A Cascade of bistable switches controls TGF-β-induced epithelial to mesenchymal transition

Jianhua Xing
Departments of Biological Sciences & Physics, Virginia Tech

About OMICS Group

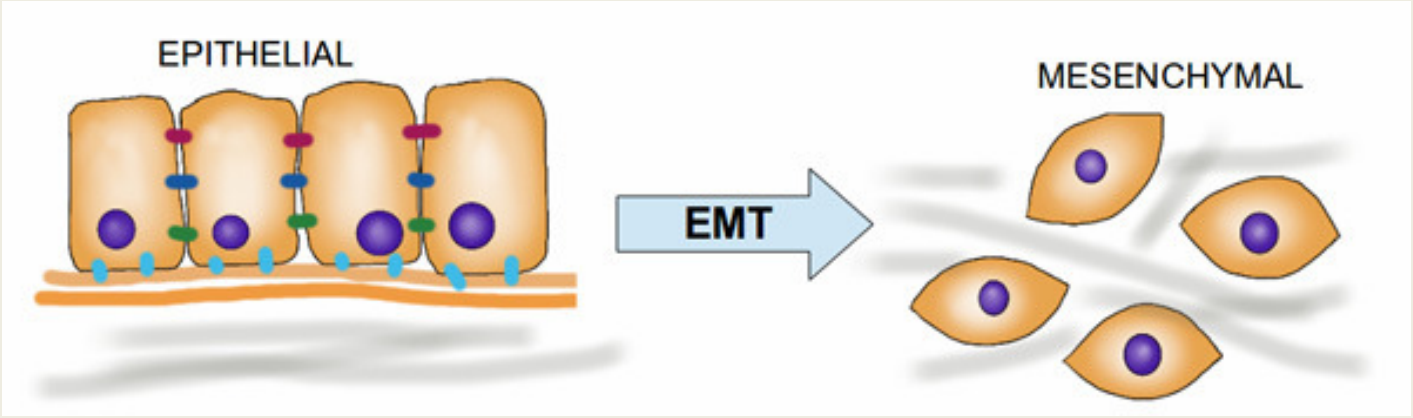
- OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

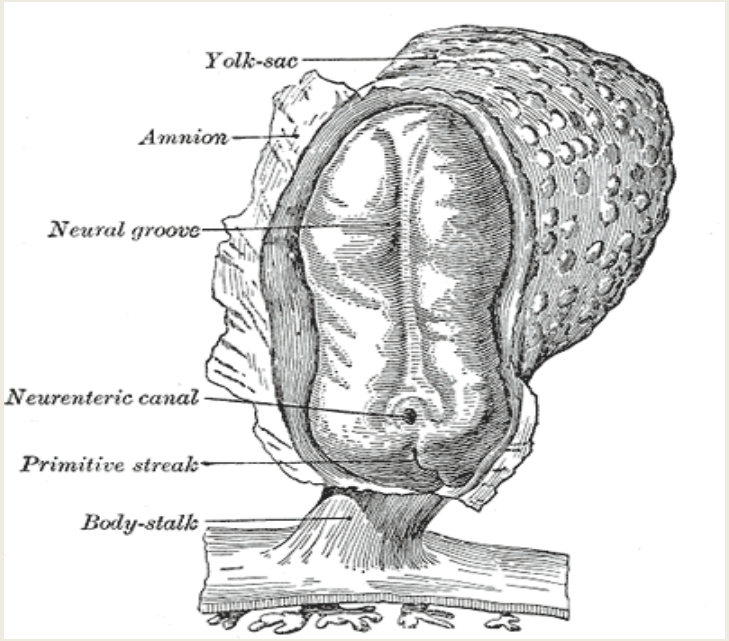
About OMICS Group Conferences

OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

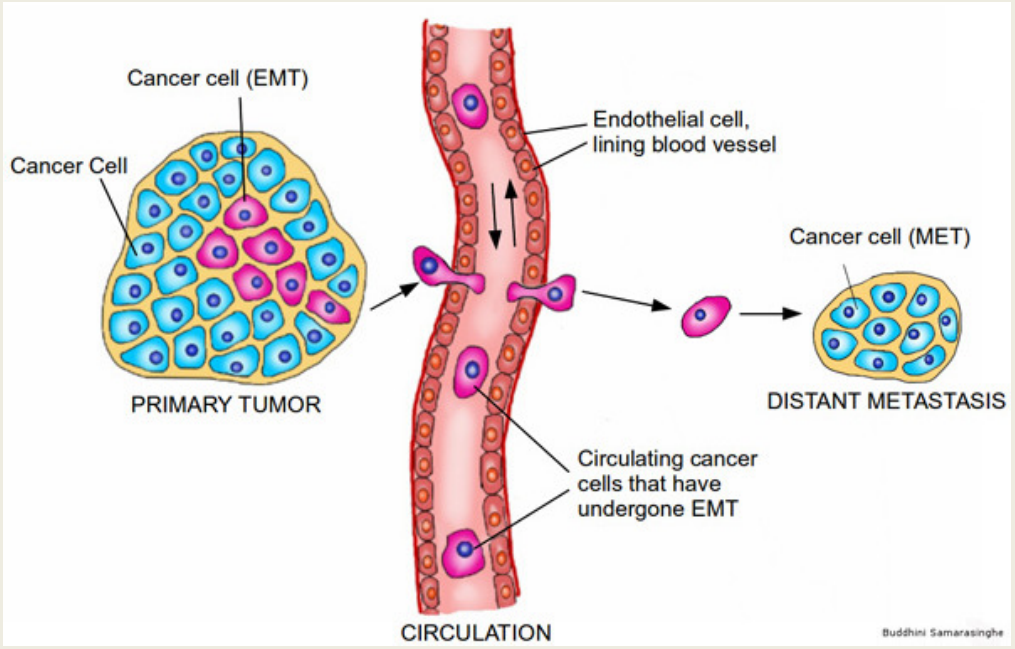
OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, SantaClara, Chicago, Philadelphia, Balti more, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bangalore and Mumbai.

Epithelial-to-Mesenchymal Transition is a fundamental cellular process



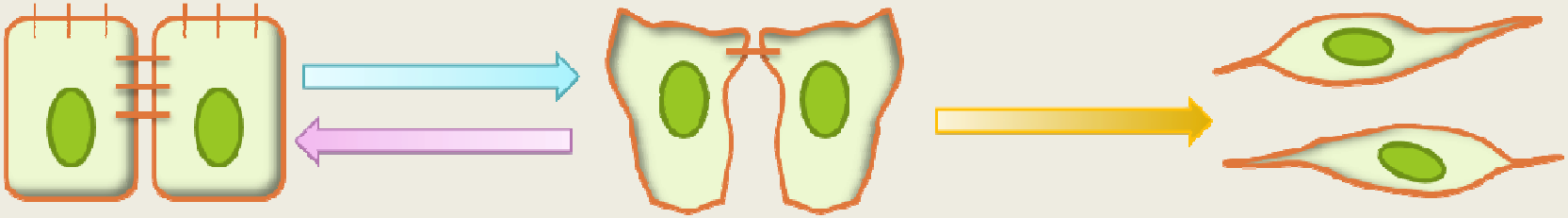


Human Embryo

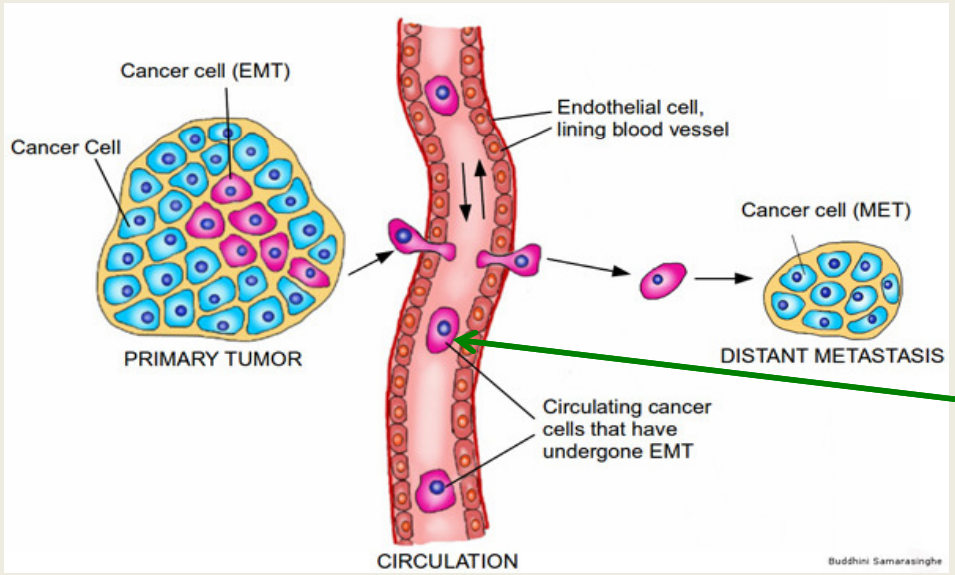


Cancer metastasis

Several EMT phenotypes have been reported



Epithelial | **Partial EMT** | **Mesenchymal**



Cancer metastasis

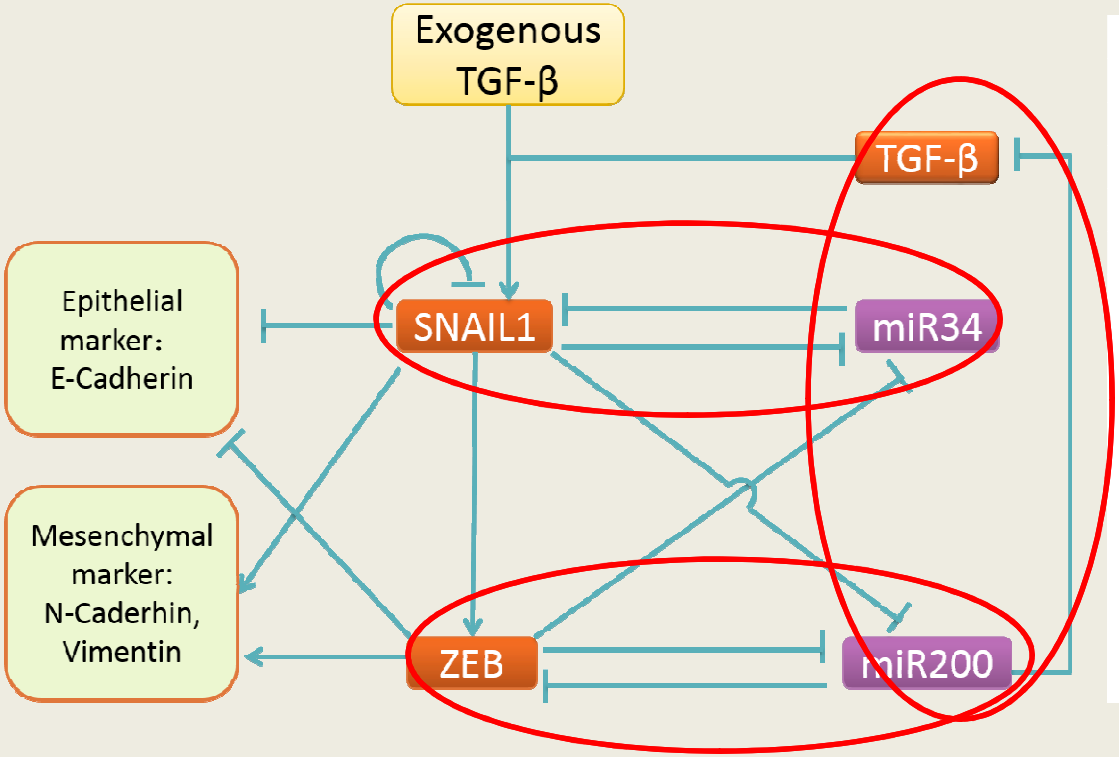
Circulating tumor cells

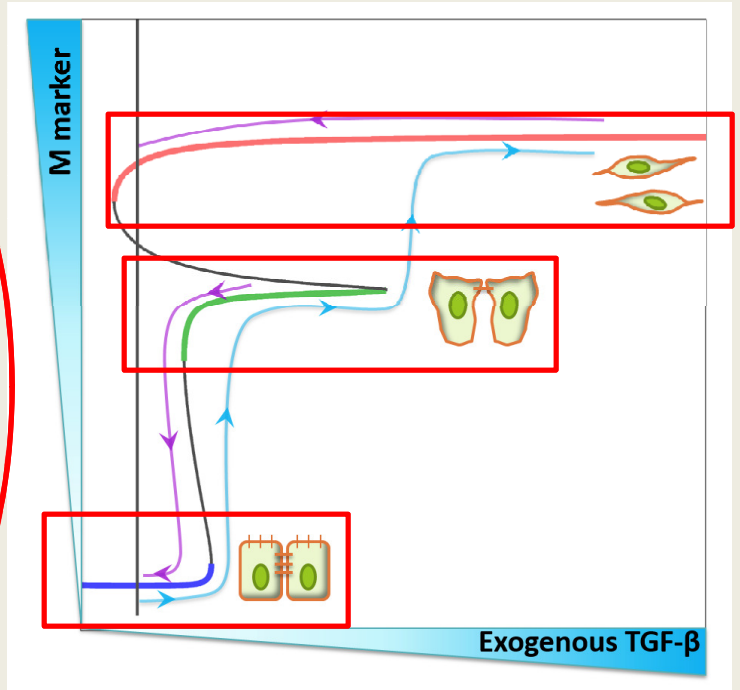
Yu et al., Science, 339:580 (2013)

Question: How are these EMT phenotypes generated?

Competing models on TGF-β induced EMT

1) Cascading binary switches (VT: CBS)





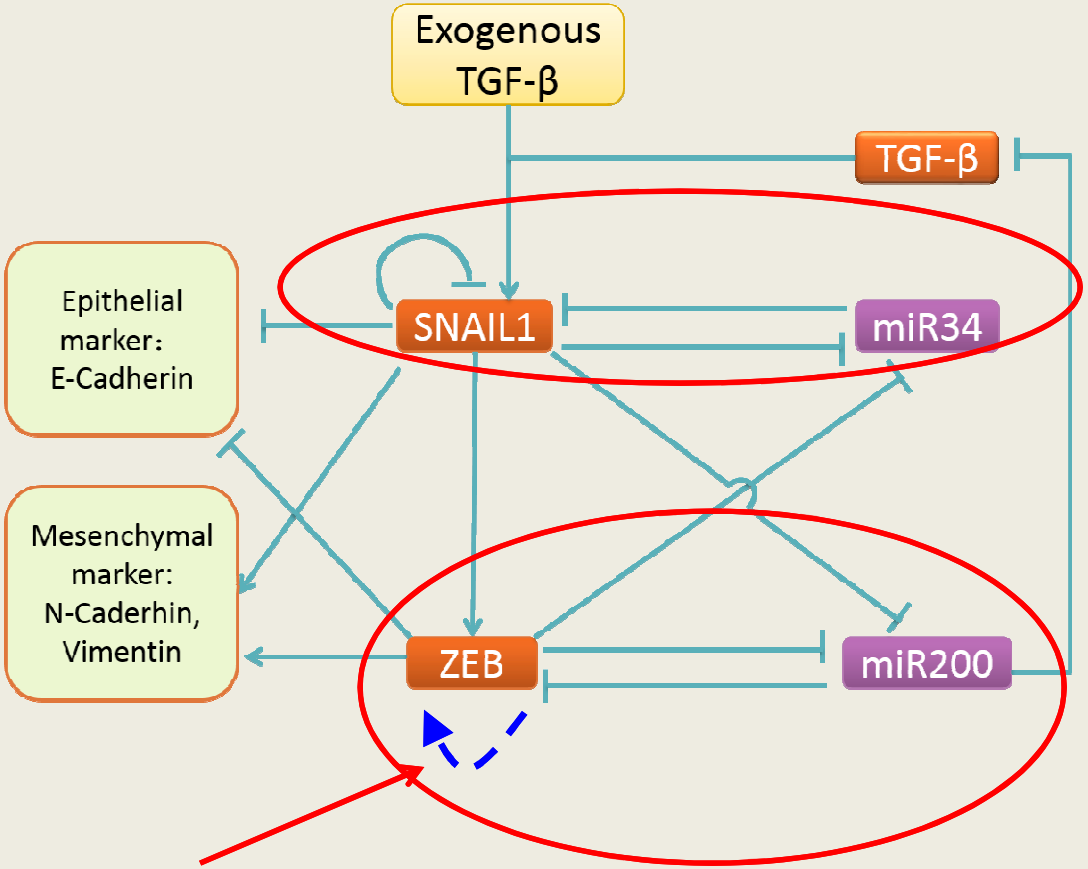
Activation

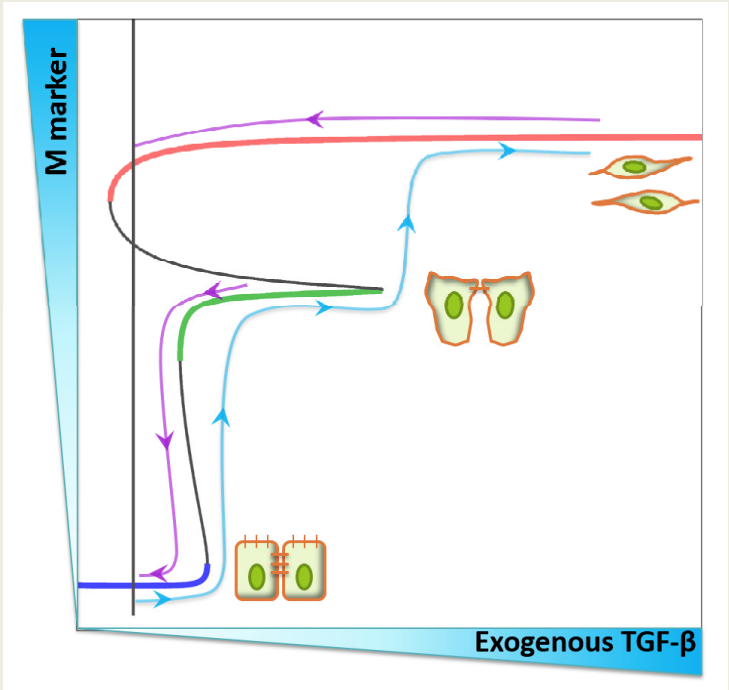
Inhibition

Tian et al., Biophys. J. 105:1079 (2013)

Competing models on EMT regulation

2) Ternary Chimera Switch (Rice: TCS)

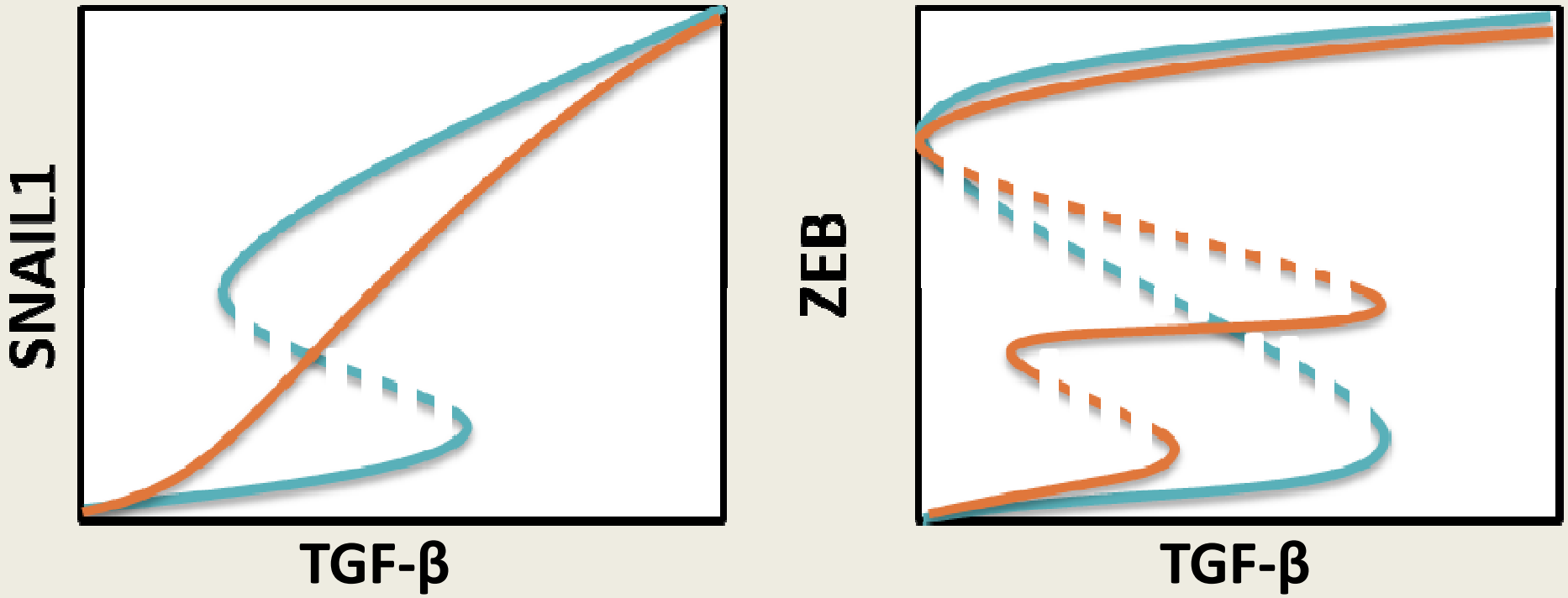




Existence of this self activation awaits for experimental confirmation

Lu et al., PNAS, 110:18144 (2013)

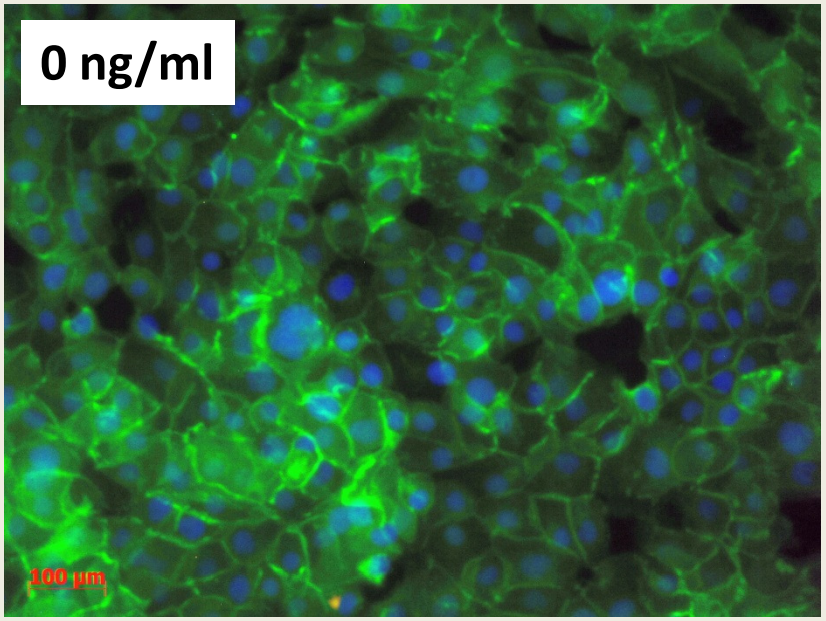
Two models make qualitatively different predictions

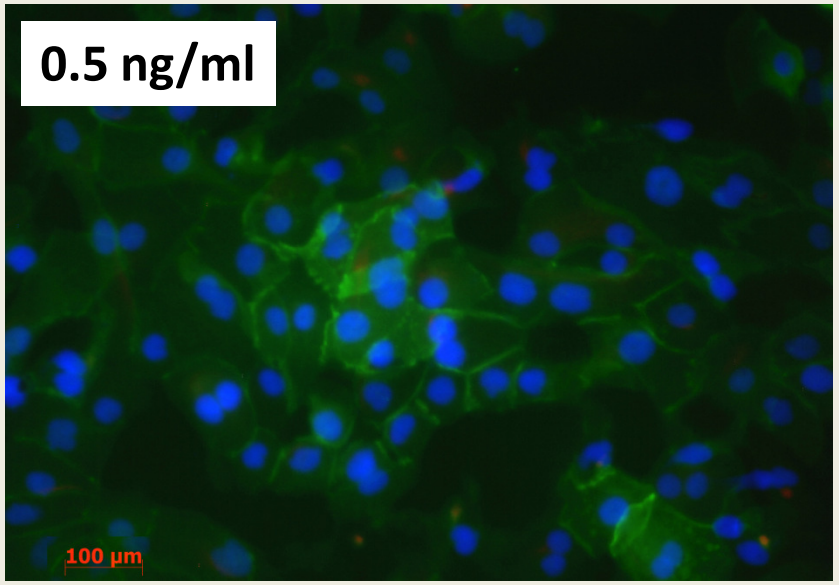


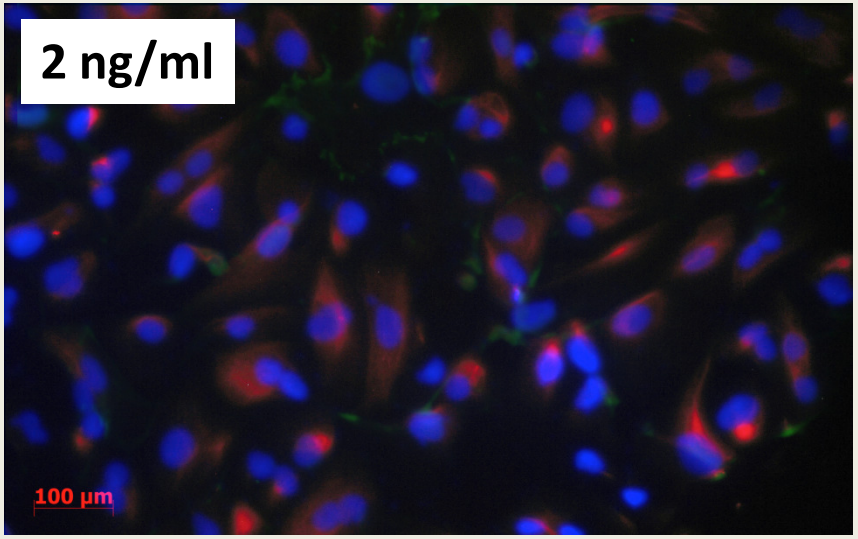
VT: CBS model prediction

Rice: TCS model prediction

TGF-β1 induced MCF10A cell EMT transition



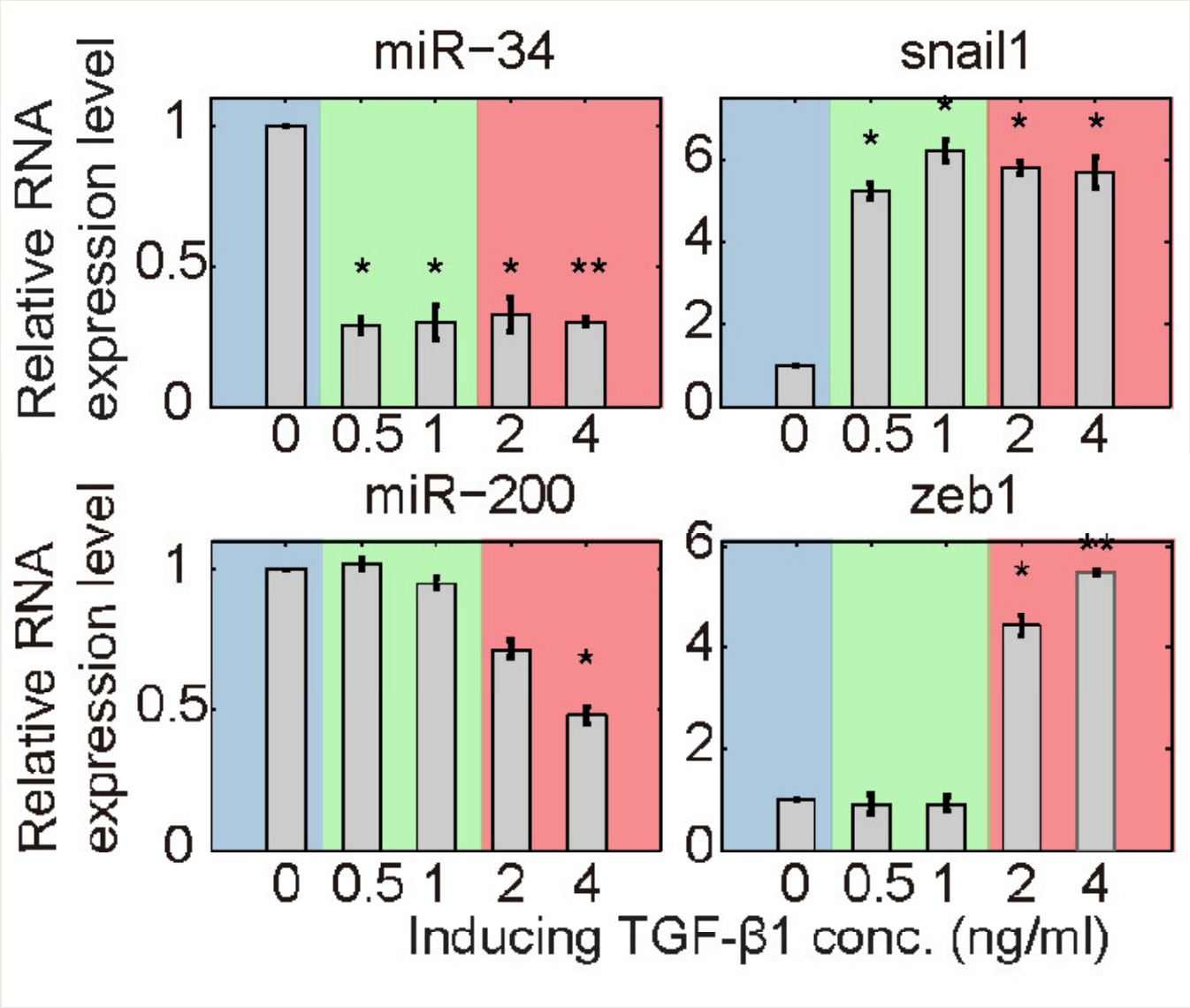




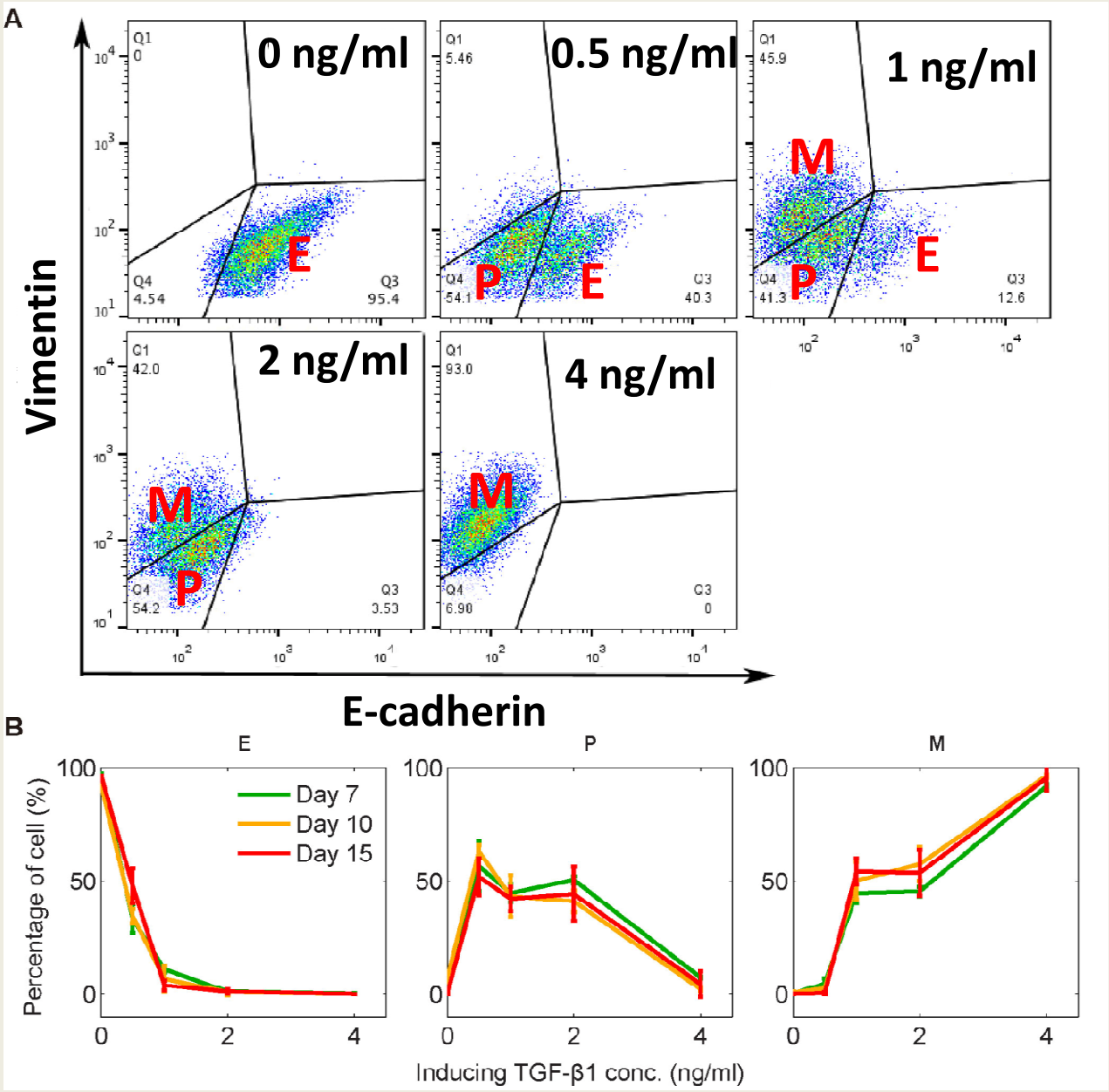
Green: E-cadherin (Epithelial marker)
Red: Vimentin (Mesenchymal marker)
Blue: nucleus

Zhang, Tian, et al., Sci Signaling, 7, ra91 (2014)

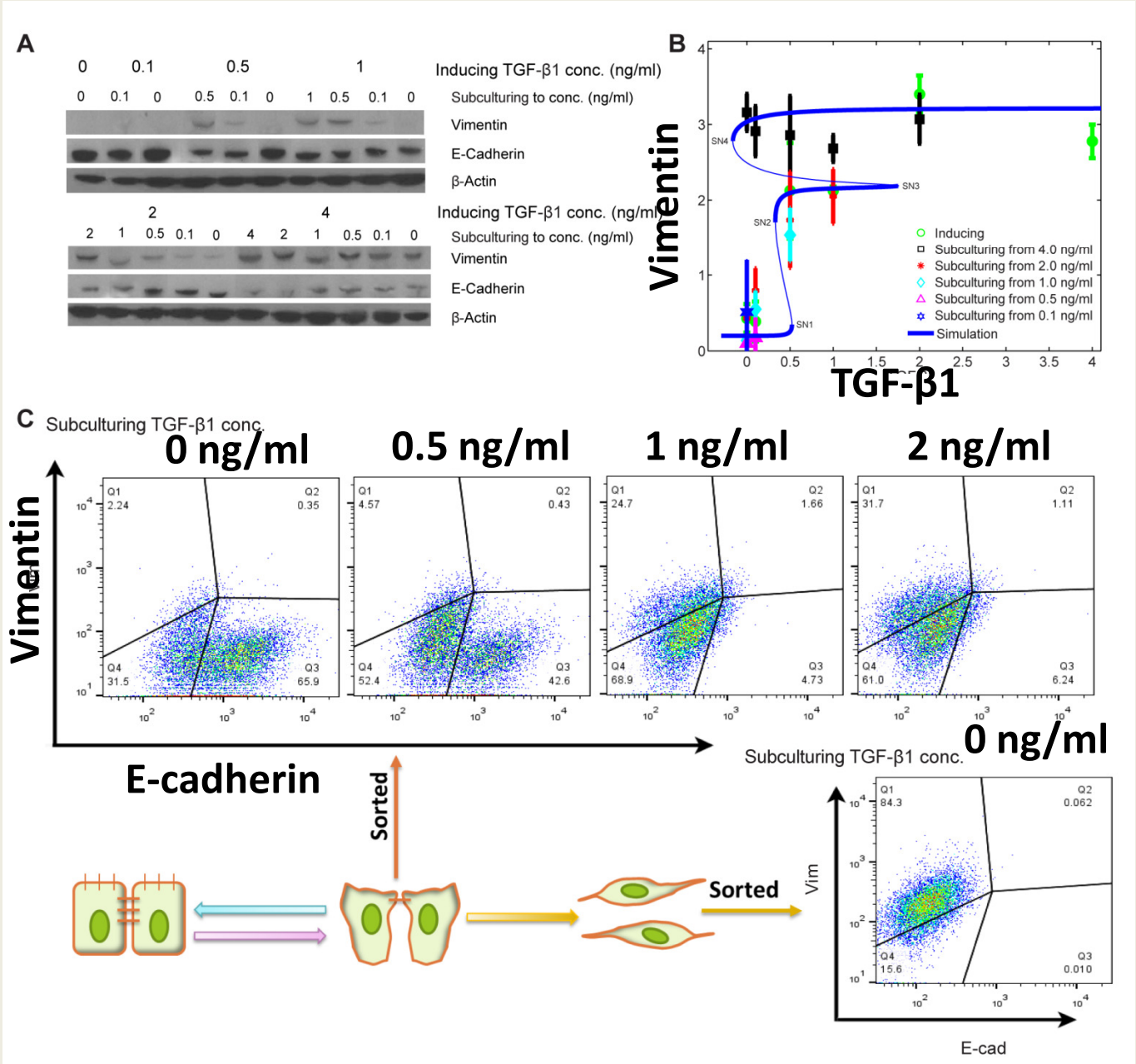
mRNA/miRNA levels show clear two-step behavior



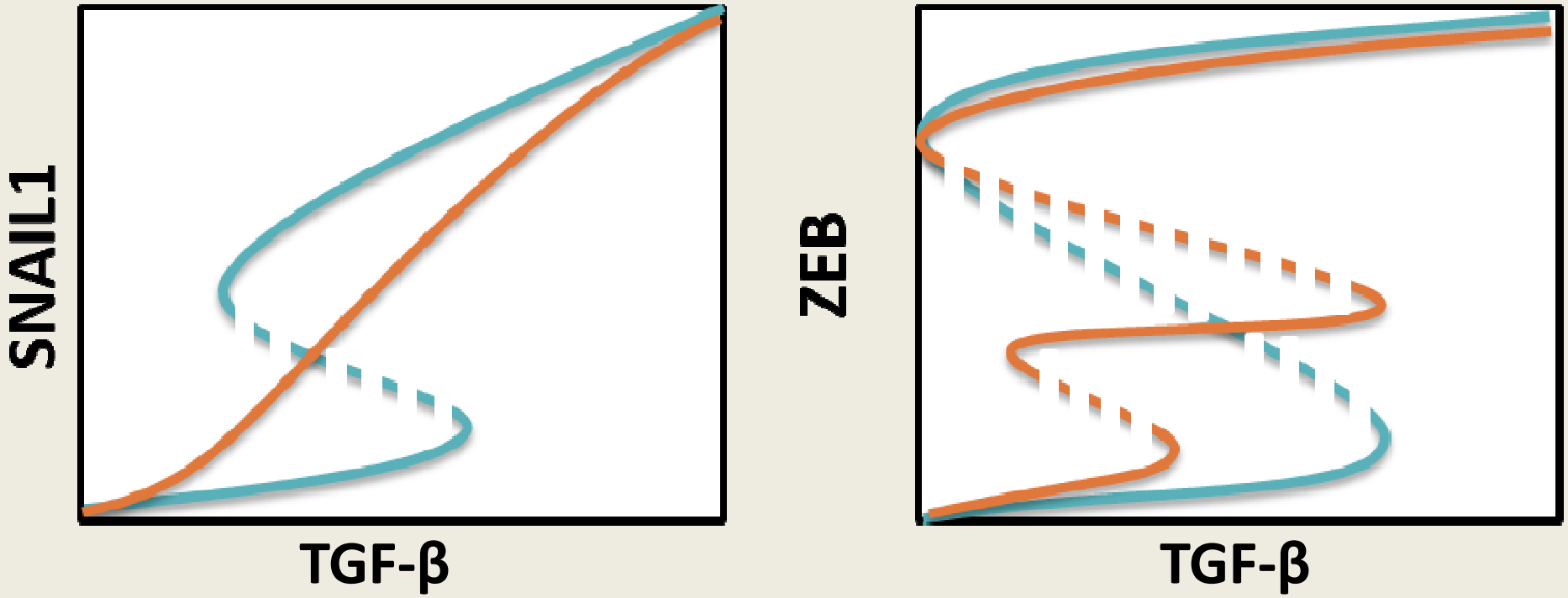
Flow cytometry data shows clear three phenotypes



Reversibility tests



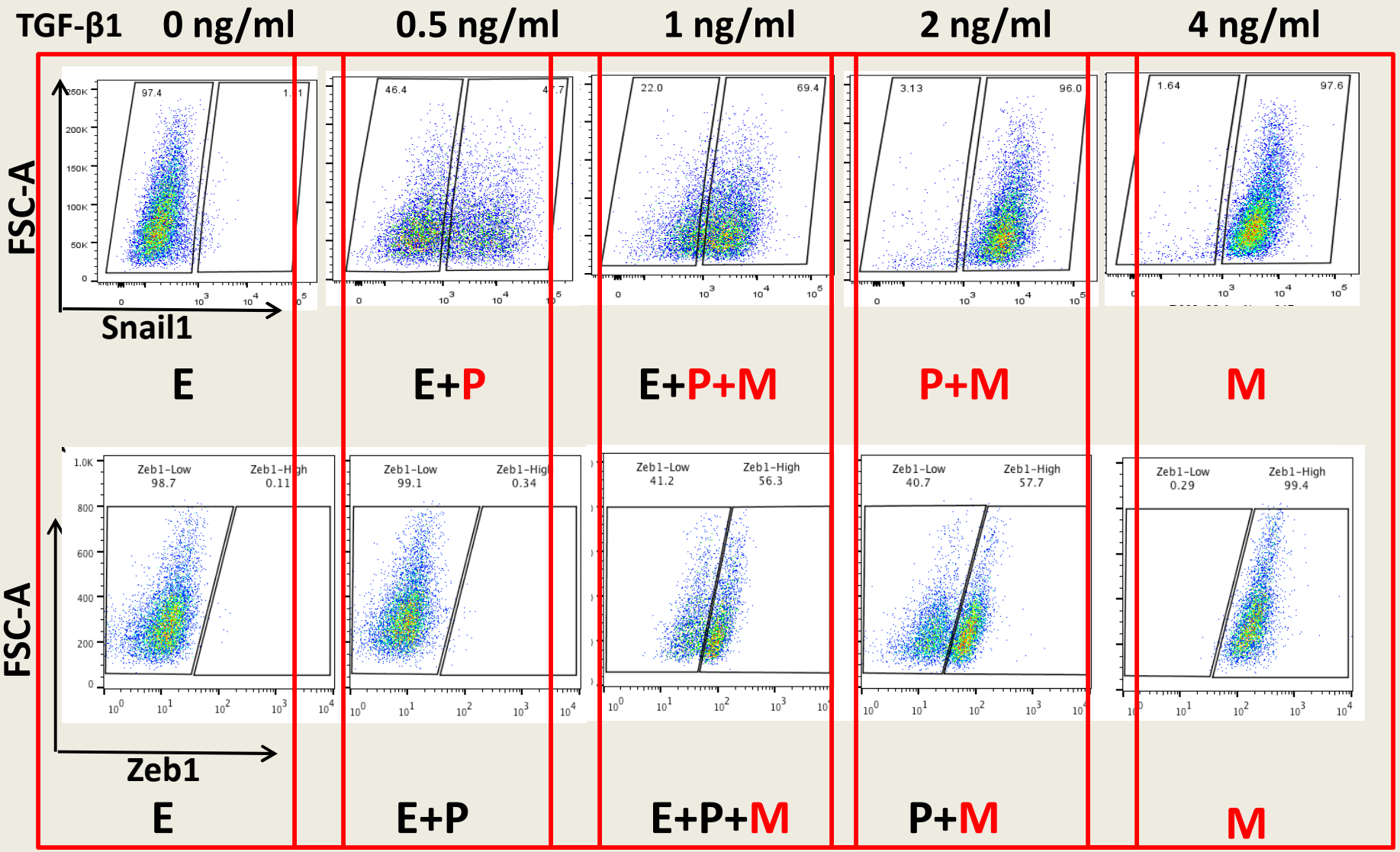
Two models make qualitatively different predictions



VT: CBS model prediction

Rice: TCS model prediction

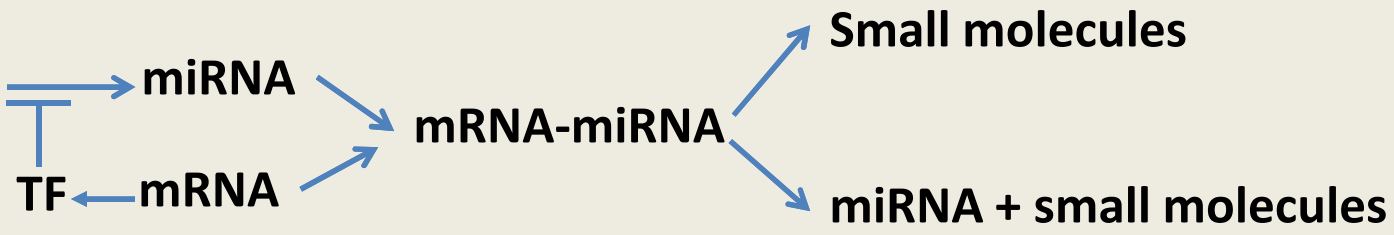
Snail1/Zeb1 measurements support the CBS model

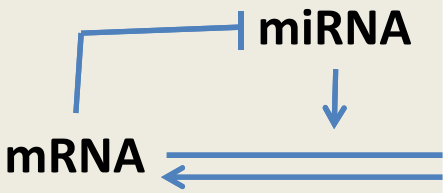


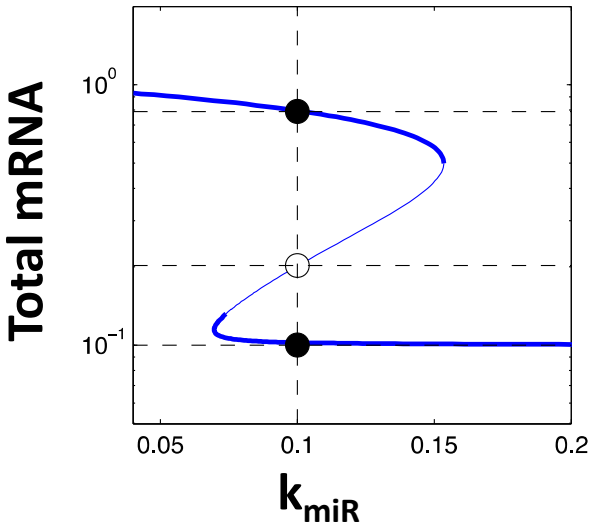
Zhang, Tian, et al., Sci Signaling, 7, ra91 (2014)

Further theoretical analysis identifies several molecular mechanisms for Snail/miR34 bistability

1. Nonlinearity from Snail1 binding to miR34 promoter
2. Ultra-sensitive-like motif with positive feedback

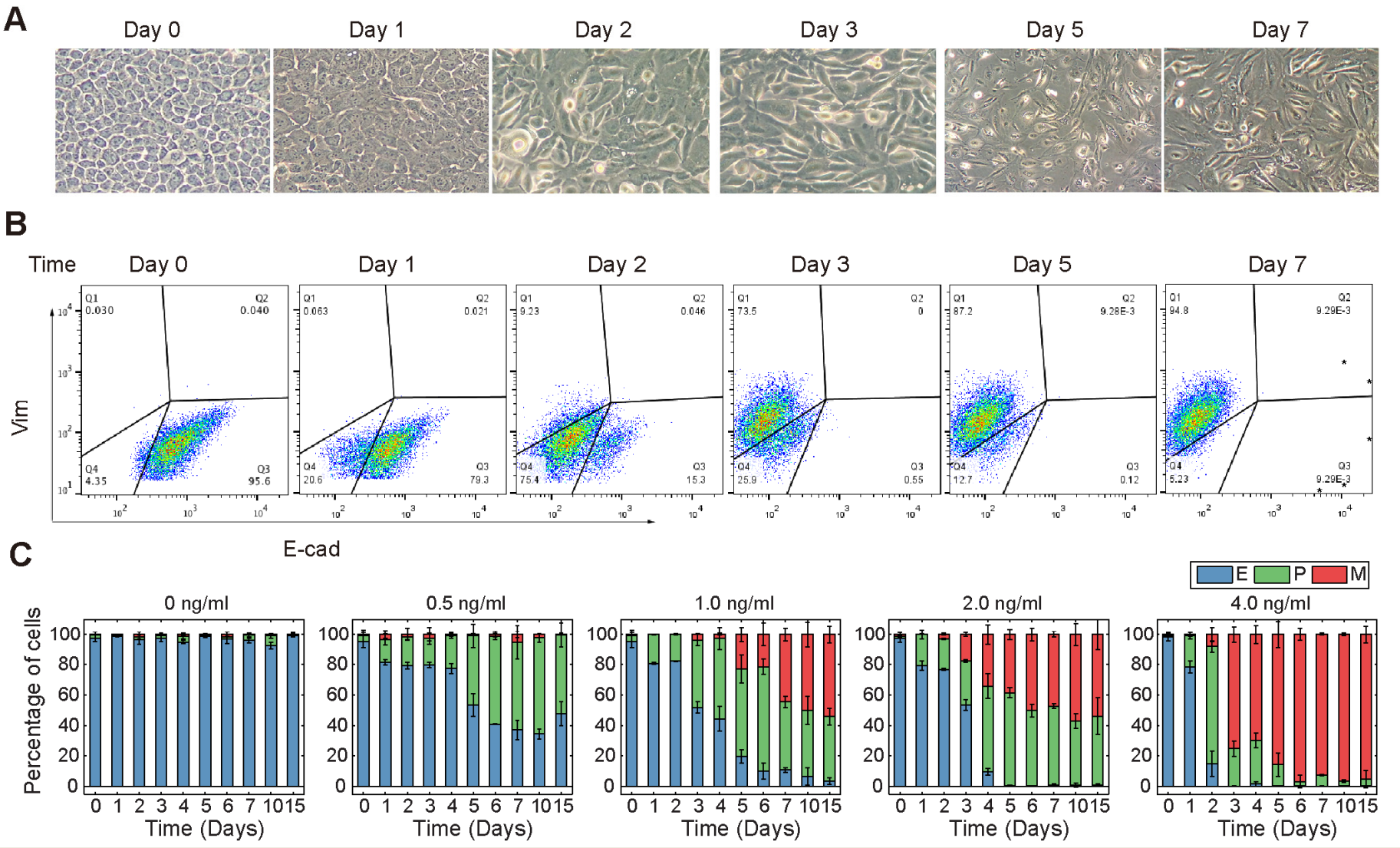






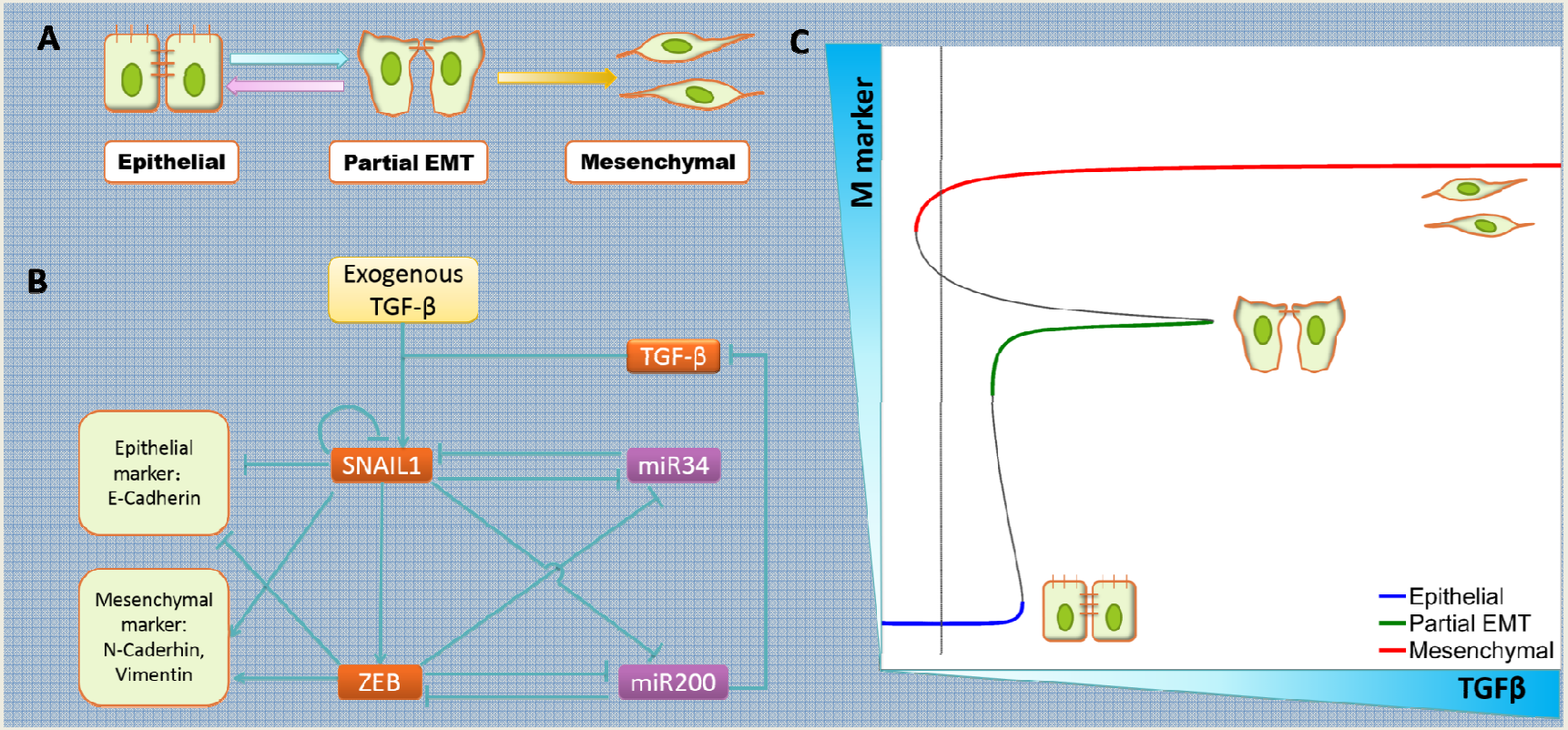
Tian, et al., in prepar

The temporal EMT dynamics also shows two-step behavior



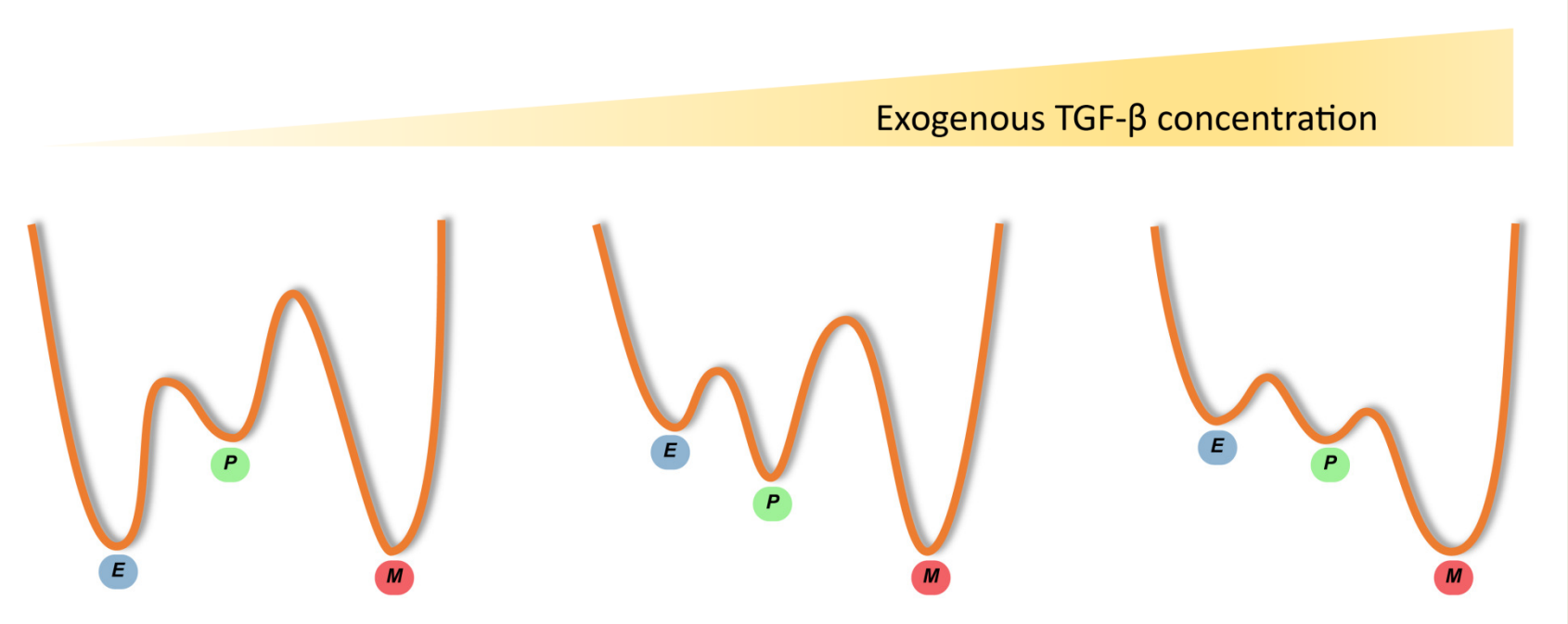
Zhang, Tian, et al., Sci Signaling, 7, ra91 (2014)

Summary and ongoing efforts

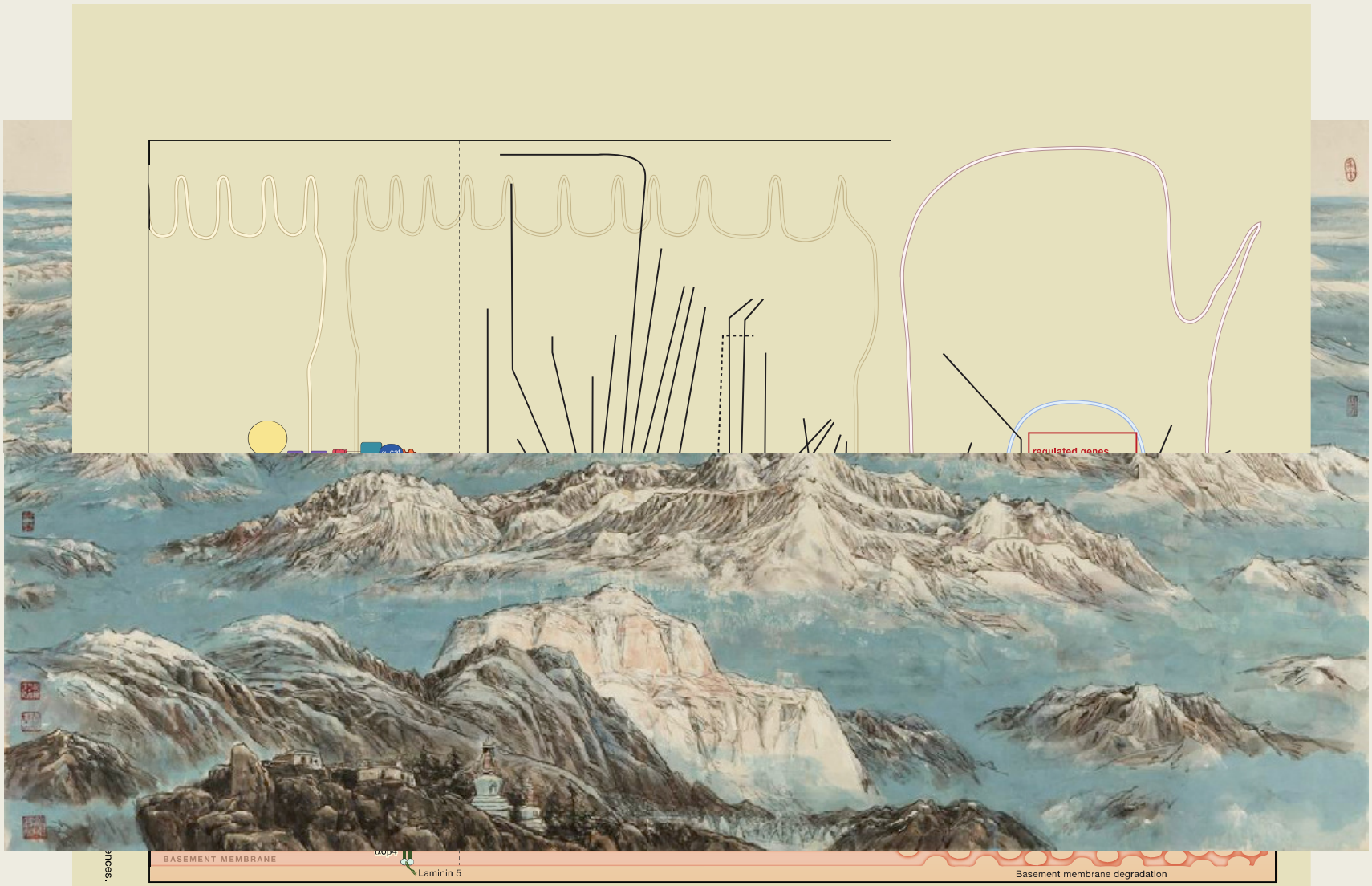


TGF-β1 induced EMT in MCF10 A cells is regulated by a cascade of binary switches.

Analogous landscape picture

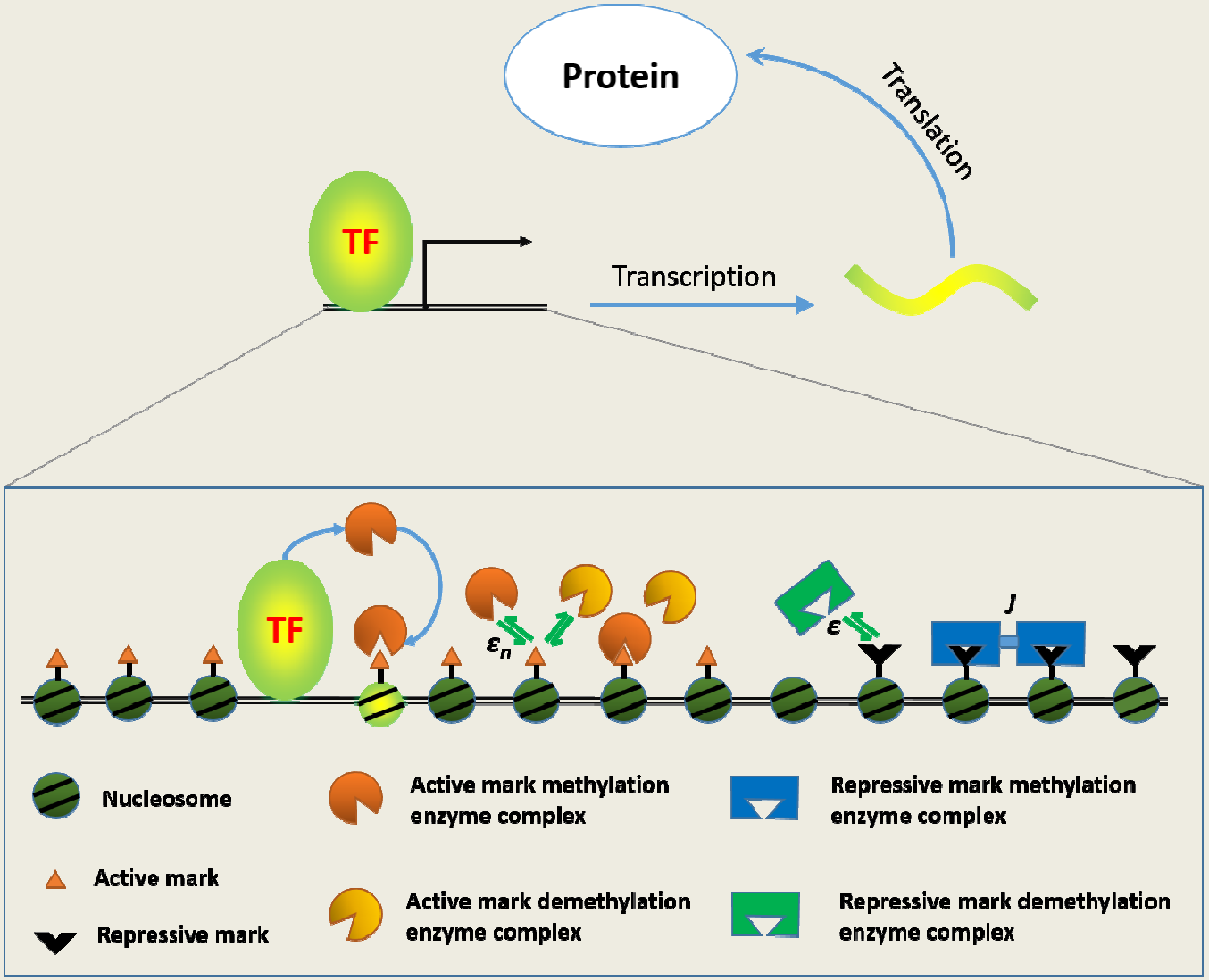


Have we seen the whole elephant?



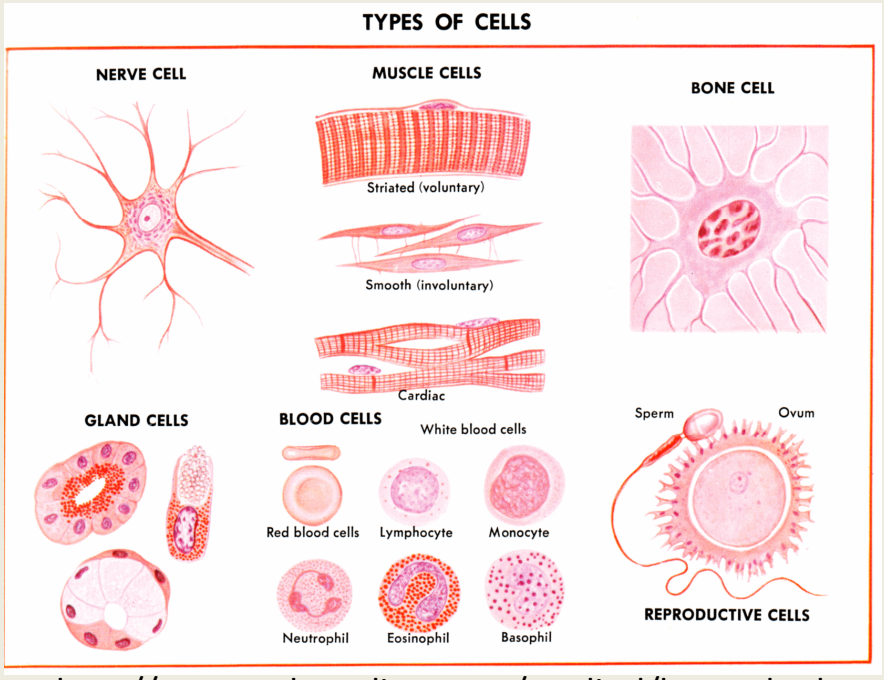
We may discover more complex cell phenotype landscapes

Epigenetic modification also play essential role in EMT

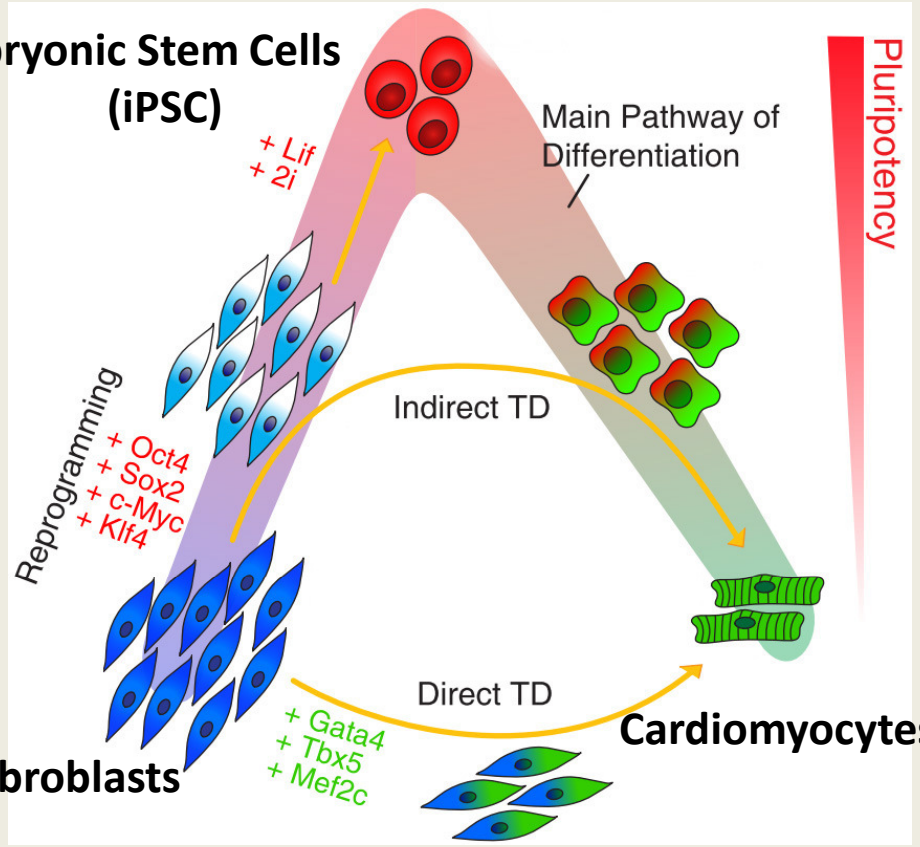


Zhang, et. al., Phys. Rev. Lett., 112:068101 (2014)

A central question we ask: how cells maintain a robustly stable yet plastic phenotype?



http://www.arthursclipart.org/medical/humanbody/cell%20types.gif

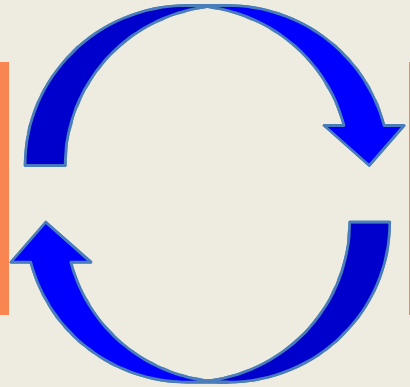


Wang, et al., Interface Focus, 4:20130068 (2014)

How can an fertilized egg develop into over 200 cell types?
How can a cell maintain its type over generations?
How can a cell collectively revise its expression program during a phenotypic transition?

Systems biology approaches are needed for complex cell phenotypic transition processes

Mathematical modeling
Computer simulations
Theoretical analysis



Experimental studies, esp. single cell and high throughput techniques

Acknowledgements

Xing lab:

Current:

Dr Xiaojun Tian

Hang Zhang

Abhishek Mukhopadhyay

Jingyu Zhang

Collaborator:

Subbiah Elanekumaran (VT)

Fan Bai (Peking University)

Ruoyan Li (Peking University)

Yue Teng (Beijing Institute of Microbiology and Epidemiology)

Financial support:

- The Thomas F. Jeffress and Kate Miller Jeffress Memorial Trust
- NSF Emerging Frontier Program
- NIGMS/DMS Mathematical Biology Program
- NIAID
- VT Fralin Institute

Current Xing lab website:

http://www.faculty.biol.vt.edu/xing/index.html

Email: xing1@pitt.edu

The Xing lab will move to

Dept of Computational & Systems Biology
University of Pittsburgh
(http://www.csb.pitt.edu)

Let Us Meet Again

We welcome you all to our future conferences of OMICS Group International

Please Visit:

www.omicsgroup.com

www.conferenceseries.com

http://tissuescience-regenerativemedicine.conferenceseries.com/