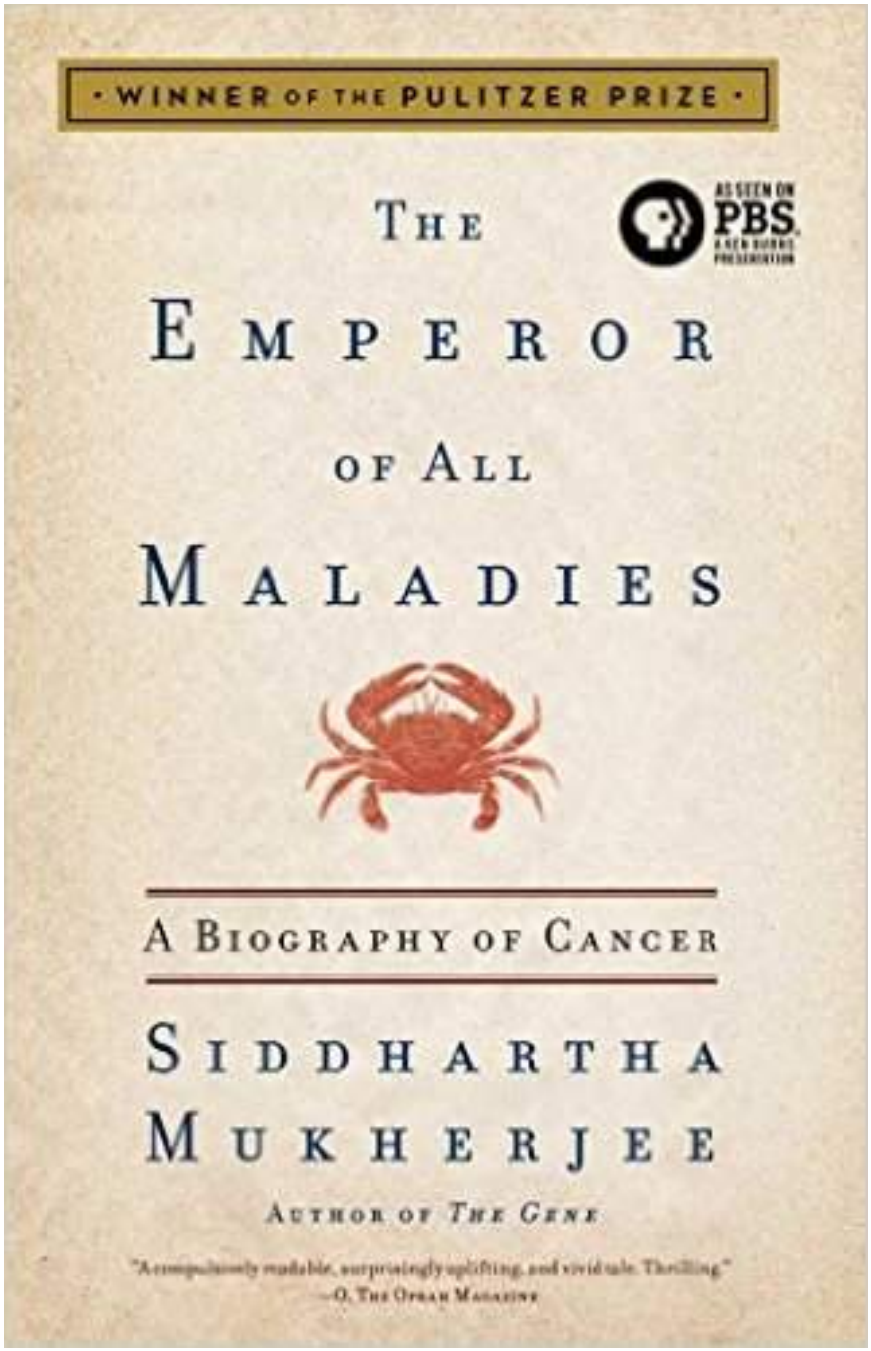
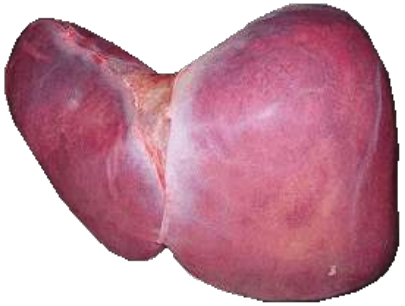
Dynamical systems biology of cancer metastasis

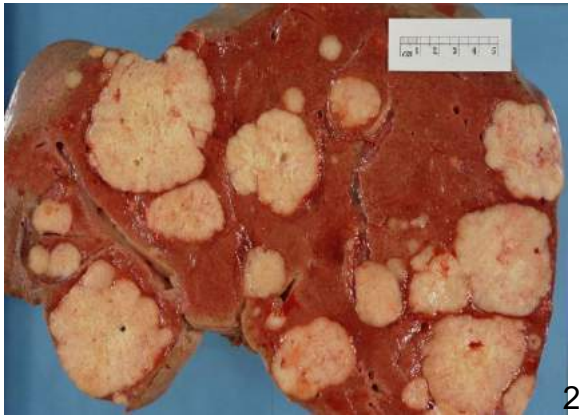
Mohit Kumar Jolly
Assistant Professor
Centre for Biosystems Science and Engineering, IISc, Bangalore
mkjolly@iisc.ac.in

July 5, 2019
DMPH 2019 | ICTS Bangalore

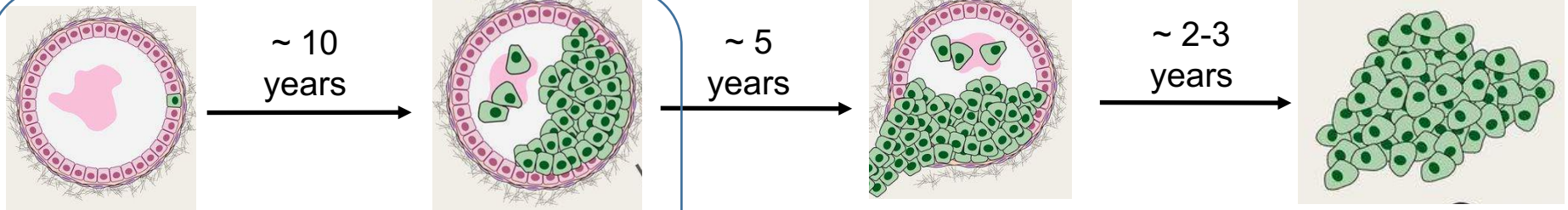




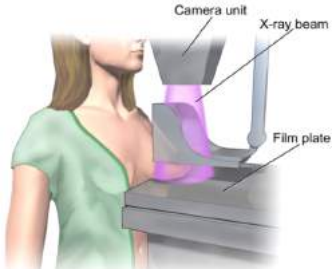
Uncontrolled growth of abnormal cells



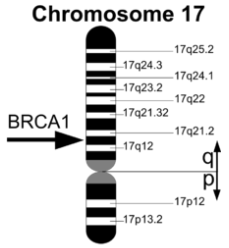
Stages of cancer progression



Remarkable progress made in:



Diagnosing cancer early



Listing the genes involved

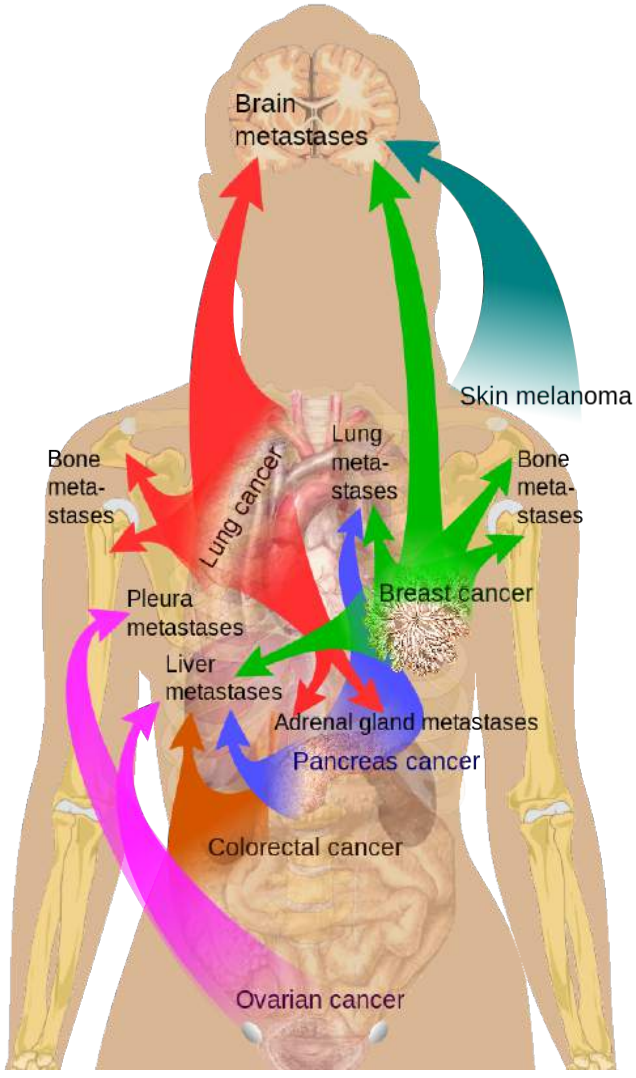
Identifying risk factors

?

Developing new therapies

Sas-Chen *et al.* Biochem Soc Trans 2017

Metastasis : the cause of 90% of all cancer deaths



More than 80% cancers happen in epithelial organs, i.e. cells that do NOT move/invade.

What traits cells need to successfully metastasize?

- Metastasis is a highly inefficient process.
- It requires dynamic/adaptive changes in:

✓ Adhering to their neighbors

✓ Ability to migrate and invade

✓ Evading attacks by immune system

✓ Settling down in a new organ and colonizing it

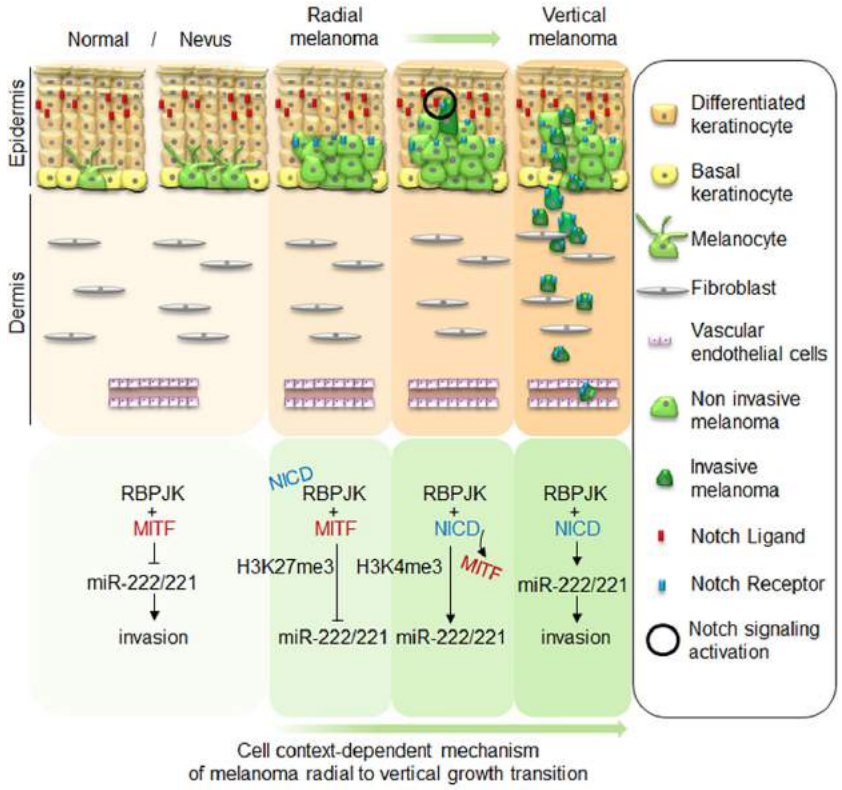
✓ Resist multiple therapies/drugs given to patients

Thus, to restrict metastasis, we first need a dynamic and systems-level understanding of the process to identify how cells alter these multiple traits together

Is genetics the answer? Not always

- Large amount of money spent on cancer genomics, but no unique signature has emerged for metastasis

- An example: Melanoma metastasis

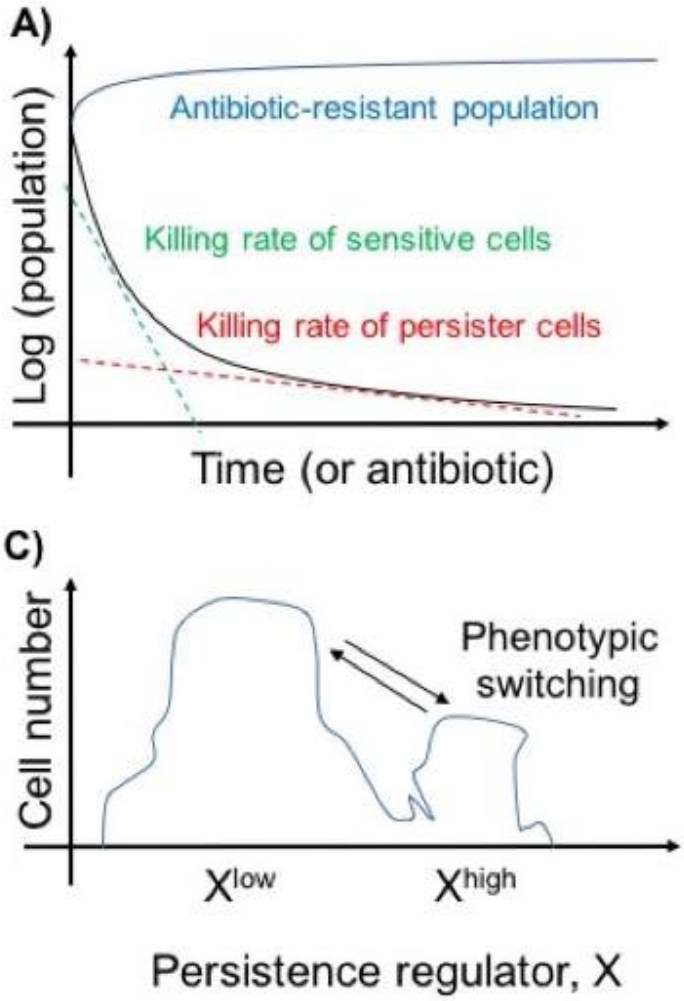


Cells become metastatic competent by being exposed to a new chemical environment

Phenotypic transition is not caused by additional mutations

Golan *et al.* Mol Cancer 2015

Can cancer proceed without mutations? Perhaps!



A Chromatin-Mediated Reversible Drug-Tolerant State in Cancer Cell Subpopulations

Sreenath V. Sharma,[1] Diana Y. Lee,[1] Bihua Li,[1] Margaret P. Quinlan,[1] Fumiyuki Takahashi,[1] Shyamala Maheswaran,[1] Ultan McDermott,[1] Nancy Azizian,[1] Lee Zou,[1] Michael A. Fischbach,[1] Kwok-Kin Wong,[2] Kathleyn Brandstetter,[2] Ben Wittner,[1] Sridhar Ramaswamy,[1] Marie Classon,[1,3,*] and Jeff Settleman[1,3,*]
[1]Massachusetts General Hospital Cancer Center, 149 13th Street, Charlestown, MA 02129, USA
[2]Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115, USA
[3]These authors contributed equally to this work
*Correspondence: classon@helix.mgh.harvard.edu (M.C.), settleman@helix.mgh.harvard.edu (J.S.)
DOI 10.1016/j.cell.2010.02.027

Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition

Aaron N Hata[1,2,14], Matthew J Niederst[1,2,14], Hannah L Archibald[1], Maria Gomez-Caraballo[1], Faria M Siddiqui[1], Hillary E Mulvey[1], Yosef E Maruvka[1,3], Fei Ji[4], Hyo-eun C Bhang[5], Viveksagar Krishnamurthy Radhakrishna[5], Giulia Siravegna[6,7], Haichuan Hu[1], Sana Raoof[1,2], Elizabeth Lockerman[1], Anuj Kalsy[1], Dana Lee[1], Celina L Keating[5], David A Ruddy[8], Leah J Damon[1], Adam S Crystal[1,13], Carlotta Costa[1,2], Zofia Piotrowska[1,2], Alberto Bardelli[6,7], Anthony J Iafrate[9], Ruslan I Sadreyev[4,9], Frank Stegmeier[5], Gad Getz[1,3,9,10], Lecia V Sequist[1,2], Anthony C Faber[11,12] & Jeffrey A Engelman[1,2]

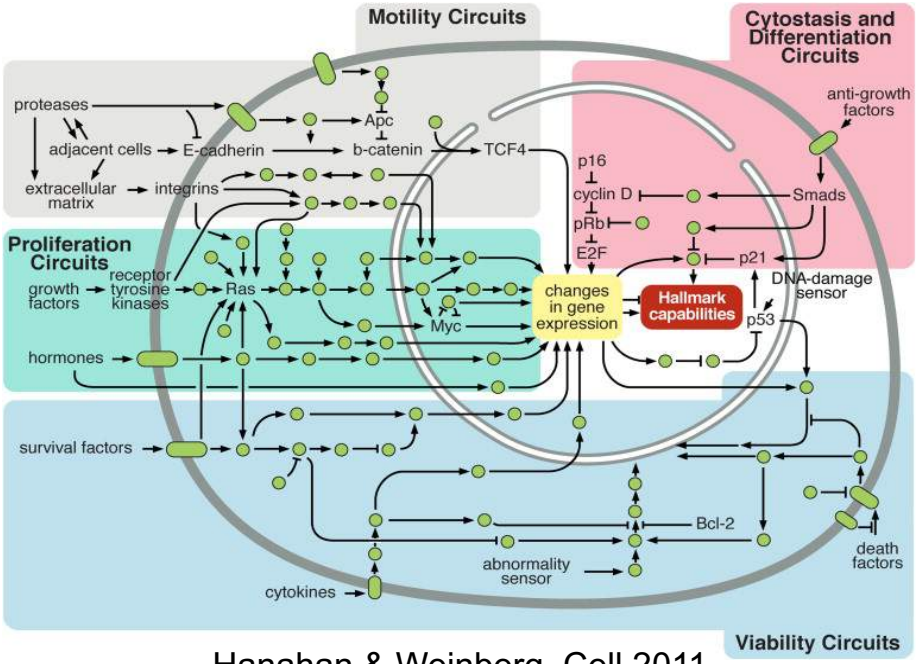
Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance

Sydney M. Shaffer[1,2], Margaret C. Dunagin[1], Stefan R. Torborg[1,3], Eduardo A. Torre[1,2], Benjamin Emert[2,4], Clemens Krepler[5], Marilda Beqiri[5], Katrin Sproesser[5], Patricia A. Brafford[5], Min Xiao[5], Elliott Eggan[2], Ioannis N. Anastopoulos[2], Cesar A. Vargas-Garcia[6], Abhyudai Singh[6,7], Katherine L. Nathanson[2], Meenhard Herlyn[5] & Arjun Raj[1,8]

Non-heritable mechanisms of drug resistance observed in bacterial and viral populations, and more recently in cancer

Balaban *et al*. Science 2004
Shaffer *et al.* Nature 2017
Sharma *et al.* Cell 2010
Hata *et al.* Nat Med 2014
Padmanabhan & Dixit, Nat Comm 2015

Can a ‘systems’ view help ‘understand’ cancer?



Hanahan & Weinberg, Cell 2011

What information does it lack?

- Time/spatial scale(s)
- Strength of regulation
- Direct/indirect
- Nonlinearity of interaction
- Combinatorial effects

Assumptions are hidden in a “black box” and can have unpleasant surprises in the clinic (ex: anti-angiogenesis therapy)

“One day, we imagine that cancer biology and treatment……will become a science with a conceptual structure and logical coherence that rivals that of chemistry or physics.”

- Hanahan & Weinberg, Cell 2000

“And, as before, we continue to foresee cancer research as an increasingly logical science, in which myriad phenotypic complexities are manifestations of a small set of underlying organizing principles.”

- Hanahan & Weinberg, Cell 2011

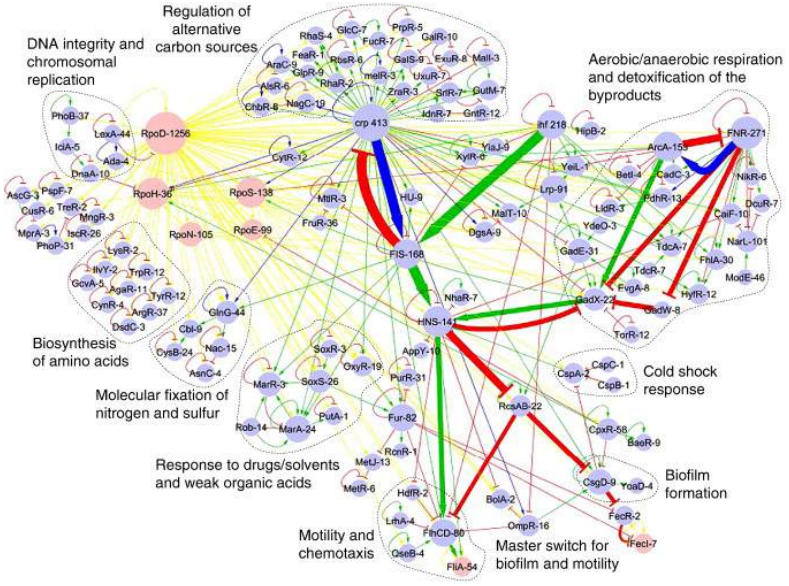
Example of ‘systems’ approach

Engineered systems:

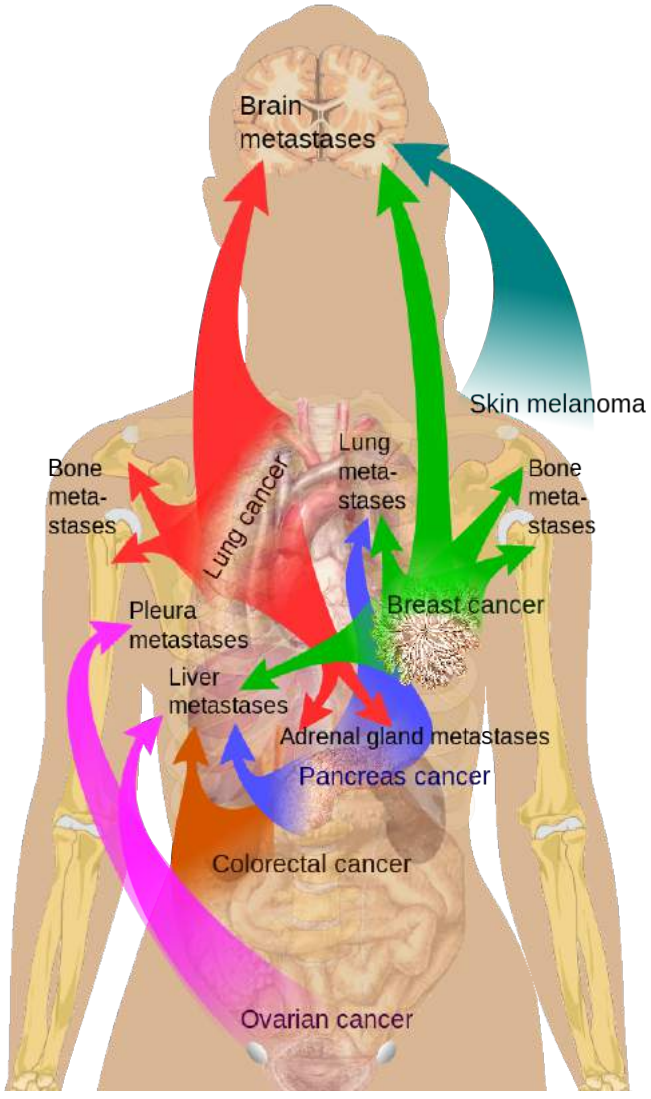
- 1000+ computers/chips
- 100s of feedback loops
- Design manual available
- Largely automated
- “Bottom-up” approach

Biological systems (*E. coli*):

- 1000s of feedback loops
- No design manual available
- Evolved (not automated)
- How do we understand and “fix” such systems?



Metastasis : the cause of 90% of all cancer deaths



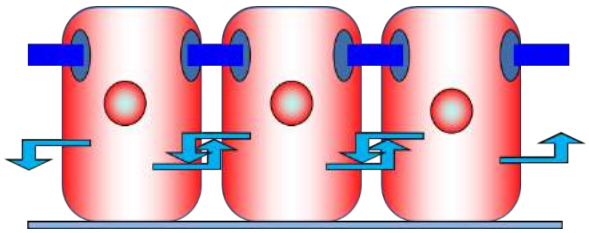
More than 80% cancers happen in epithelial organs, i.e. cells that do NOT move/invade.

We are…

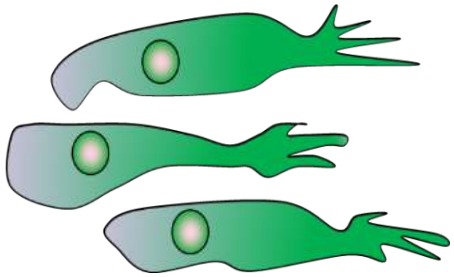
- **Not** inferring networks by data-mining from "omics" data
- **Not** focusing exclusively on one dataset or even on one type of cancer

- **We are** attempting to build a conceptual framework, a quantitative version of the framework that biologists build to help think through their data

EMT/MET: The engine of metastasis

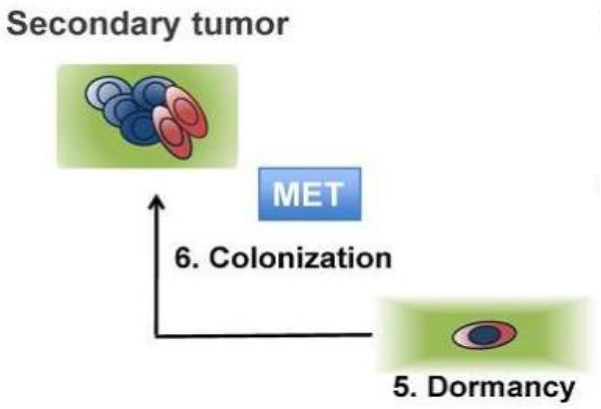


Adhere to neighbors
Do NOT migrate or invade
Epithelial (E)

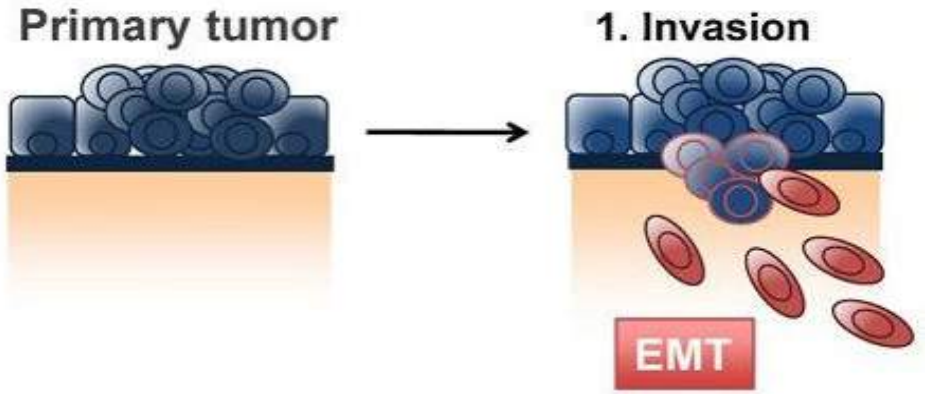


Do NOT adhere to neighbors
Migrate and invade
Mesenchymal (M)

Mesenchymal-to-Epithelial Transition (MET)

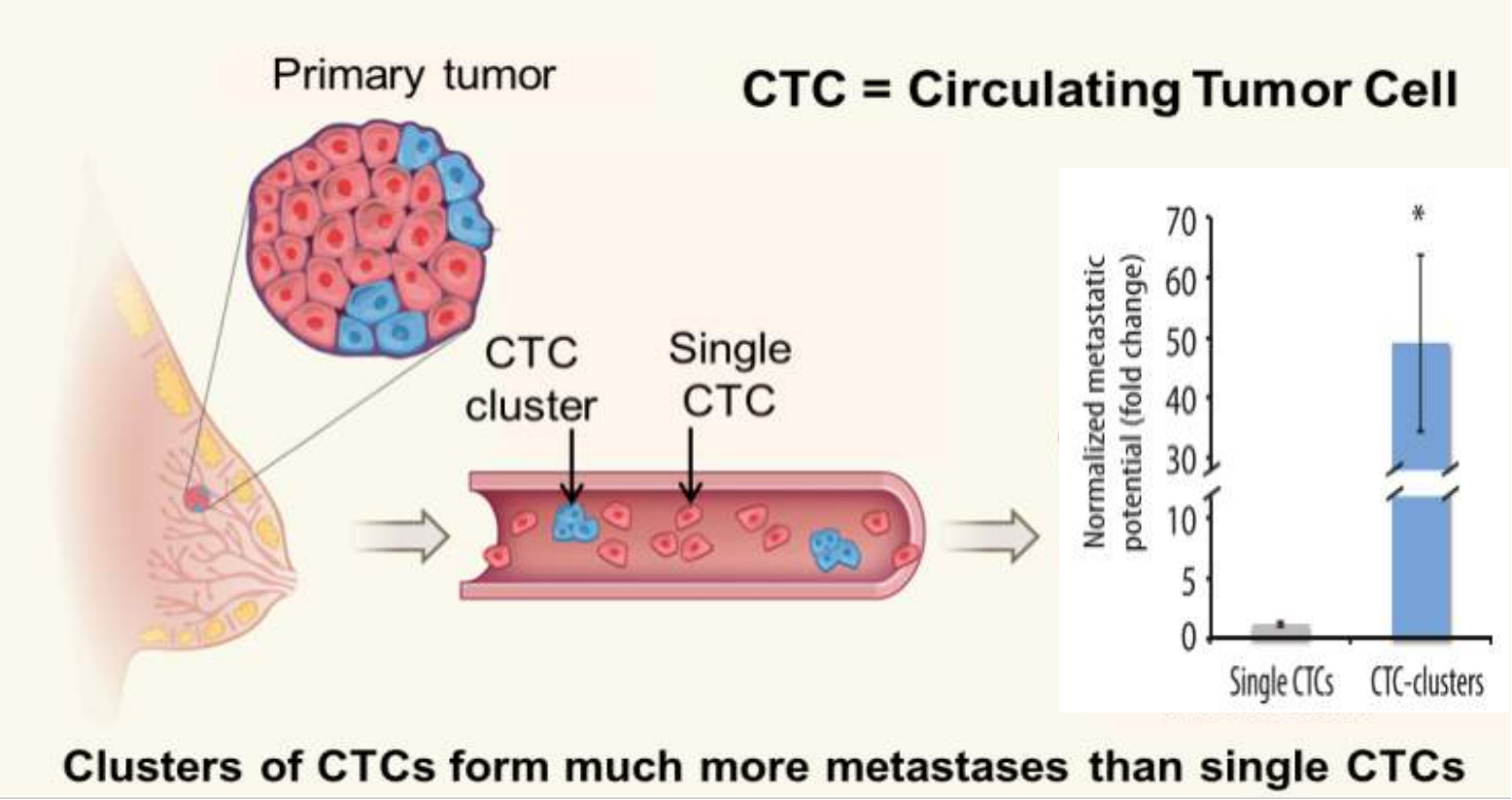


Epithelial-to-Mesenchymal Transition (EMT)



Scheel & Weinberg, Semin Cancer Bio 2012

Metastasis: a journey taken in groups

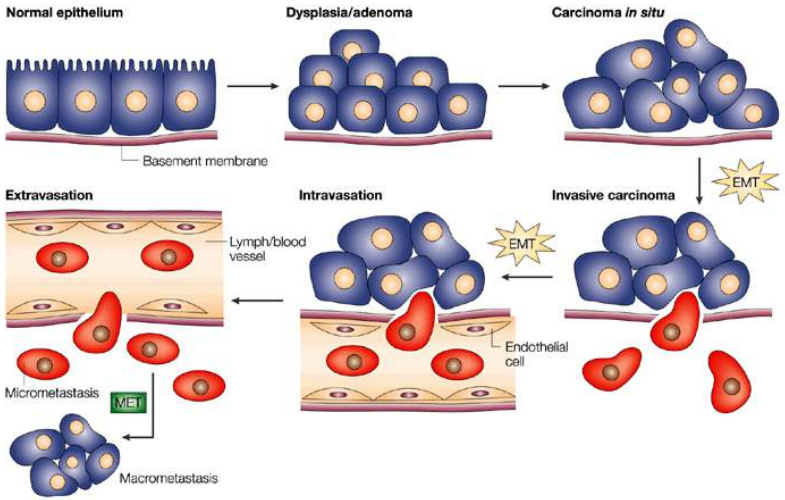


Clusters of CTCs:

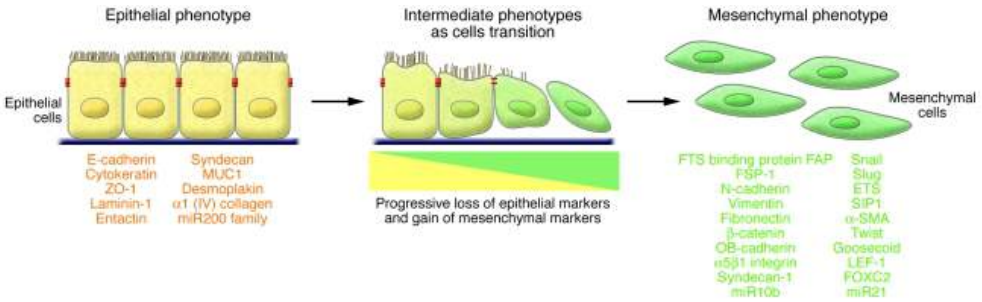
- Comprise of 5-8 cells
- Associate with worse patient survival
- Resist cell death in circulation
- Are formed before entering the circulation

Aceto *et al.* Cell 2014
Bottos & Hynes, Nature 2014
Cheung *et al.* PNAS 2016

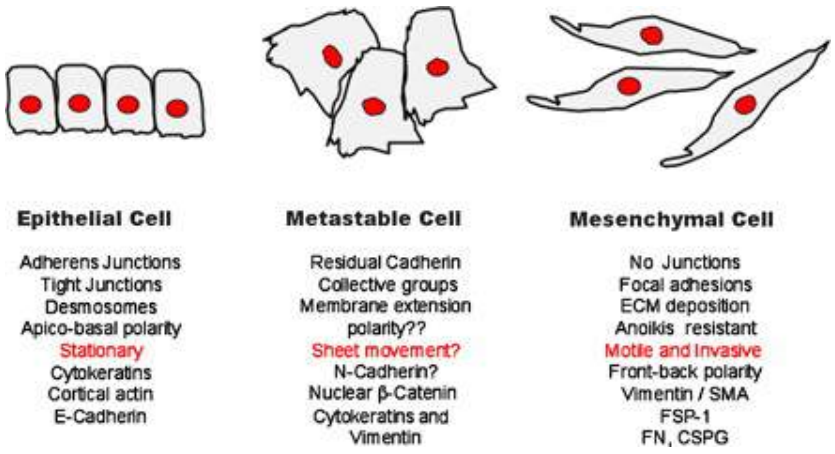
How do clusters reconcile with (binary) EMT?



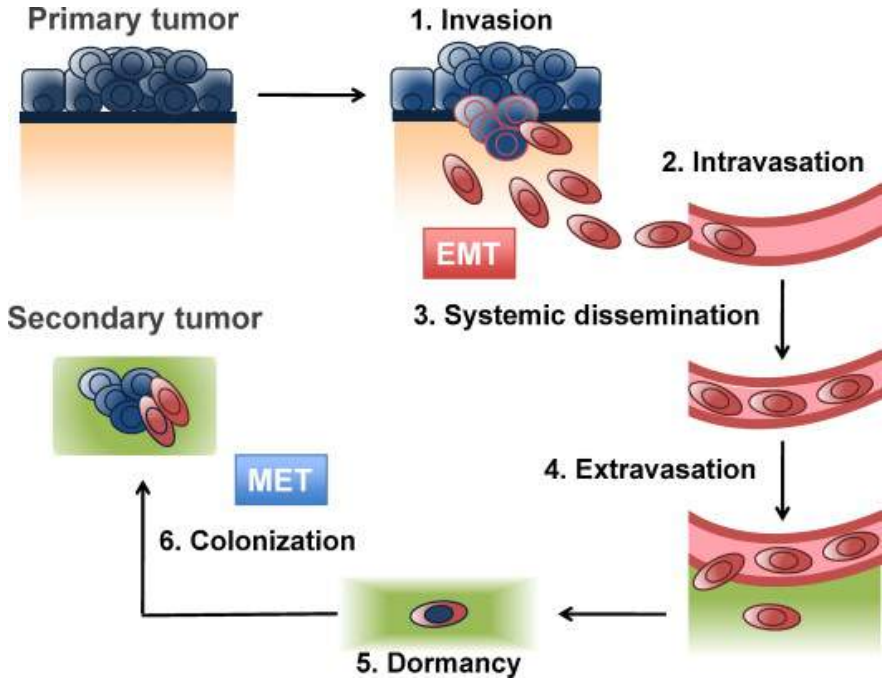
Thiery JP, Nat Rev Cancer 2002



Kalluri & Weinberg, J Clin Invest 2009

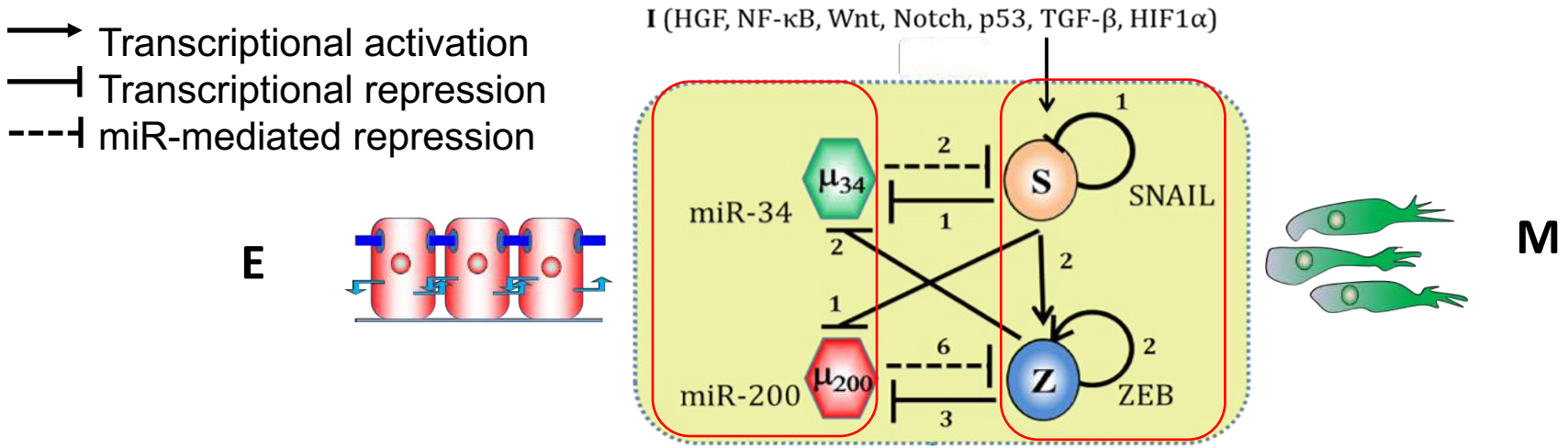


Lee *et al.* J Cell Biol 2006



Scheel & Weinberg, Semin Cancer Biol 2012

Systems biology model for EMT/MET



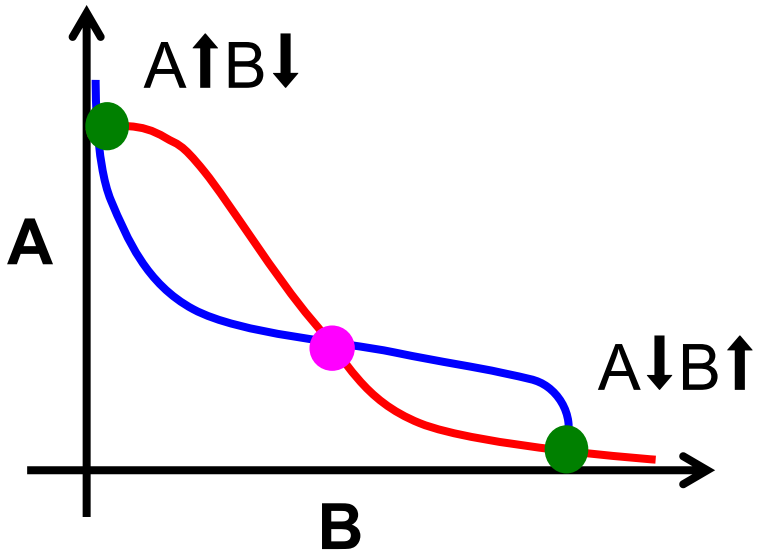
Lu*, Jolly* *et al.* PNAS 2013

- Each arrow is a quantitative relationship between the input and output levels
- This has been done for many transcription circuits, e.g. in microorganisms
- We needed to develop a new method for translation regulation

Toggle switch: A systems biology model

Bistability
(A, B) = (high, low)
(A, B) = (low, high)

Huang, PloS Biology 2013
Gardner *et al.* Nature 2000



$$\frac{dA}{dt} = g_A \frac{(B_0)^{n_B}}{(B_0)^{n_B} + B^{n_B}} - k_A A$$

$$\frac{dB}{dt} = g_B \frac{(A_0)^{n_A}}{(A_0)^{n_A} + A^{n_A}} - k_B B$$

Production

Regulation

Degradation

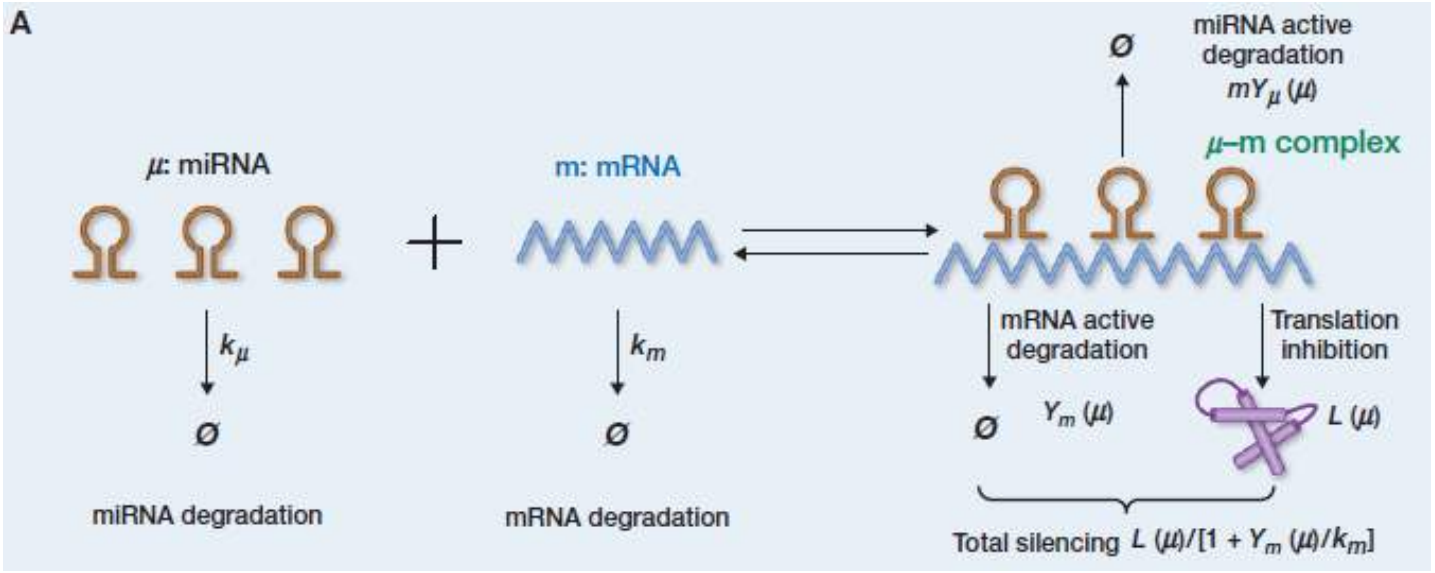
A_0 , B_0 = Threshold concentrations

Steps involved:

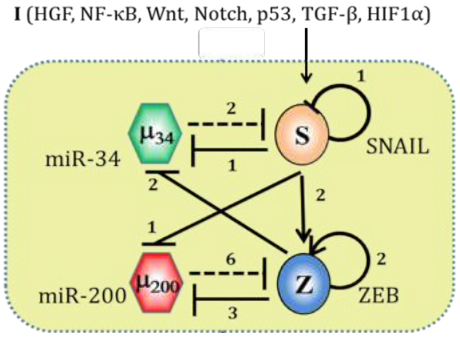
- Solving ODEs, plotting nullclines
- Stability analysis (Jacobian Matrix)
- Sensitivity analysis
- Bifurcation analysis
- Phase diagrams

- Hallmark of cell-fate decision making during embryonic development
- One of the first synthetic bio circuits designed

Theoretical framework for miRNA-based circuits



Lu*, Jolly* *et al.* PNAS 2013



Production

Degradation

miR regulation

TF regulation

$$\frac{d\mu_{200}}{dt} = g_{\mu_{200}} H^S(Z,\lambda_{Z,\mu_{200}}) H^S(S,\lambda_{Z,\mu_{200}}) - m_Z Y_\mu(\mu_{200}) - k_{\mu_{200}}\mu_{200}$$ miR-200

$$\frac{dm_Z}{dt} = g_{m_Z} H^S(Z,\lambda_{Z,m_Z}) H^S(S,\lambda_{S,m_Z}) - m_Z Y_m(\mu_{200}) - k_{m_Z} m_Z$$ ZEB mRNA

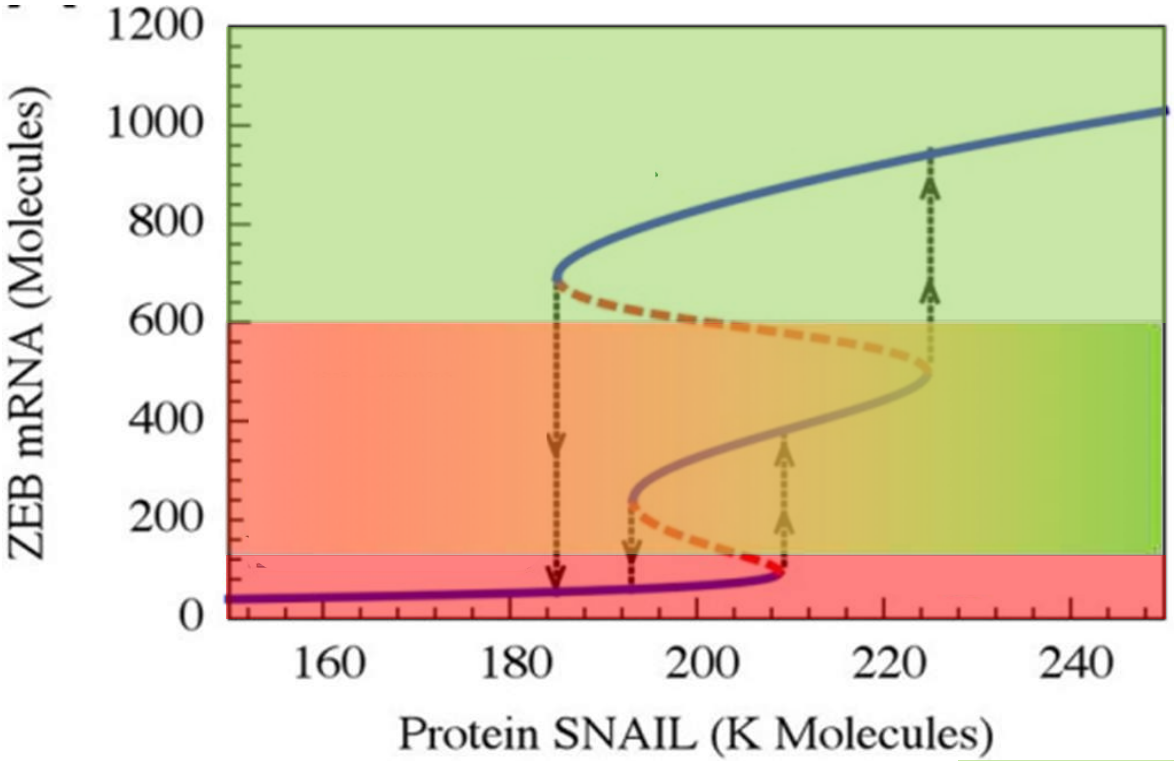
$$\frac{dZ}{dt} = g_Z m_Z L(\mu_{200}) - k_Z Z$$ ZEB

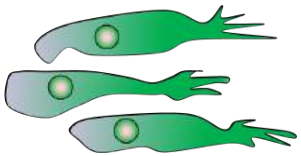
$$\frac{d\mu_{34}}{dt} = g_{\mu_{34}} H^S(Z,\lambda_{Z,\mu_{34}}) H^S(S,\lambda_{Z,\mu_{340}}) - m_S Y_\mu(\mu_{34}) - k_{\mu_{34}}\mu_{34}$$ miR-34

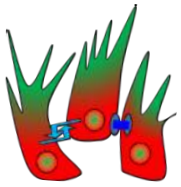
$$\frac{dm_S}{dt} = g_{m_S} H^S(S,\lambda_{S,m_S}) H^S(I,\lambda_{I,m_S}) - m_S Y_m(\mu_{34}) - k_{m_S} m_S$$ SNAIL mRNA

$$\frac{dS}{dt} = g_S m_S L(\mu_{34}) - k_S S$$ SNAIL

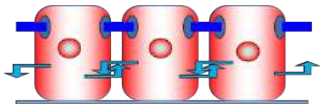
Tristability in the underlying EMT network

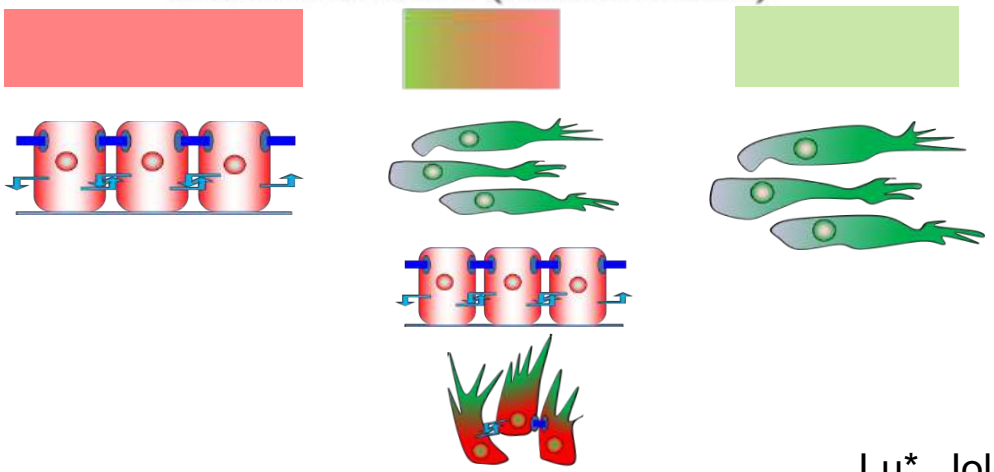


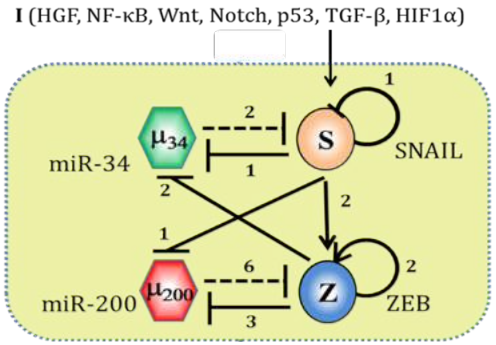




Hybrid E/M
Adhere AND
migrate collectively

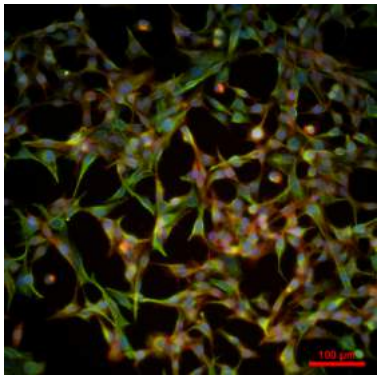




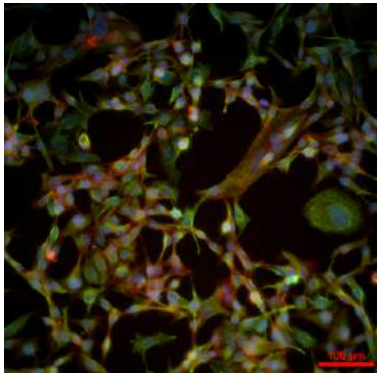


Lu*, Jolly* *et al.* PNAS 2013

Hybrid E/M can be a stable phenotype



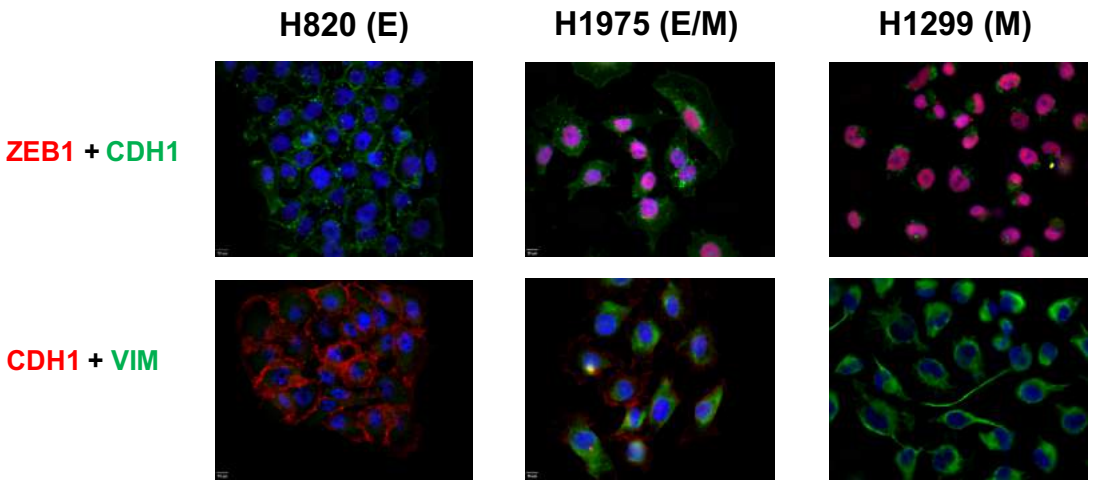
H1975, T=0

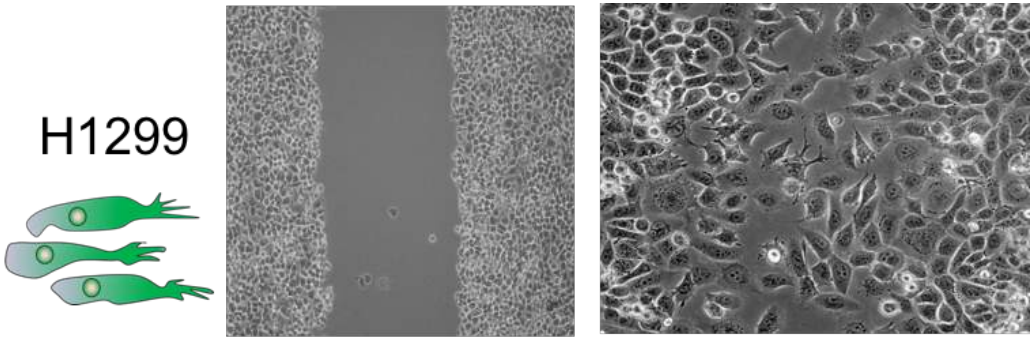


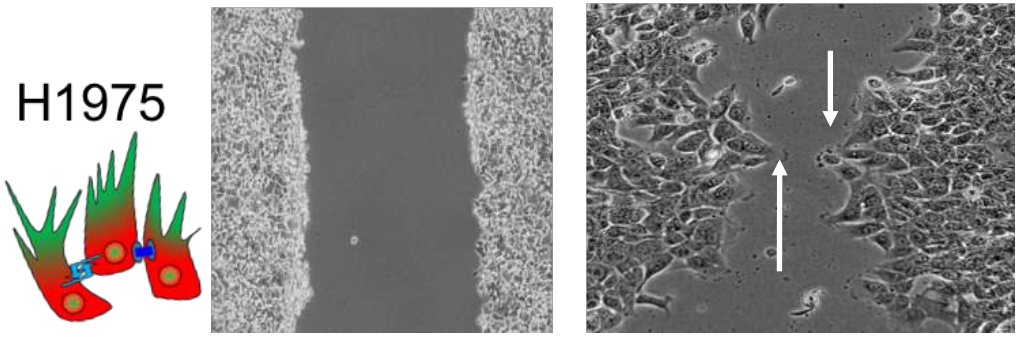
H1975, T=2 months

CDH1 + VIM

Jolly *et al.* Oncotarget 2016
Jolly *et al.* Mol Oncol 2017
Satyendra Tripathi,
Sam Hanash (MDACC)

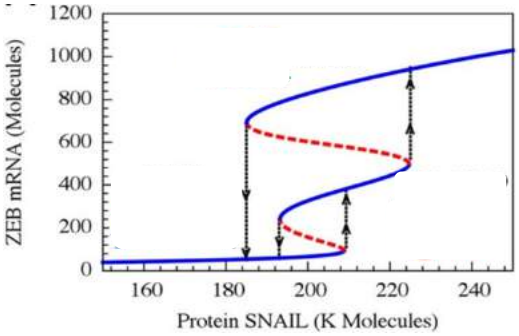






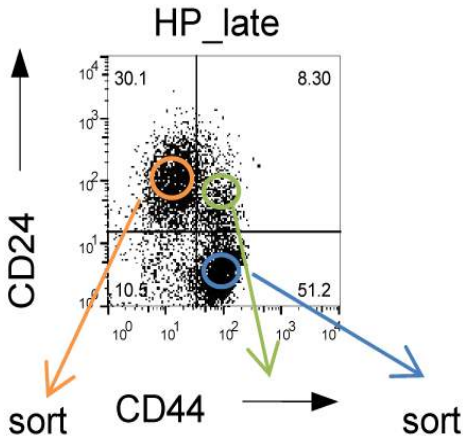
Co-existence of phenotypes seen experimentally

Theoretical prediction



Lu*, Jolly* *et al.* PNAS 2013

Experimental validation

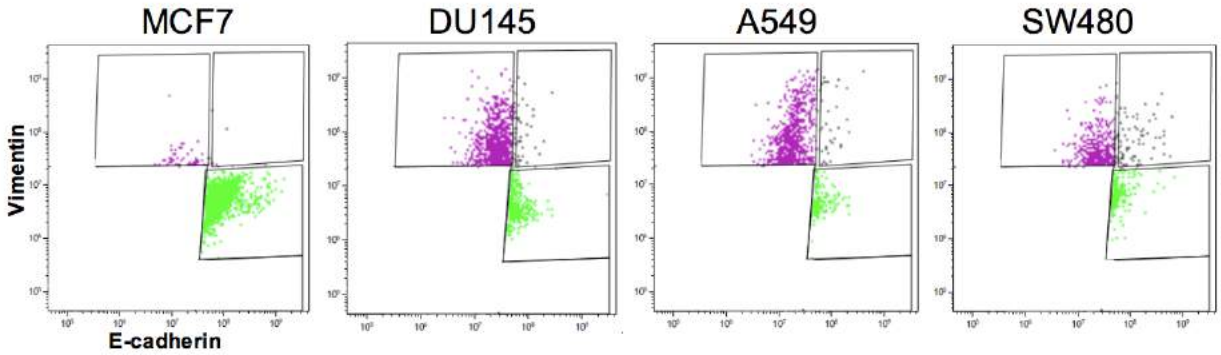


Grosse-Wilde *et al.* PLoS ONE 2015

Quantification of cells in different phenotypic states

Cell line	E (%)	E=M (%)	M (%)
A549	82	10.2	7.80
LT73	24.5	28.6	46.9
H460	19.5	4.8	75.6
H460_ miR-200c	39.5	20.8	39.6

Andriani *et al.* Mol Oncol 2016



George*, Jolly* *et al.* Cancer Res 2017

Shengnan Xu, Jason A Somarelli (Duke University)

Quantifying the EMT spectrum of states

Hybrid E/M state(s) also predicted by other computational models:

- Xing group (Pittsburgh)

Tian *et al.* Biophys J 2013
Zhang *et al.* Sci Signal 2014

- Albert group (Penn State)

Steinway *et al.* Cancer Res 2014
Steinway *et al.* NPJ Syst Bio Appl 2014

- Zapperi group (U Milan)

Font-Clos *et al.* PNAS 2018

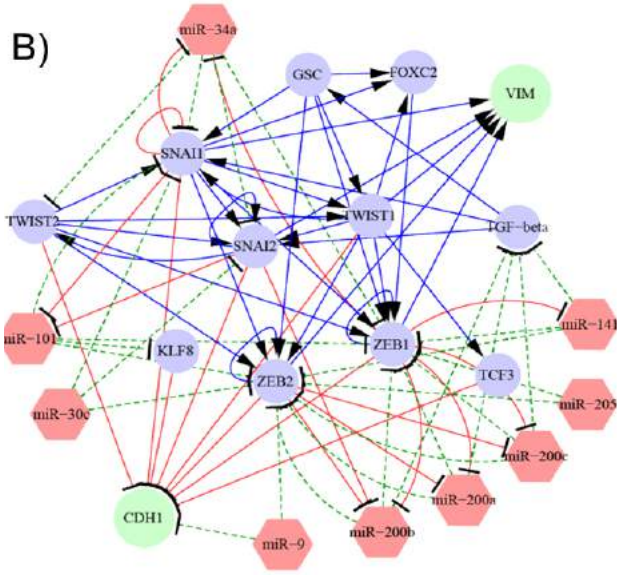
- Nie group (UC Irvine)

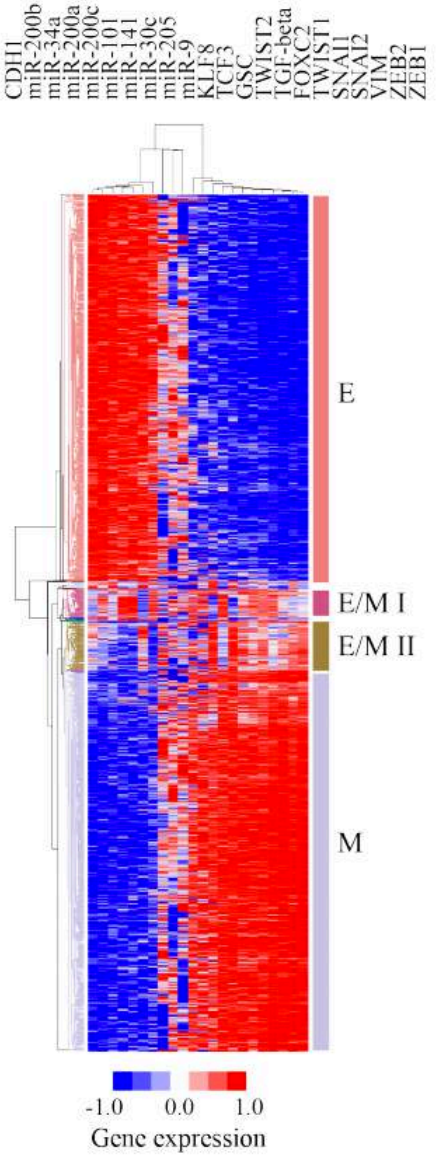
Hong *et al.* PLoS Comp Bio 2015
Li *et al.* Phys Chem Chem Phys 2016
Ta *et al.* Disc Contin Dyn Syst Ser B

- Huang group (ISB Seattle)

Joo *et al.* Sci Rep 2018

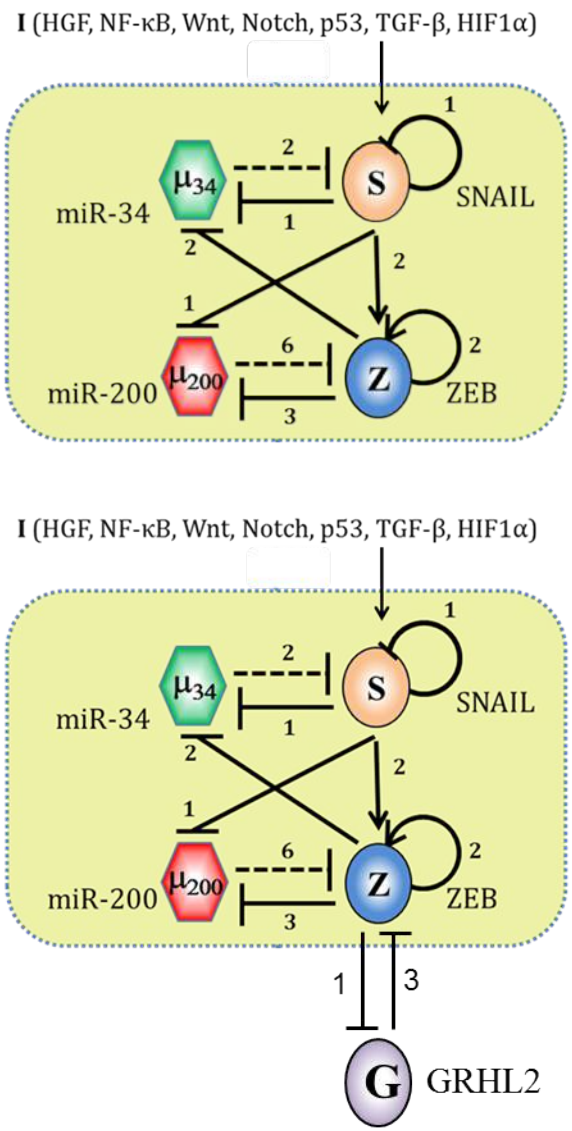
Ensemble of kinetic models with fixed circuit topology but with randomly selected parameters also enable hybrid E/M state(s)

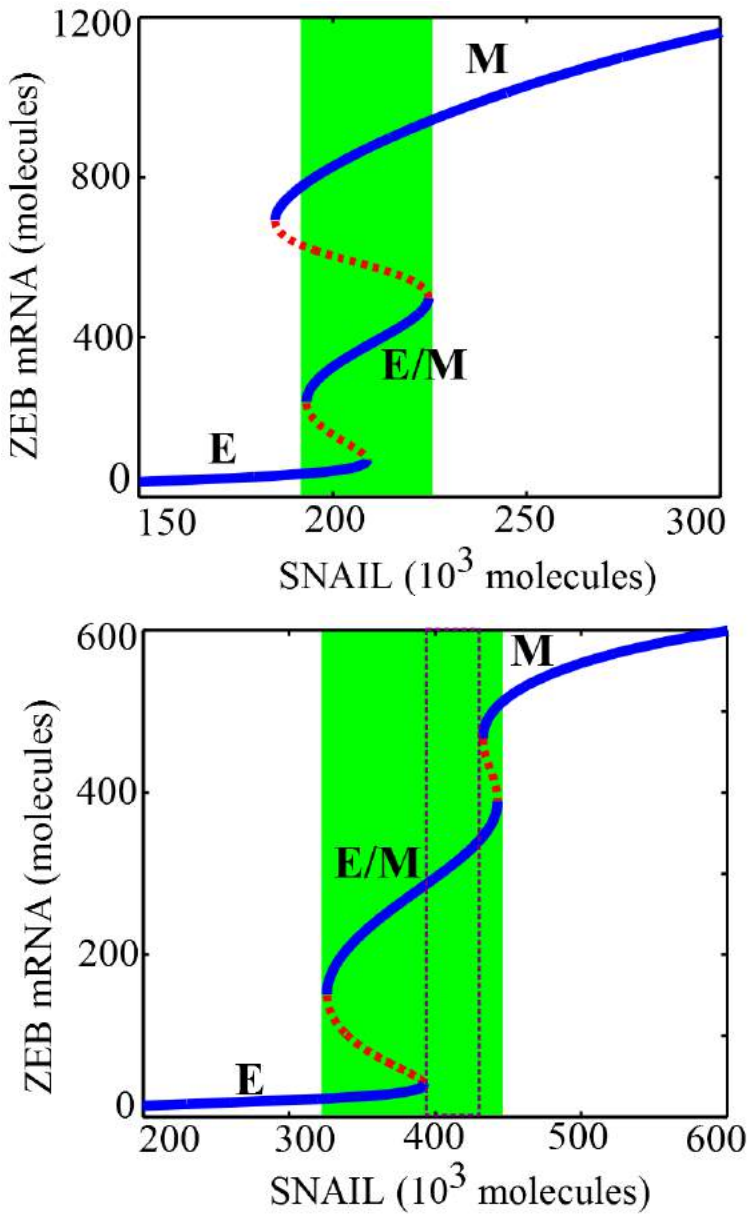




Huang *et al.* PLoS Comp Bio 2017
Huang *et al.* BMC Sys Bio 2018

Identifying ‘phenotypic stability factors’ (PSFs)





Jolly *et al*. Oncotarget 2016

Other PSFs:

- OVOL2

(Jia*, Jolly* *et al.* Oncotarget 2015; Watanabe *et al.* Dev Cell 2014; Hong *et al.* PLoS Comp Biol 2015)

- ΔNP63α

(Jolly *et al.* NPJ Br Cancer 2017; Dang *et al.* Cancer Res 2015)

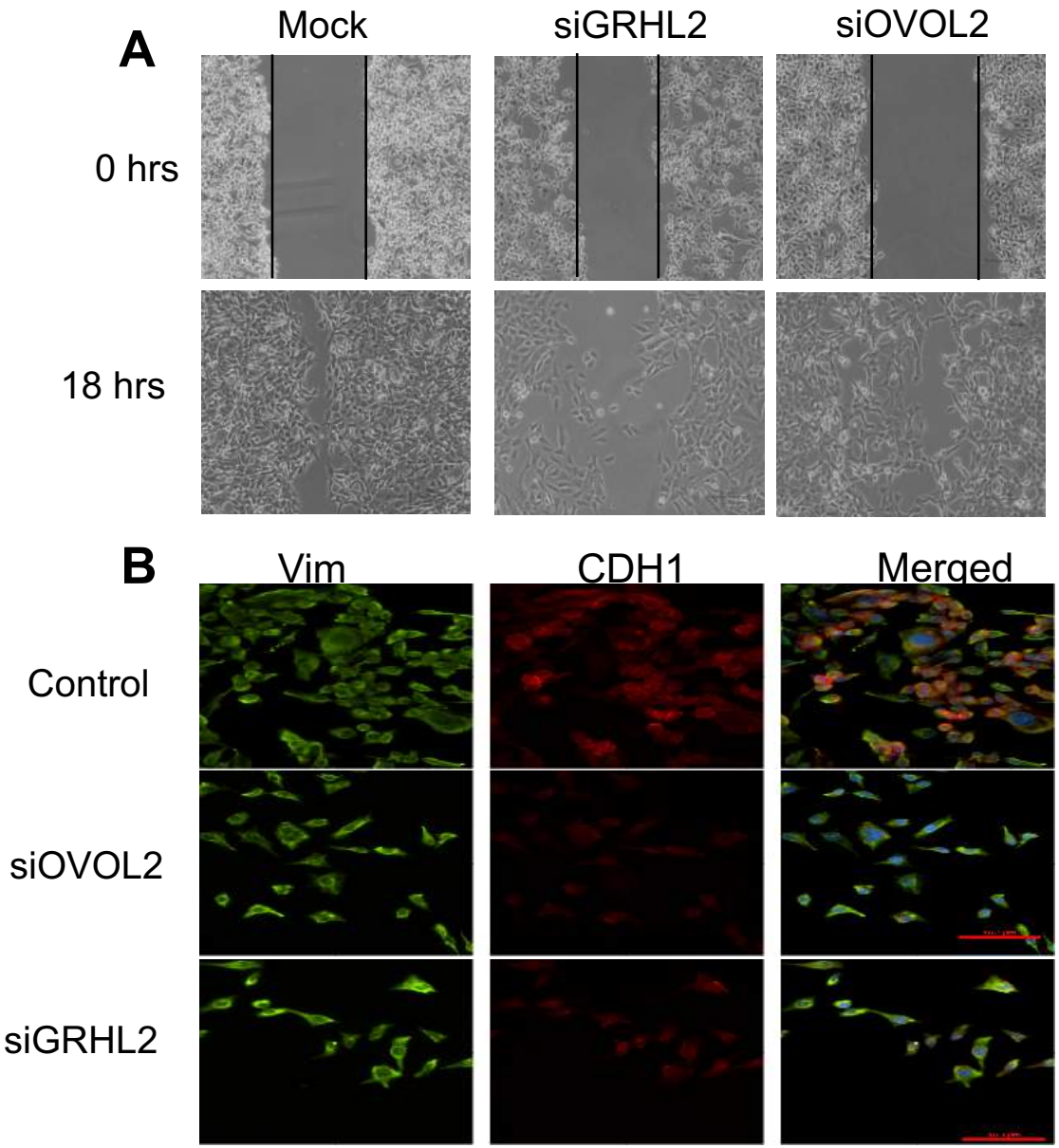
- NUMB

(Bocci*, Jolly* *et al.* J R Soc Interface 2017)

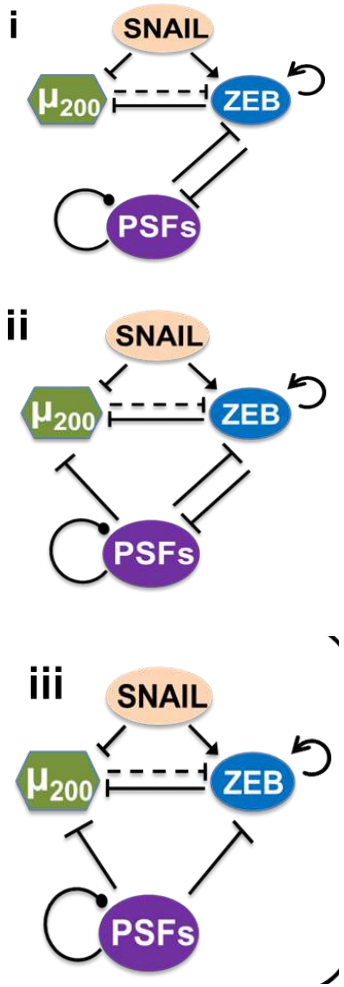
- NRF2

(Bocci *et al.*,; bioRxiv: **390237**)

Knockdown of PSFs can drive a complete EMT



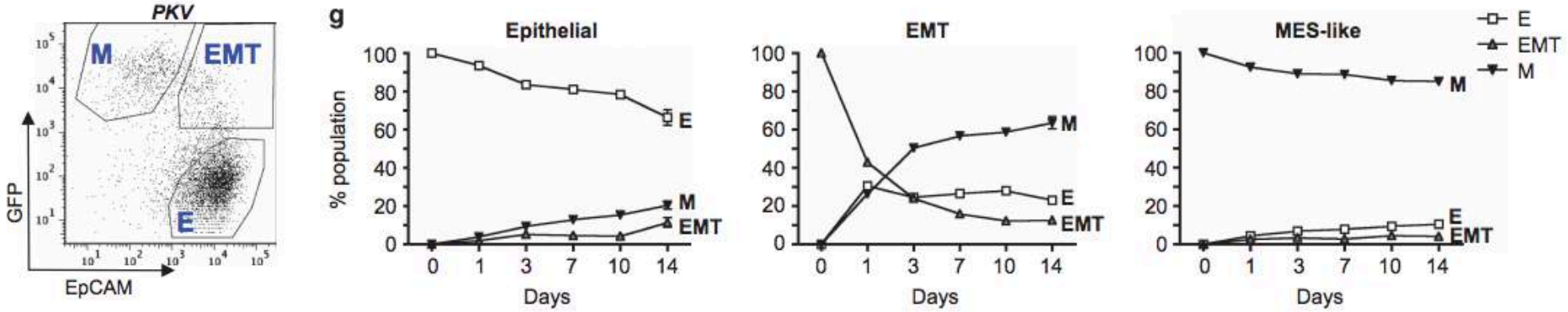
Network motifs for identifying additional PSFs



Satyendra Tripathi, Sam Hanash (MDACC)

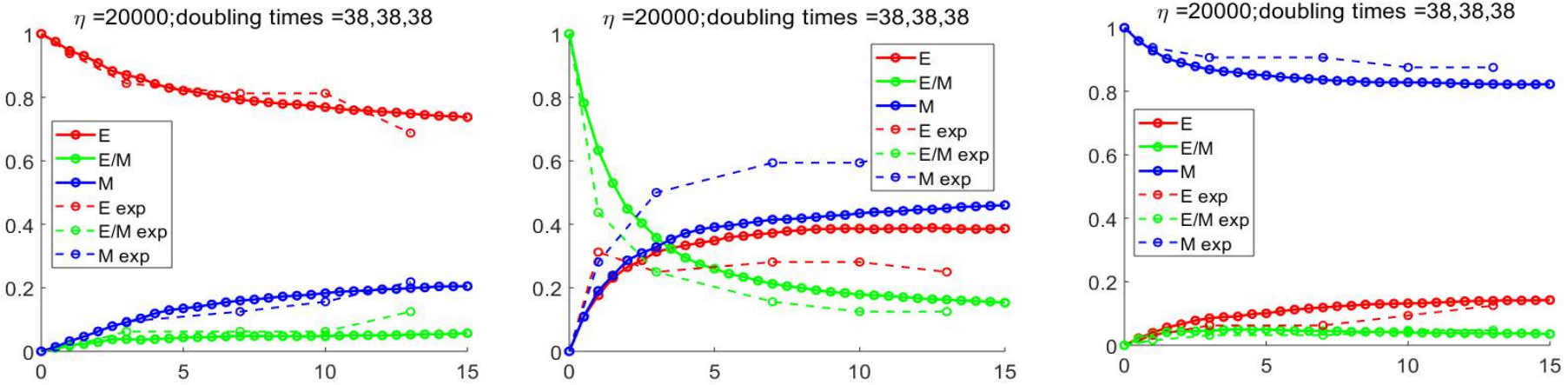
Jolly *et al.* Oncotarget 2016

Spontaneous switching among phenotypes



Ruscetti *et al.* Oncogene 2016

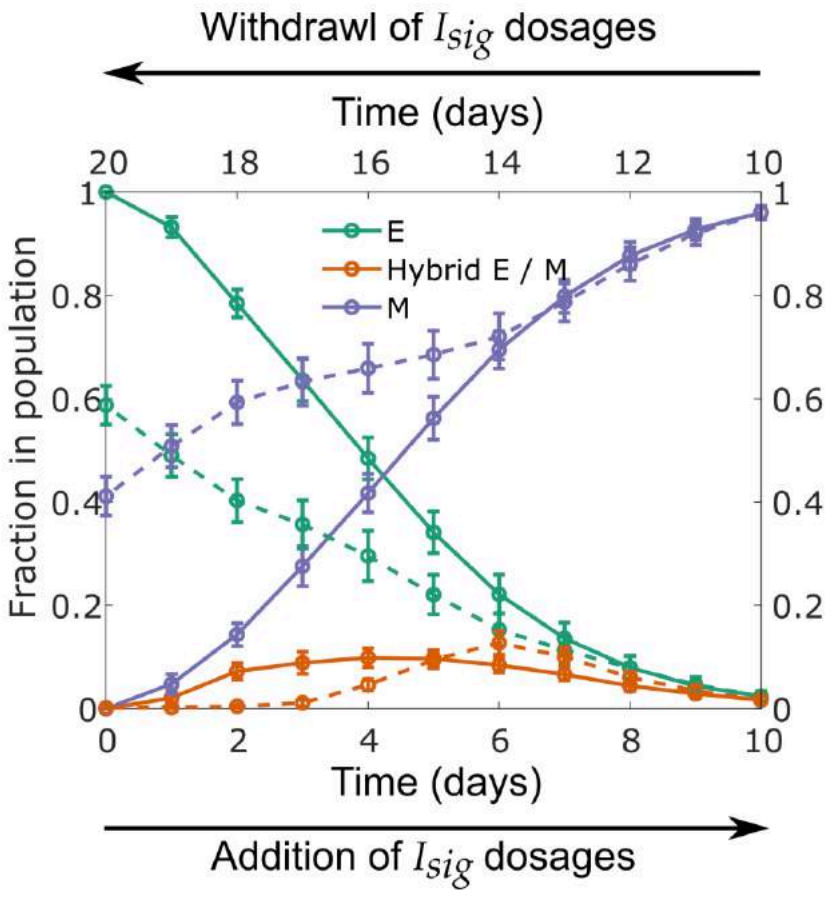
Can we explain these features of the population dynamics of EMT?



Tripathi, Levine & Jolly, bioRxiv: **592691**

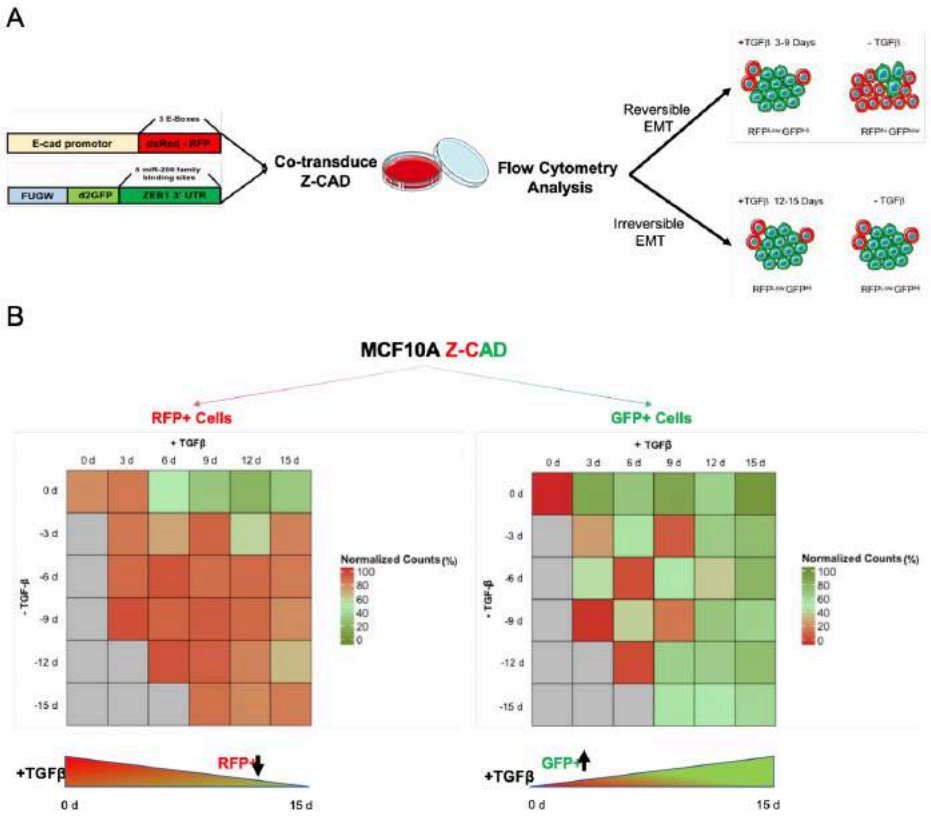
Is EMT always reversible?

Theoretical prediction



Tripathi, Levine & Jolly, bioRixiv: **592691**

Experimental validation



Jia, Deshmukh, Mani, Jolly & Levine, bioRxiv: **651620**

Cells may get ‘locked’ in mesenchymal state, losing phenotypic plasticity

How EMT alters tumor-initiation ability (stemness)?

The Epithelial-Mesenchymal Transition Generates Cells with Properties of Stem Cells

Sendurai A. Mani,[1,3,10,*] Wenjun Guo,[1,10] Mai-Jing Liao,[1,10] Elinor Ng. Eaton,[1] Ayyakkannu Ayyanan,[4] Alicia Y. Zhou,[1,2] Mary Brooks,[1] Ferenc Reinhard,[1] Cheng Cheng Zhang,[1] Michail Shipitsin,[5,6] Lauren L. Campbell,[5,7] Kornelia Polyak,[5,6,7] Cathrin Brisken,[4] Jing Yang,[8] and Robert A. Weinberg[1,2,9,*]

Mani *et al.* Cell 2008

Epithelial-mesenchymal transition can suppress major attributes of human epithelial tumor-initiating cells

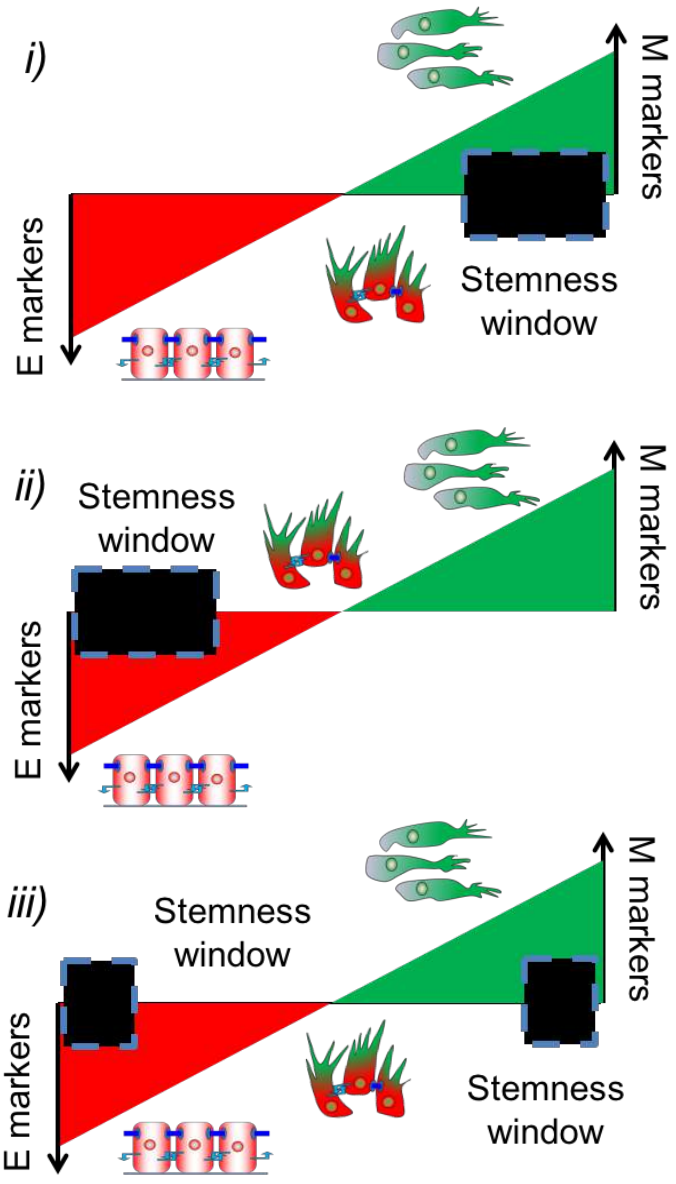
Toni Celià-Terrassa,[1] Óscar Meca-Cortés,[1] Francesca Mateo,[1] Alexia Martínez de Paz,[1] Nuria Rubio,[2] Anna Arnal-Estapé,[3] Brian J. Ell,[4] Raquel Bermudo,[5,6] Alba Díaz,[6] Marta Guerra-Rebollo,[2] Juan José Lozano,[7] Conchi Estarás,[8] Catalina Ulloa,[1] Daniel Álvarez-Simón,[1] Jordi Milà,[9] Ramón Vilella,[9] Rosanna Paciucci,[10] Marian Martínez-Balbás,[8] Antonio García de Herreros,[11] Roger R. Gomis,[3,12] Yibin Kang,[4] Jerónimo Blanco,[2] Pedro L. Fernández,[5,6,13] and Timothy M. Thomson[1]

Celia-Terrassa *et al.* J Clin Invest 2012

Breast Cancer Stem Cells Transition between Epithelial and Mesenchymal States Reflective of their Normal Counterparts

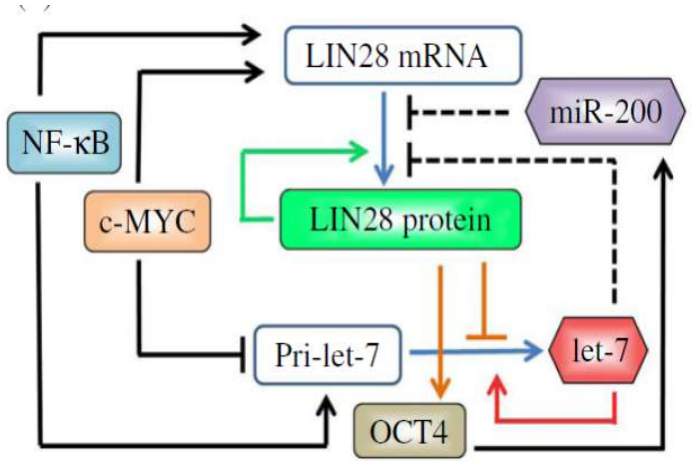
Suling Liu,[1,6,*] Yang Cong,[2,6] Dong Wang,[1] Yu Sun,[1] Lu Deng,[1] Yajing Liu,[3] Rachel Martin-Trevino,[3] Li Shang,[3] Sean P. McDermott,[3] Melissa D. Landis,[4] Suhyung Hong,[3] April Adams,[3] Rosemarie D'Angelo,[3] Christophe Ginestier,[5] Emmanuelle Charafe-Jauffret,[5] Shawn G. Clouthier,[3] Daniel Birnbaum,[5] Stephen T. Wong,[2] Ming Zhan,[2,7] Jenny C. Chang,[4,7] and Max S. Wicha[3,7,*]

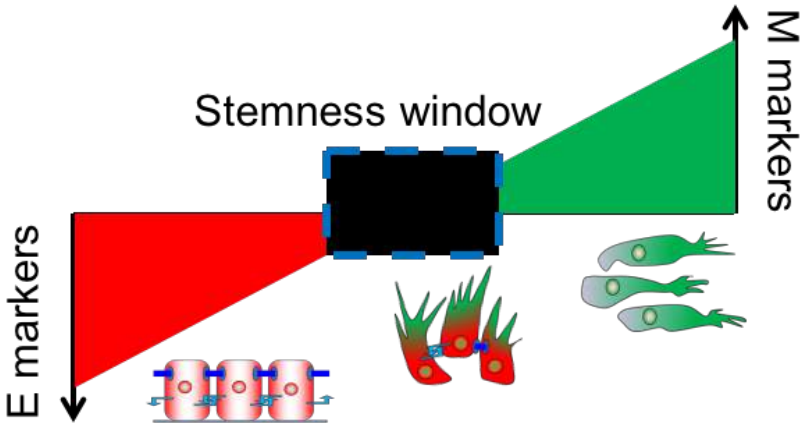
Liu *et al.* Stem Cell Reports 2013



Hybrid E/M cells can form many more tumors

Theoretical prediction

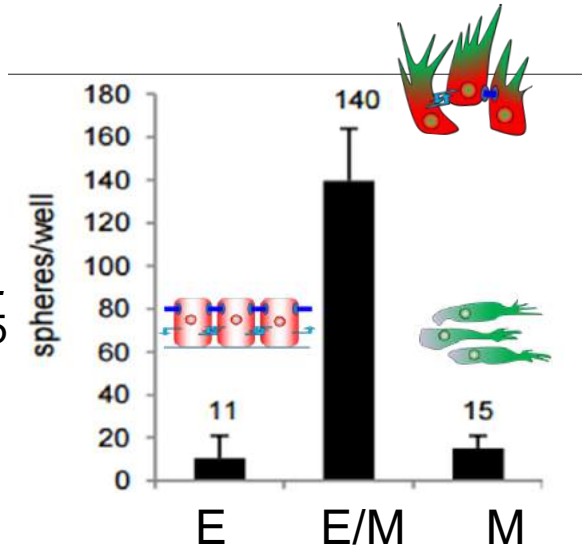




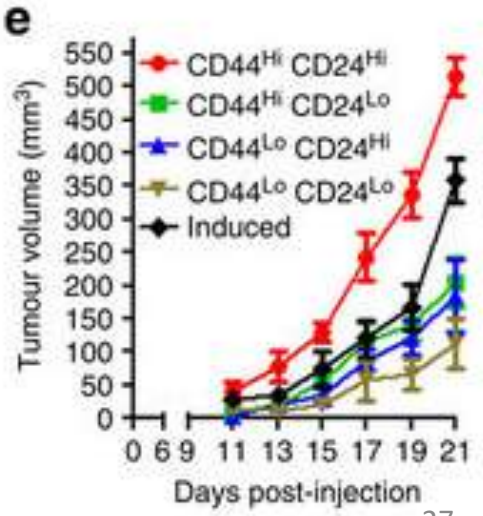
Jolly *et al.* J R Soc Interface 2014
Jolly*, Jia* *et al.* Oncotarget 2015

Experimental validation

Grosse-Wilde *et al.*
PLoS ONE 2015



Goldman *et al.*
Nat Comm 2015



Hybrid E/M cells can form many more tumors

Acquisition of a hybrid E/M state is essential for tumorigenicity of basal breast cancer cells

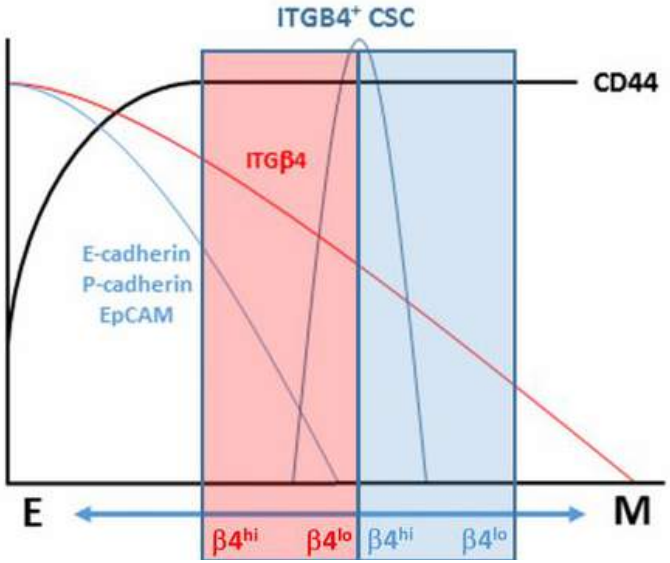
Cornelia Kröger[a], Alexander Afeyan[a,b], Jasmin Mraz[a,c], Elinor Ng Eaton[a], Ferenc Reinhardt[a], Yevgenia L. Khodor[d], Prathapan Thiru[a], Brian Bierie[a], Xin Ye[a,e], Christopher B. Burge[d], and Robert A. Weinberg[a,f,g,1]

Kroger *et al.* PNAS 2019

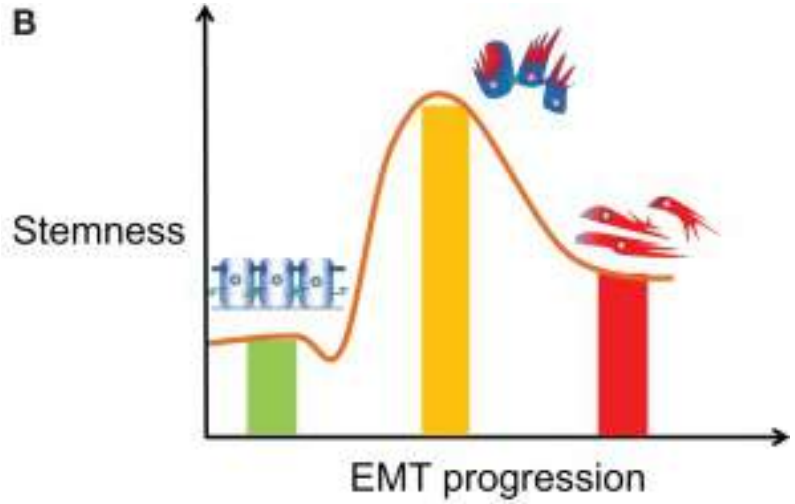
Heterogeneity of Human Breast Stem and Progenitor Cells as Revealed by Transcriptional Profiling

Justin A. Colacino,[1,2,3,*] Ebrahim Azizi,[3,4] Michael D. Brooks,[3,4] Ramdane Harouaka,[3,4] Shamileh Fouladdel,[3,4] Sean P. McDermott,[3,4] Michael Lee,[4] David Hill,[4] Julie Madden,[5] Julie Boerner,[5] Michele L. Cote,[5,6] Maureen A. Sartor,[3,7] Laura S. Rozek,[1,3] and Max S. Wicha[3,4,*]

Colacino *et al.* Stem Cell Reports 2018



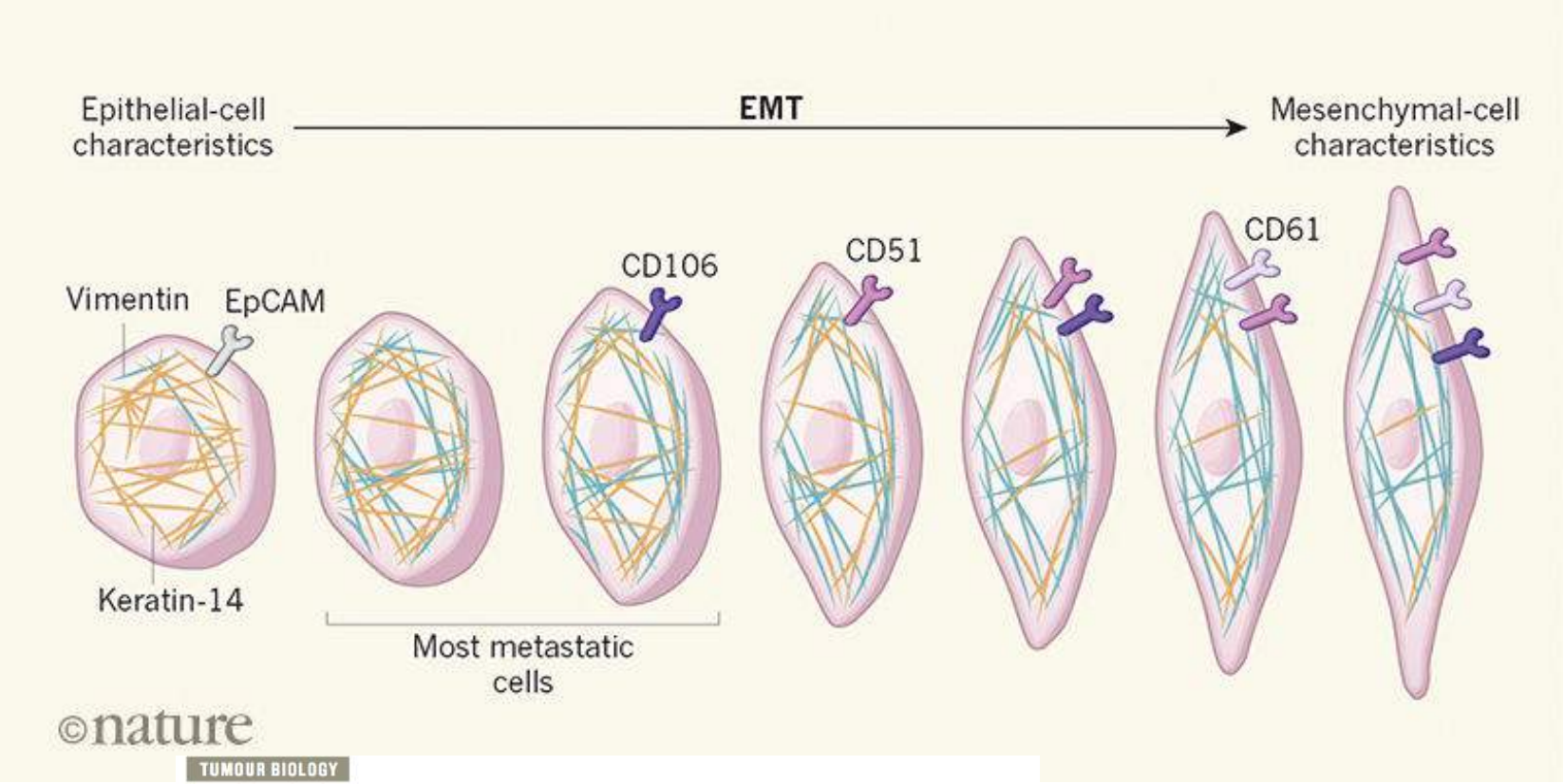
Bierie *et al.* PNAS 2017



Jolly *et al.* Front Oncol 2015

Jolly *et al.* Pharmacol Ther 2018

In vivo spontaneous EMT model highlights the aggressive behavior of hybrid E/M phenotype(s)



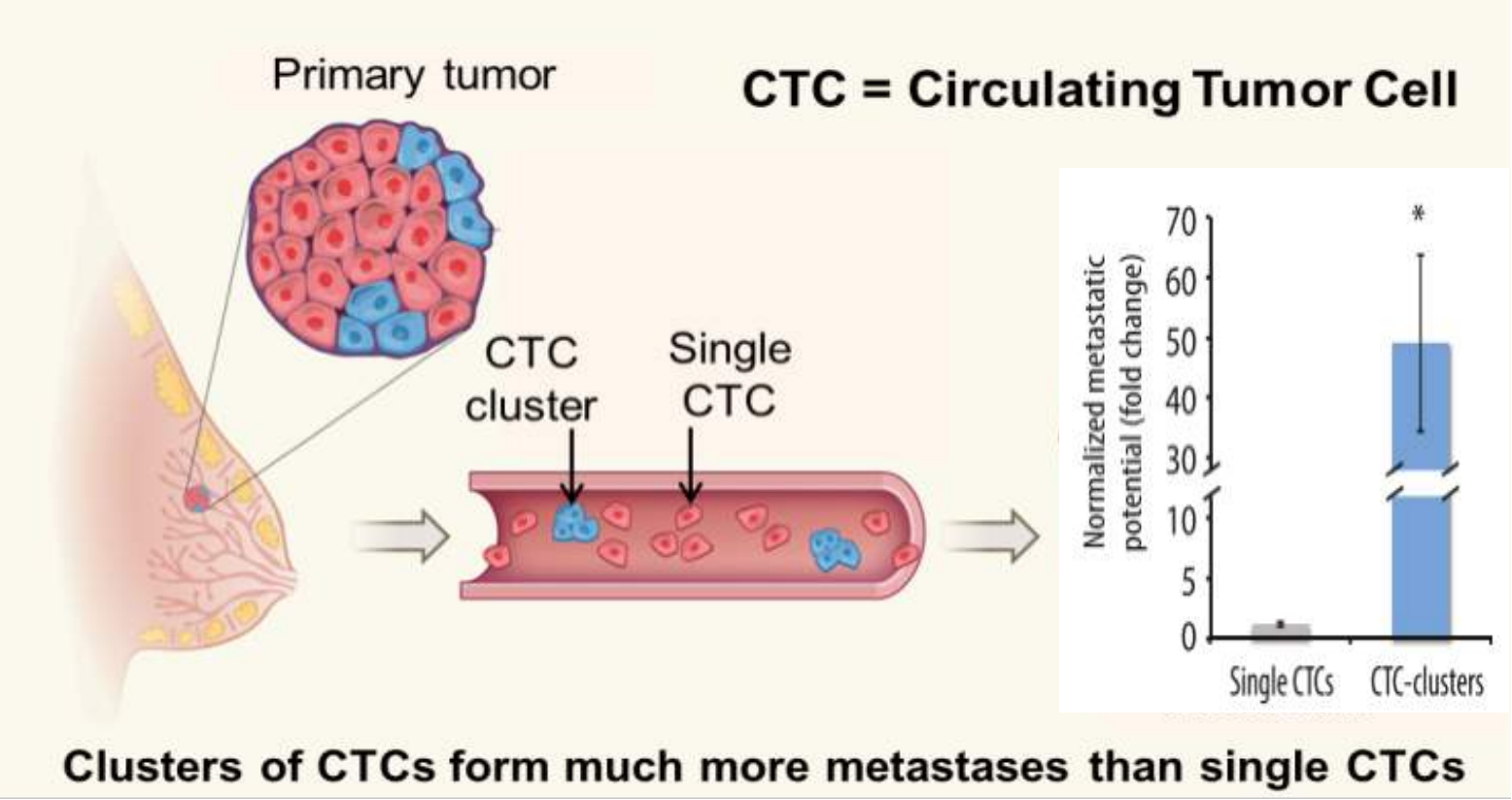
TUMOUR BIOLOGY

Transition states that allow cancer to spread

Cancers of epithelial-cell origin often contain some tumour cells that have acquired traits of mesenchymal cells. How this leads to cancer spread has now been illuminated in mouse models. SEE ARTICLE P.463

Thompson & Nagaraj, Nature 2018
Patushenko *et al.* Nature 2018

Hybrid E/M phenotype may form CTC clusters

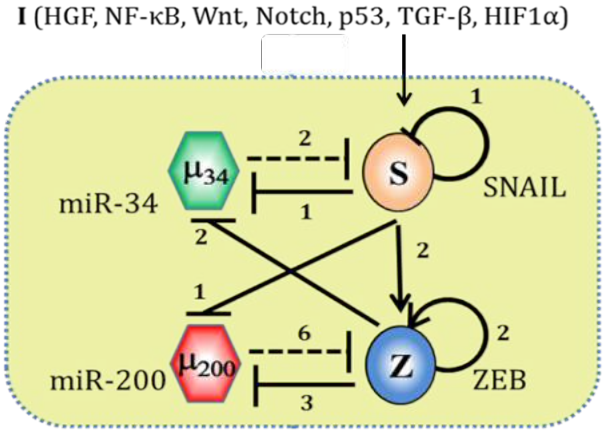


Clusters of CTCs:

- Comprise of 5-8 cells
- Associate with worse patient survival
- Resist cell death in circulation
- Are formed before entering the circulation

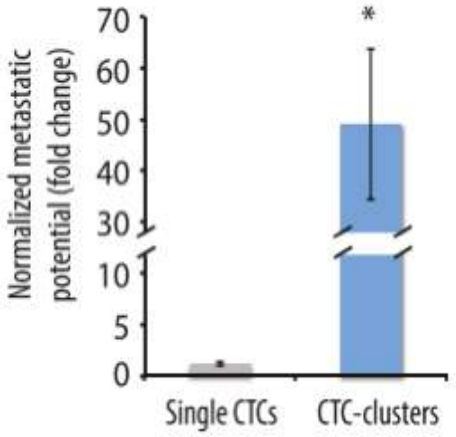
Aceto *et al.* Cell 2014
Bottos & Hynes, Nature 2014
Cheung *et al.* PNAS 2016

How are CTC clusters formed?



Existence of Hybrid E/M Phenotype

Cell-Cell Signaling

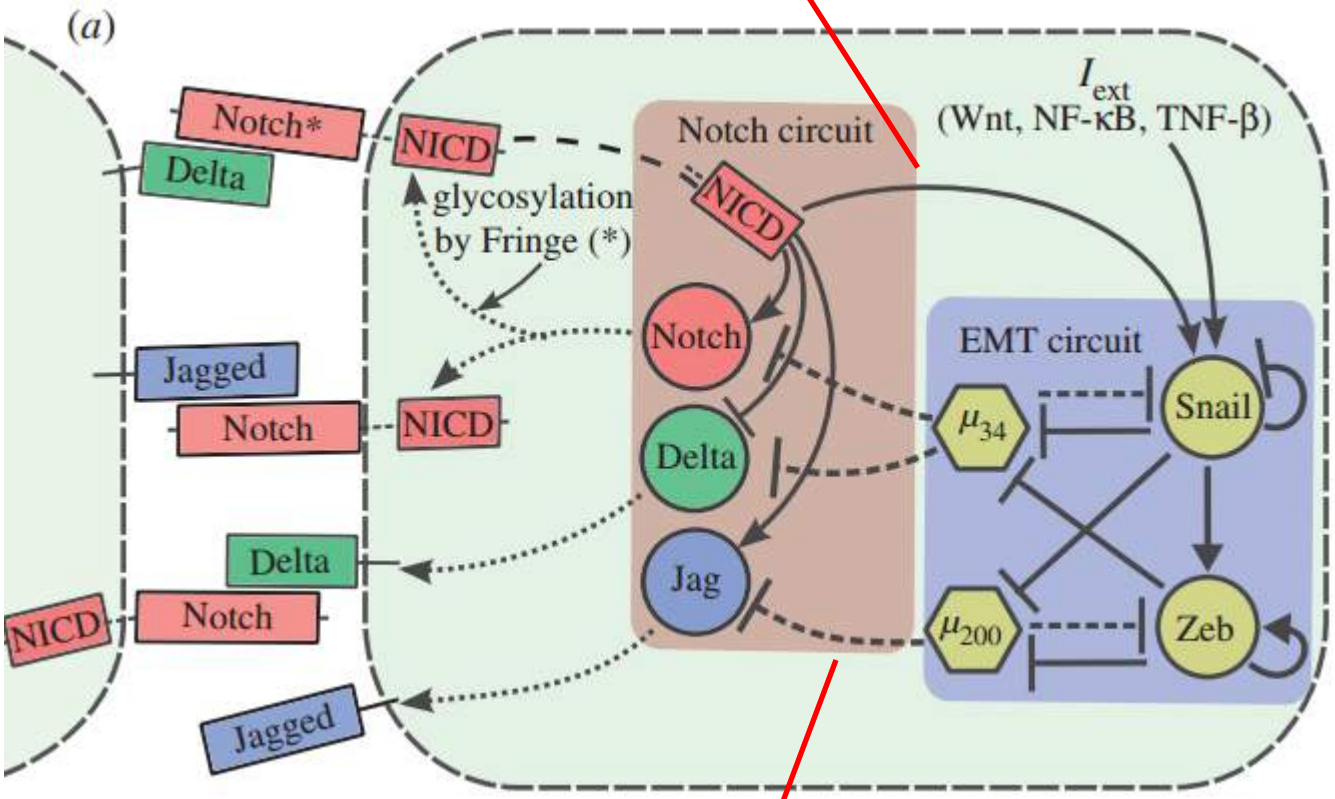


Clusters of CTCs

Cell-cell communication may help coordinate the spatial proximity of hybrid E/M cells to form CTC clusters

Crosstalk between EMT and Notch pathways

Notch signaling activates EMT

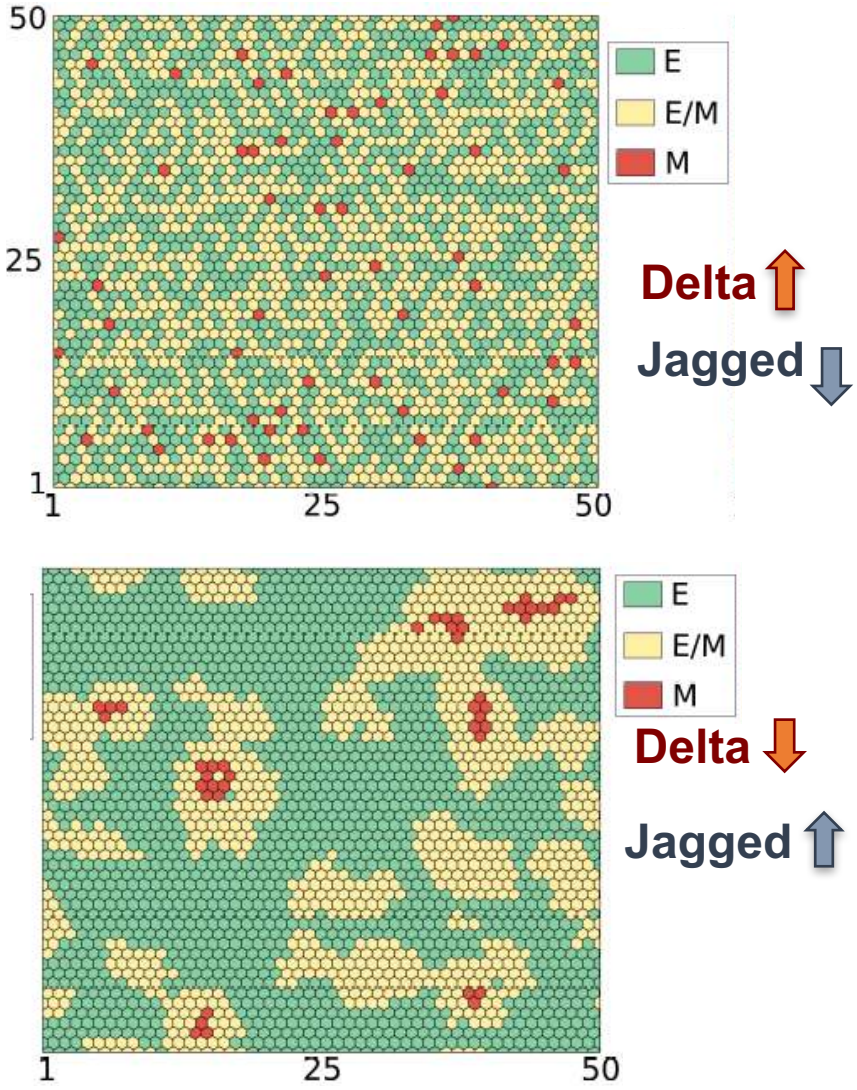


microRNAs inhibit Notch signaling

Can cell-cell communication via Notch signaling enable forming CTC clusters?

Notch-Jagged signaling can form CTC clusters

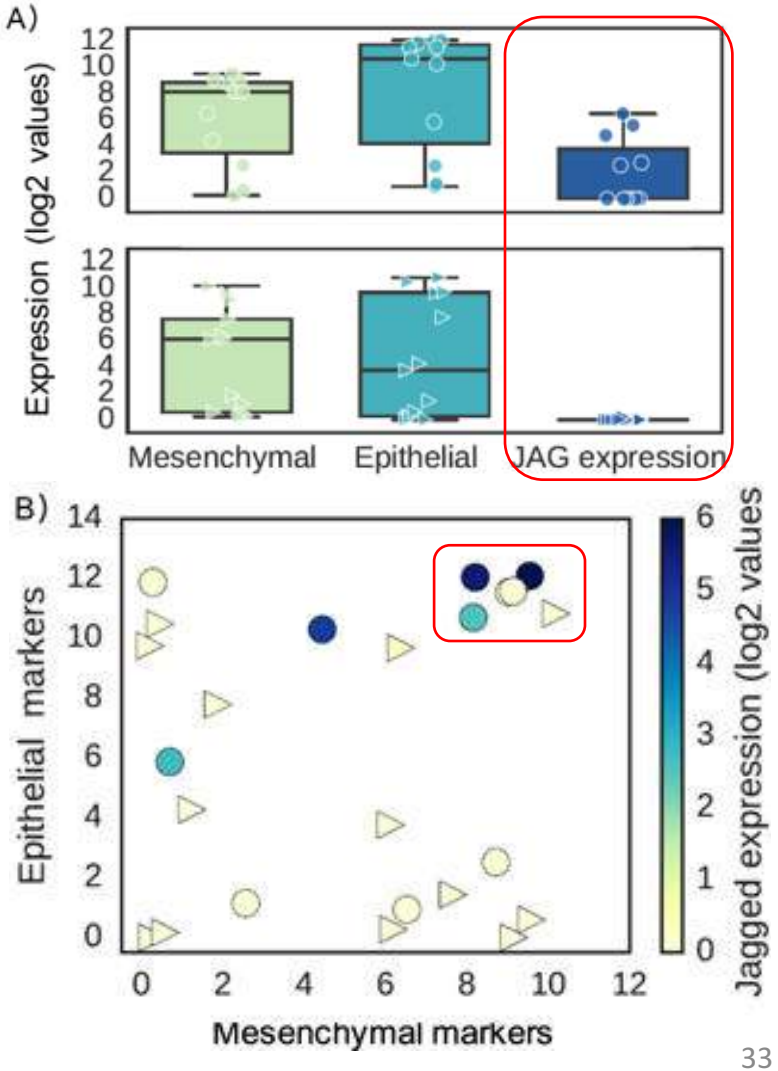
Theoretical prediction



Boareto, Jolly *et al*. J R Soc Interface 2016

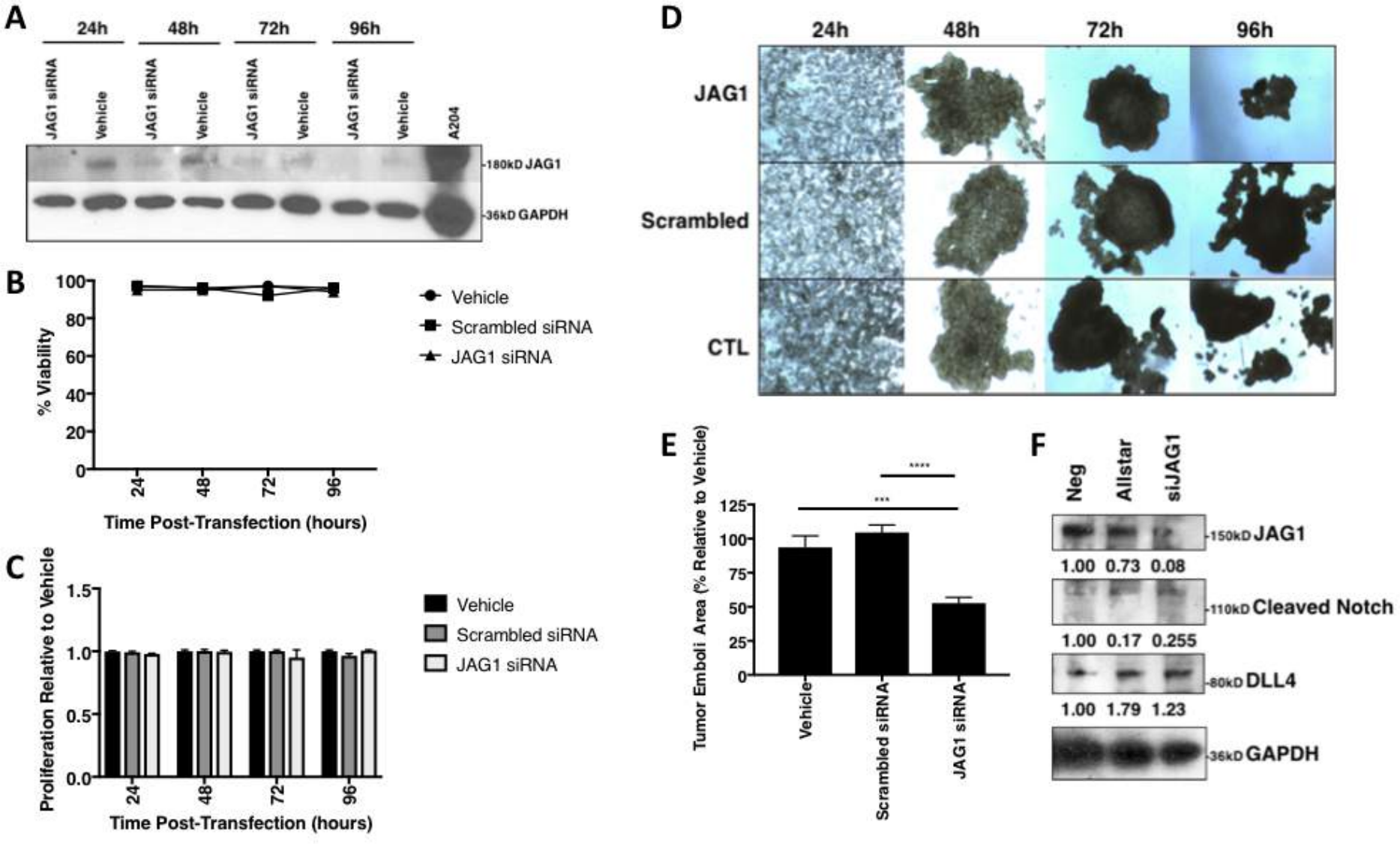
Experimental validation

Patient data for CTC clusters vs. single CTCs



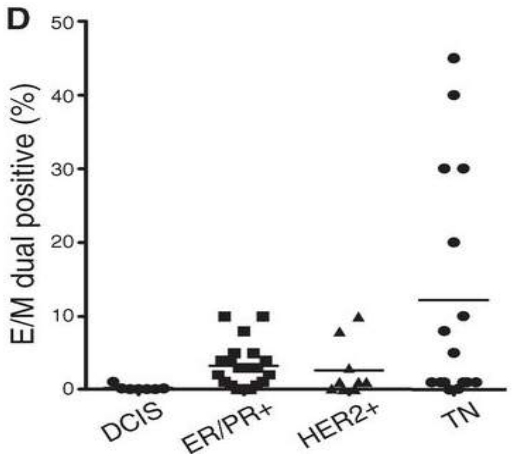
Jolly *et al.* NPJ Br Cancer 2017

JAG1 knockdown diminishes emboli formation

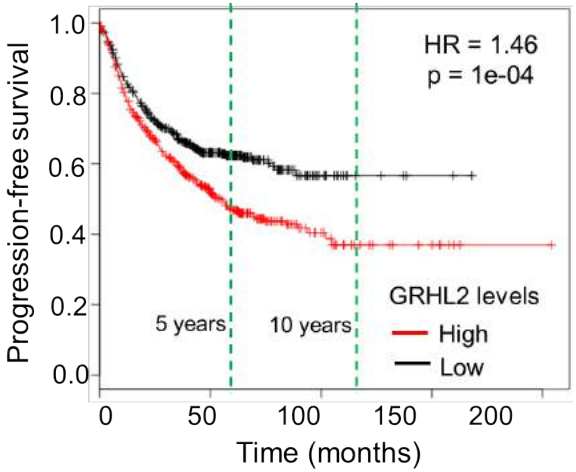


Bocci….. Jolly, PNAS 2018

Why do hybrid E/M cells matter in the clinic?

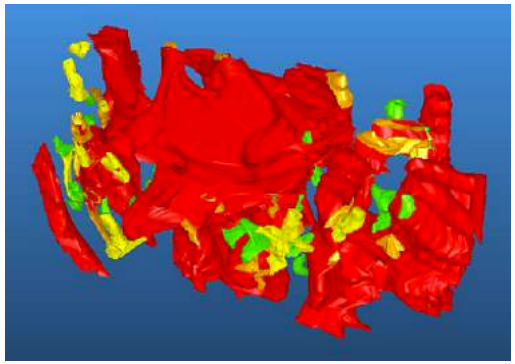


Yu *et al*. Science 2013



Jolly *et al*. Oncotarget 2016

n = 982 (lung cancer)



Single-cell migration is very rare, if any, in cancer

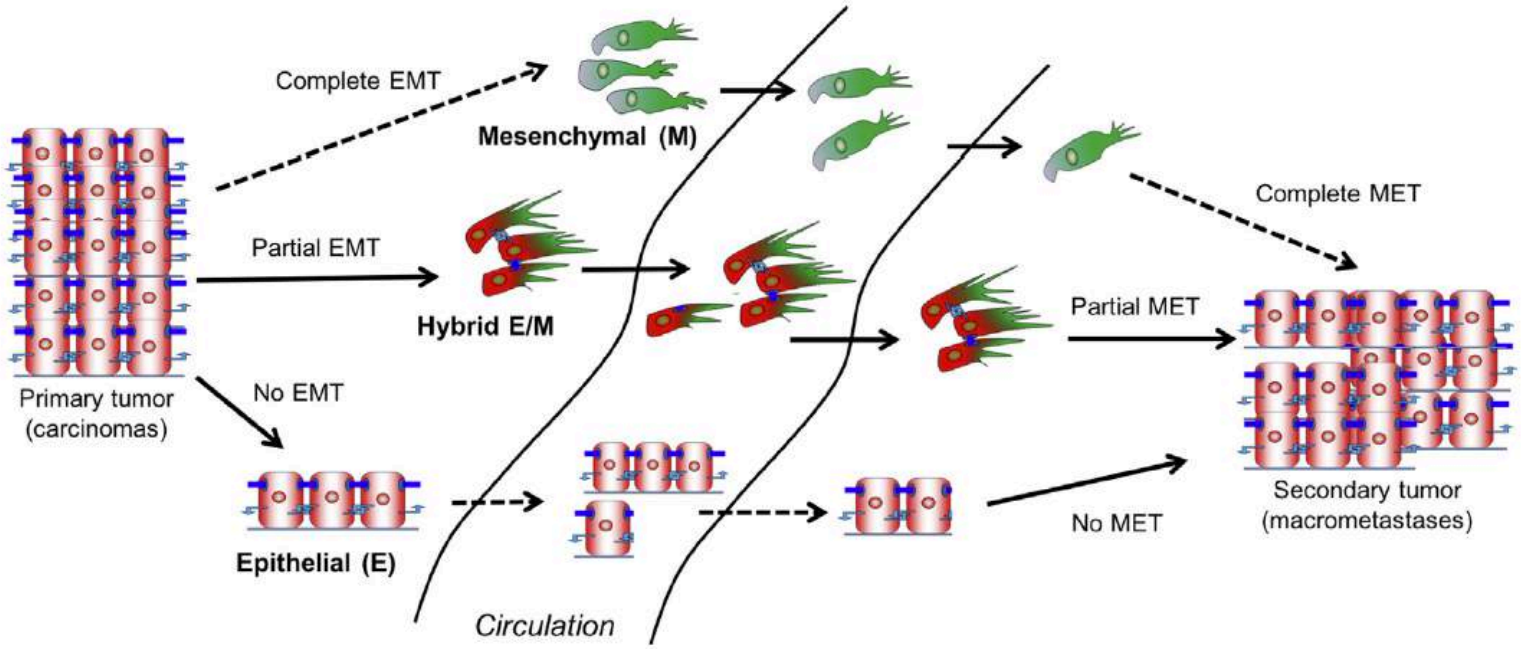
Co-expression of nuclear ZEB1 and membranous E-cad - a 'partial EMT' status of 'tumor buds'

Hybrid E/M may be more aggressive than a complete EMT

Bronsert *et al.* J Pathol 2014

Grigore*, Jolly* *et al.* J Clin Med 2016

Hybrid E/M: the 'fittest' for metastasis?



United cancer cells stand, divided they fall!

- Cells can help each other develop resistance against cell death
- Clusters can navigate more effectively
- Hybrid E/M cells can more easily initiate new tumors
- Hybrid E/M cells can generate more heterogeneity driving cooperation

Jolly *et al.* BBA Rev Cancer 2018

Conclusion

Existing framework:

Hybrid E/M state is transient, and the more the EMT, the more aggressive the cancer

Tam and Weinberg, Nat Med 2013, Savagner P Curr Opin Dev Biol 2015

Proposed framework:

Hybrid E/M state is stable and may be more aggressive than a complete EMT

Jolly *et al.* Front Oncol 2015, Jolly *et al.* Oncotarget 2016

with biophysical models. Computational modeling, including those that consider the mutual inhibitory loops between several microRNAs (miRNAs) and EMT transcriptional drivers like Snail1 and Zeb1, also accepts an intermediate hybrid EMT state that could favor the progress of developmental programs and metastatic potential (Jolly et al., 2015; Lu et al., 2013; Tian et al., 2013; Zhang et al., 2014). The inclusion of additional reciprocal inhibitory loops that involve other transcription factors (e.g., Zeb1 with Ovol2 and Grhl2) and the description of these as phenotypic stability factors indicates that the network is capable of generating additional intermediate stabilized states that, therefore, are not necessarily metastable (Hong et al., 2015; Jolly et al., 2016).

Nieto MA, Thiery JP, Cell 2016

"Instead, there is growing evidence that a cell that has undergone only a partial EMT, thereby expressing both retained epithelial and acquired mesenchymal traits, is best positioned to acquire stem-like properties (Grosse-Wilde et al., 2015; **Jolly et al., 2015 a,b**, Andriani et al., 2016)"

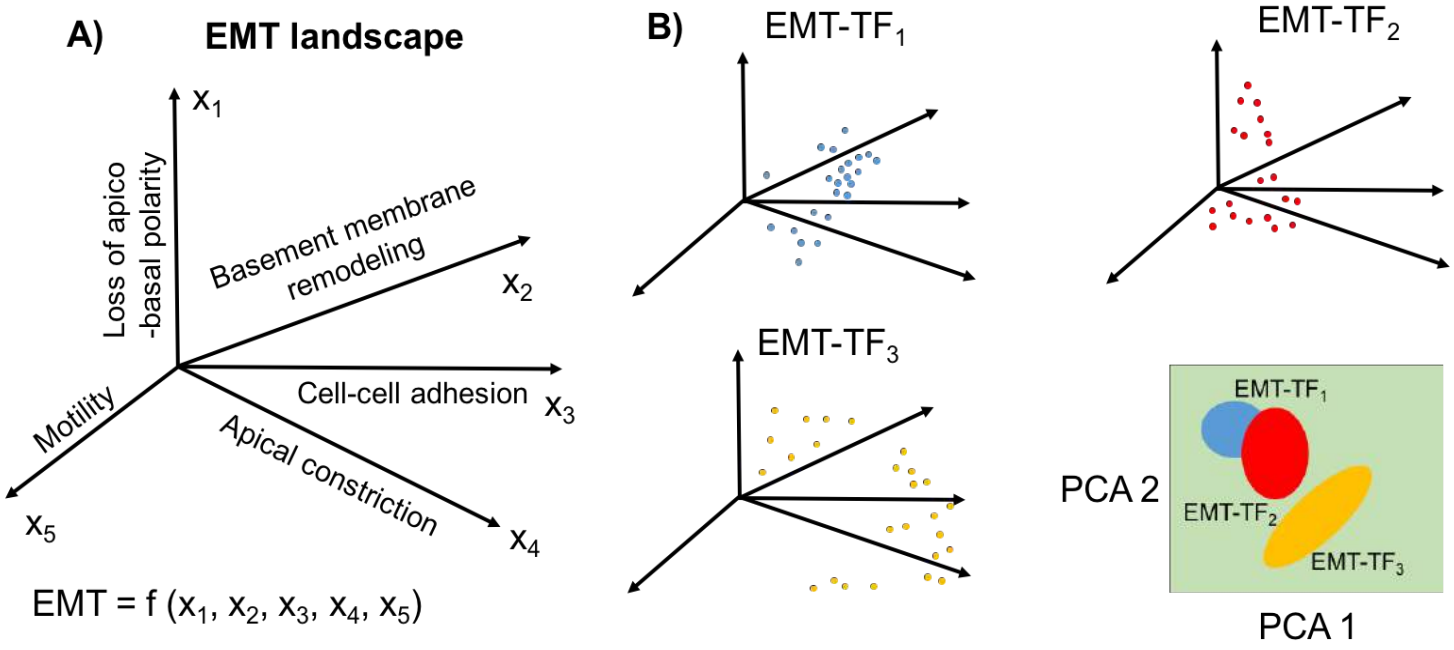
Pattabiraman & Weinberg, CSHL Quant Bio 2017

Ongoing questions/debate

Epithelial–to–mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer

Xiaofeng Zheng[1]*, Julienne L. Carstens[1]*, Jiha Kim[1], Matthew Scheible[1], Judith Kaye[1], Hikaru Sugimoto[1], Chia-Chin Wu[2], Valerie S. LeBleu[1] & Raghu Kalluri[1,3,4]

Zheng *et al.* Nature 2015
Fischer *et al.* Nature 2015
Krebs *et al.* Nat Cell Biol 2017



- EMT is a highly non-linear and multi-dimensional process
- Connections between genetics and biophysics of EMT are still being elucidated

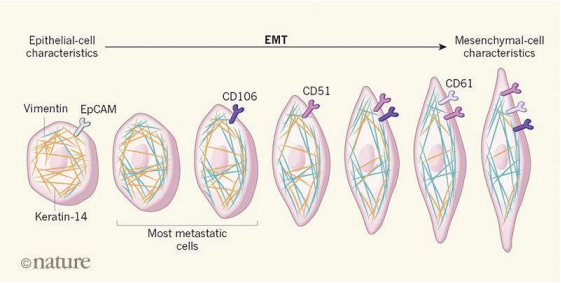
Jolly *et al.* Mol Oncol 2017

Fifty (or more) shades of cellular plasticity

A box contains 6 white balls, 3 red balls, and 3 blue balls. In how many ways can one pick one white ball, one red ball, and one blue ball?

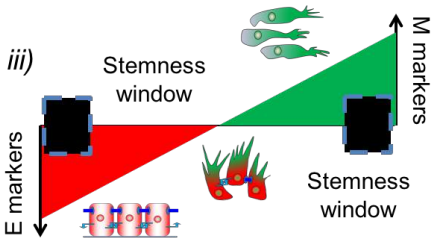
- No. of EMT states >= 6

Pastushenko et al. Nature 2018
Huang et al. EMBO Mol Med 2014
Schliekelman et al. Cancer Res 2015
Yu et al. Science 2013
Biddle et al. EBioMedicine 2016
Varankar et al., bioRxiv: 307934



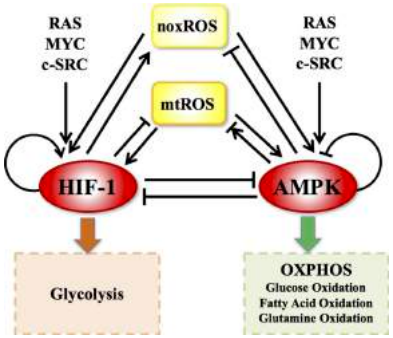
- No. of stem-like states >= 3

Liu et al. Stem Cell Reports 2014
Colacino et al. Stem Cell Reports 2018
Ruscetti et al. Oncogene 2015, 2016



- No. of metabolic states > = 3

Yu et al. Cancer Res 2017
Saha et al. Cancer Res 2018



- **Total no. of states = 6*3*3*…..?**

Acknowledgements

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

S C Tripathi
Samir Hanash
A Deshmukh
Sendurai A Mani

Annapoorni Rangarajan
Saurav Kumar

IISER PUNE

Kundan Sengupta
Maithilee Khot
Apoorva Kulkarni

NCCS National Centre for Cell Science

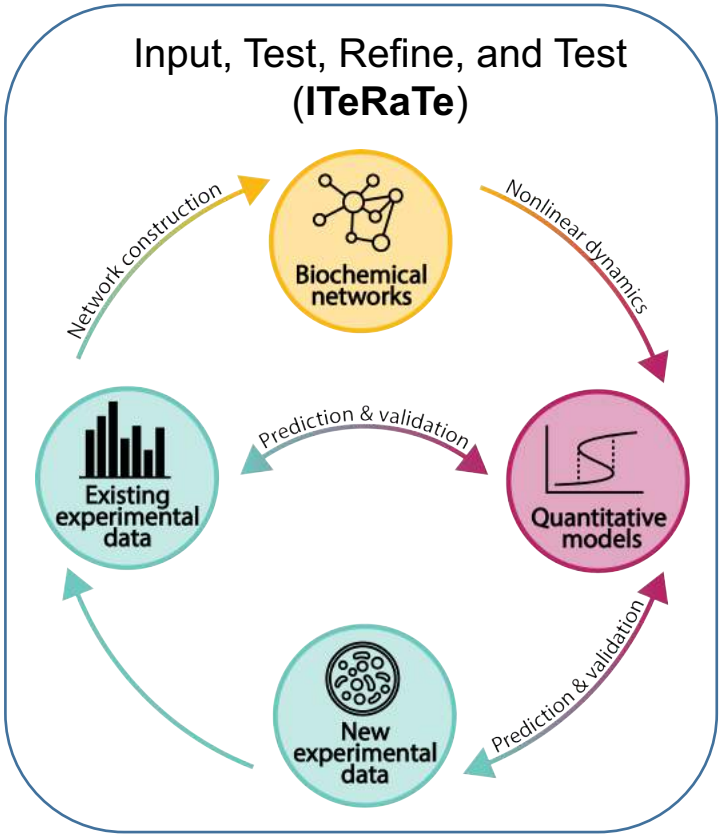
Sharmila A Bapat
Sagar Varankar

Duke UNIVERSITY

Jason A Somarelli
Andrew J Armstrong
Gayathri R Devi
L Gearhart-Serna
Kathyrn E Ware
Shengnan Xu

City of Hope

Ravi Salgia
Prakash Kulkarni
Blake Hewelt
Arjun Kalvala



CPRIT SERB DIA NSF

Thank you!

mkjolly@iisc.ac.in

RICE

CTBP

Herbert Levine
Jose N Onuchic
Eshel Ben-Jacob
Michael W Deem
MC Farach-Carson
Dongya Jia
Federico Bocci
Jason T George
Shubham Tripathi
Marcelo Boareto
Xuefei Li
Mingyang Lu
Wen Jia

Govindan Rangarajan
HAS Shri Kishore

Partha Sharthi Dutta
Sudipta Sinha
Sukanta Sarkar

IISER KOLKATA

Anandmohan Ghosh
Kuheli Biswas

MIT

Aaron Goldman
Shiladitya Sengupta