A theoretical (bio)physicist looks at cancer metastasis

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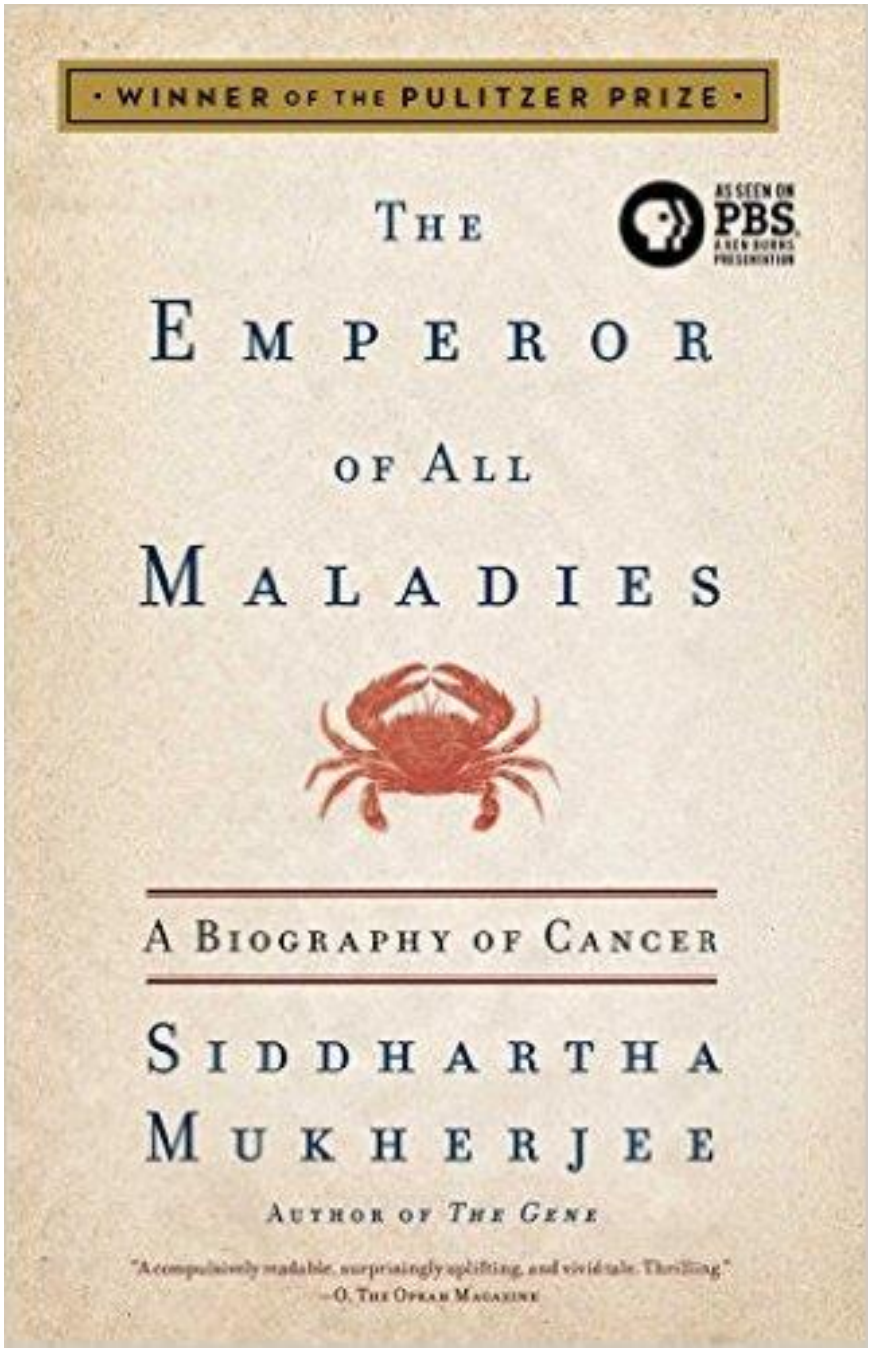
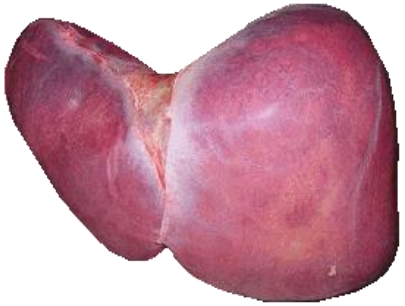
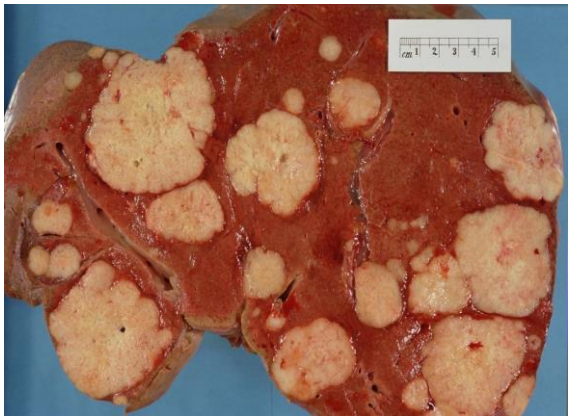
(Mentors: Prof. Herbert Levine (Rice U), Prof. Samir Hanash (MDACC))

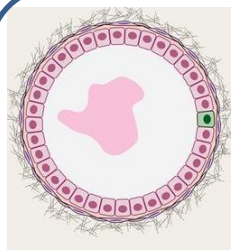




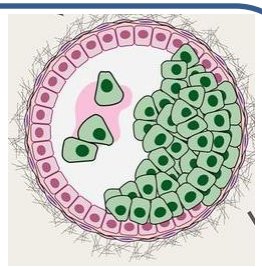
Uncontrolled growth of abnormal cells



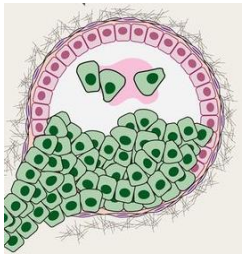
Stages of cancer progression



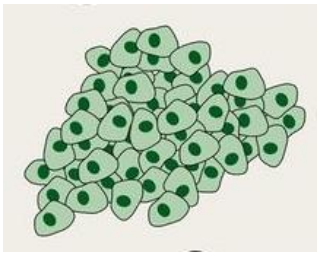
~ 10 years



~ 5 years



~ 2-3 years



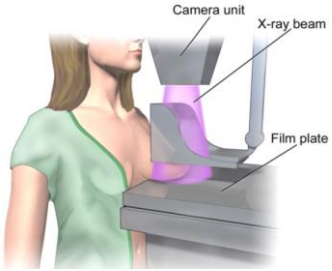
Tumor initiation

Localized disease (primary tumor)

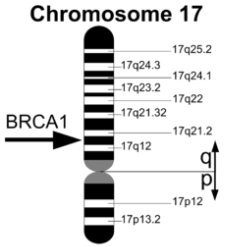
Invasive spread

Metastasis (secondary tumors)

Remarkable progress made in:



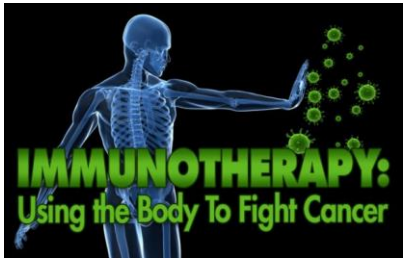
Diagnosing cancer early



Listing the genes involved

Identifying risk factors

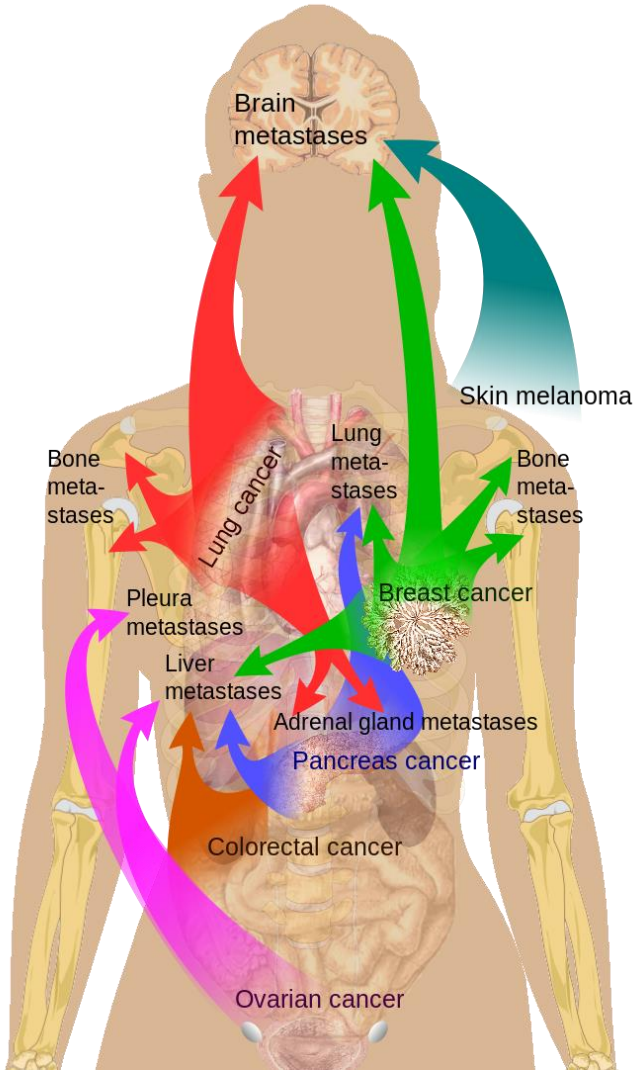
?



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.

Is genetics the answer? Not always

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

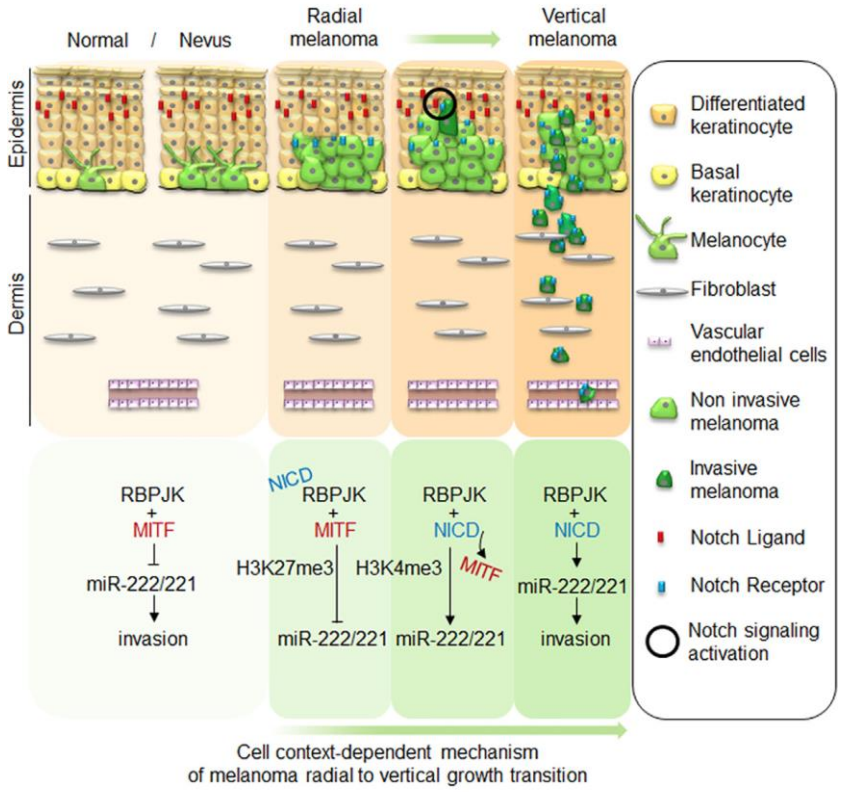
- One example: Inflammatory Breast Cancer (IBC)
  - About 30% of IBC patients have distant metastases at the time of diagnosis as compared to only 5% of non-IBC type
  - Though only 2-4% of breast cancer cases each year are of IBC type, IBC patients account for 10% of the annual breast cancer related mortalities
  - Despite several studies, no robust gene signature associated with IBC has yet been identified.

Jolly *et al.* NPJ Br Cancer 2017

Is genetics the answer? Not always

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

- Another example: Melanoma metastasis

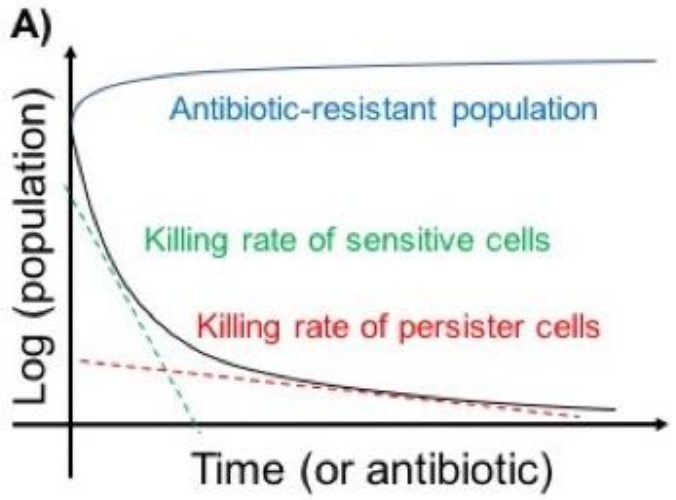


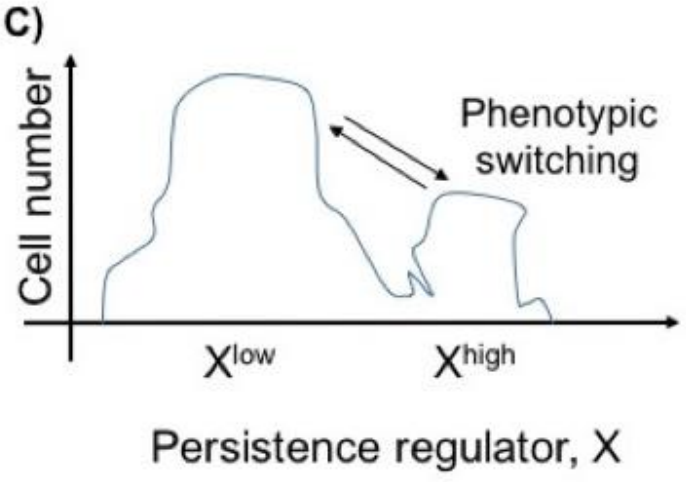
Cells become metastatic competent by being exposed to a new chemical environment

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,*]
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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]

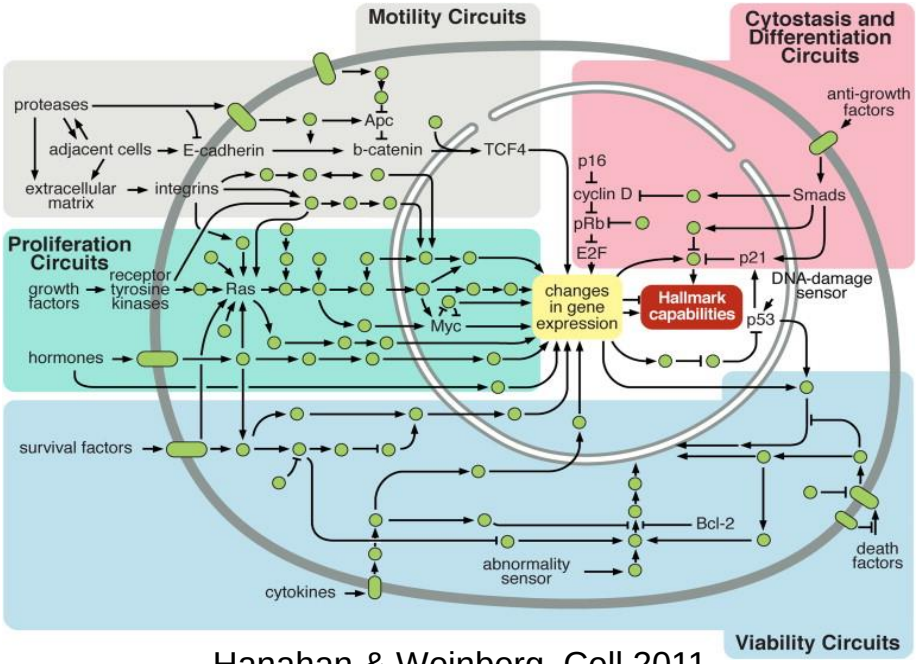
Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance

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)

Can physicists help decode cancer? Yes!



Hanahan & Weinberg, Cell 2011

Cellular phenotypes = 'attractors' or stable states of this multi-dimensional system

Switching between different states in response to internal or external signals = phenotypic plasticity

"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

Cancer biology still needs physicists

Considering game theory and the role of physical forces could lead to better treatments for cancer, says **Robert Austin**.

- Inventing new experimental methods (MRI, e.g.)
- Enhancing existing treatments (radiation therapy)
- Applying physical perturbations to tissues (heating via nanoparticles, for example)
- Developing sophisticated data analysis tools
- …

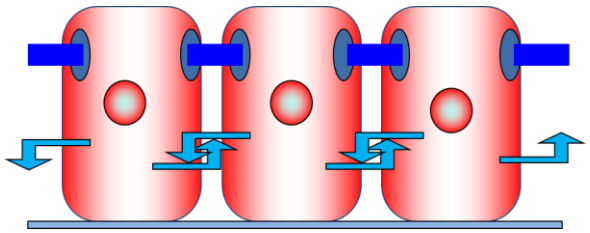
- Here: Using mathematical models to isolate the mechanisms underlying observed phenomena. Analogous to the use of physics in other complex systems, such as climate change.

We are…

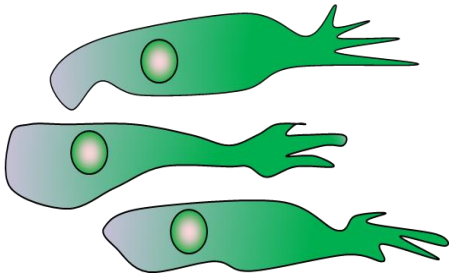
- **Not** inferring networks by data-mining from “omics” data
- **Not** focusing exclusively on one dataset or even on one type of cancer

- **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

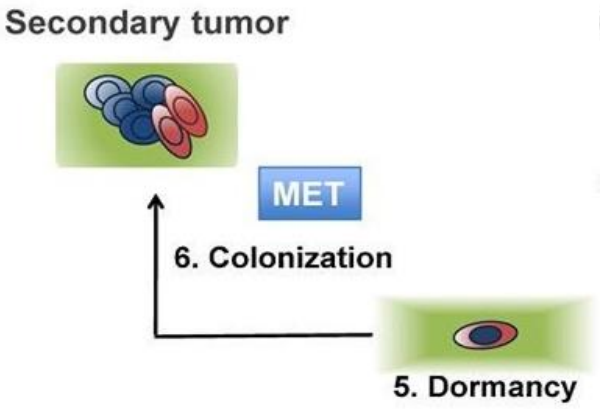


Adhere to neighbors
Do NOT migrate or invade
Epithelial (E)

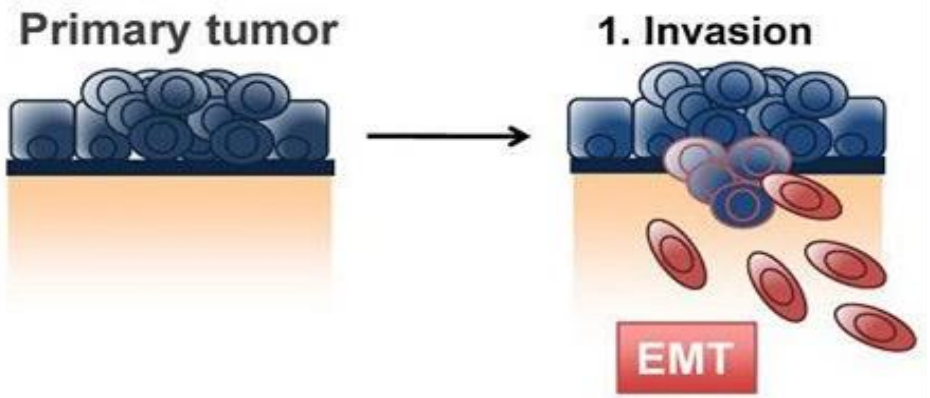


Do NOT adhere to neighbors
Migrate and invade
Mesenchymal (M)

Mesenchymal-to-Epithelial Transition (MET)



Epithelial-to-Mesenchymal Transition (EMT)



Scheel & Weinberg, Semin Cancer Bio 2012

EMT/MET: motor of cellular plasticity

Boareto, **Jolly** *et al.*
J R Soc Interface 2016
Tripathi…**Jolly** *et al.*
Cancer Res 2017

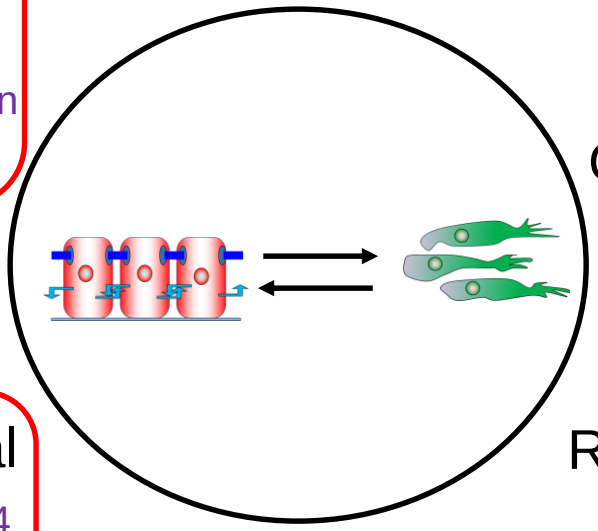
Chemoresistance

Lu*, **Jolly*** *et al.* PNAS 2013
Jia*, **Jolly*** et al. Oncotarget 2015
Huang, **Jolly** et al. Sci Rep 2016
Jolly *et al.* Oncotarget 2016
Jolly *et al.* NPJ Br Cancer 2017
Boekhorst..**Jolly** *et al.*, in preparation

Migration and invasion

Somarelli, Shelter, **Jolly** *et al.*
Mol Cell Biol 2016 (Cover article)
Kulkarni, **Jolly** *et al.*, in revision
Eichelberger... **Jolly** *et al.*, in preparation

Genomic/epigenetic reprogramming



Tumor-initiation potential

Jolly *et al.* J R Soc Interface 2014
Jolly*, Jia* *et al.* Oncotarget 2015
Jolly *et al.* NPJ Br Cancer 2017
Jolly *et al.*, in preparation

Resistance to cell death

Evans.. **Jolly** *et al.,* in revision
Gearhart .. **Jolly** *et al*., in preparation
Somarelli.. **Jolly** *et al.,* in preparation

Evasion of immune system

Tripathi…**Jolly** *et al.*
PNAS 2016
Li, **Jolly** *et al.,* in preparation

A systems biology approach to investigate EMT

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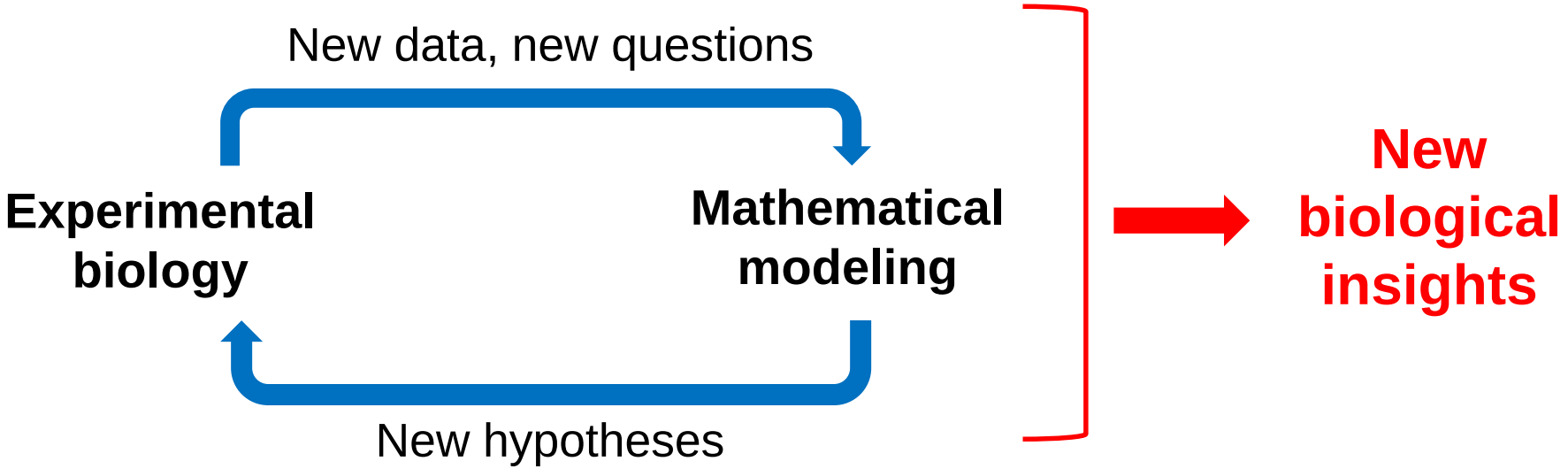
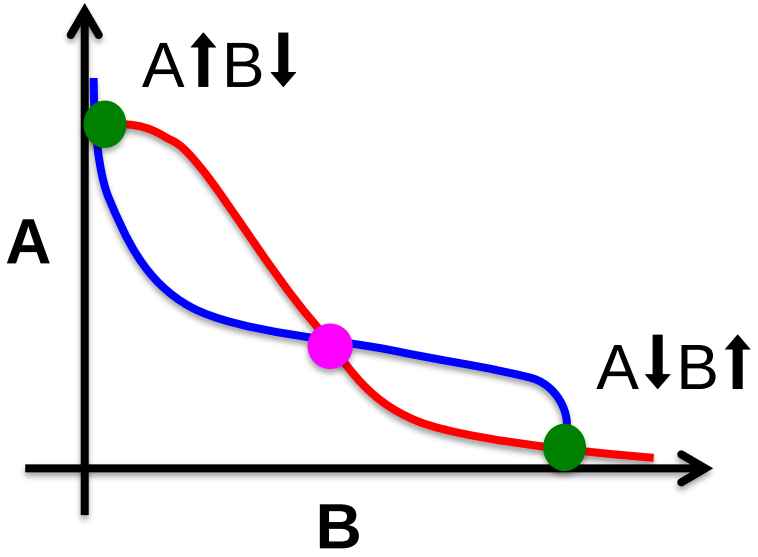
Can a systems or engineering approach help defeat cancer metastasis?



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

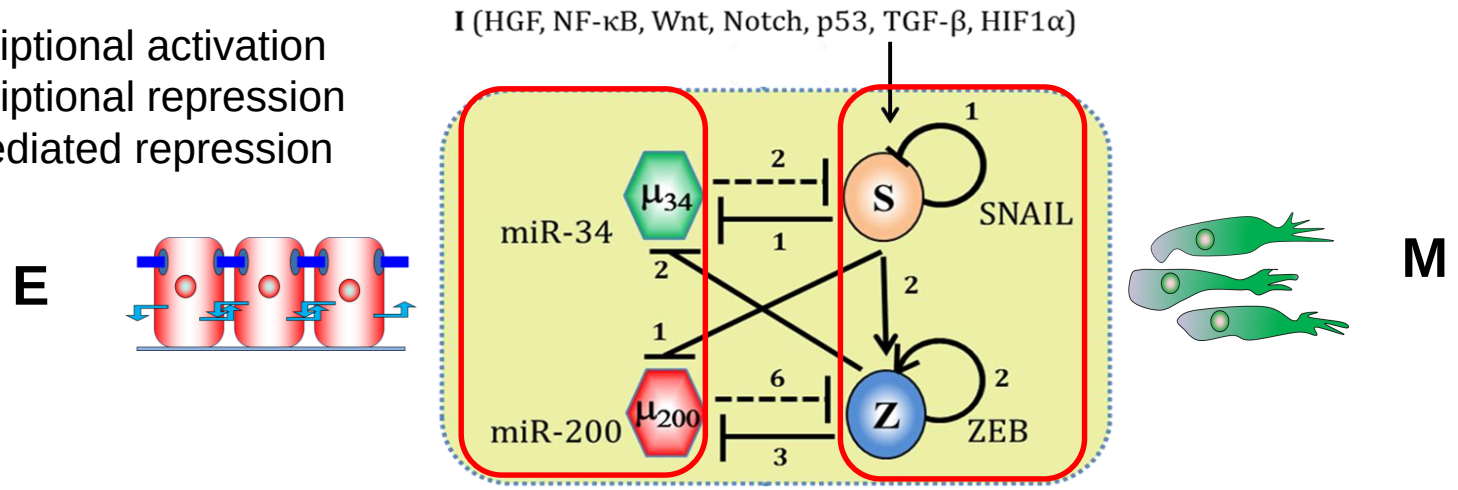
Steps involved:

- 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

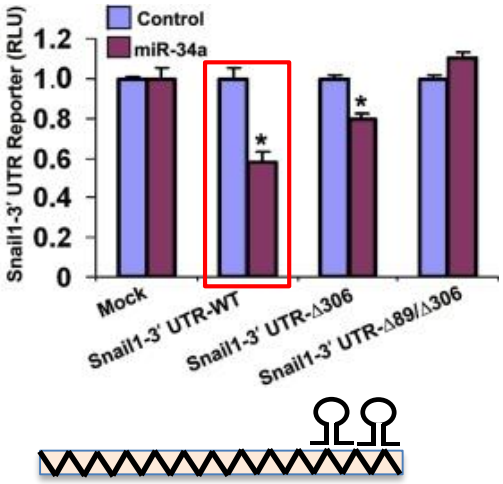
Systems biology model for EMT/MET

Transcriptional activation
Transcriptional repression
miR-mediated repression

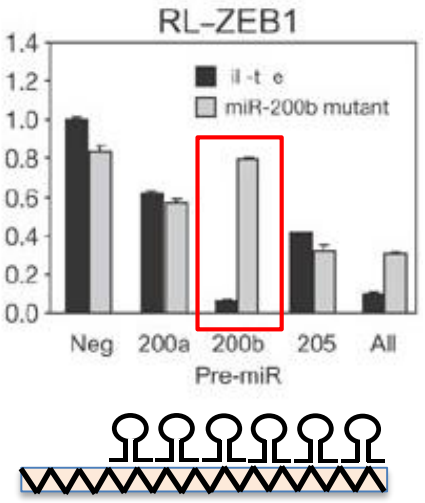


Lu*, Jolly* *et al.* PNAS 2013

Example input data for the model:

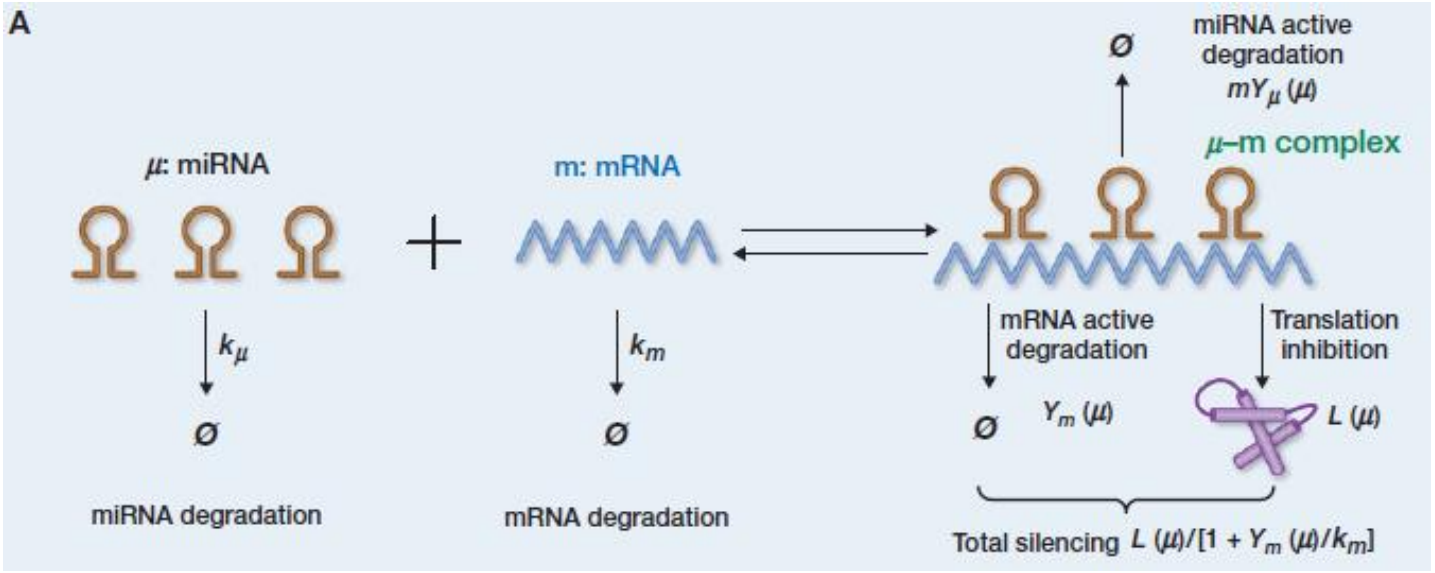


Kim *et al.* J Cell Biol 2011

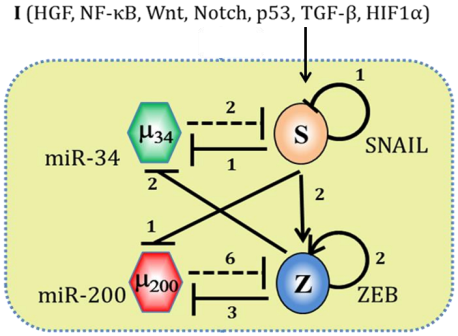


Gregory *et al.* Nat Cell Biol 2008

Theoretical framework for miRNA-based circuits



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



Production

Degradation

miR regulation

TF regulation

$$\frac{dm_{200}}{dt} = g_{m_{200}} H^S(Z, I_{Z,m_{200}}) H^S(S, I_{Z,m_{200}}) - m_Z Y_m(m_{200}) - k_{m_{200}} m_{200}$$ miR-200

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

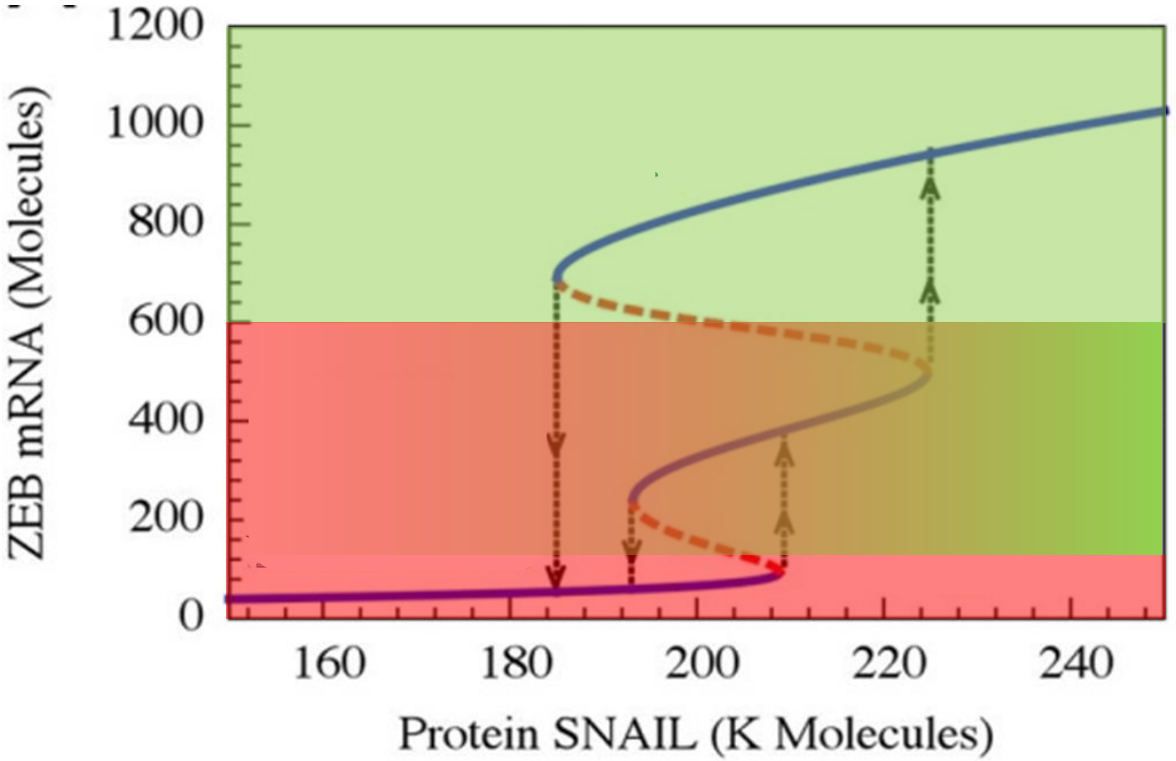
$$\frac{dZ}{dt} = g_Z m_Z L(m_{200}) - k_Z Z$$ ZEB

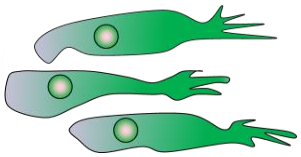
$$\frac{dm_{34}}{dt} = g_{m_{34}} H^S(Z, I_{Z,m_{34}}) H^S(S, I_{Z,m_{340}}) - m_S Y_m(m_{34}) - k_{m_{34}} m_{34}$$ miR-34

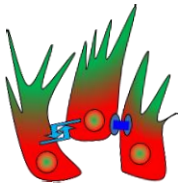
$$\frac{dm_S}{dt} = g_{m_S} H^S(S, I_{S,m_S}) H^S(I, I_{I,m_S}) - m_S Y_m(m_{34}) - k_{m_S} m_S$$ SNAIL mRNA

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

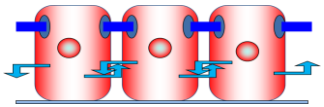
Tristability in the underlying EMT network

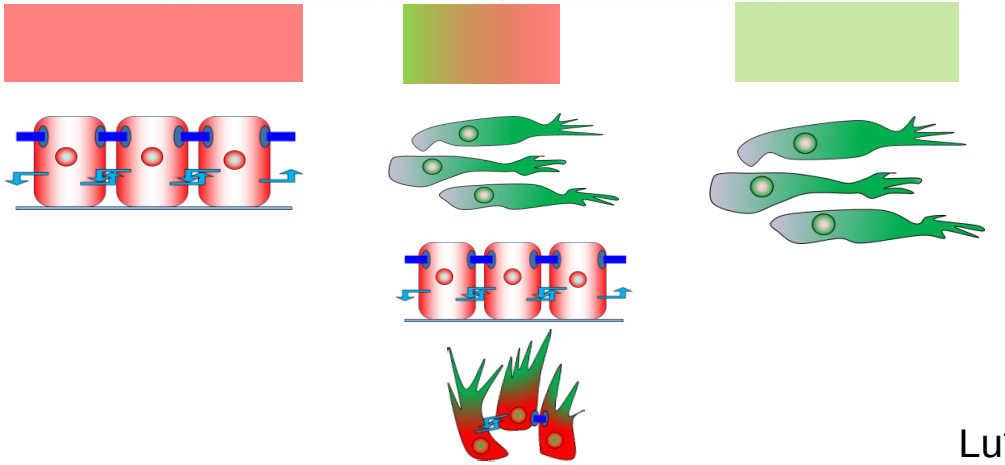






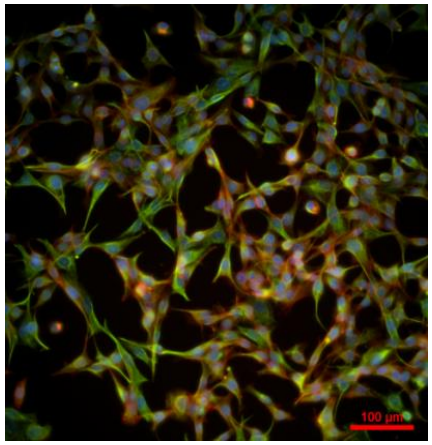
Hybrid E/M
Adhere AND
migrate collectively



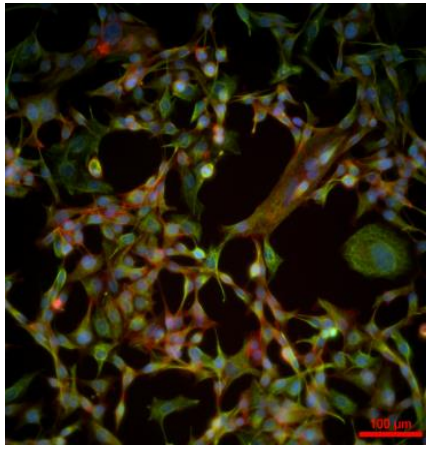


Lu*, Jolly* *et al.* PNAS 2013

Hybrid E/M can be a stable phenotype

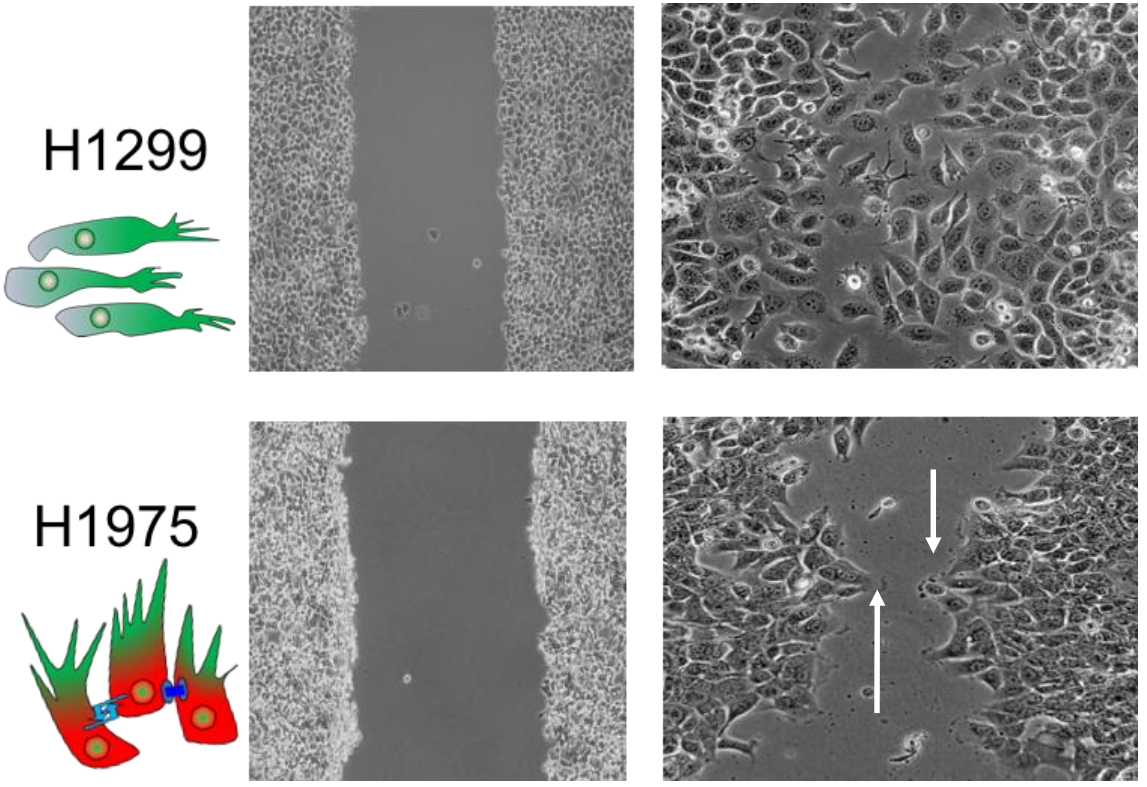


H1975, T=0



H1975, T=2 months

CDH1 (E-marker)
VIM (M-marker)

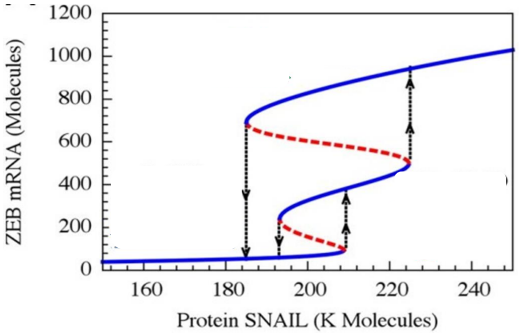


Hybrid E/M cells tend to move collectively

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

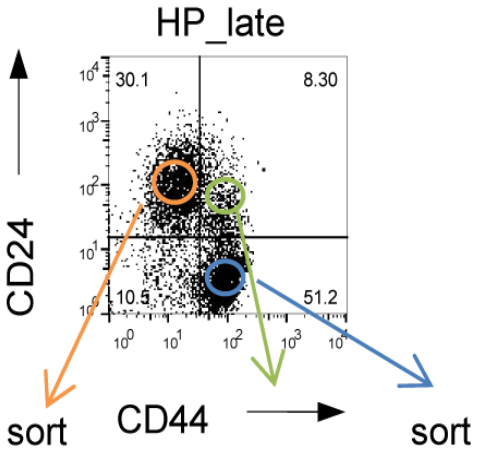
Co-existence of phenotypes seen experimentally

Theoretical prediction



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

Experimental validation

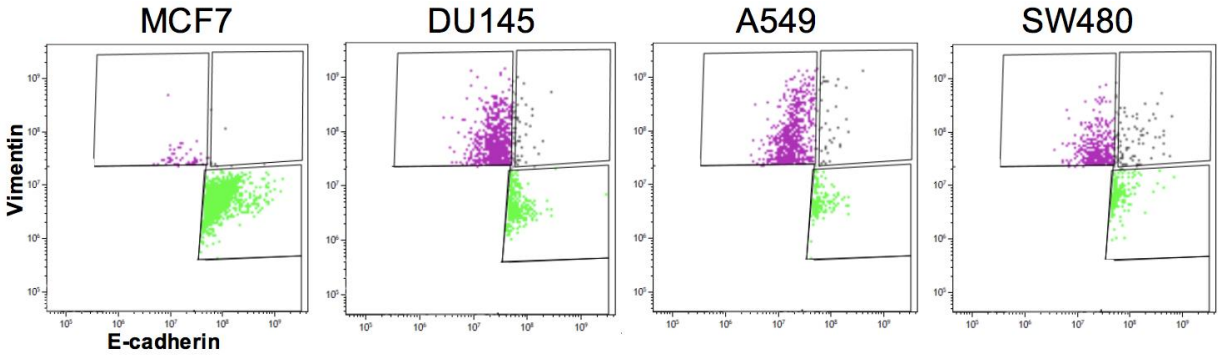


Grosse-Wilde *et al.* PLoS ONE 2015

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:

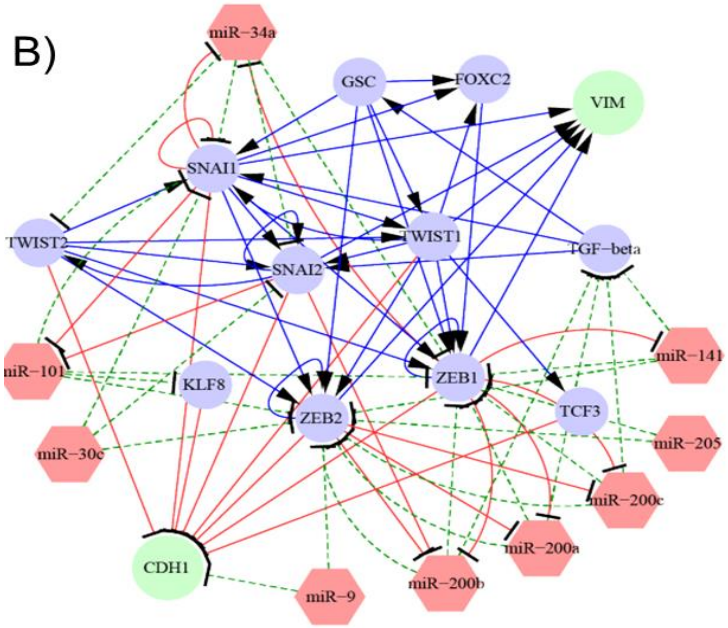
- Xing group (Pittsburgh)

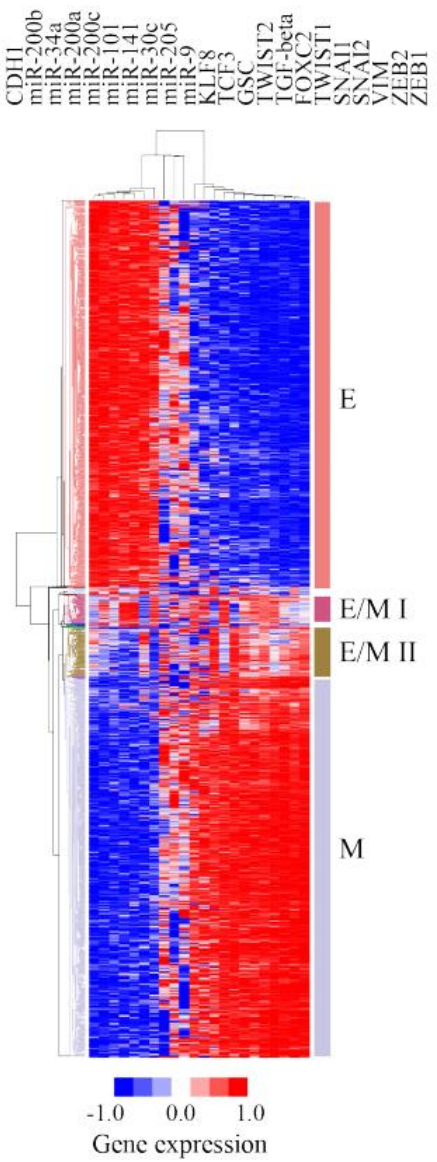
(Tian *et al.* Biophys J 2013, Zhang *et al.* Sci Signal 2014)

- Albert group (Penn State Univ)

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

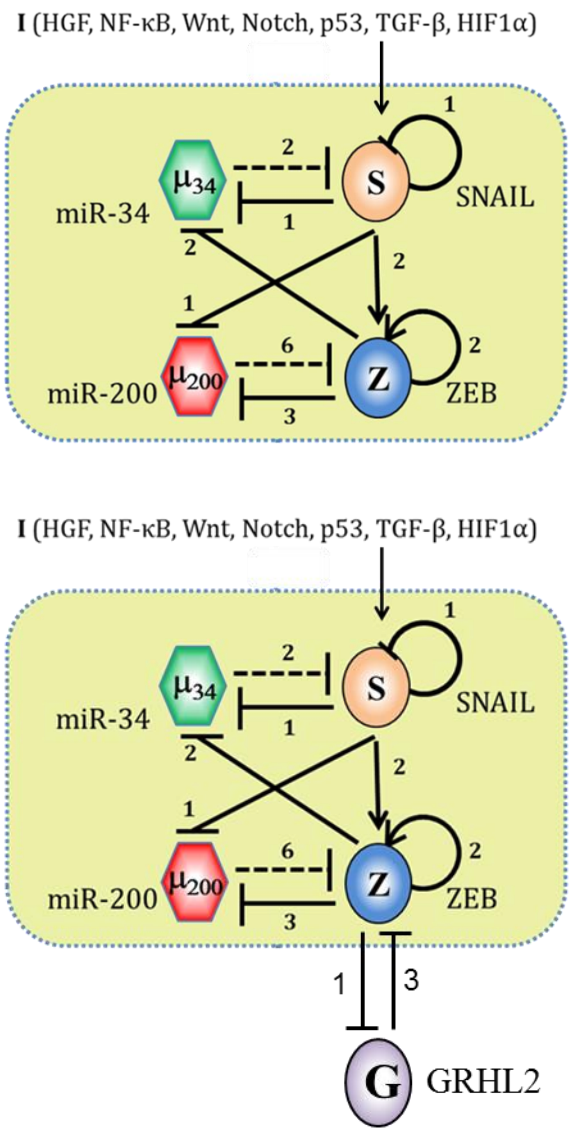
Ensemble of kinetic models with fixed circuit topology but with randomly selected parameters also enable hybrid E/M state(s)

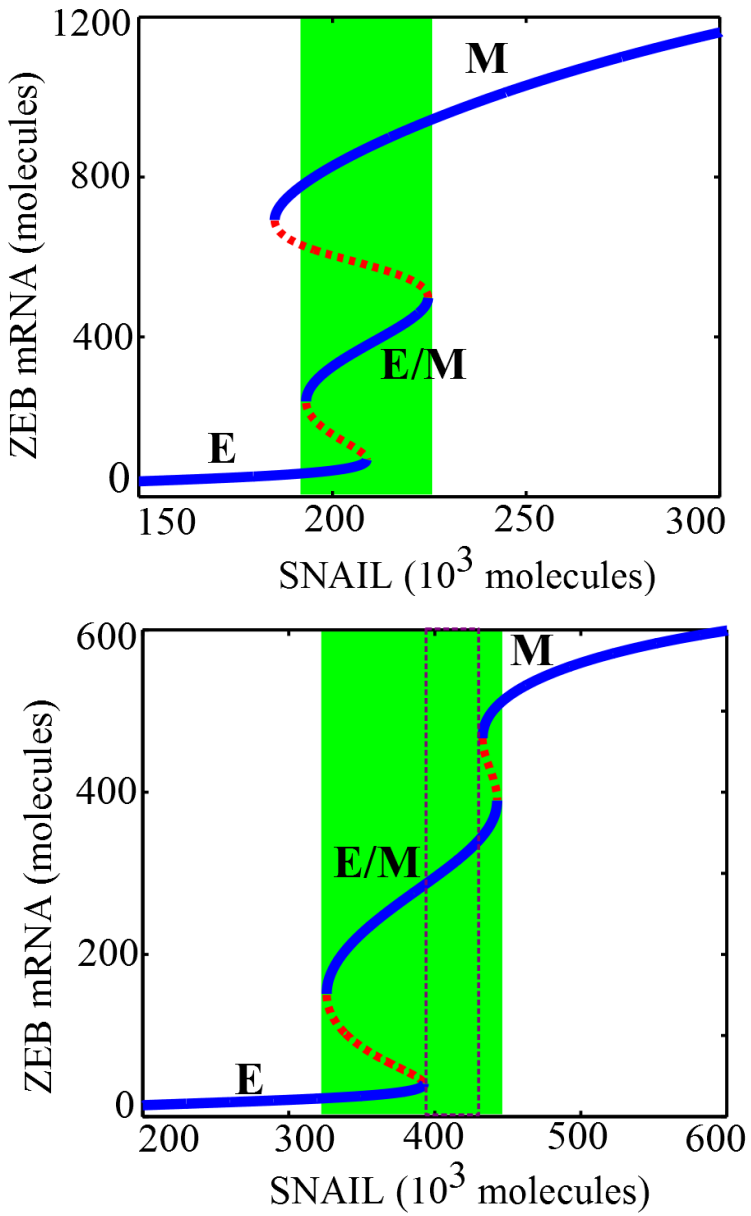




Huang *et al.* PLoS Comp Bio 2017

Identifying ‘phenotypic stability factors’ (PSFs)



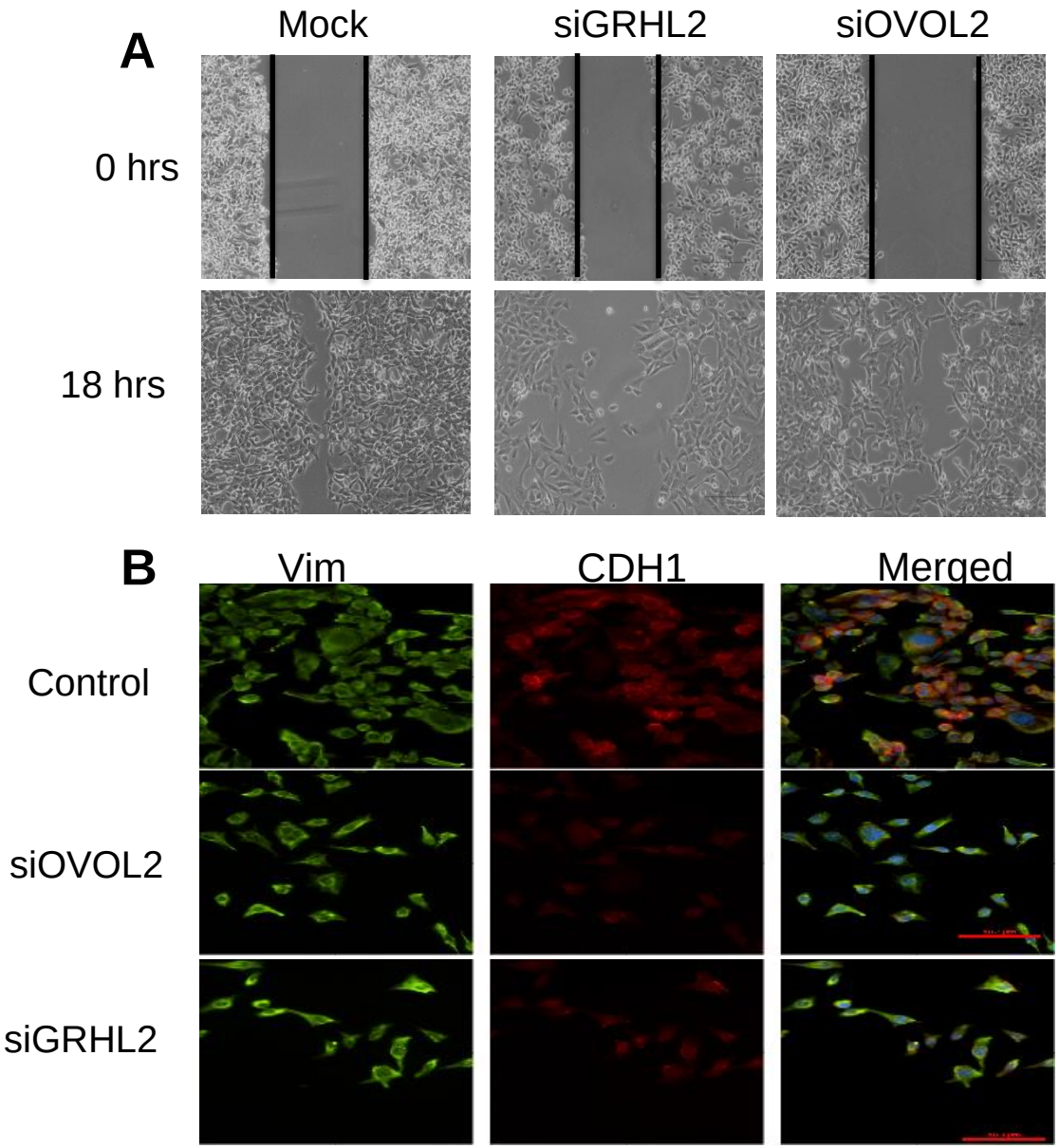


Jolly *et al*. Oncotarget 2016

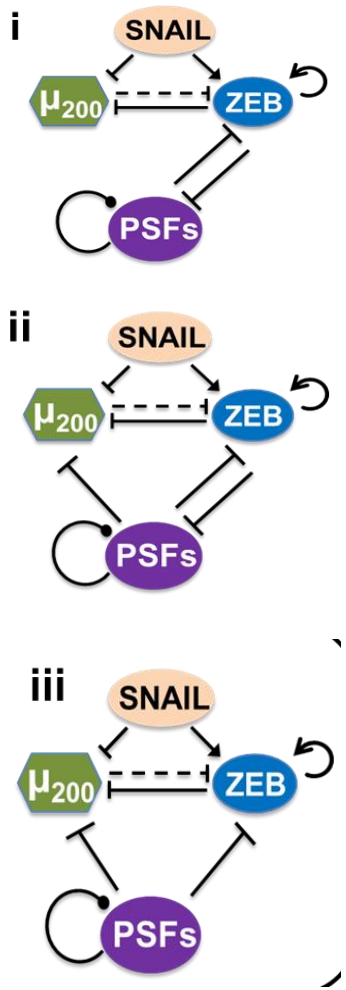
Other PSFs:

- 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, Jolly *et al.*, in preparation)

Knockdown of PSFs can drive a complete EMT



Network motifs for identifying additional PSFs



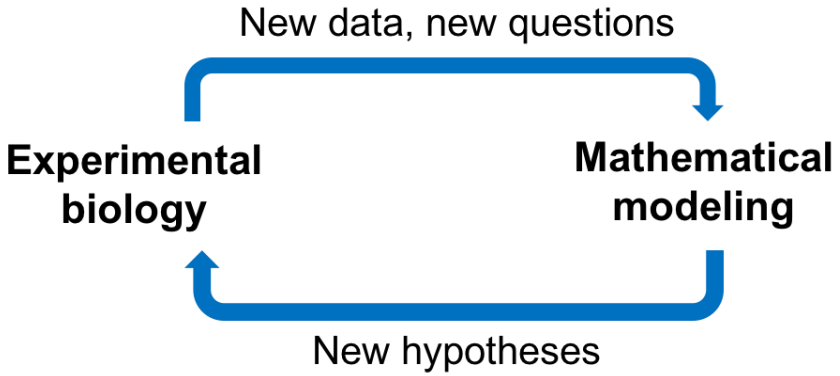
Satyendra Tripathi, Sam Hanash (MDACC)

Jolly *et al.* Oncotarget 2016

Summary: Systems Biology of EMT

How do miR-200/ miR-34/SNAIL/ZEB regulate EMT progression?

This circuit can enable three stable states/phenotypes in clonal populations



How do H1975 maintain a hybrid E/M phenotype stably?

GRHL2 or OVOL2 can stabilize a hybrid E/M state

EMT/MET: motor of cellular plasticity

Lu*, **Jolly*** *et al.* PNAS 2013
Jia*, **Jolly*** et al. Oncotarget 2015
Huang, **Jolly** et al. Sci Rep 2016
Jolly *et al.* Oncotarget 2016
Jolly *et al.* NPJ Br Cancer 2017
Boekhorst..**Jolly** *et al.*, in preparation

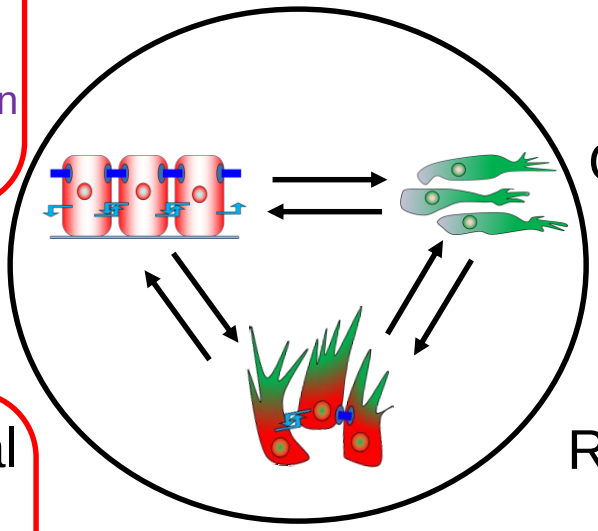
Migration and invasion

Boareto, **Jolly** *et al.*
J R Soc Interface 2016
Tripathi…**Jolly** *et al.*
Cancer Res 2017

Chemoresistance

Somarelli, Shelter, **Jolly** *et al.*
Mol Cell Biol 2016 **(Cover article)**
Kulkarni, **Jolly** *et al.*, in revision
Eichelberger... **Jolly** *et al.*, in preparation

Genomic/epigenetic reprogramming



Tumor-initiation potential (Stemness)

Jolly *et al.* J R Soc Interface 2014
Jolly*, Jia* *et al.* Oncotarget 2015
Jolly *et al.* NPJ Br Cancer 2017
Jolly *et al.*, in preparation

Evasion of immune system

Tripathi…**Jolly** *et al.*
PNAS 2016
Li, **Jolly** *et al.,* in preparation

Resistance to cell death

Evans.. **Jolly** *et al.,* in revision
Gearhart .. **Jolly** *et al*., in preparation
Somarelli.. **Jolly** *et al.,* in preparation

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

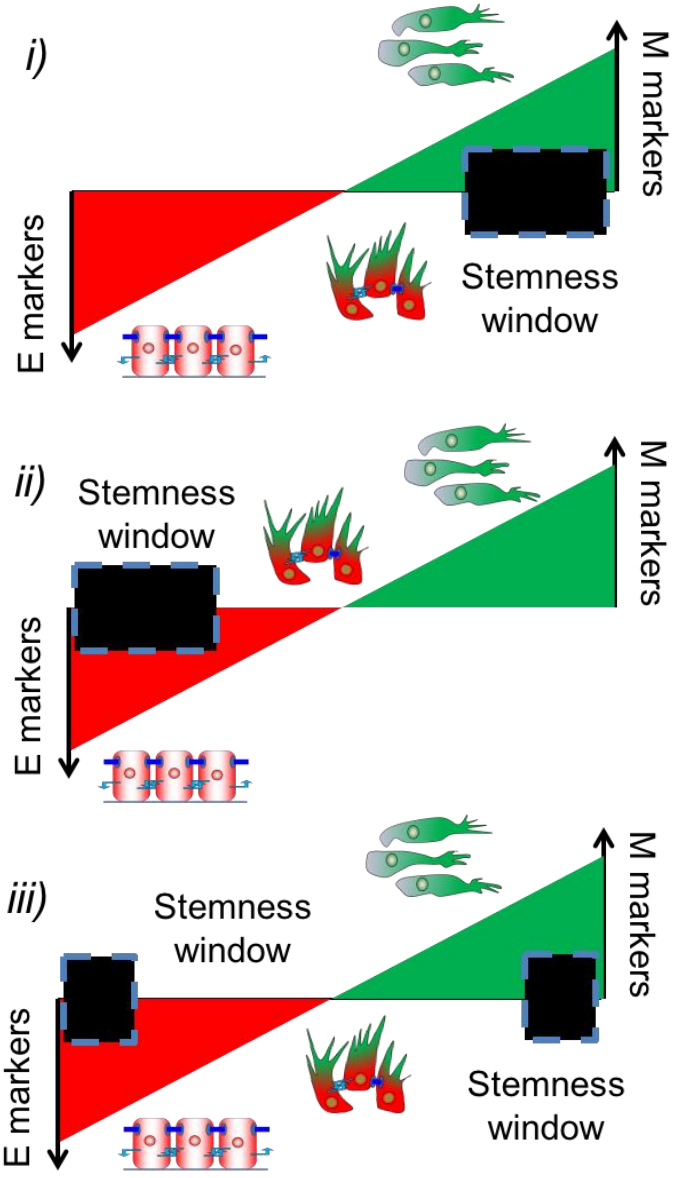
Toni Celià-Terrassa,[1] Óscar Meca-Cortés,[1] Francesca Mateo,[1] Alexia Martínez de Paz,[1] Nuria Rubio,[2] Anna Arnal-Estapé,[3] Brian J. Ell,[4] Raquel Bermudo,[5,6] Alba Díaz,[6] Marta Guerra-Rebollo,[2] Juan José Lozano,[7] Conchi Estarás,[8] Catalina Ulloa,[1] Daniel Álvarez-Simón,[1] Jordi Milà,[9] 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

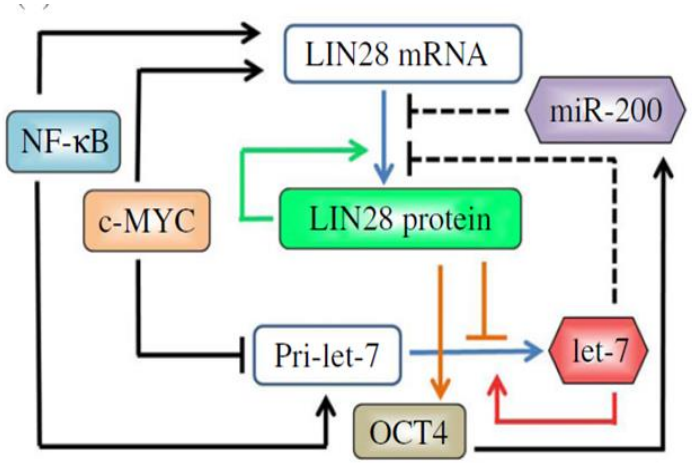
Suling Liu,[1,6,*] Yang Cong,[2,6] Dong Wang,[1] Yu Sun,[1] Lu Deng,[1] Yajing Liu,[3] Rachel Martin-Trevino,[3] Li Shang,[3] Sean P. McDermott,[3] Melissa D. Landis,[4] Suhyung Hong,[3] April Adams,[3] Rosemarie D'Angelo,[3] Christophe Ginestier,[5] Emmanuelle Charafe-Jauffret,[5] Shawn G. Clouthier,[3]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

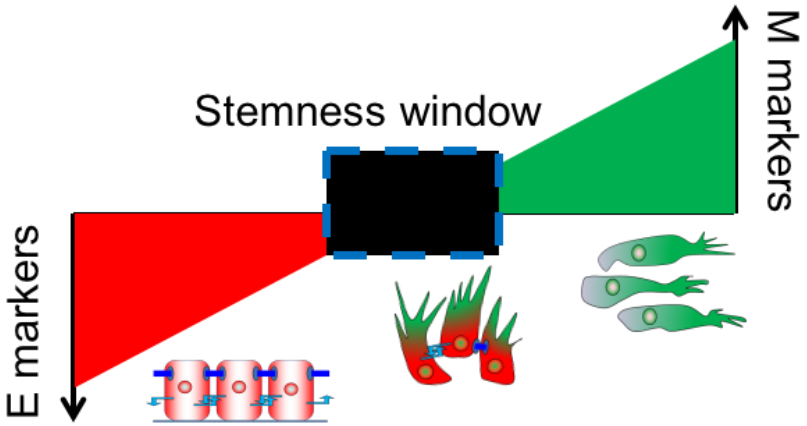
Liu *et al.* Stem Cell Reports 2013



Hybrid E/M cells can form many more tumors

Theoretical prediction

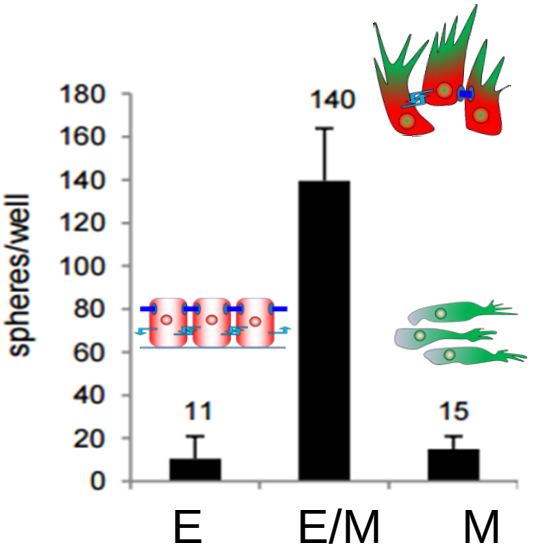




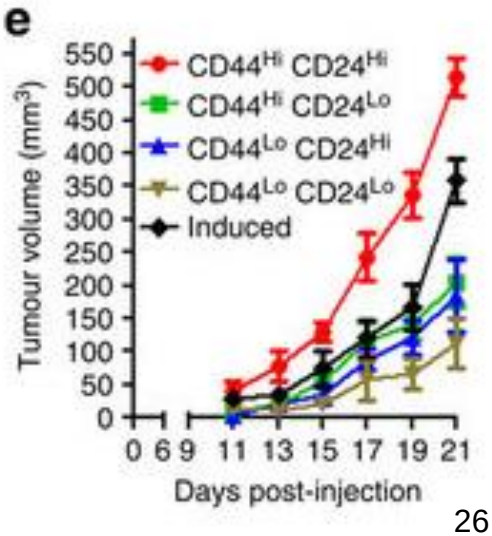
Jolly *et al.* J R Soc Interface 2014
Jolly*, Jia* *et al.* Oncotarget 2015

Experimental validation

Grosse-Wilde *et al.*
PLoS ONE 2015



Goldman *et al.*
Nat Comm 2015



Hybrid E/M cells can form many more tumors

Integrin-β4 identifies cancer stem cell-enriched populations of partially mesenchymal carcinoma cells

Brian Bierie[a], Sarah E. Pierce[b], Cornelia Kroeger[a], Daniel G. Stover[c], Diwakar R. Pattabiraman[a], Prathapan Thiru[a], Joana Liu Donaher[a], Ferenc Reinhardt[a], Christine L. Chaffer[a], Zuzana Keckesova[a], and Robert A. Weinberg[a,d,e,1]

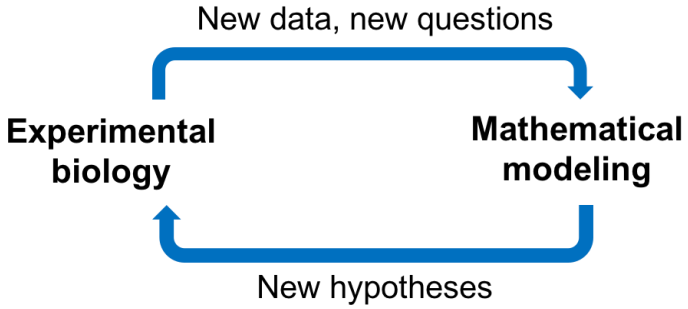
Bierie *et al.* PNAS 2017

Heterogeneity of normal 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], Shamileh Fouladdel[3,4], Sean P. McDermott[3,4], Michael Lee[4], David Hill[4], Maureen A. Sartor[3,5], Laura S. Rozek[1,3], Max S. Wicha[3,4,*]

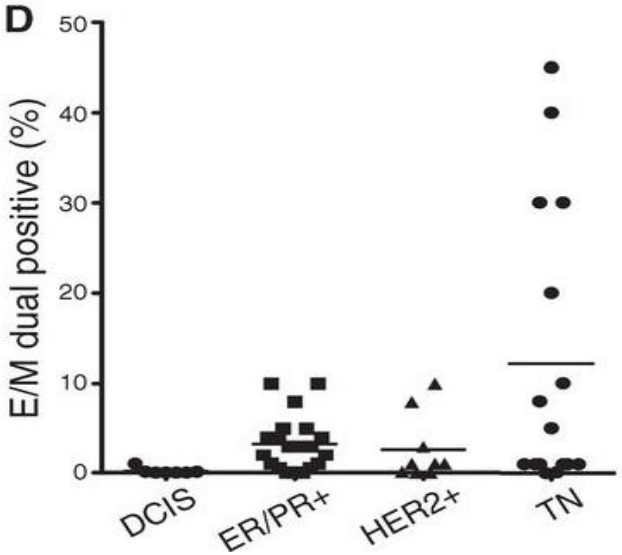
Colacino *et al.* biorxiv 2017

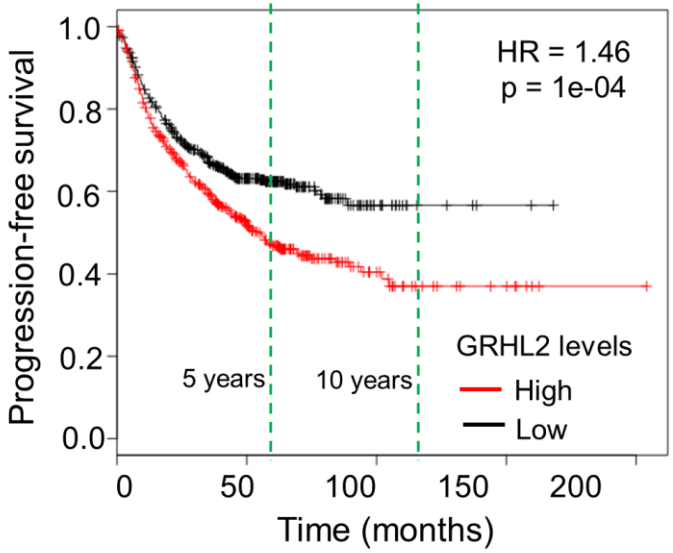
Where does 'stemness window' lie on 'EMT axis'?



Hybrid E/M phenotype is more likely to be stem-like than E or M.

Clinical implications of hybrid E/M cells



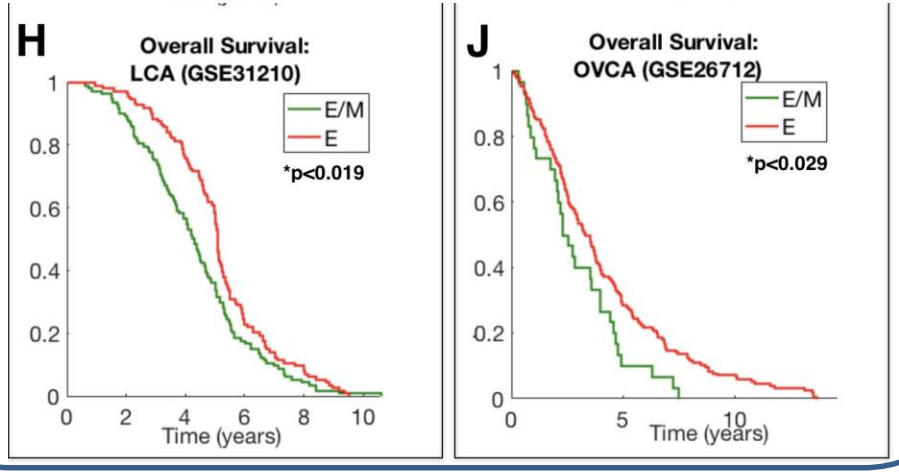


Higher levels of GRHL2 associate with worse prognosis

The more **aggressive** the cancer, the higher the number of **hybrid** E/M cells

Yu *et al*. Science 2013

Correlate EMT score (on a scale of 0 to 2) with data on drug sensitivity and patient outcome across cancer types

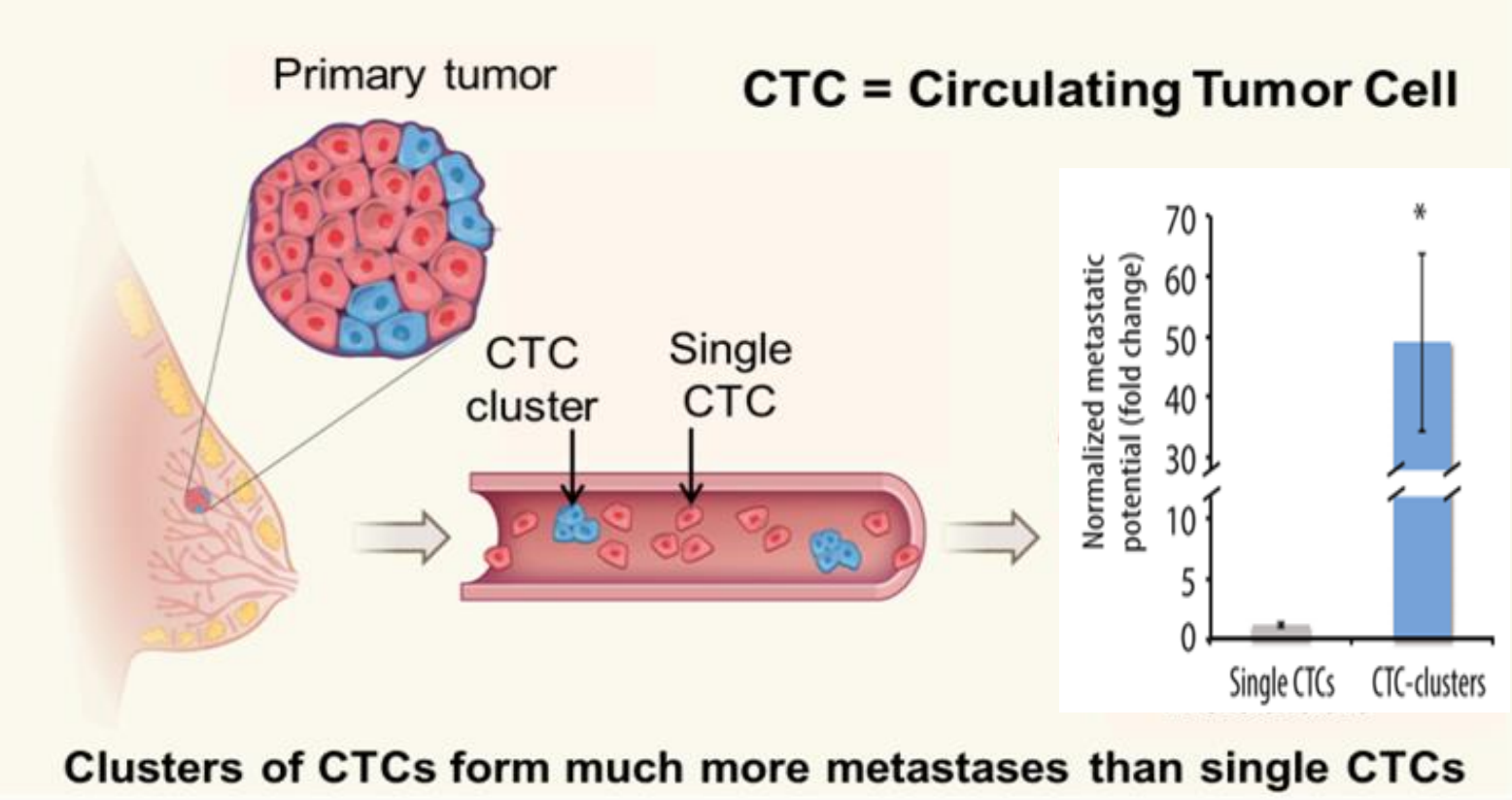


Hybrid E/M phenotype may be more aggressive than a complete EMT

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

Jolly *et al.* Oncotarget 2016

Hybrid E/M phenotype may form CTC clusters

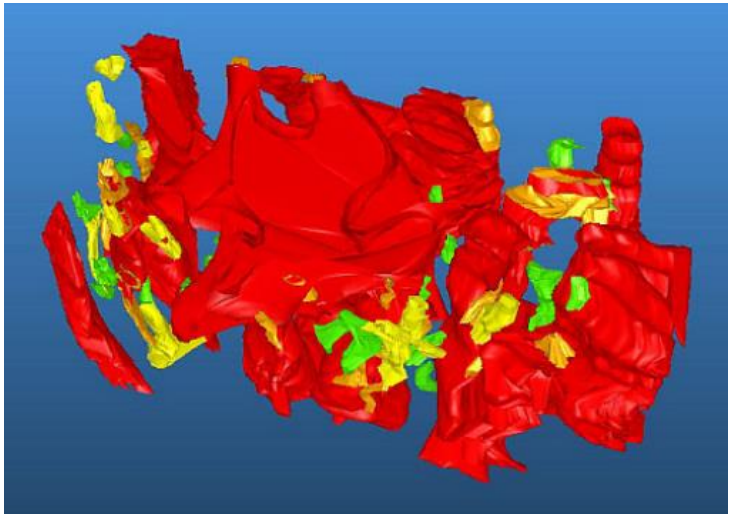


Clusters of CTCs:

- 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

Collective motility may lead to CTC clusters



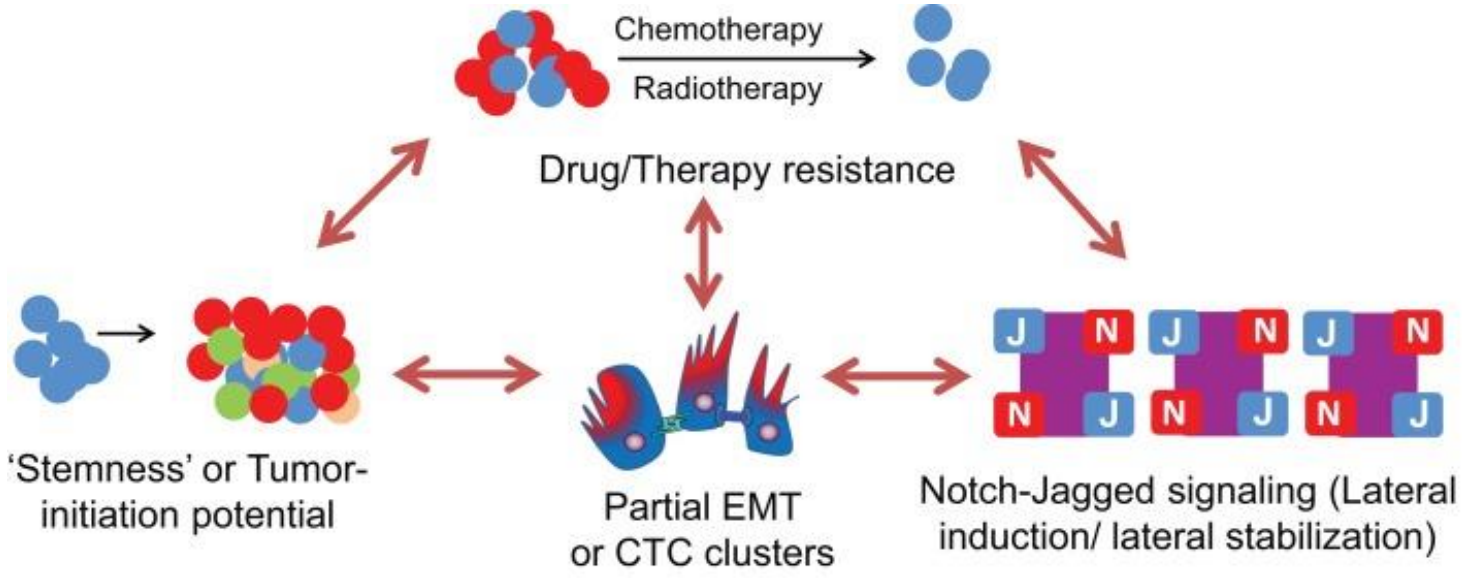
- Clusters are typically composed of several cells
- Cells in cluster express ZEB1, reduced membrane resident E-cadherin
- Hypothesized to be partial EMT phenotype

Main tumor = red, multicellular buds = green (Bronsert et J. Path (2014))

Clusters can be better at metastasis!

- Cells can help each other develop anoikis resistance
- Clusters can navigate more effectively
- Clusters can survive stresses in the circulation
- Hybrid E/M cells can more easily initiate new tumors

Biological insights gained



- Elucidated **how** tumor cells form stable clusters of Circulating Tumor Cells (CTCs) – the primary 'villains' of metastasis
- Offered a potential mechanistic understanding of **why** clusters of CTCs form much more metastases
- Identified potential **targets** that maintain these clusters and enhance their tumor forming ability – **GRHL2, OVOL2, JAG1**

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

Why does having a theoretical framework help?

- What do we mean by theoretical framework?
  - An integrated understanding of how all the complex pieces fit together to get cancer phenotypes
  - Understanding the connections between EMT and other “hallmarks” will help prevent surprise side effects of treatment options

- Theory can point to the most critical experiments and most useful data analysis approaches
  - This role is becoming increasingly prevalent in basic cell and developmental biology and should be imported to cancer biology field

Can we define EMT mathematically?

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

Epithelial–mesenchymal transition (EMT) and metastasis: yes, no, maybe?

Maren Diepenbruck and Gerhard Christofori

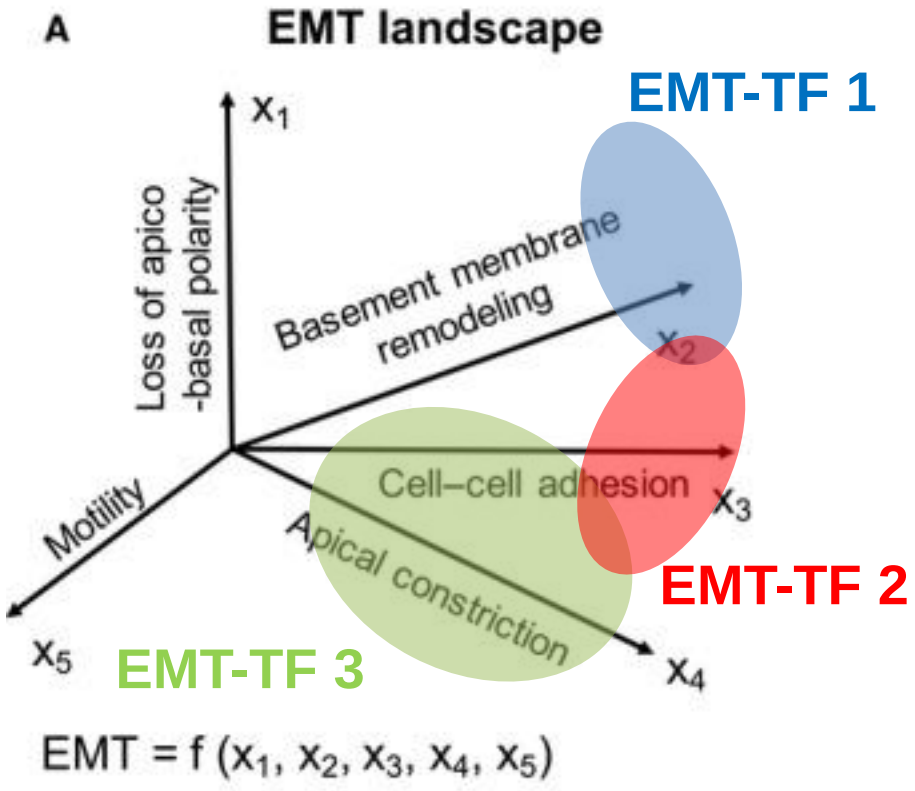
Molecular Oncology

FEBS PRESS

EMT and MET: necessary or permissive for metastasis?

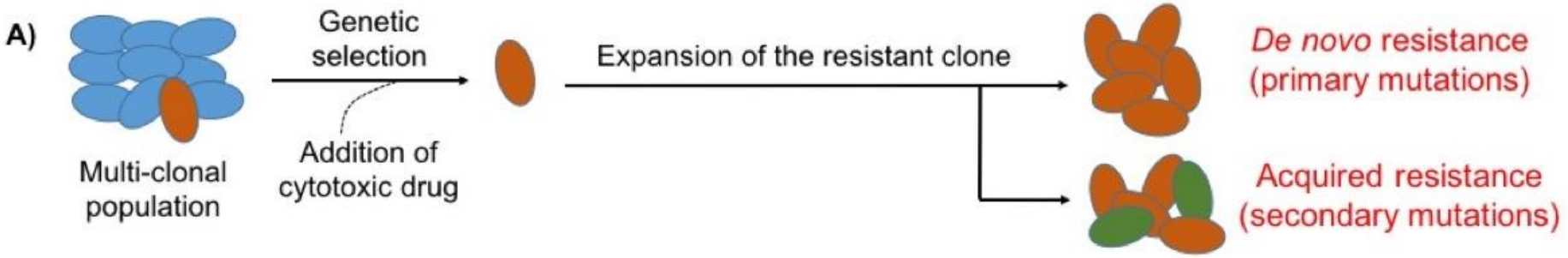
Mohit Kumar Jolly[1], Kathryn E. Ware[2], Shivee Gilja[2], Jason A. Somarelli[2] and Herbert Levine[1]

Jolly *et al.* Mol Oncol 2017

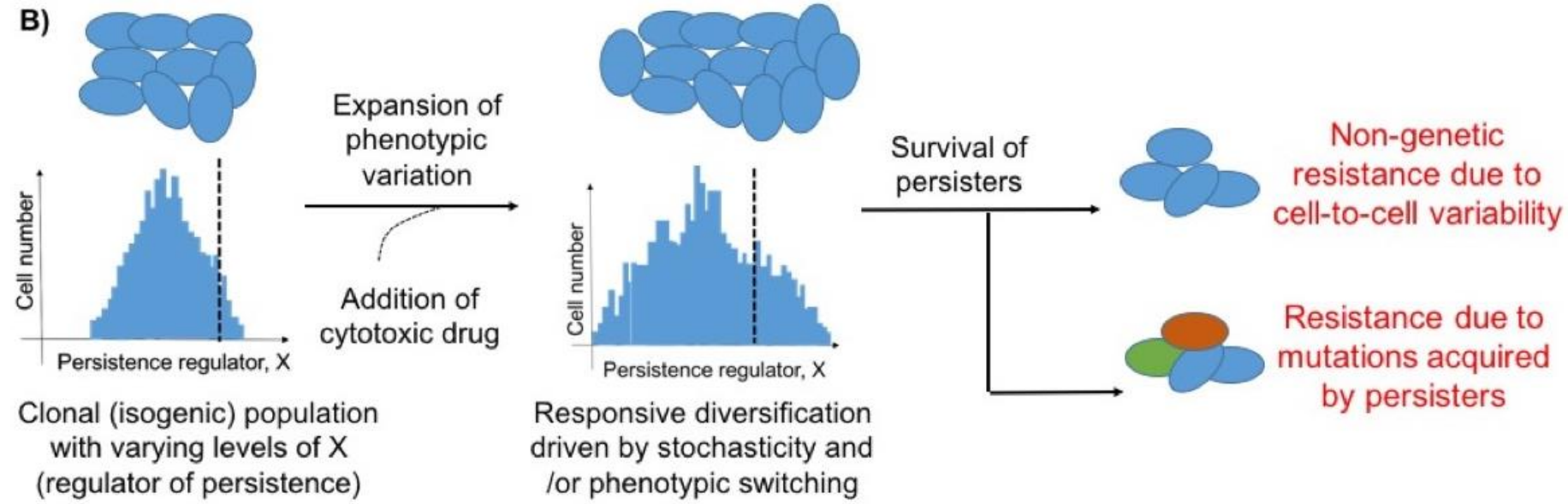


- EMT is a highly non-linear and multi-dimensional process
- Connections among genetics and biophysics of EMT still being elucidated

Role for phenotypic plasticity in cancer



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



Jolly *et al.* Nat Rev Urol 2017, under review

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MD Anderson Cancer Center

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