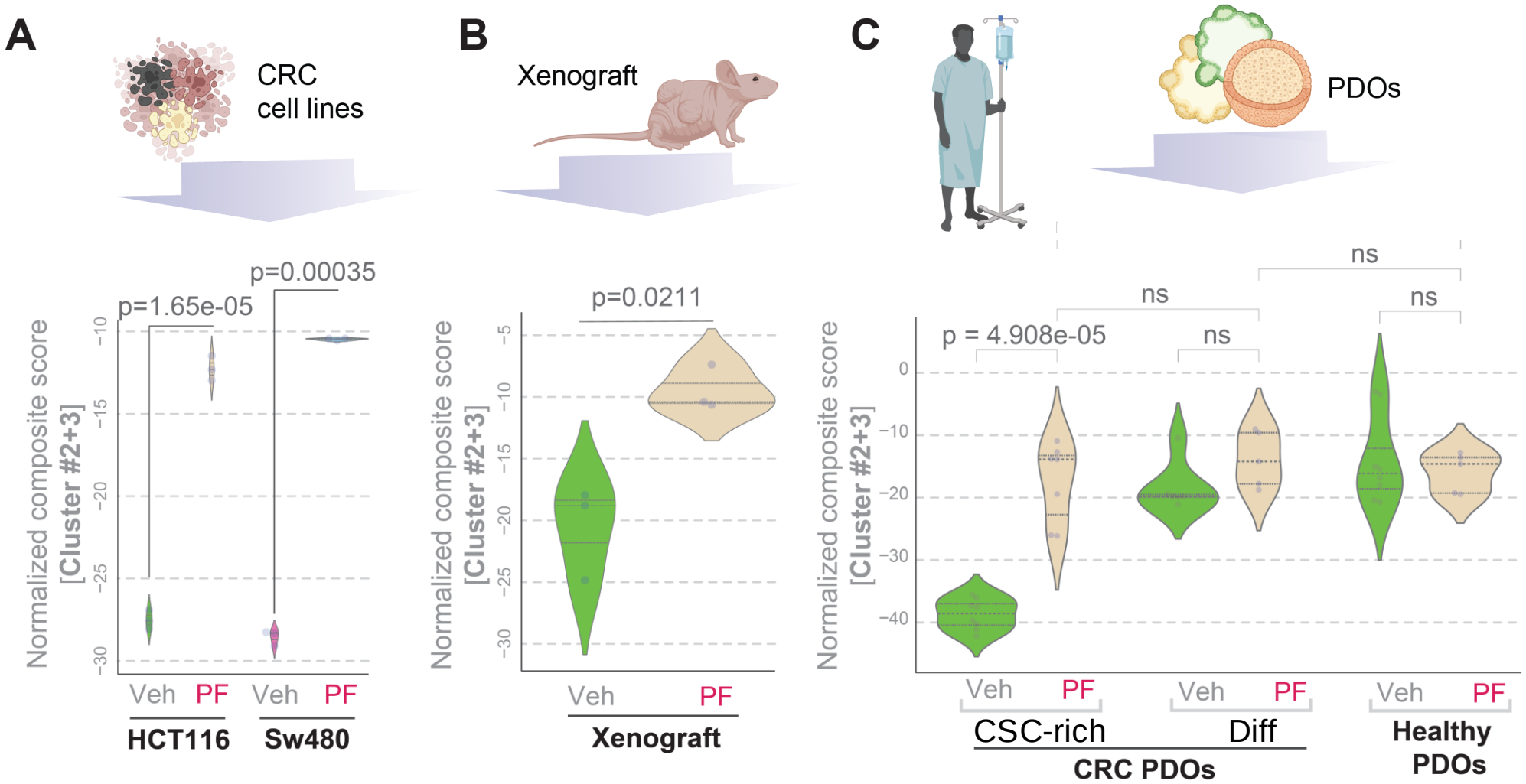
OBJECTIVE METRICS:

- ❑ Reinstate CDX2;
- ❑ Reverse differentiation-axis;
- ❑ Reset the network

Sahar Taheri
(GSR, CSE)

Saptarshi Sinha
(PDF, CMM)

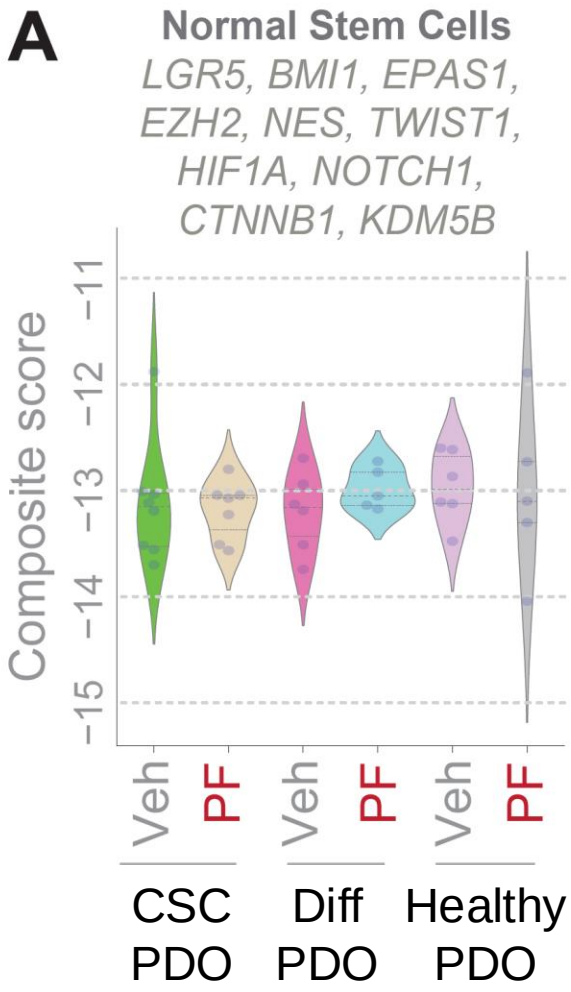
Impact on Network
[Induction of C #2+3]



CAN WE MEASURE IMPACT?

1) SAFETY
2) EFFICACY [SAVE LIVES]
3) OTHER RX MODALITIES

SELECTIVITY: RX KILLS CSCs; NOT NORMAL STEM OR DIFFERENTIATED CELLS

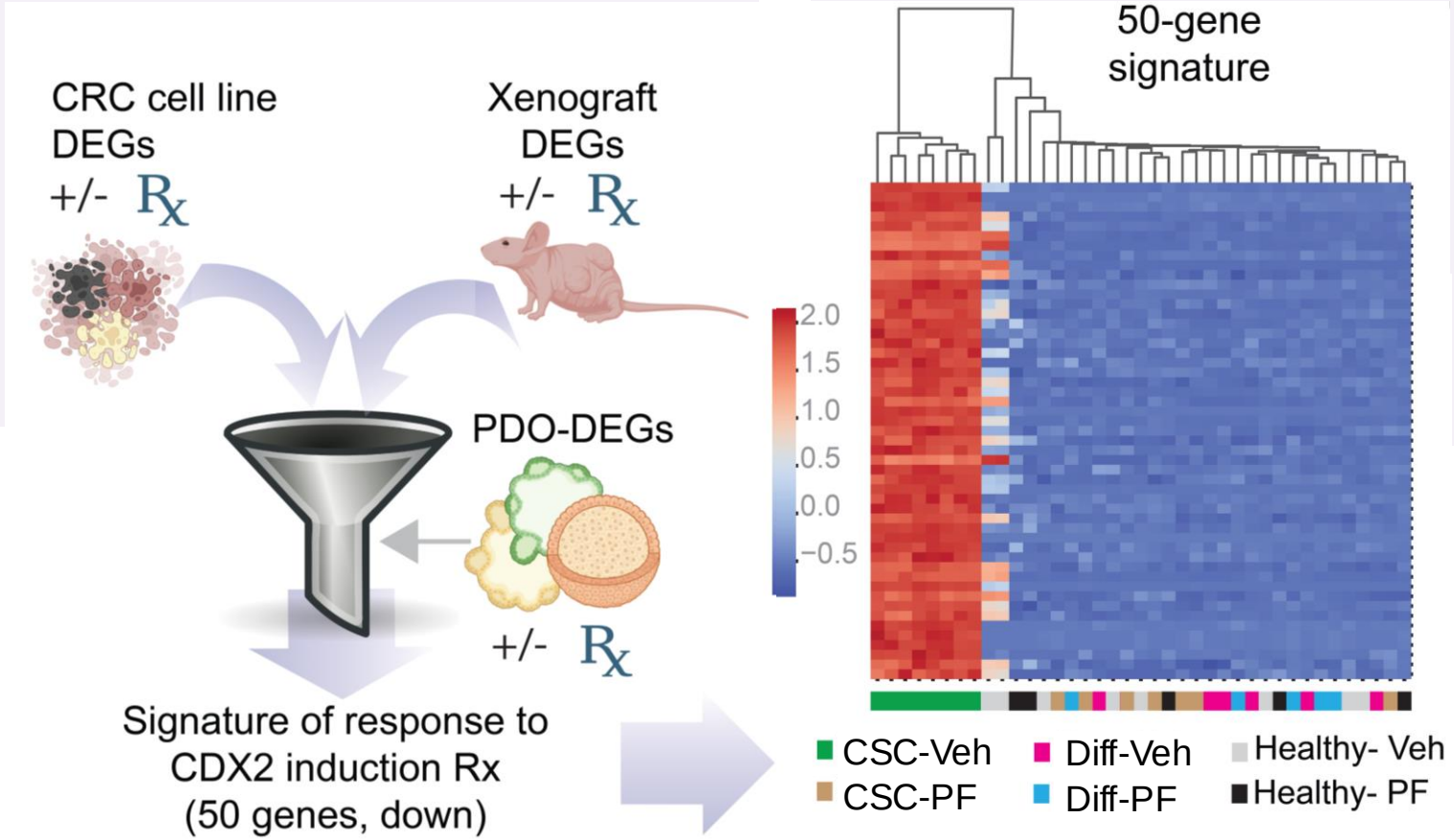


CAN WE MEASURE THE IMPACT OF RX ON LIVES OF PATIENTS?

Step 4: Impact of Differentiation Therapy

Estimation of the impact of therapeutic reinstatement of CDX2 on disease-free/relapse-free (DFS/RFS) and overall (OS) survival

Integrated differential expression analysis between treated vs untreated samples using all 3 models



CAN WE MEASURE THE IMPACT OF RX ON LIVES OF PATIENTS?

Step 4: Impact of Differentiation Therapy

Estimation of the impact of therapeutic reinstatement of CDX2 on disease-free/relapse-free (DFS/RFS) and overall (OS) survival

Integrated differential expression analysis between treated vs untreated samples using all 3 models

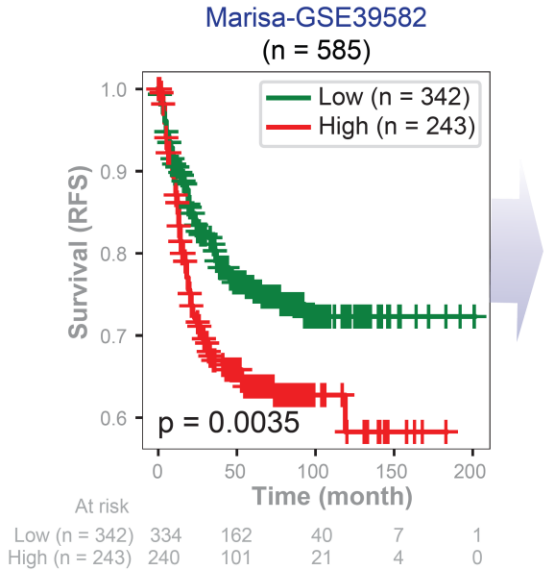
→ Derivation of a 50-gene signature of therapeutic response

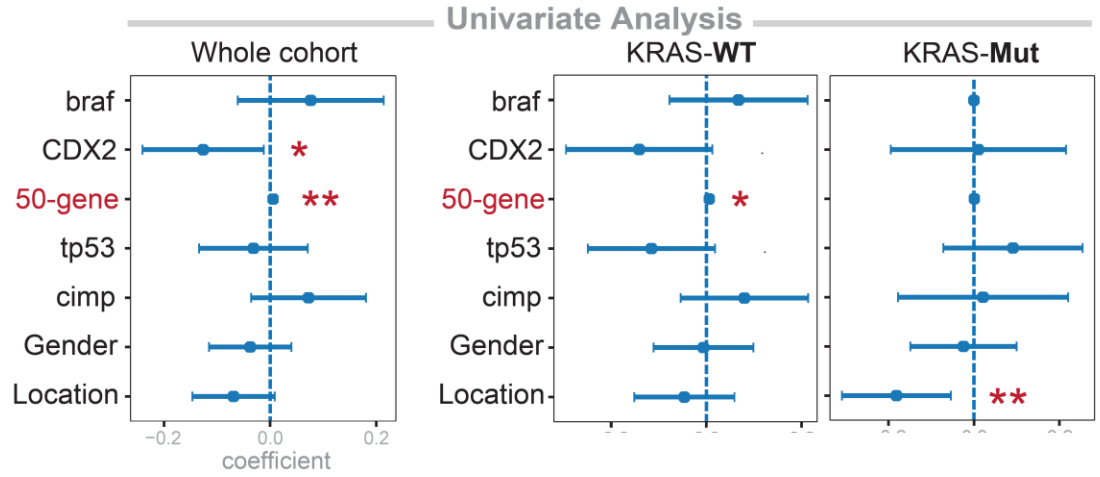
↓

Prognostic impact of the 50-gene signature assessed on 2472 unique subjects with CRCs in 10 independent cohorts

Univariate analysis based on the Cox-proportional hazards method on 585-patient cohort

SUPPRESSION OF 50-GENE SIGNATURE SHOULD IMPROVE SURVIVAL





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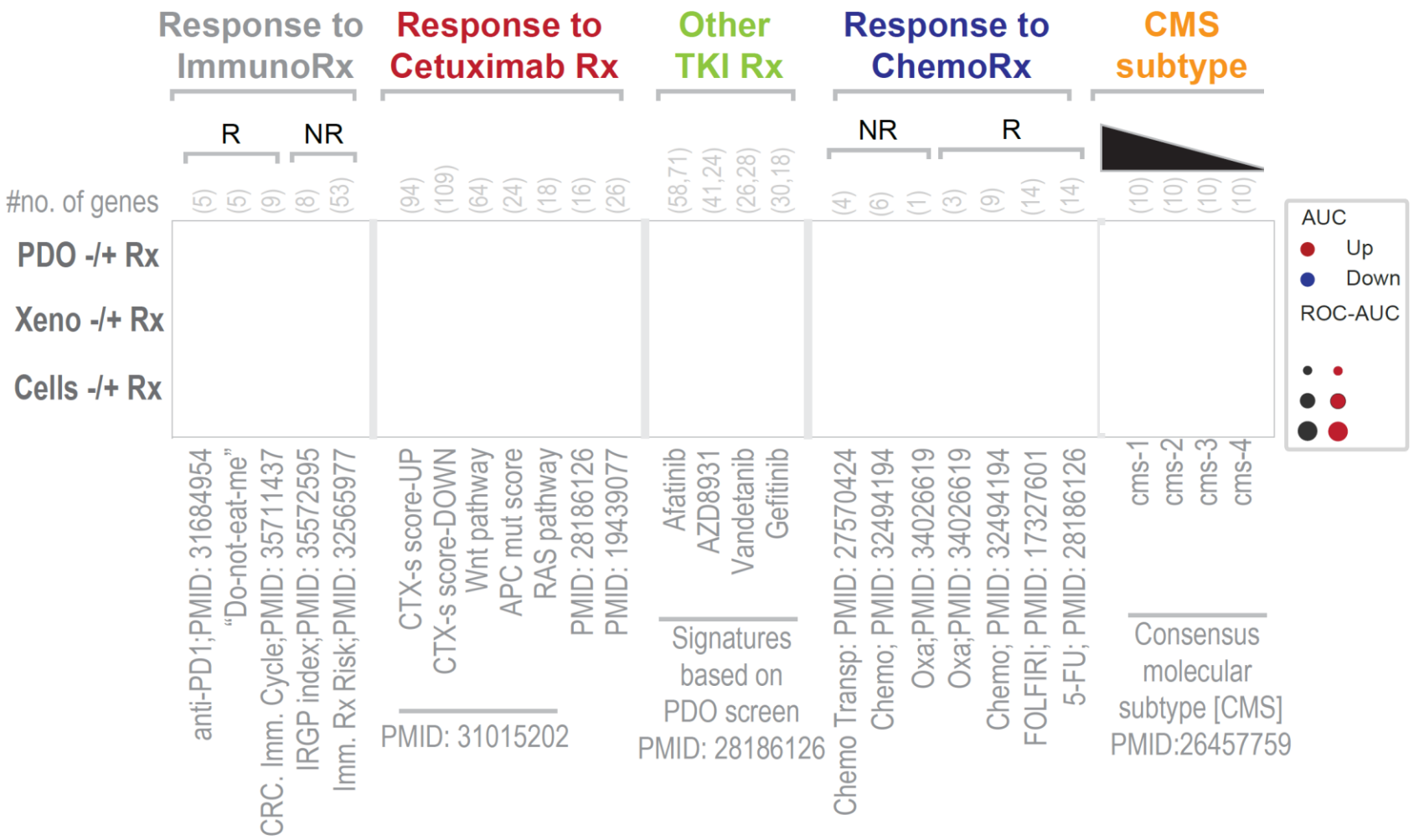
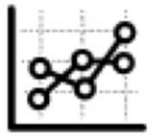
EXPECT SYNERGY WITH EXISTING MODALITIES



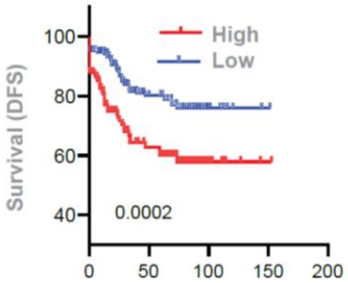
Evaluating Our Metrics Of Success

Network-based Metrics of Success & Impact



Predictable network perturbation

Rx specificity, Synergy with other Rx modalities



Relapse-free survival

MEET US AT PHASE '0'

Thank You

Precision Computational Systems Network

PreCSN

Curate

Build

Validate

Targets

Institute for Network Medicine

Create

Validate

Phase '0'

Center of Research Excellence

HUMANOID™

USING BOOLEAN NETWORK EXPLORER [BoNE]

USING HUMAN ORGANOID-BASED MODELS OF DISEASES

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