Coordinated angiogenic movement of tip endothelial cell revealed by experiments combined with mathematical modeling

Koichi Nishiyama, M.D, Ph.D.

International Research Center for Medical Sciences (IRCMS), Kumamoto University

Angiogenesis

Multicellular morphogenesis

Development

Endothelial cell (EC)

Wound healing

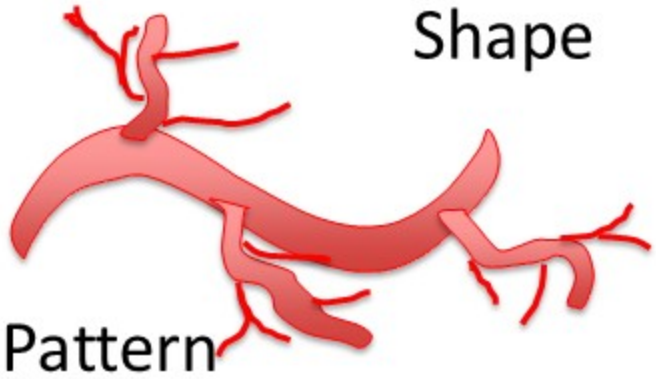
Ischemia

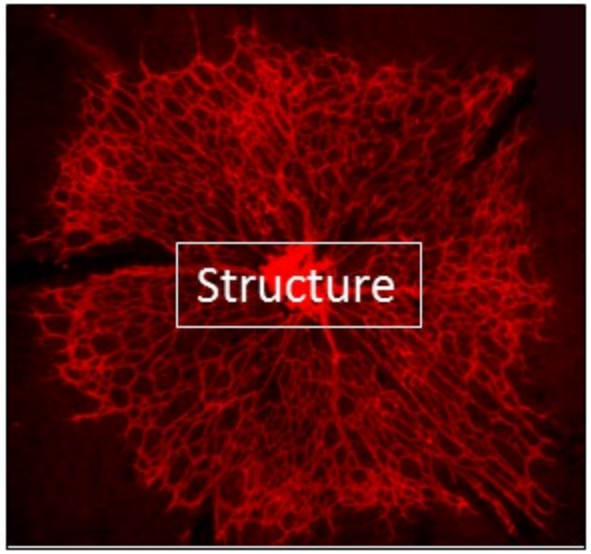
Components

Inflammation

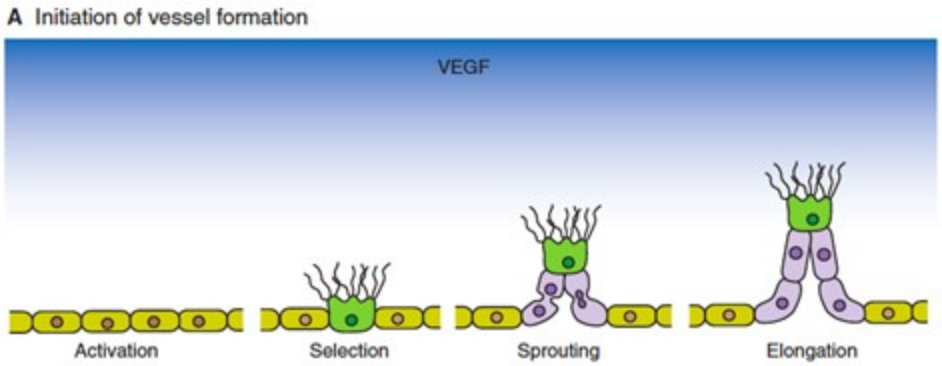
Tumor

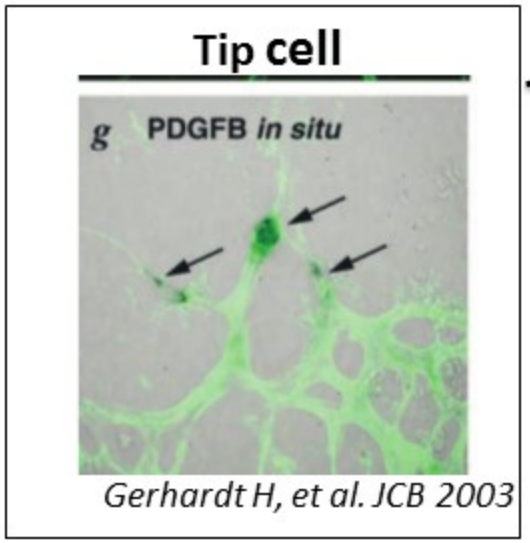
Pre-existing vessel



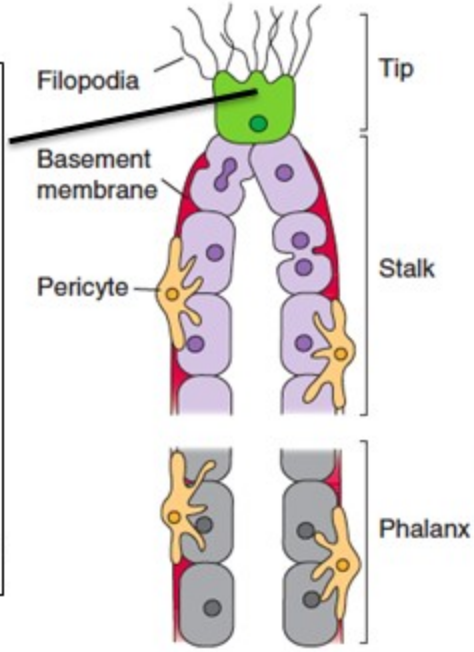


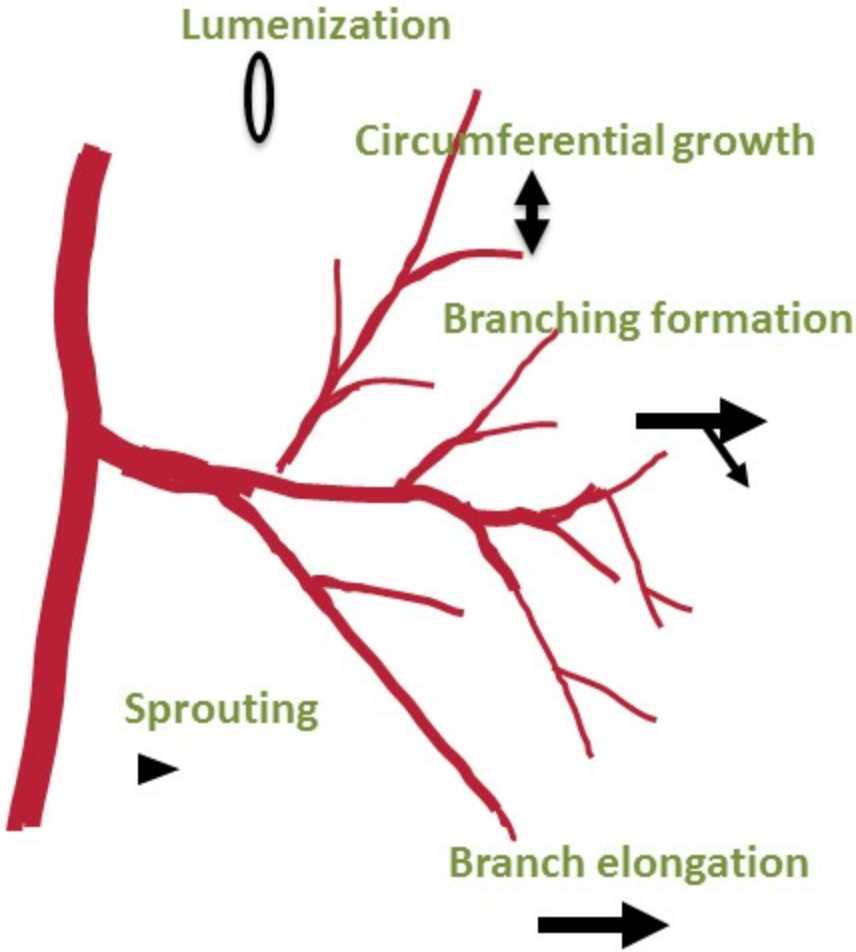
Angiogenesis





Gerhardt H, et al. JCB 2003

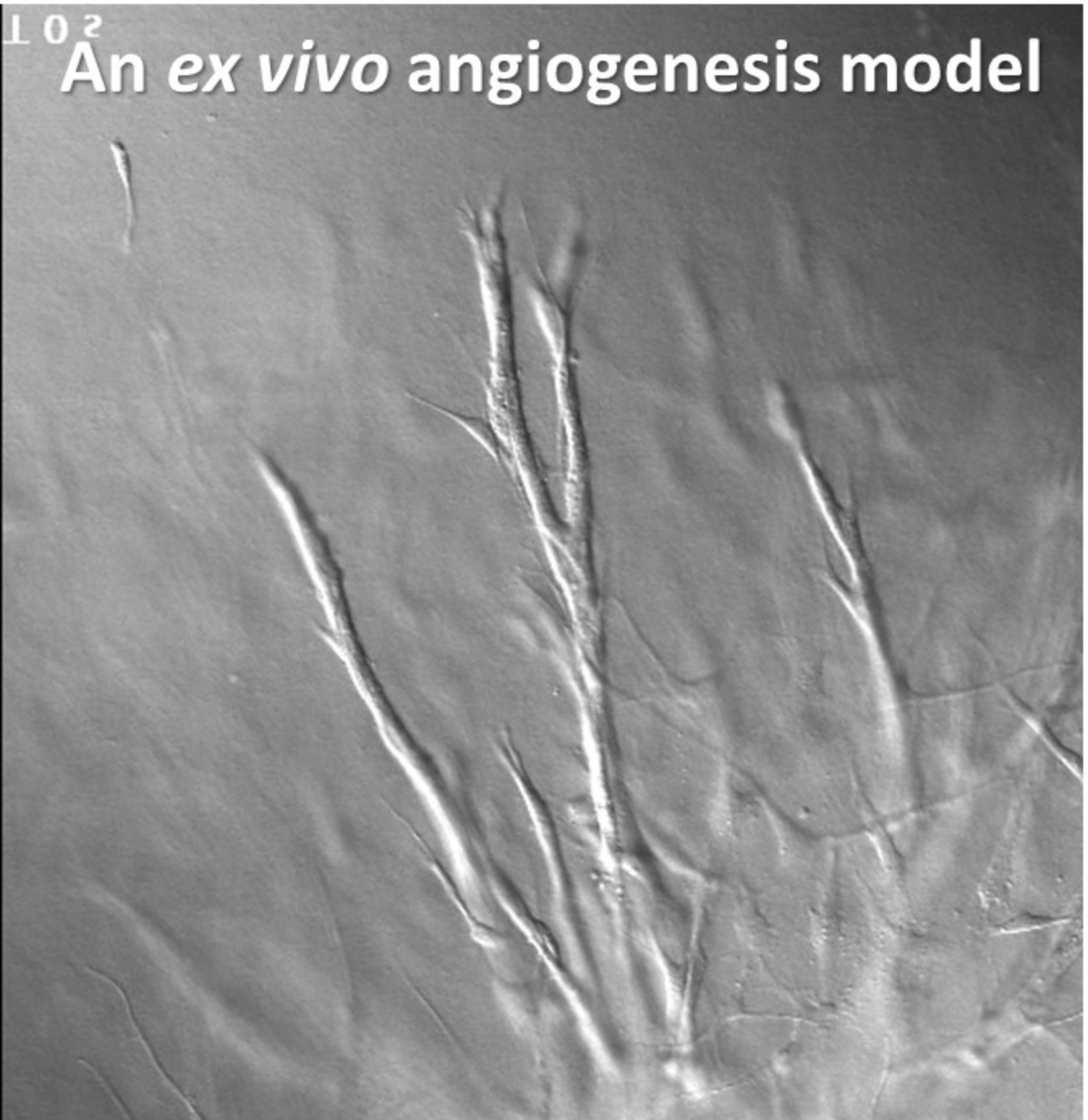




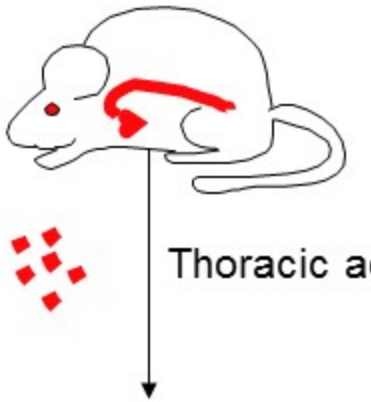
Angiogenic modules

Adapted from Development 2011;138:4569-83

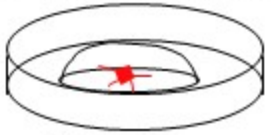
An *ex vivo* angiogenesis model



Mouse aortic ring assay

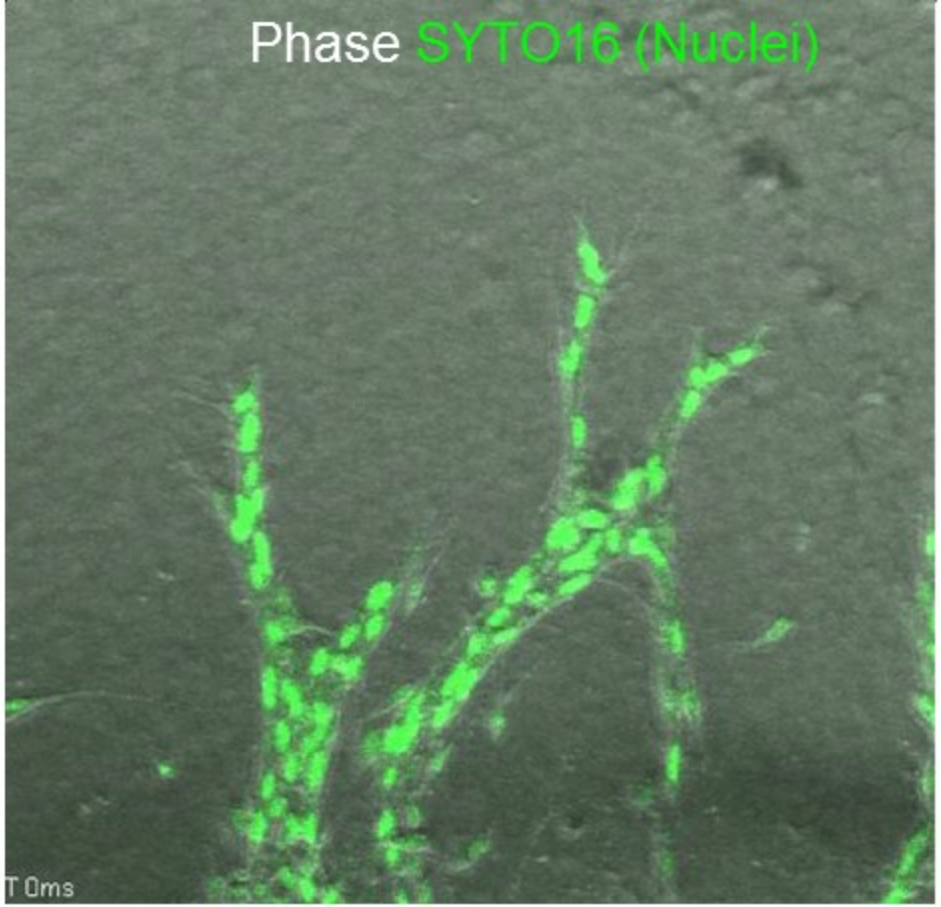


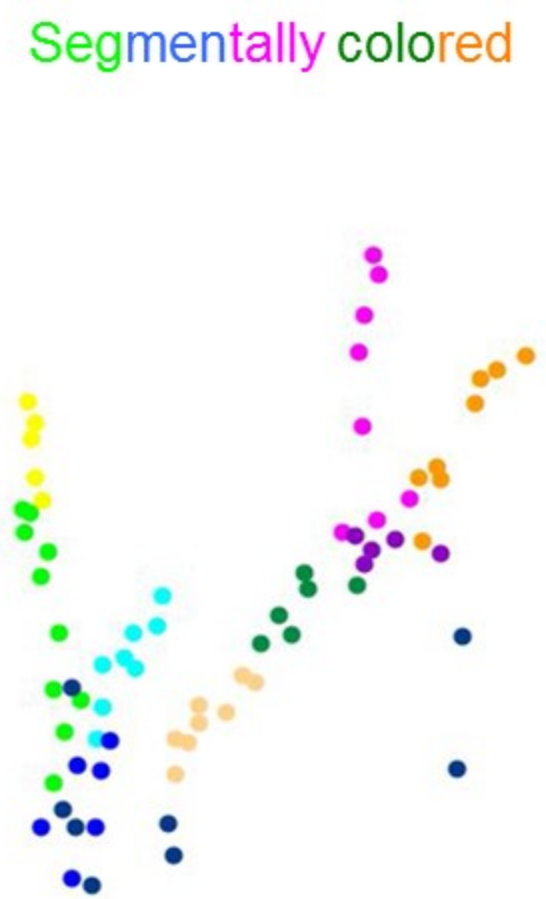
In type-1 collagen gel

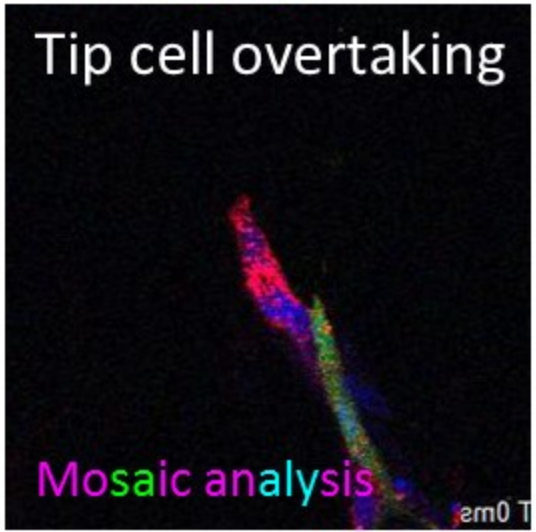


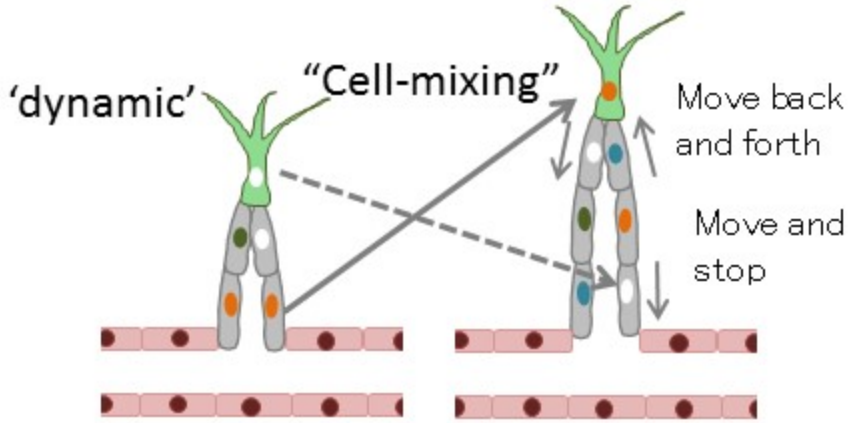
3D culture

Time-lapse imaging





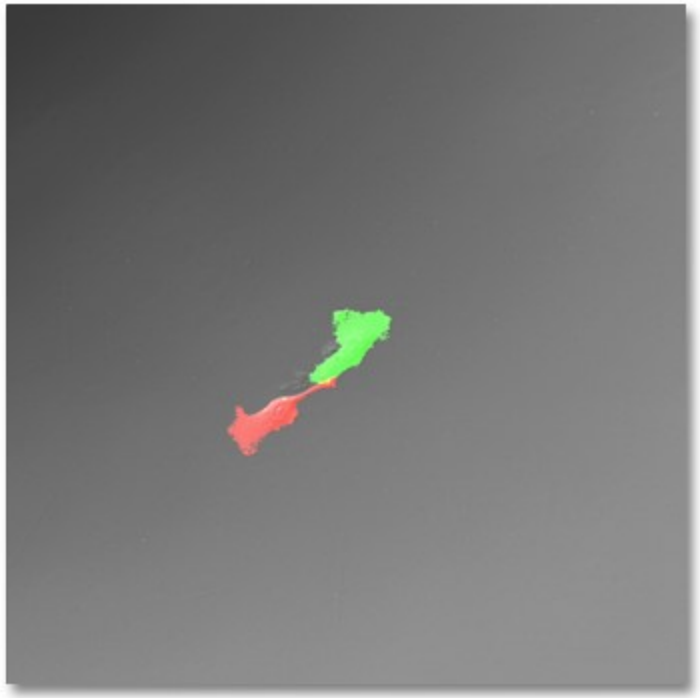




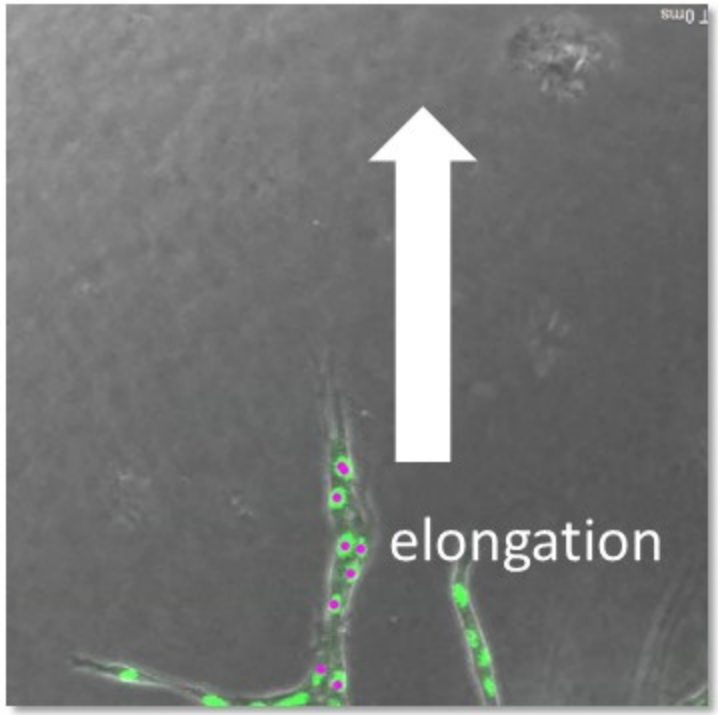
(Arima S, Nishiyama K, et al. Development 2011)

What is the governing system?

Individual EC movements



Multicellular angiogenic movements



Branch elongation model

1. Cell emergence

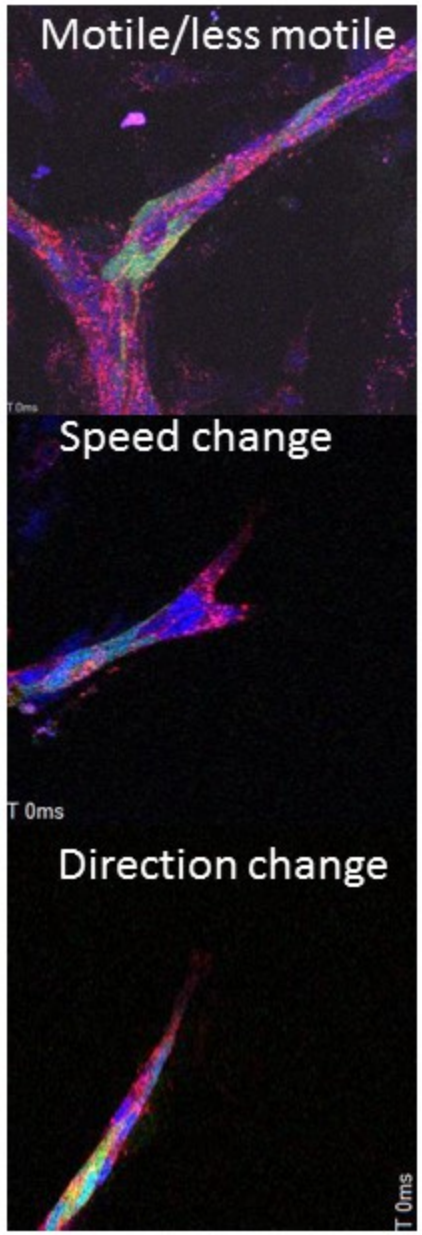
(1) Motility:

1/2

or

② Time interval: *c* (const.

Vessel elongation



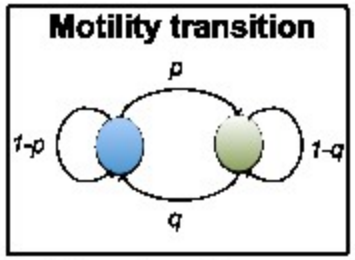
Assumption: speed and direction change stochastically

08:25:25

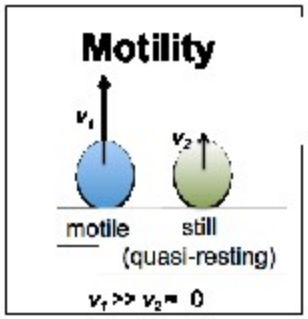
Continuous model

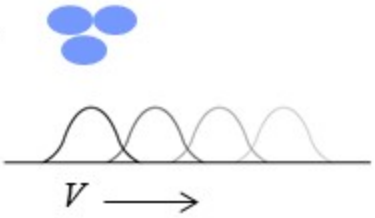
- Governing equation

Reaction



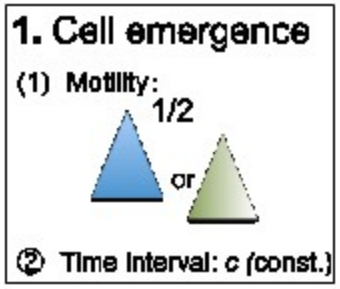
Advection



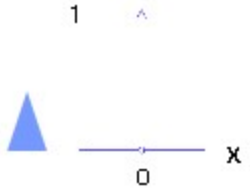


$$\frac{\partial u}{\partial t} = -V\frac{\partial u}{\partial x}$$

Source



$\delta(x)$



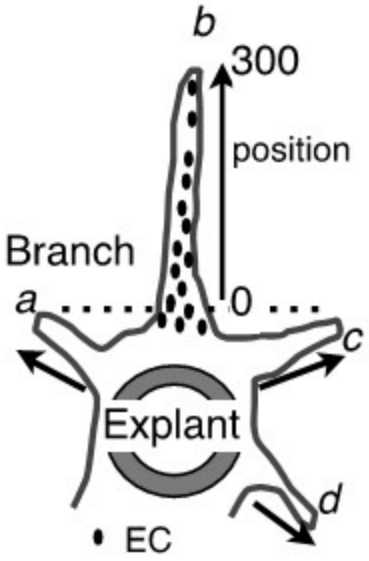
$x \neq 0,\ \delta(x) = 0$

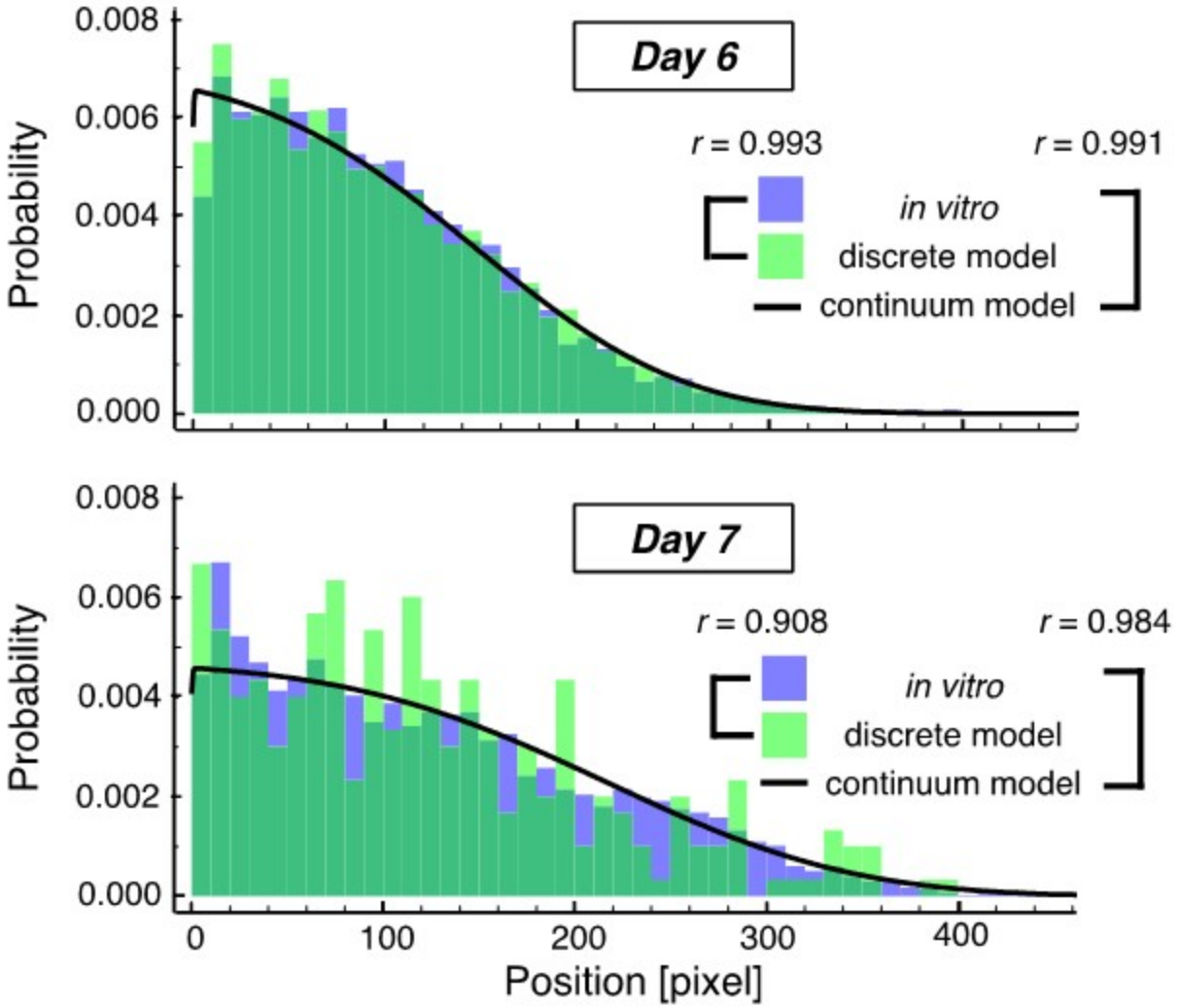
$$\int_{-\infty}^{\infty} \delta(x)dx = 1$$

$$\begin{cases} \dfrac{\partial u}{\partial t} = -ru + sw - V\dfrac{\partial u}{\partial x} + \dfrac{\delta(x)}{c}, \\ \dfrac{\partial w}{\partial t} = ru - sw + V\dfrac{\partial w}{\partial x}. \end{cases}$$

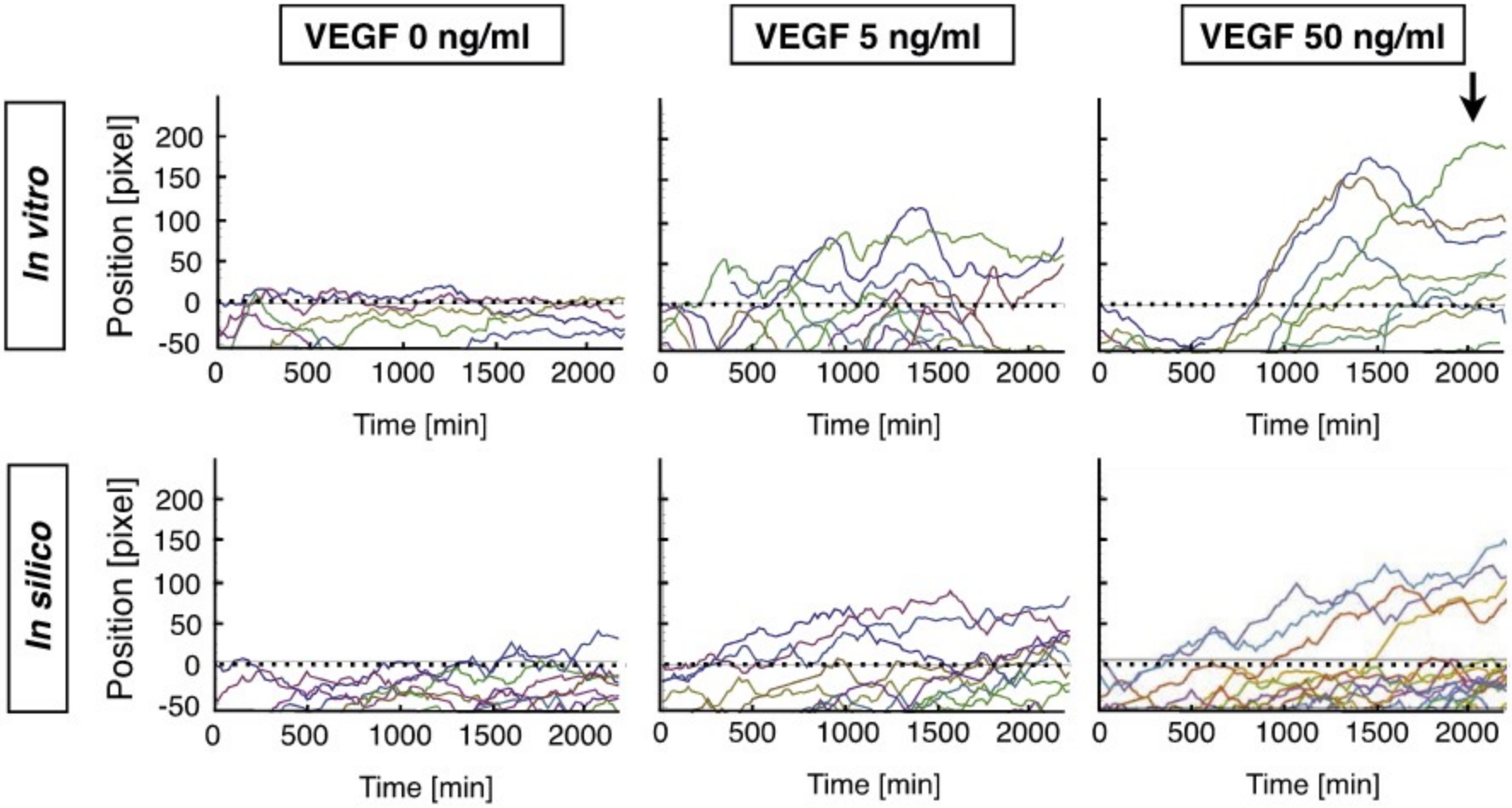
In collaboration with Dr. Takashi Miura and Dr. Ryo Kobayashi

Existence probabilities of individual ECs



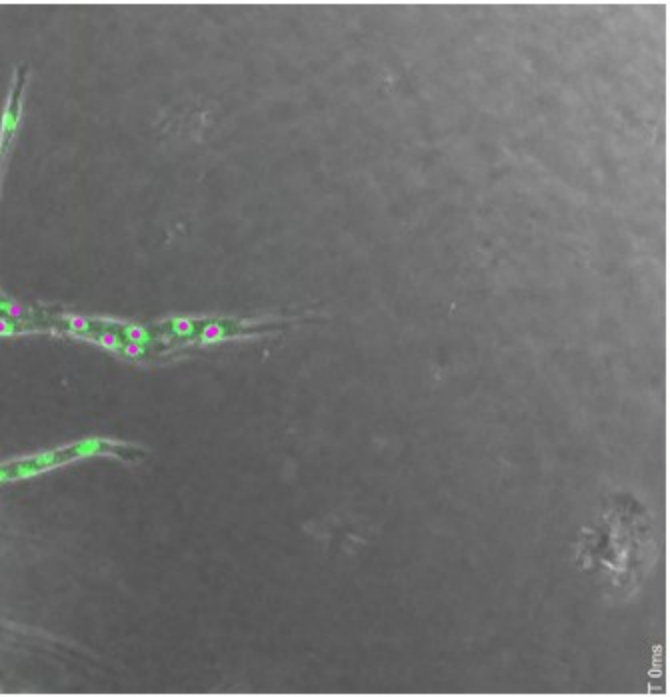


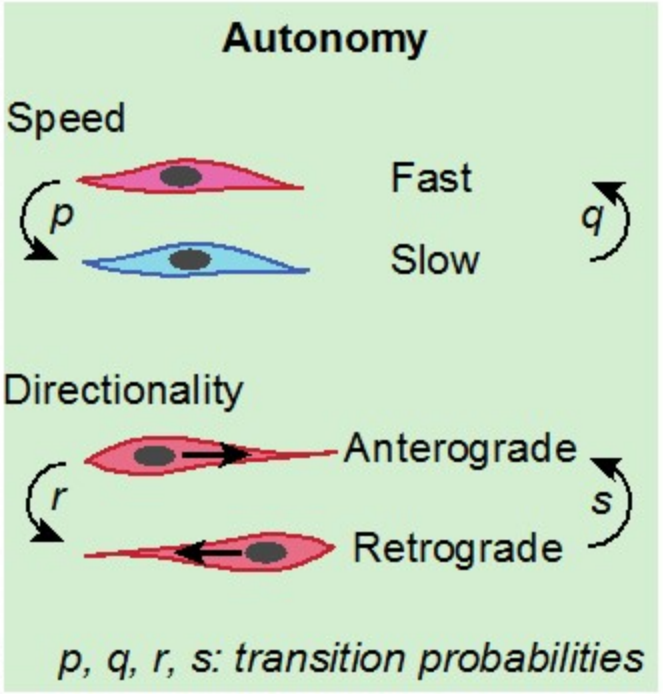
EC movements during branch elongation



Summary

1. Stochastic changes in the motility of an individual ECs are sufficiently explained core features of angiogenic EC dynamics in branch elongation.



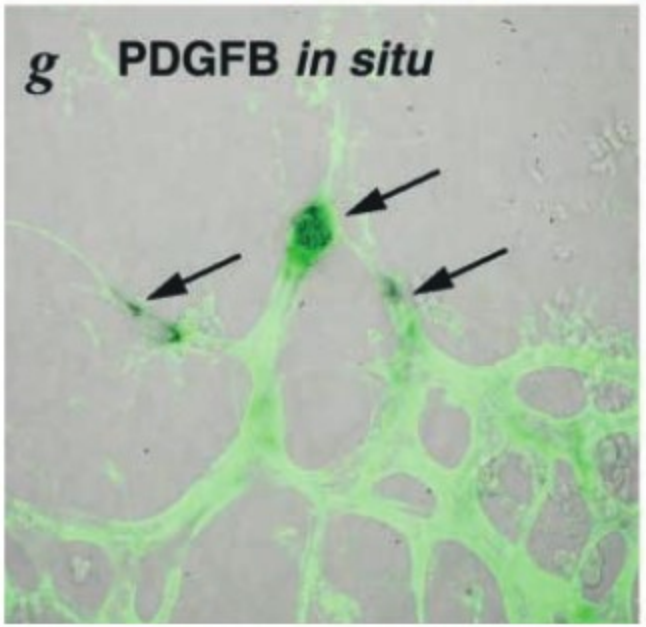


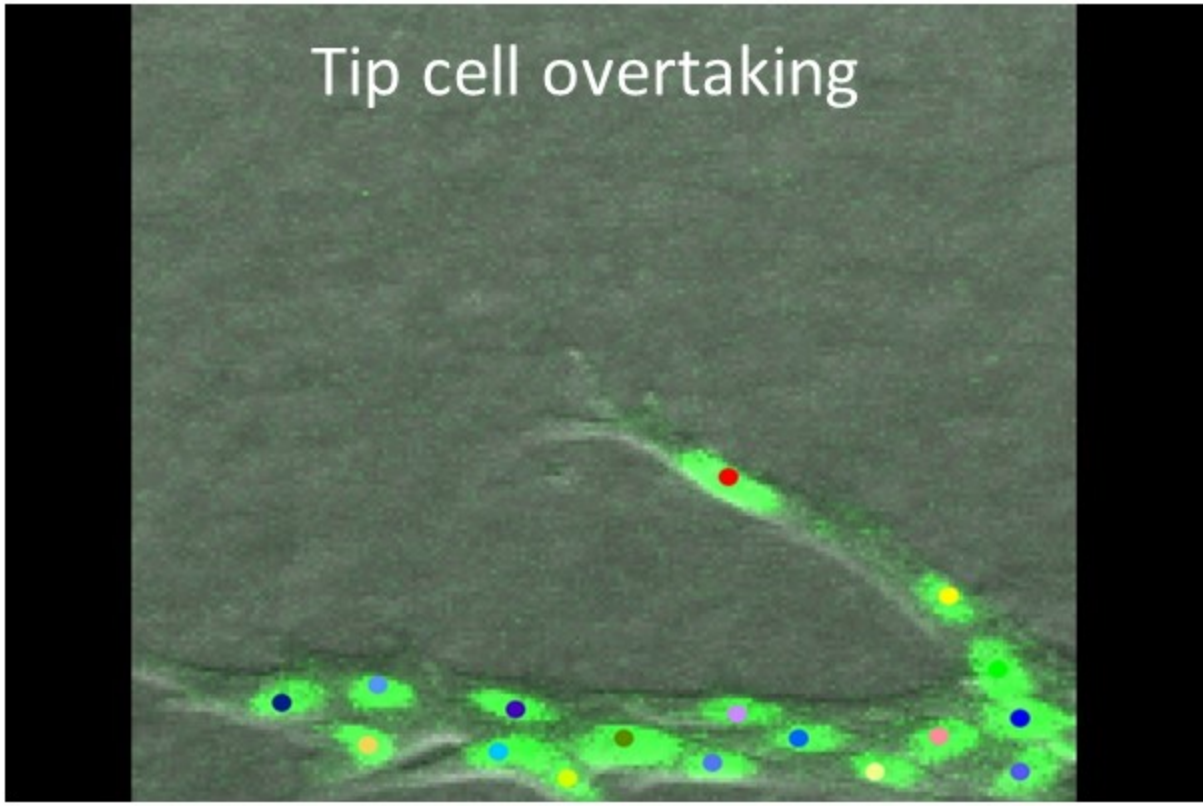
$$\begin{cases} \dfrac{\partial u}{\partial t} = -ru + sw - V\dfrac{\partial u}{\partial x} + \dfrac{\delta(x)}{c}, \\ \dfrac{\partial w}{\partial t} = ru - sw + V\dfrac{\partial w}{\partial x}. \end{cases}$$

(Sugihara K, Nishiyama K et al. ***Cell Rep*** 2015)

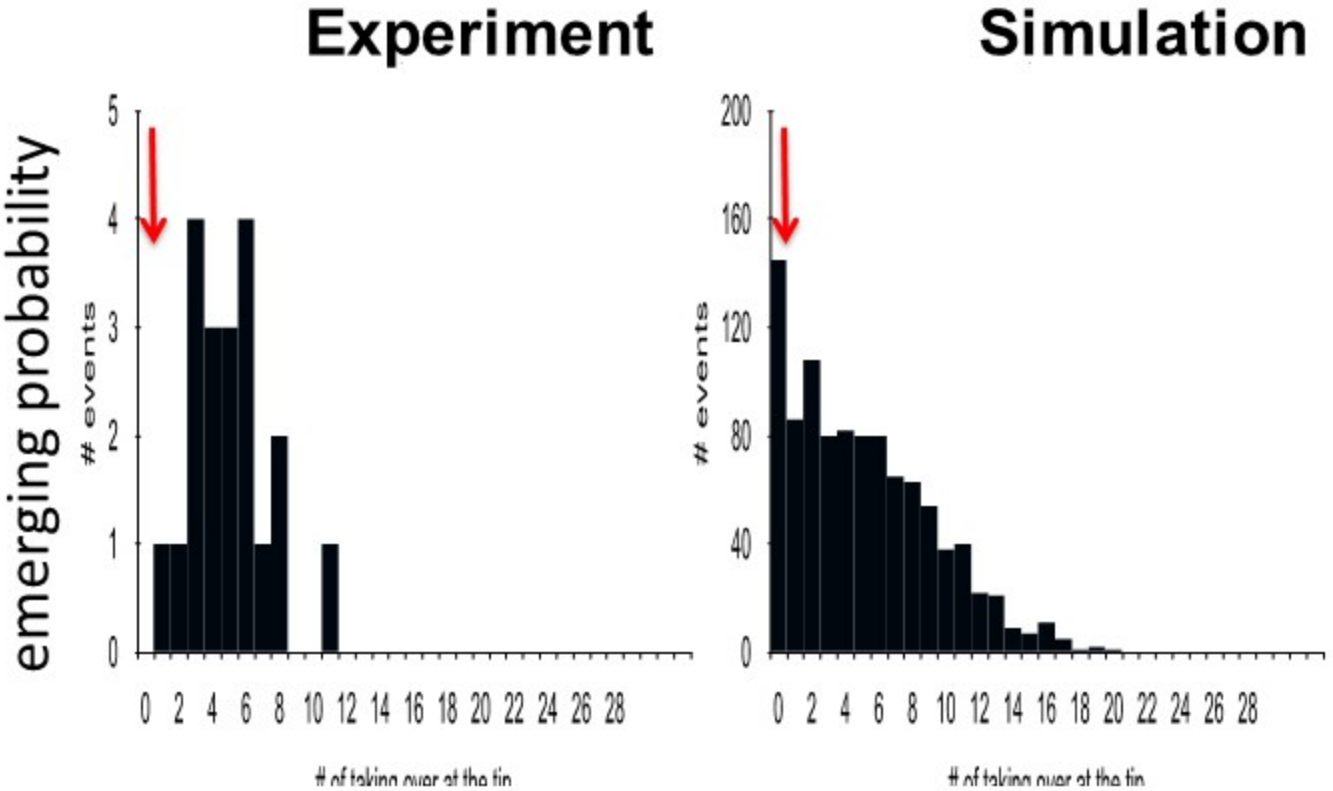
Tip EC dynamics

Tip EC





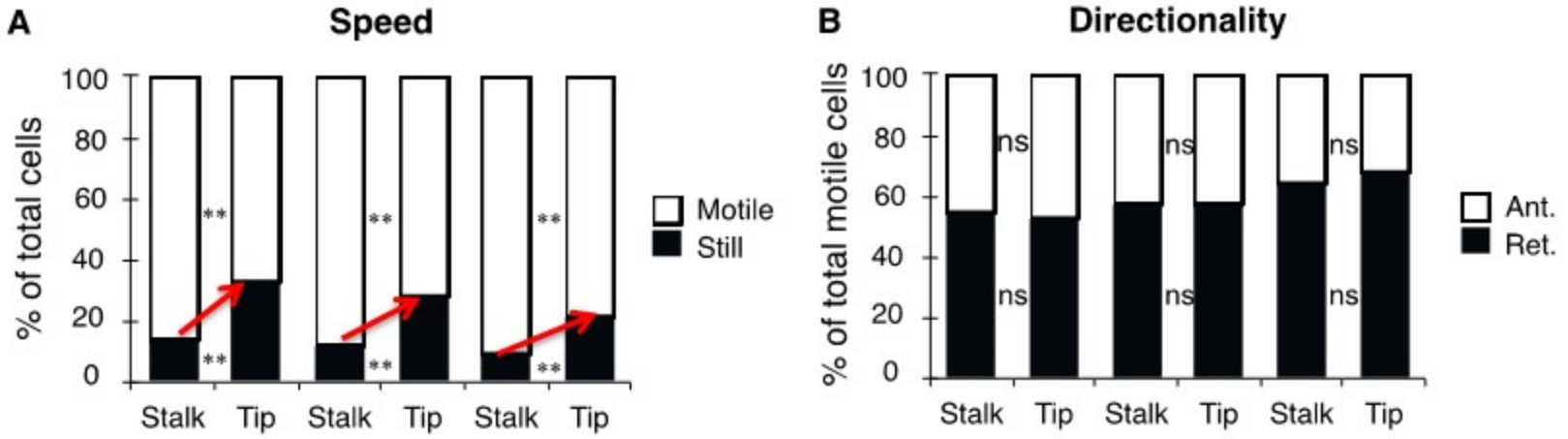
A discrepancy between simulation and experiment in appearance pattern of tip EC overtaking



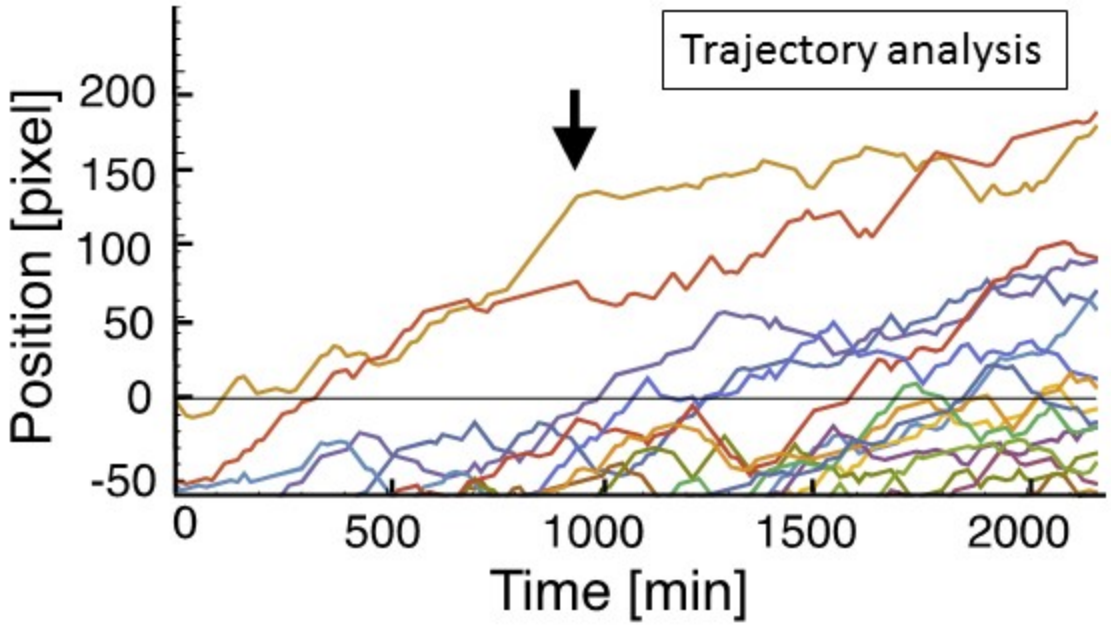
Number of tip EC overtaking event

EC behaviors might be controlled in additional ways

Tip cell dynamics in experiments



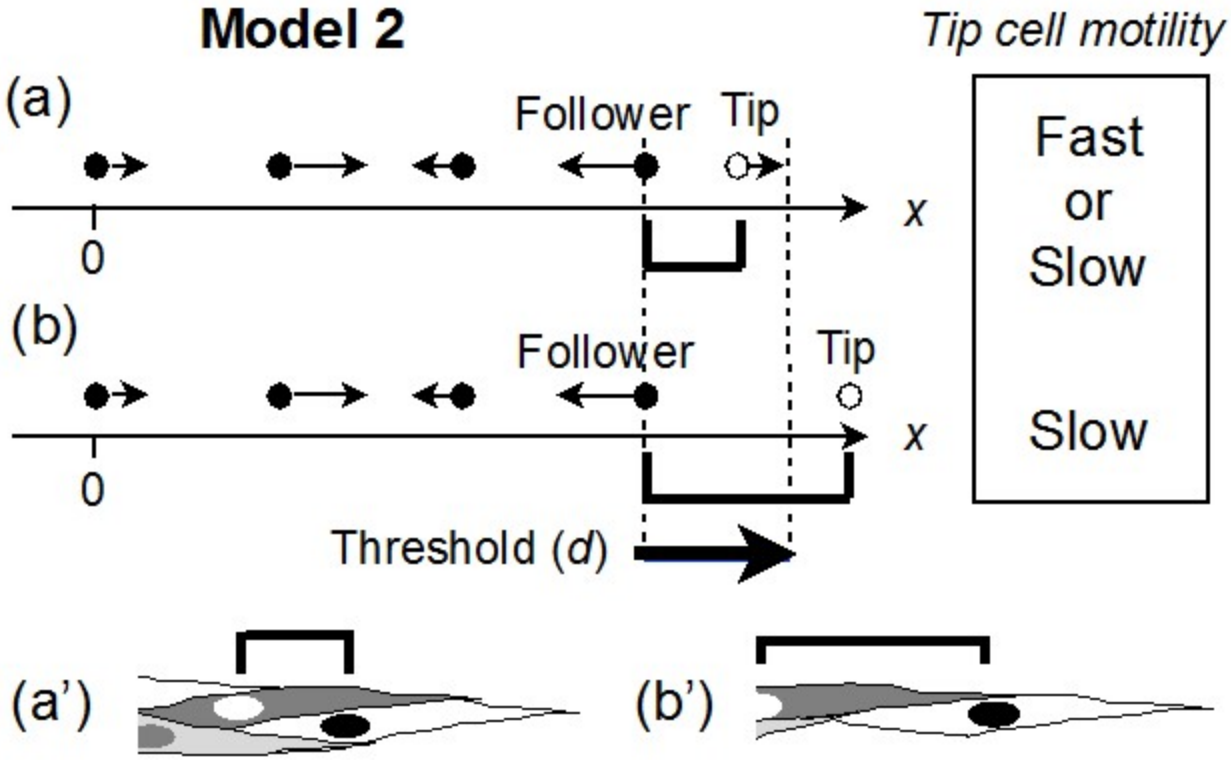
Additional mechanisms restrict forward movement of tip EC



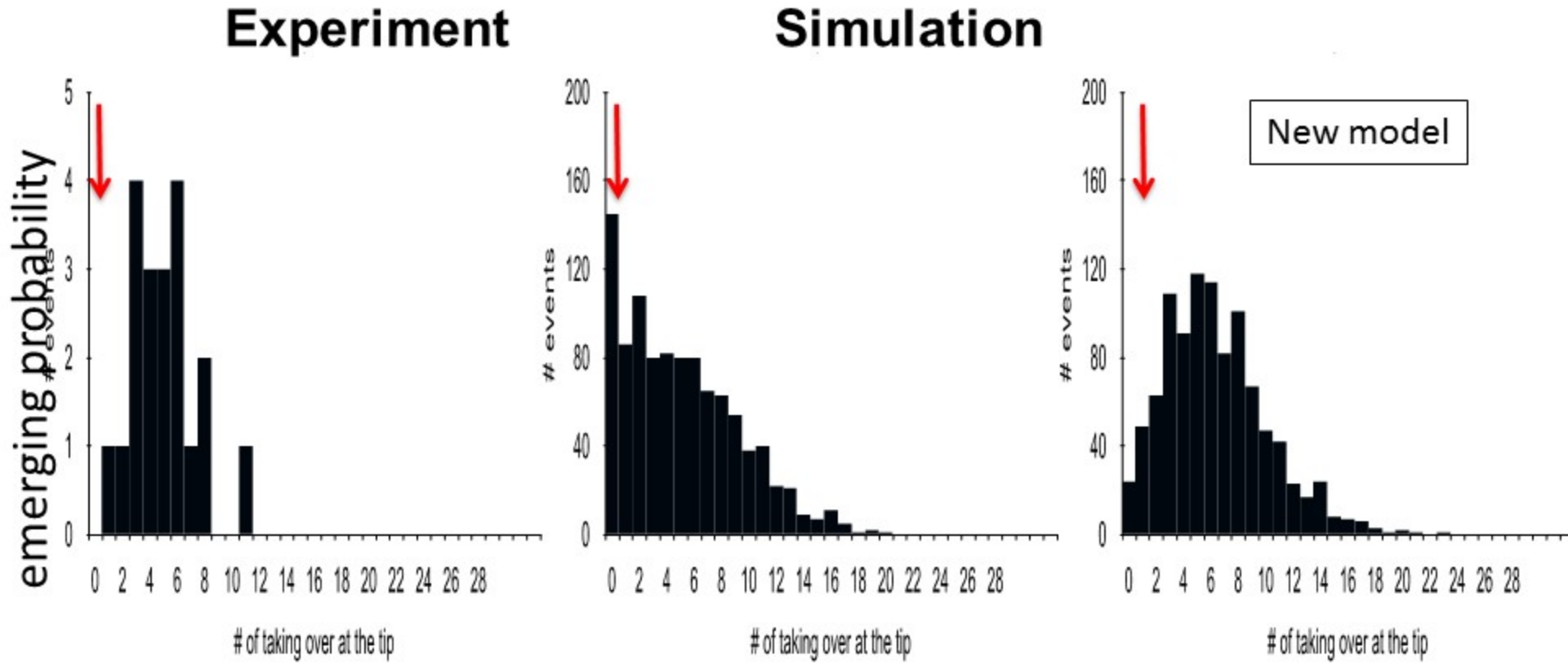
Additional rule for tip cell dynamics

Hypothesis:

Follow-up by stalk EC is necessary for keeping tip cell forward movement



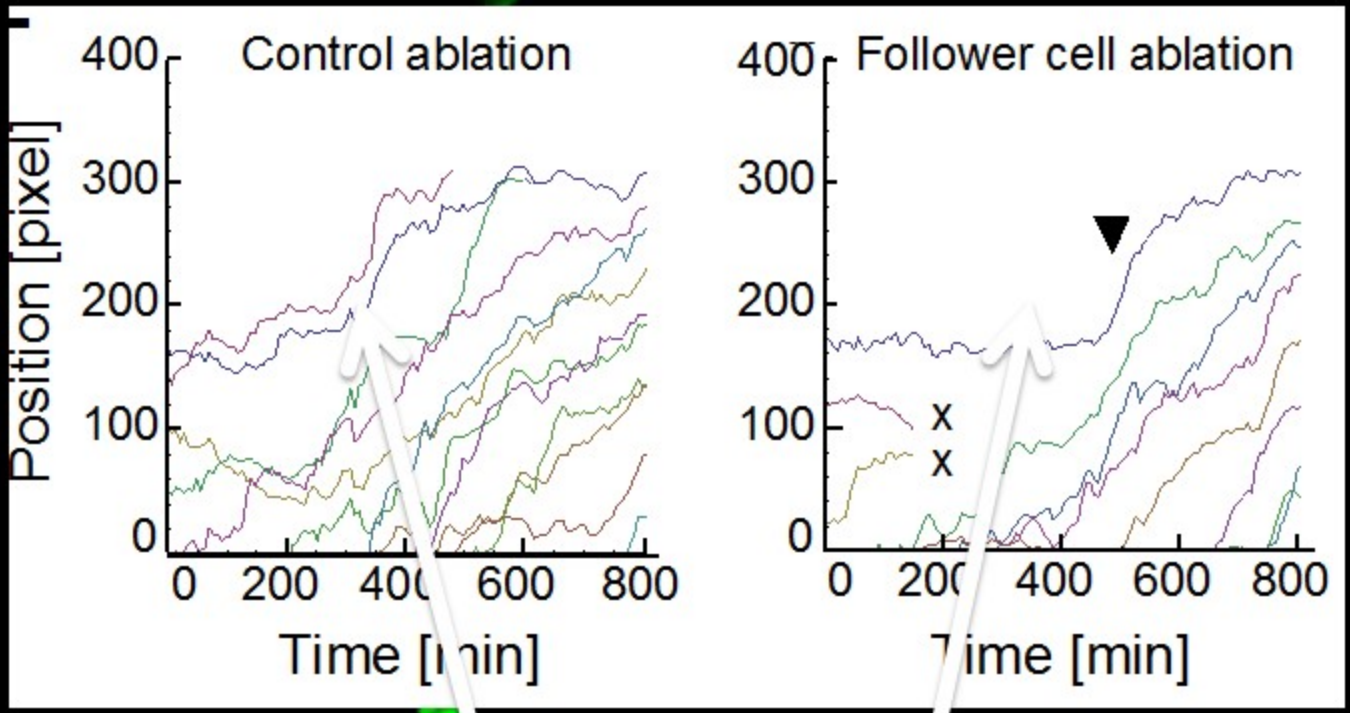
Tip cell dynamics were reproduced more accurately

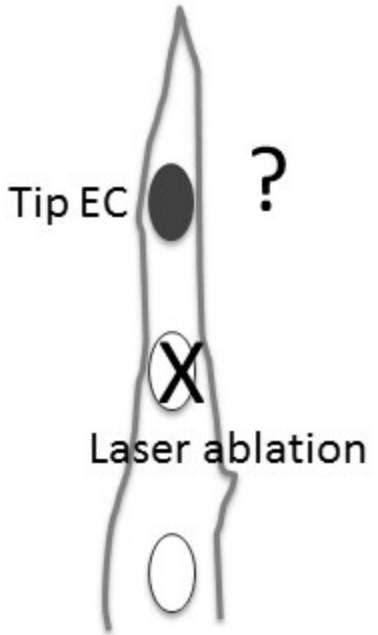


Number of tip EC overtaking event

00:00:00.000

A coordinated mode of tip EC movement





Follower cell attachment is necessary for Tip EC forward movement?

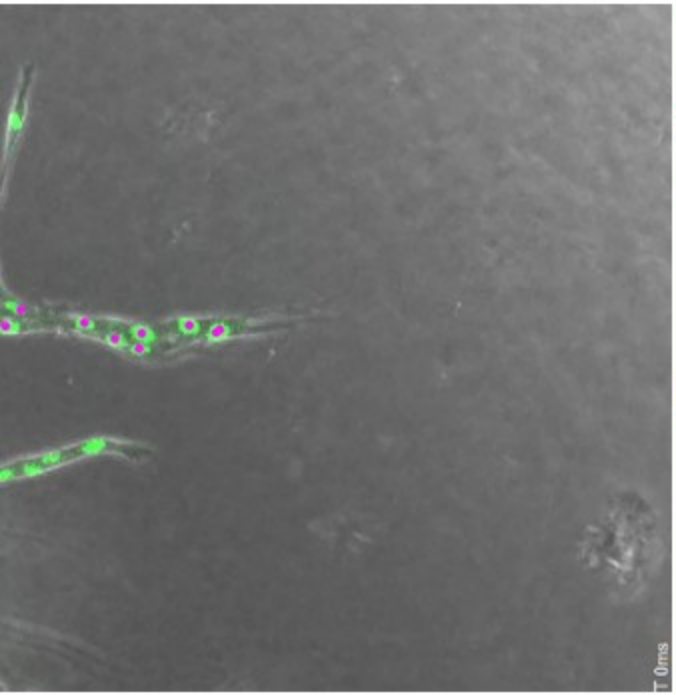
Mesencephalic vein in Zebrafish embryo

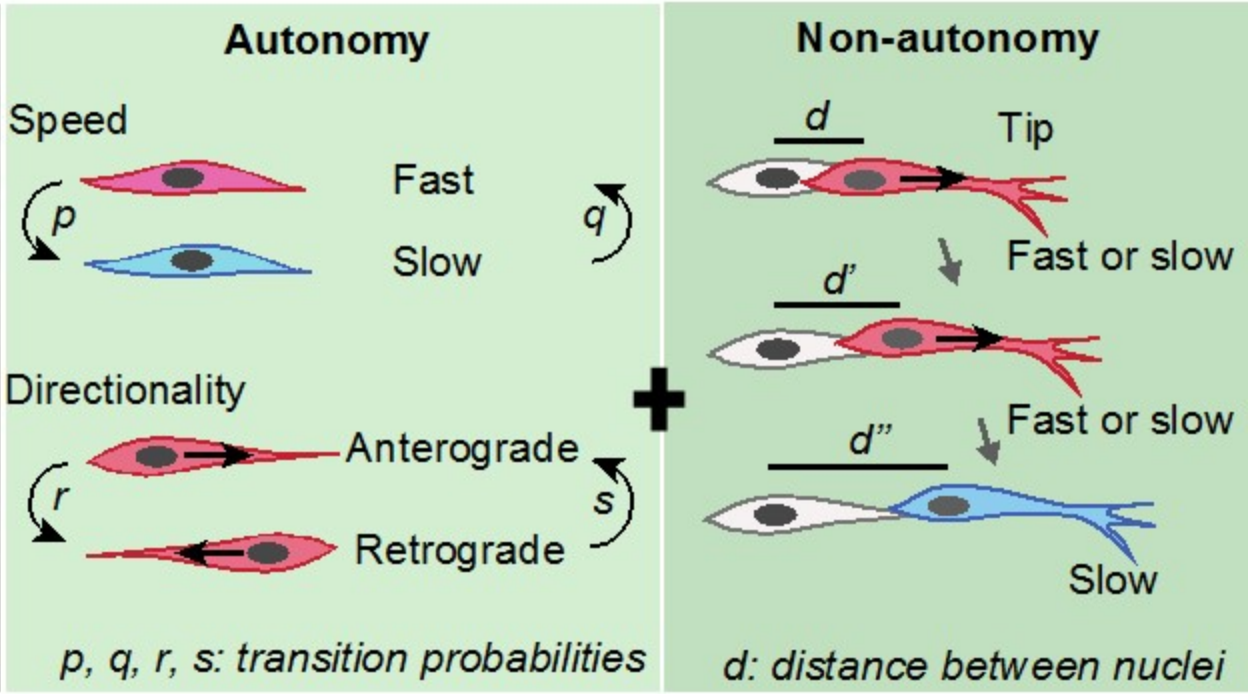
Endothelial cell nuclei In collaboration with Prof. Fukuhara and Prof. Mochizuki

08:25:25

Summary and Conclusion

1. Stochastic changes in the motility of an individual ECs are sufficiently explained core features of angiogenic EC dynamics in branch elongation.
2. Tip cell behaviors are also regulated in a deterministic way. Follow-up by stalk cell is necessary for appropriate tip cell forward movement.
3. Sufficient cell attachment may induce tip EC polarization and the resultant forward movement.





(Sugihara K, Nishiyama K et al. ***Cell Rep*** 2015 and unpublished data)

Acknowledgements

IRCMS, Kumamoto University

Yuichiro Arima
Michie Uchikawa
Yoshimi Yamaguchi
Chiharu Esumi
Nao Shogenji

The University of Tokyo

Hiroki Kurihara
Satoshi Arima
Kei Sugihara

Nihon Medical School

Shigetomo Fukuhara

NCVC

Naoki Mochizuki

Technische Universität Dresden

Walter de Back

Universitetet i Oslo

Alvaro Köhn-Luque

Hiroshima University

Ryo Kobayashi

Kyusyu University

Takashi Miura