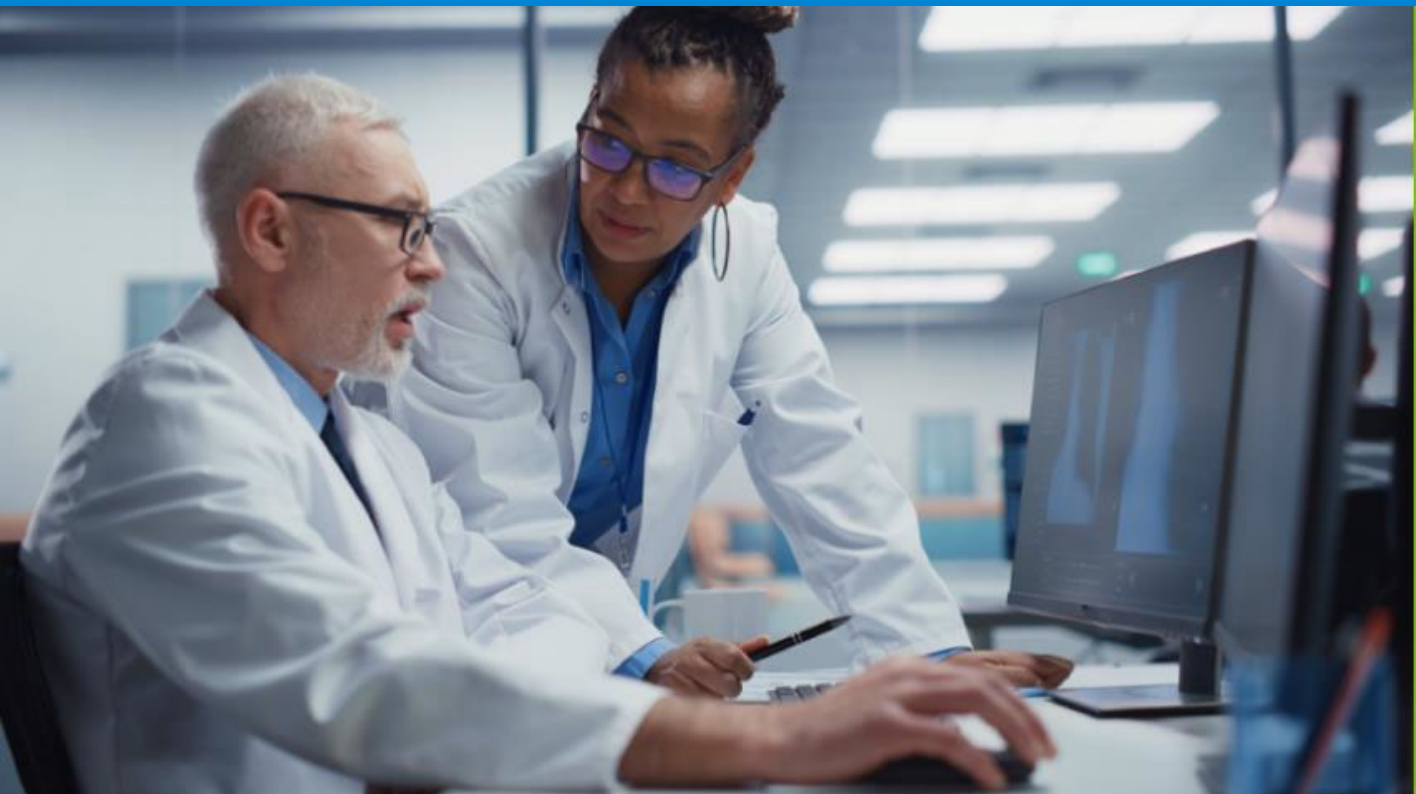




The Intricate Understanding of Cell Function and Metabolism in Cancer



Agilent AACR
Media Briefing

April 7, 2024

San Diego, CA

Safe Harbor

This presentation contains forward-looking statements (including, without limitation, information and future guidance on the company's goals, priorities, growth opportunities, customer service and innovation plans, new product introductions, financial condition and considerations, and the continued strengths and expected growth of the markets the company sells into, operations) **that involve risks and uncertainties that could cause results of Agilent to differ materially from management's current expectations.** The words "anticipate," "plan," "estimate," "expect," "intend," "will," "should" "forecast" "project" and similar expressions, as they relate to the company, are intended to identify forward-looking statements.

In addition, other risks that the company faces in running its operations include the ability to execute successfully through business cycles; the ability to successfully adapt its cost structures to continuing changes in business conditions; ongoing competitive, pricing and gross margin pressures; the risk that our strategic and cost-cutting initiatives will impair our ability to develop products and remain competitive and to operate effectively; the impact of geopolitical uncertainties on our markets and our ability to conduct business; the impact of currency exchange rates on our financial results; the ability to improve asset performance to adapt to changes in demand; the ability to successfully introduce new products at the right time, price and mix, and other risks detailed in the company's filings with the Securities and Exchange Commission, including our annual report on Form 10-K for the year ended October 31, 2023.

The company assumes no obligation to update the information in these presentations. This presentation include non-GAAP measures. Non-GAAP measures exclude primarily the impacts of asset impairments, amortization of intangibles, transformational initiatives, acquisition and integration costs, change in fair value of contingent consideration, loss on extinguishment of debt, business exit and divestiture costs, pension settlement loss and net gain on equity securities. We also exclude any tax benefits that are not directly related to ongoing operations, and which are either isolated or are not expected to occur again with any regularity or predictability. With respect to the company's guidance, most of these excluded amounts pertain to events that have not yet occurred and are not currently possible to estimate with a reasonable degree of accuracy. Accordingly, no reconciliation to GAAP amounts has been provided.



**San Diego Zoo
Wildlife Alliance**

Today's Presenters



Todd Christian

Vice President and
General Manager,
Cell Analysis Division,
Agilent



Roddy O'Connor

BSc, MS, Ph.D., Research
Assistant Professor of Pathology
and Laboratory Medicine,
Perelman School of Medicine,
University of Pennsylvania



Pradipta Gosh

M.D., Professor,
Medicine and Cellular
and Molecular Medicine,
UC San Diego

Todd Christian

Vice President and General Manager,
Cell Analysis Division, Agilent



Mission and Market Focus

A global, collaborative team, serving vital industries in 6 key markets



Our Mission

Advancing the **quality of life**,
by providing
trusted answers



Committed to

Accelerating the
advancement of science

Providing complete,
integrated solutions

Championing our
customers' success

Technology and Solutions

Agilent provides the technology and solutions researchers need throughout the cancer continuum

UNCOVER

How cancer cells behave and avoid the immune system

DISCOVER

The genetic changes which drive cancer

TRANSLATE

Advance your discoveries from basic to clinical research

ENABLE

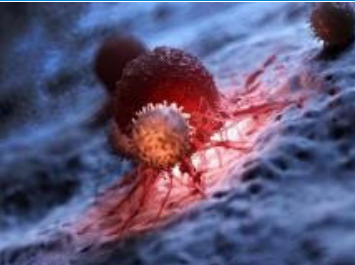
The diagnosis with trusted pathology solutions

DELIVER

Precision diagnostics to guide therapeutic decision making

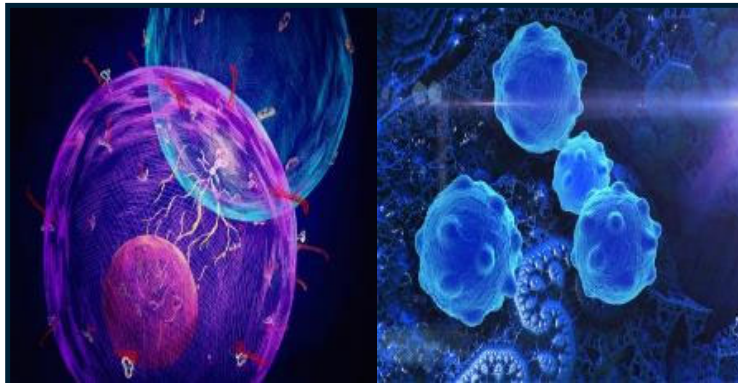
FIGHT

Drive cutting edge molecular and cellular therapies



Why Cell Analysis...

Unique opportunity to address important challenges



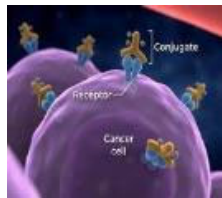
Moving from a molecular basis of understanding disease to using the cellular ecosystem to target & treat disease

- The most debilitating, costly, and lethal **diseases are cell-related, mediated, or treated.**
- Modeling the integrated activities comprised within a **living cell** is essential for disease research
- Advances in cell analysis and genome editing have created a **revolution in cell engineering**
- **Cell, Gene & Immuno-therapies** rapidly emerging as a pillar in therapeutics, driving an evolution of cell analysis tools

Traditional Techniques Evolving with **Emerging Live-cell** Capabilities

Scientists are *using* immunology and the immune system to treat cancer and fight infectious disease

\$5B⁽¹⁾ Opportunity with attractive growth drivers; 5-7%⁽²⁾



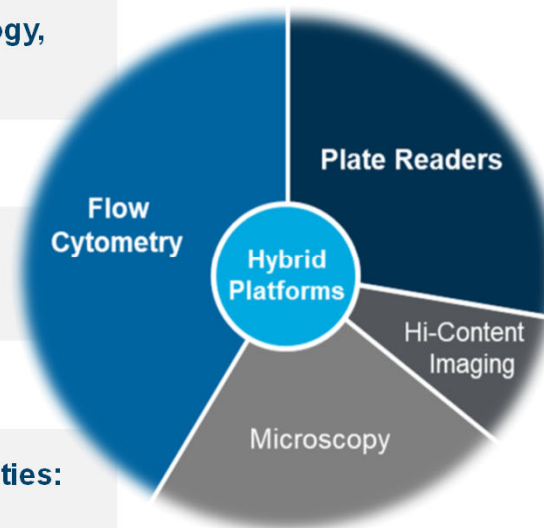
**Immunology, Immuno-oncology,
and Immunotherapy**



**Infectious Disease, Virology,
and Vaccine Research**



**Emerging Therapeutic Modalities:
Cell & Gene Therapy**



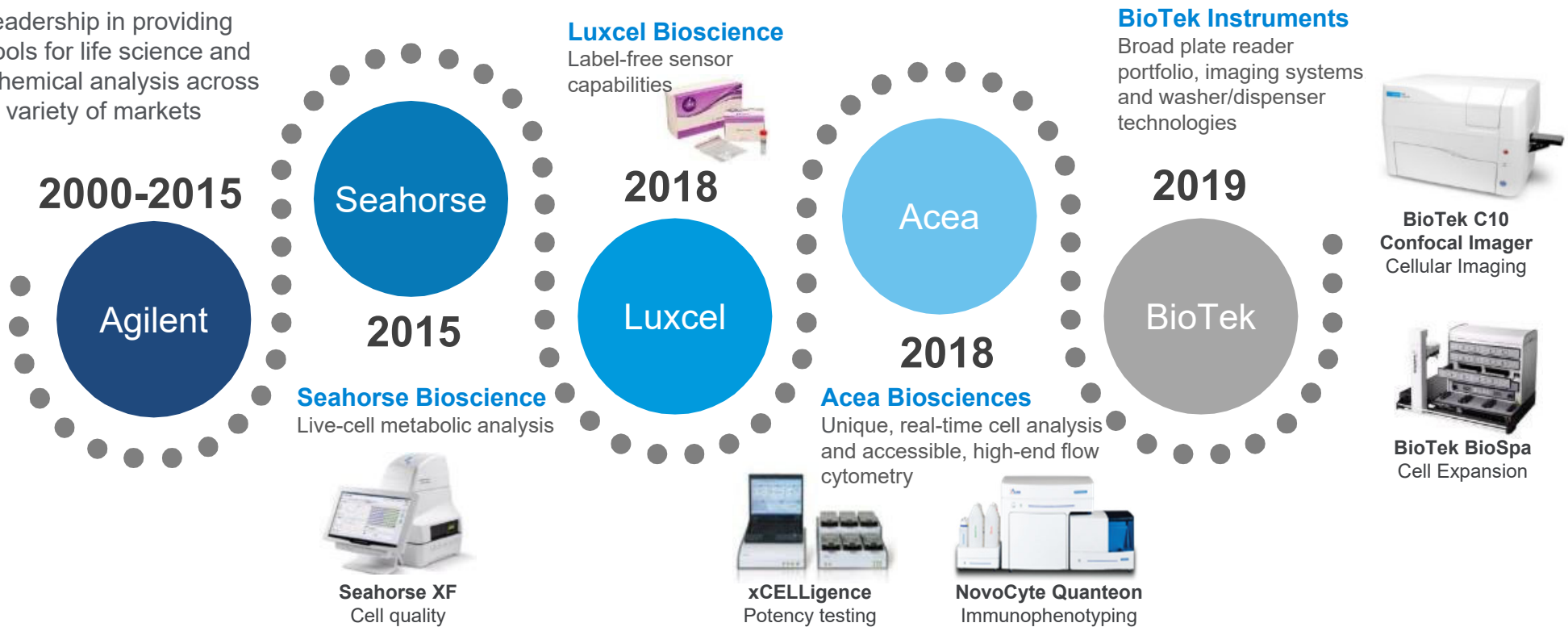
- Emergence of promising new biologic therapeutic modalities
- Increased need for accelerated vaccine development to address evolving and persistent infectious diseases
- Need to understand the entire cellular ecosystem, in context of disease and immune response
- Simultaneous use of traditional platforms and live-cell, real-time techniques
- Coordinated workflows across multiple techniques

(1) and (2) based on internal company estimates

Our Journey

Enabling a deeper understanding of the cellular environment

Agilent has a long history of innovation and leadership in providing tools for life science and chemical analysis across a variety of markets



Thank you!

Roddy O'Connor

BSc, MS, Ph.D., Research Assistant
Professor of Pathology and Laboratory
Medicine, Perelman School of Medicine,
University of Pennsylvania



^{13}C tracing my scientific journey and career fate so far...

Roddy O'Connor, Ph.D.

Research Assistant Professor
Center for Cellular Immunotherapies
Perelman School of Medicine



My undergraduate TME

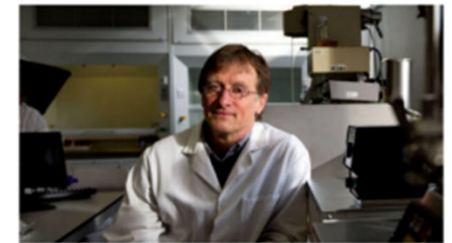


**UNIVERSITY OF
LIMERICK**
OLLSCOIL LUIMNIGH

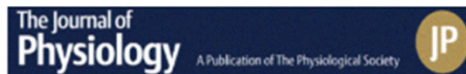


Start-up firm seeks to ace golf market with nutrition study

A drive is on to see how golfers can best to beat off hunger during those hours on the course.



Graduate School at Emory University



[J.Physiol.](#) 2008 Jun 15; 586(Pt 12): 2841–2853.
Published online 2008 Apr 17. doi: [10.1113/jphysiol.2008.151027](https://doi.org/10.1113/jphysiol.2008.151027)

PMCID: PMC2517193
PMID: [18420707](https://pubmed.ncbi.nlm.nih.gov/18420707/)

Phosphocreatine as an energy source for actin cytoskeletal rearrangements during myoblast fusion

[Roddy S. O'Connor](#)¹, [Craig M. Steeds](#)¹, [Robert W. Wiseman](#)² and [Grace K. Pavlath](#)¹

Postdoctoral adventures at UPenn



[Clin Cancer Res](#). Author manuscript; available in PMC 2012 Mar 15.

Published in final edited form as:

[Clin Cancer Res](#). 2011 Mar 15; 17(6): 1463–1473.

Published online 2011 Jan 10. doi: [10.1158/1078-0432.CCR-10-0091](https://doi.org/10.1158/1078-0432.CCR-10-0091)

PMCID: PMC3060277

NIHMSID: NIHMS239568

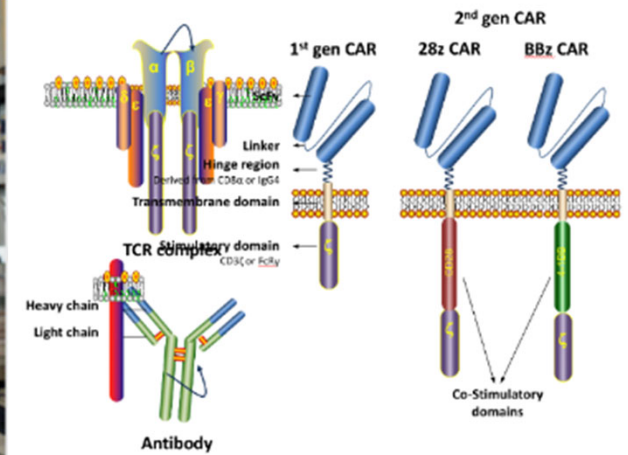
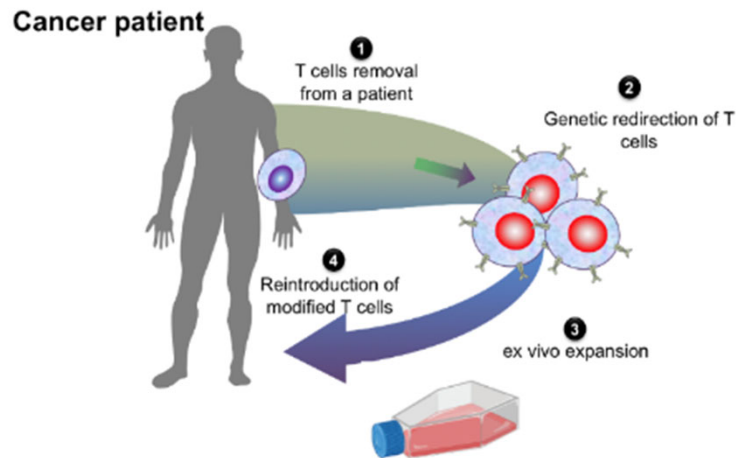
PMID: [21220470](https://pubmed.ncbi.nlm.nih.gov/21220470/)

Genomic and clinical analysis of amplification of the 13q31 chromosomal region in alveolar rhabdomyosarcoma: a report from the Children's Oncology Group^{*}

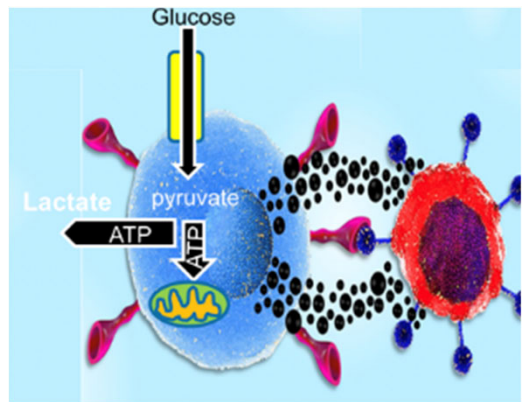
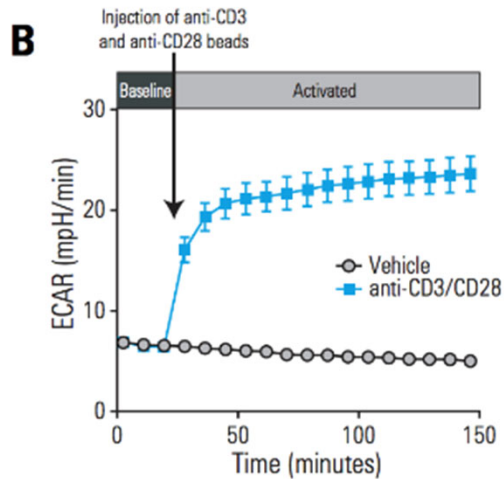
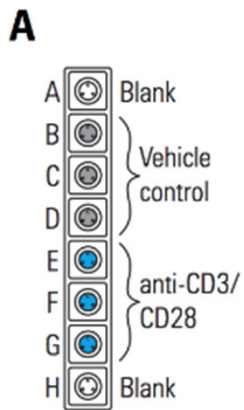
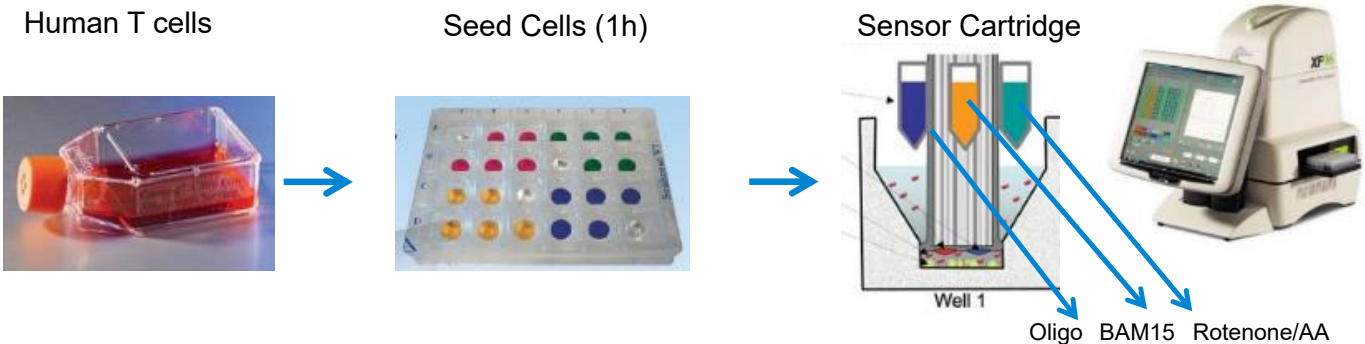
[Jennifer L. Reichel](#),^{1,2,1†} [Fenghai Duan](#),^{3,1} [Lynette M. Smith](#),^{4,5,1} [Donna M. Gustafson](#),¹ [Roddy S. O'Connor](#),¹ [Chune Zhang](#),¹ [Mandy J. Pitts](#),⁶ [Julie M. Gastier-Foster](#),^{6,7} and [Frederic G. Barr](#)^{1,8}

Learning gene delivery with Dr. Carl June

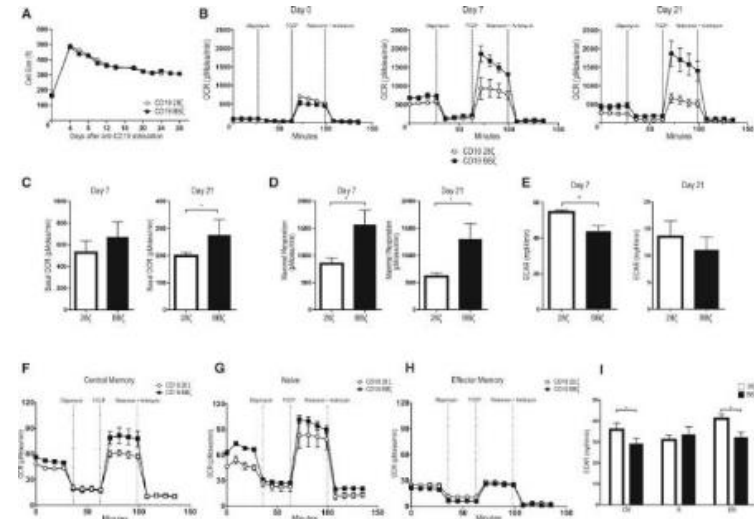
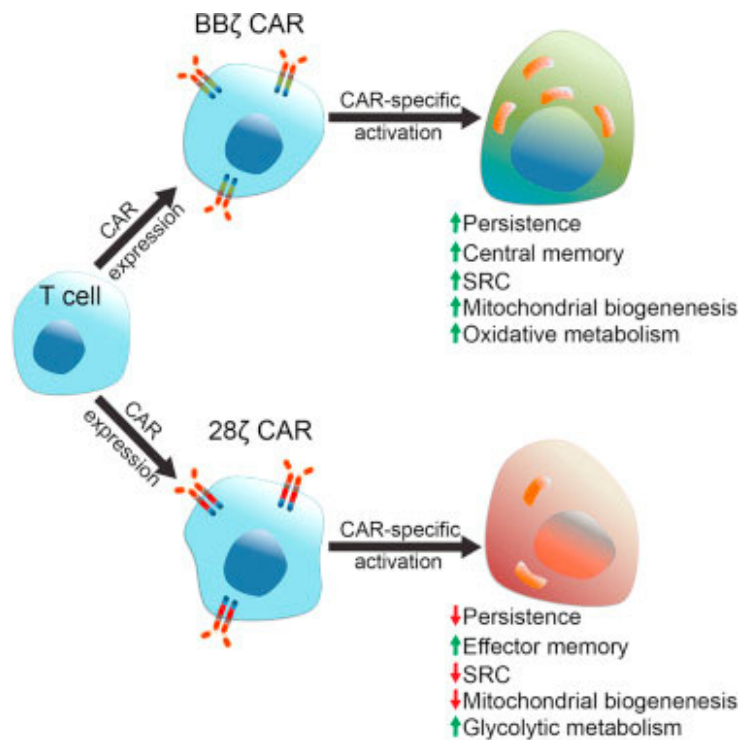
Paved the way for a second postdoc...



Activated T Cells undergo a metabolic shift to glycolysis



Leveraging XF Flux analysis to understand how CAR design impacts metabolic reprogramming



Published Erratum > *Immunity*. 2016 Mar 15;44(3):712. doi: 10.1016/j.immuni.2016.02.023. Epub 2016 Mar 15.

Distinct Signaling of Coreceptors Regulates Specific Metabolism Pathways and Impacts Memory Development in CAR T Cells

Omkar U Kawalekar, Roddy S O' Connor, Joseph A Fraietta, Lili Guo, Shannon E McGettigan, Avery D Posey Jr, Prachi R Patel, Sonia Guedan, John Scholler, Brian Keith, Nathaniel W Snyder, Ian A Blair, Michael C Milone, Carl H June

Building my own lab: CAR T cell metabolic engineering for enhanced anti-tumor function



The screenshot shows the Penn Medicine website for the Center for Cellular Immunotherapies. The header includes the Penn Medicine logo and the Center for Cellular Immunotherapies name. Below the header is a navigation bar with links for FOP, PATIENTS, Researchers, About, Shared Facilities, Richard G. Carroll Award, and Donate. The main content area is for the O'Connor Lab, featuring a profile for Roddy S. O'Connor, Ph.D. with a portrait photo and a detailed biography of his research in CAR-T cell metabolism.

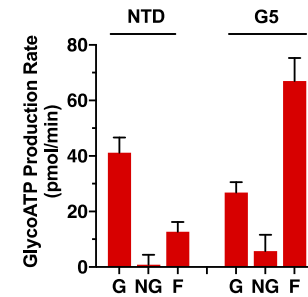
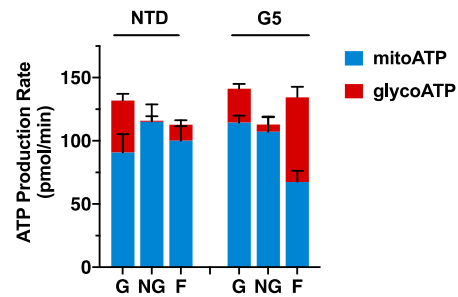
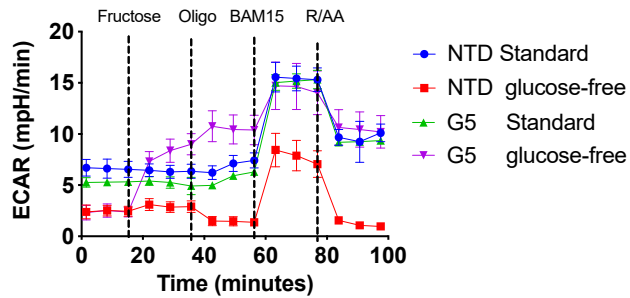
O'Connor Lab

Roddy S. O'Connor, Ph.D.

Dr. O'Connor graduated with a Bachelor's of Science from the University of Limerick (UL), Ireland. At UL, Dr. O'Connor developed his initial interests in metabolism, studying in the laboratory of the renowned metabolic biochemist Dr. Pih Jakeman. Dr. O'Connor continued his education at Emory University, studying the impact of NFAT-mediated transcription in myogenic stem cell differentiation. His work revealed how glycine, arginine, and methionine, combined as a guanidino acetate cell culture supplement, support the energy cost of stem cell fusion during tissue repair. This work received editorial praise from the *Journal of Physiology* and culminated in his Ph.D. in Molecular and Systems Pharmacology in 2007. Dr. O'Connor completed his first postdoctoral fellowship, at the University of Pennsylvania, studying the role of oncogenic microRNAs in rhabdomyosarcoma. This was followed by additional postdoctoral training with Dr. Michael Milone examining the role of metabolism in CAR-T cell differentiation. At Penn, he developed a series of approaches including metabolic flux analysis and isotopic tracer technology to understand how metabolic adjustments in CAR-T cells that have been genetically engineered to express distinct co-stimulatory domains influence central memory differentiation, increase oxidative metabolism, and promote long-lasting persistence. His skillset has led to a series of collaborators yielding high impact publications in *Immunity*, *Nature Immunology*, and *Nature Medicine*. Dr. O'Connor is a highly-regarded expert in CAR-T cell metabolism and has presented his findings at AAI, ASGCT, and the CAR-TCR Summit. Dr. O'Connor co-organizes the annual metabolomics symposium at Penn, and has presented several workshops as well as a webinar series on CAR-T cell metabolism.



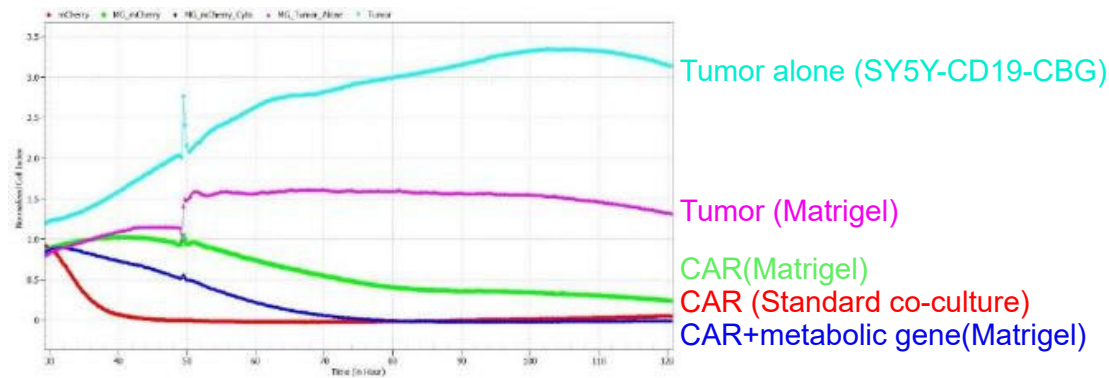
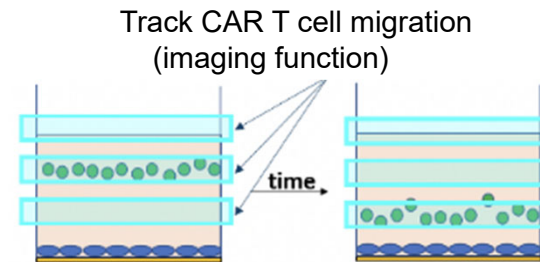
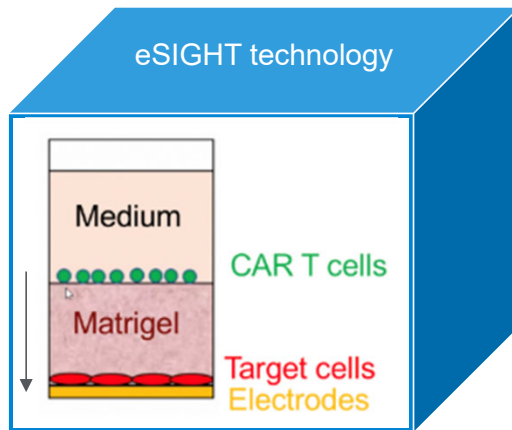
GLUT5 confers a unique metabolic flexibility to T cells



w Dr. Natalia Romero

How does metabolic reprogramming support 'hit & run' serial killing?

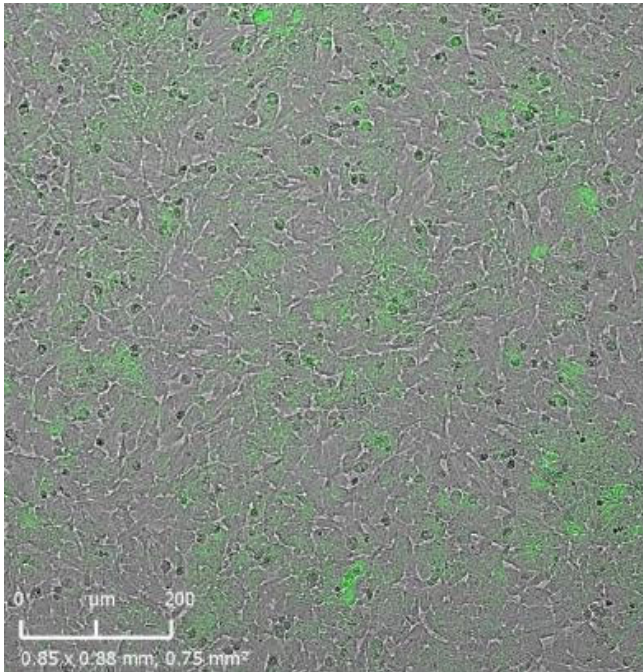
Both tumor cells and CAR T are in contact with Matrigel



A control to show tumor cells are viable in Matrigel (tumor only)

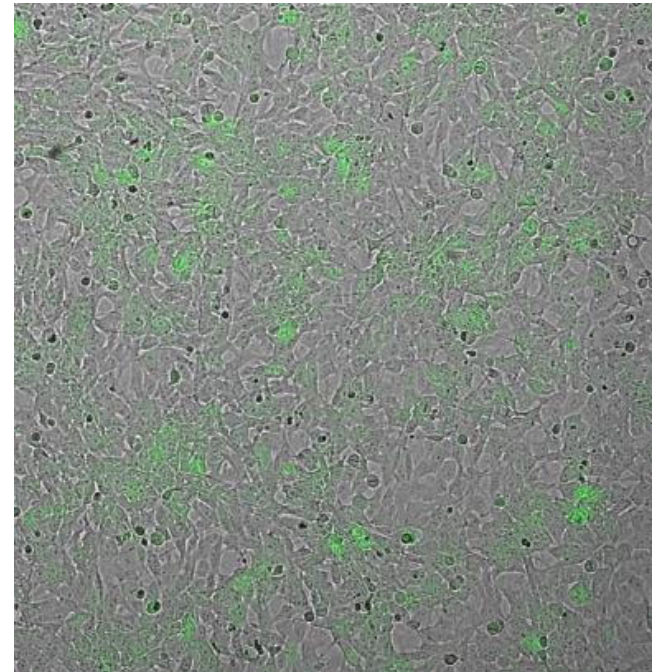
Tumor (standard)
SY5Y-CBG-CD19

34 hours



Tumor + matrigel

34 hours

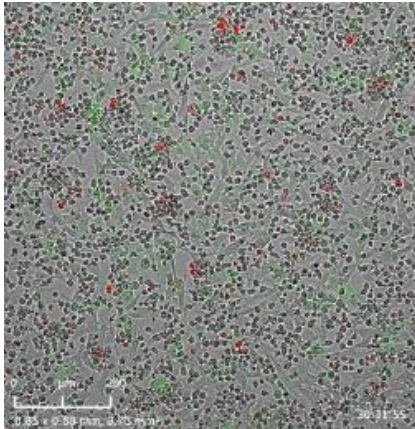


What fuels CAR T cell serial killing?

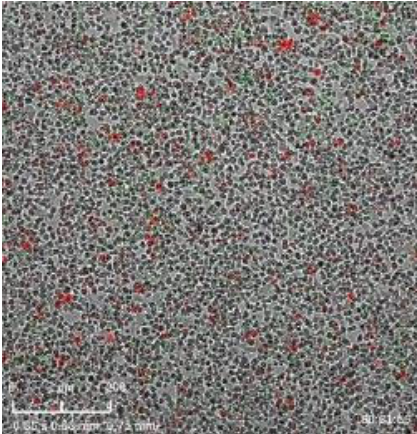
Direct
Co-culture

(Standard
approach)

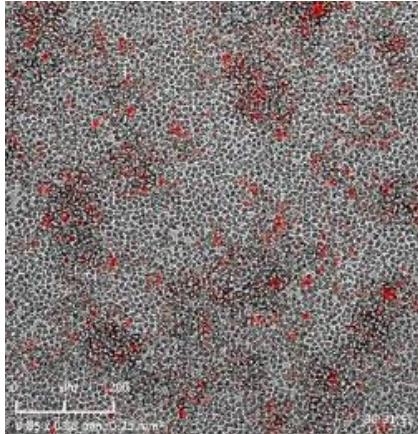
4 hours



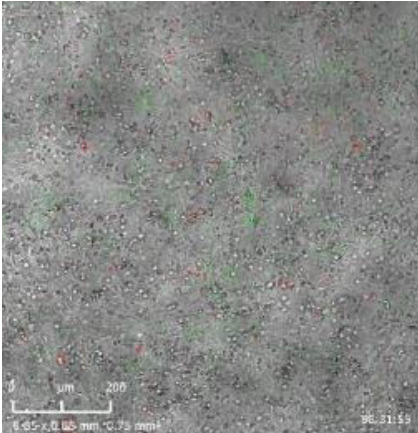
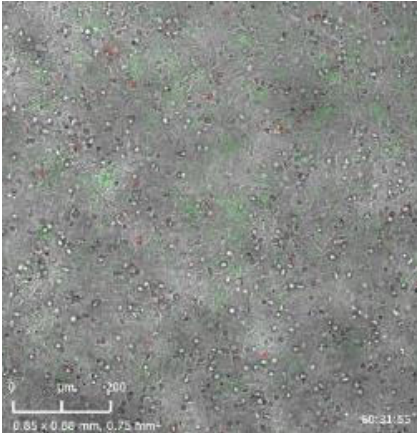
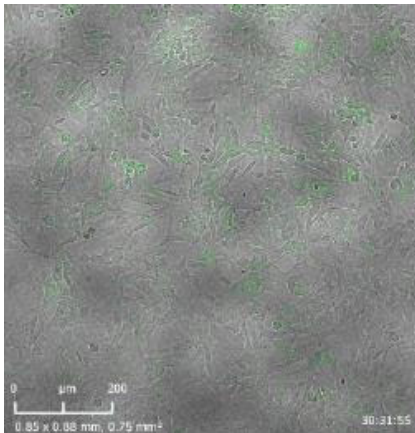
34 hours



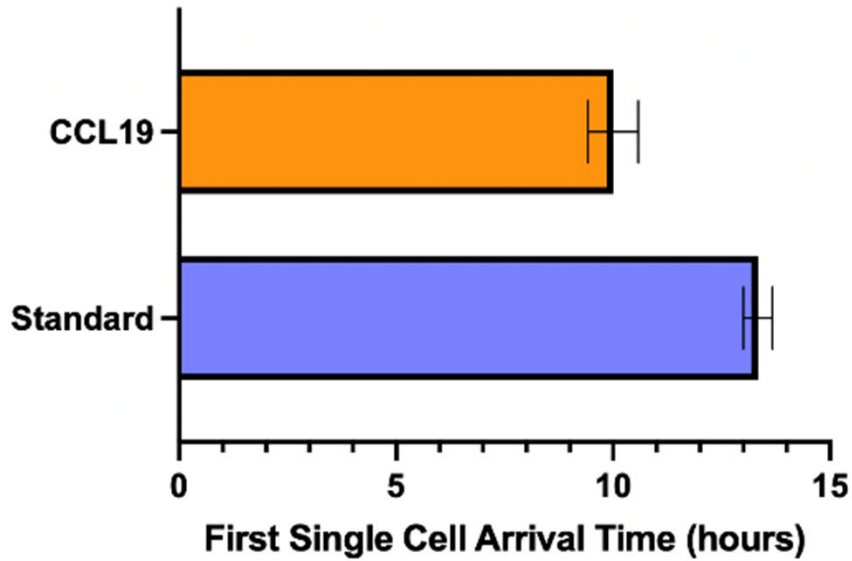
72 hours



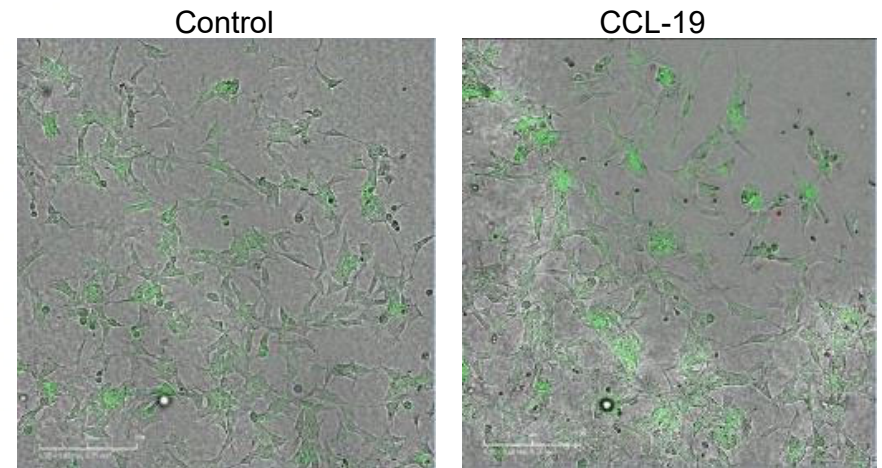
50ul
matrigel
barrier



CCL19 accelerates CAR T cell migration through Matrigel



Standard
CCL19

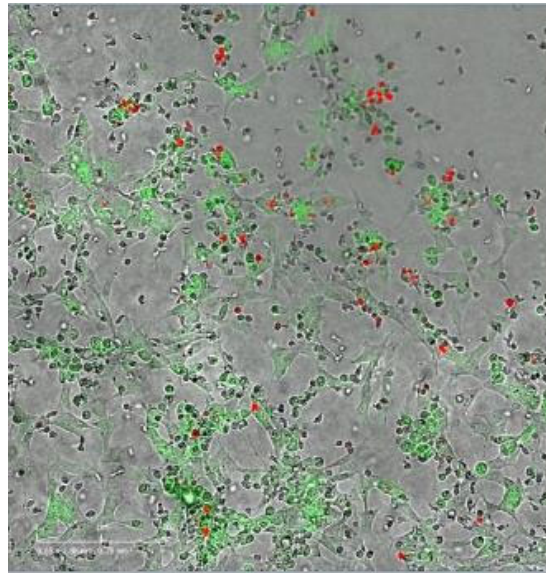


Accelerated by 3 hours

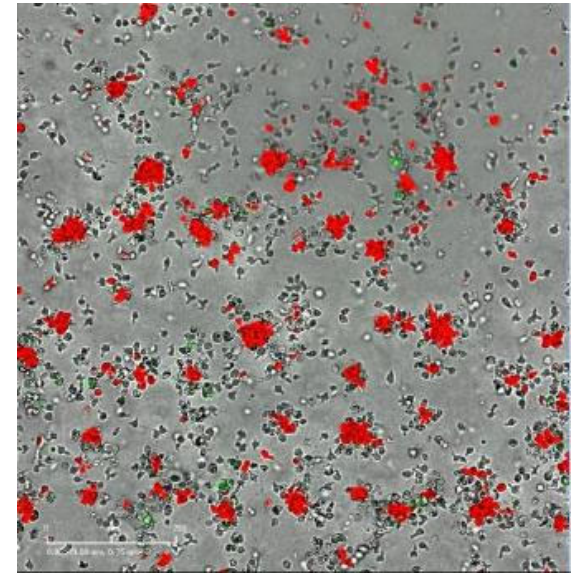
CAR T cells demonstrate cooperative killing in Matrigel co-cultures

SY5Y-CBG-CD19 target cells
CD19-CAR-mCherry

20 hour



94 hour



*CCL19 treated

Thank you!

Pradipta Ghosh, M.D.

Professor of Medicine and Cellular
and Molecular Medicine;
Founding Director, UC San Diego
Institute for Network Medicine

UC San Diego






Decoding Natural Intelligence

UC San Diego

**AGILENT CENTER OF EXCELLENCE
IN CELLULAR INTELLIGENCE**

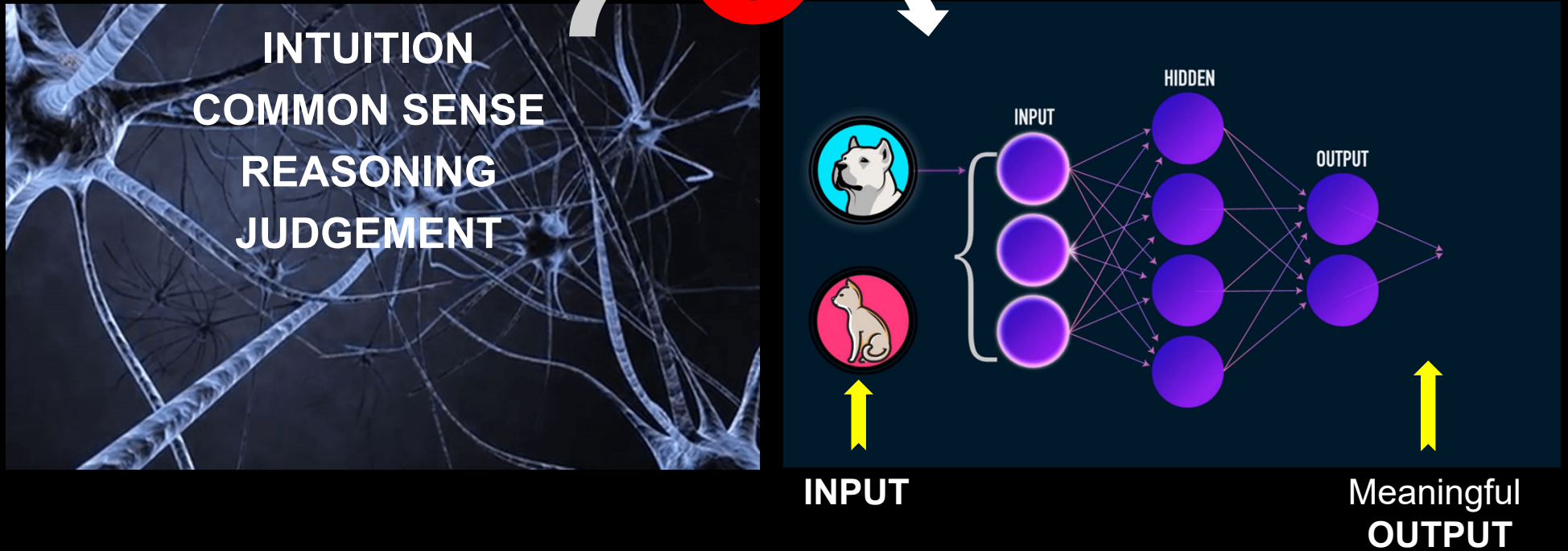


Intelligence = brain

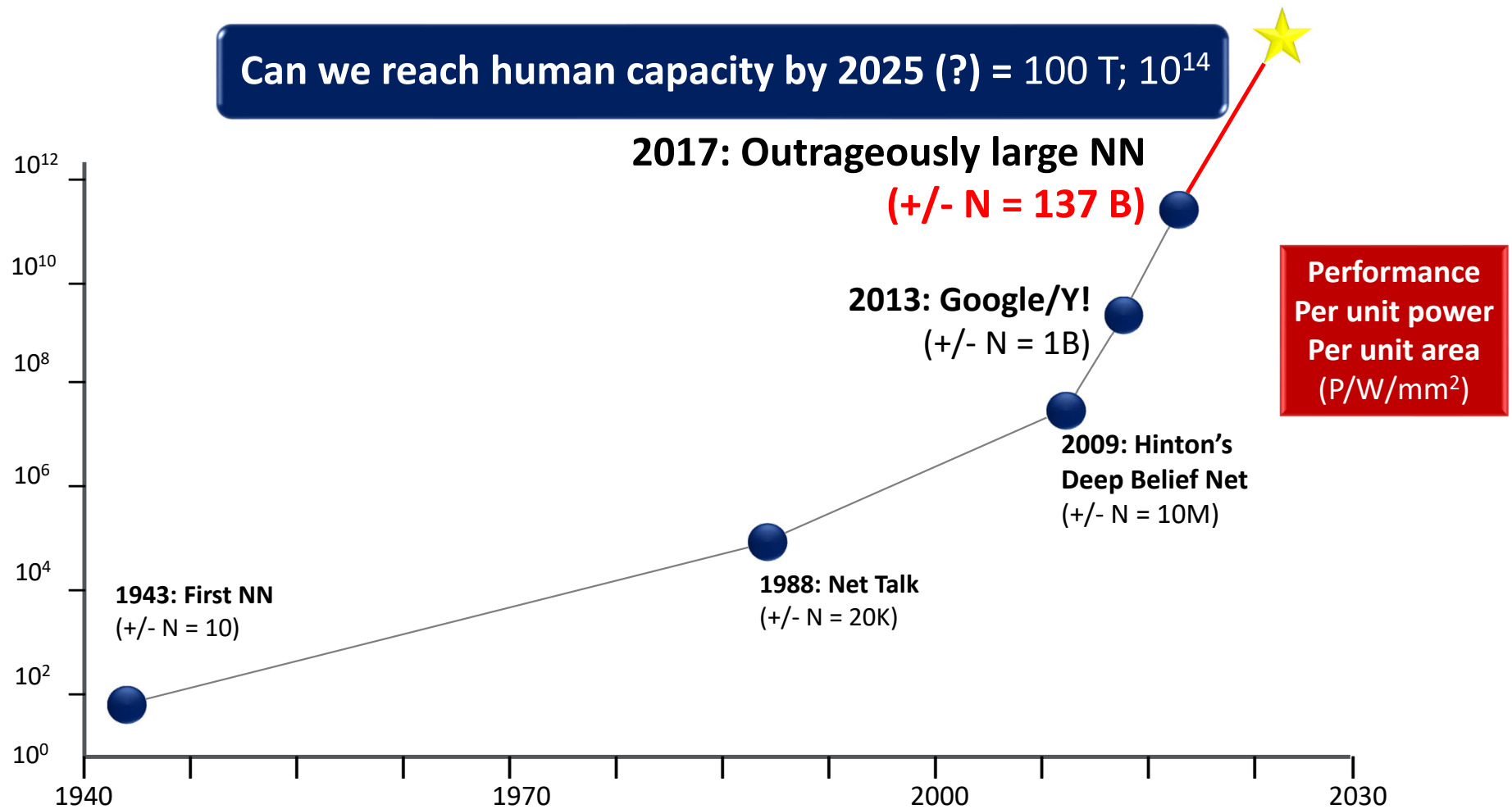


**Let's
emulate
neural
networks**

Bioinspired Artificial Neural Networks (ANN) enable a computer to learn from observational data



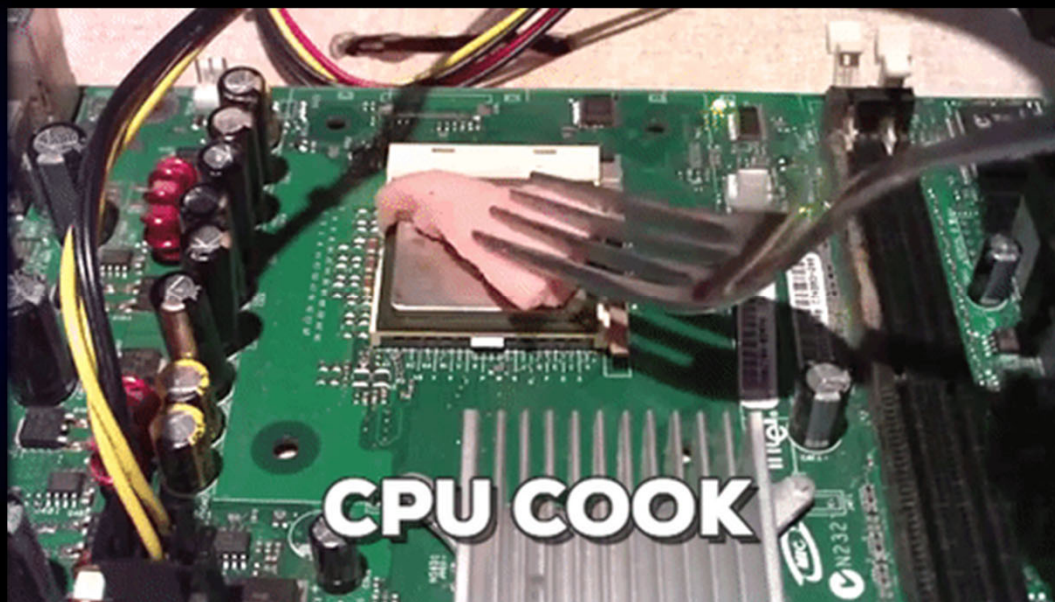
The march of Artificial Neural-Networks has stagnated



~16.3 B = Human Cognition



**~137B = Outrageously large
Neural Networks**



It's not just the number, is it?



Humans
vs
Machines

Intelligence is not the ability to beat you at a game.....

**Hey Siri, can you help
me prepare for this talk?**

...nor is it the ability to understand or speak 20+ languages

“The measure
of intelligence
is the ability
to change.”

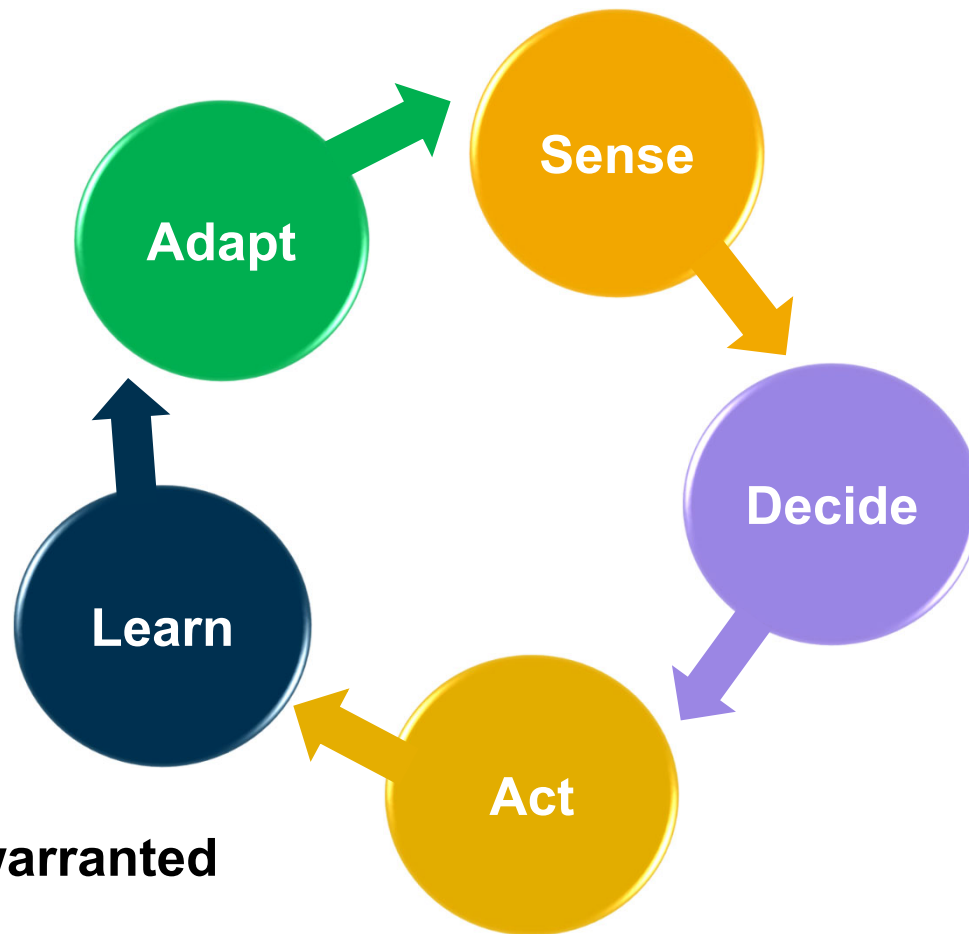
Albert Einstein

in·tel·li·gence

....the ability to acquire and apply
knowledge and skills.

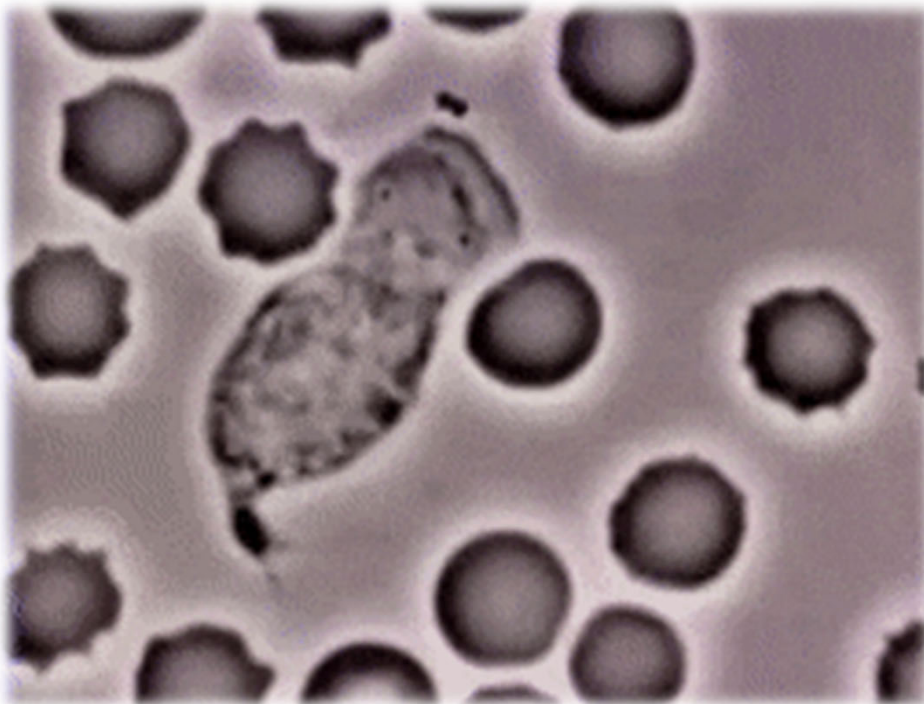


It is the ability to **sense** cues from any environment, **decide**, **act**, and eventually **learn** and **adapt** to it

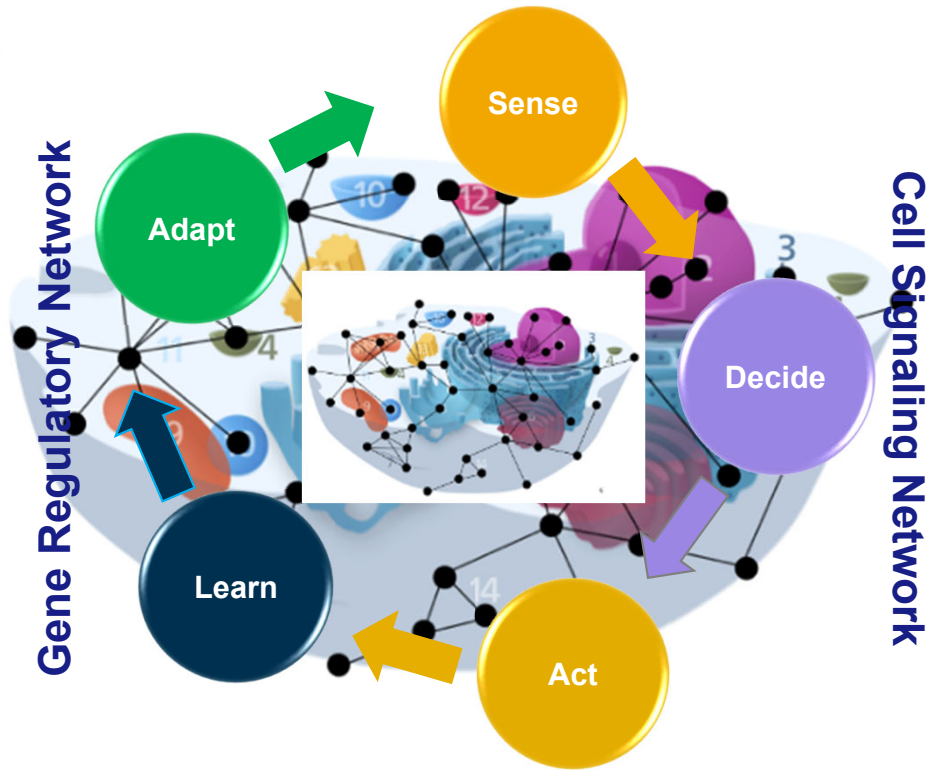


...even modify it if warranted

Cells are the tiniest autonomous units that constantly process data to adapt to any given environment



Movie: A neutrophil chasing bacteria



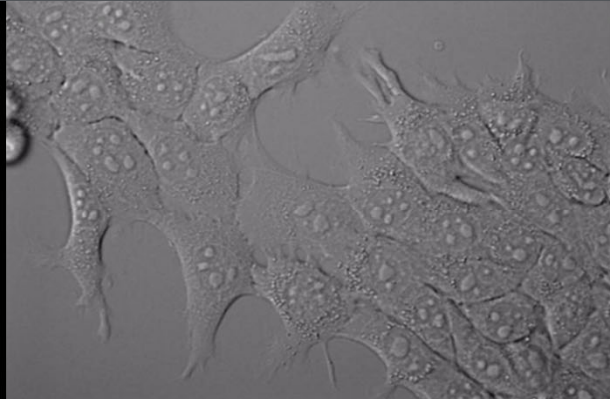
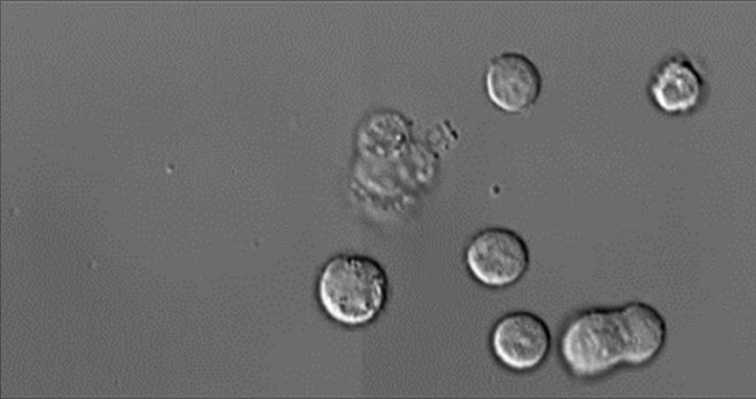
Cells represent the beginning of natural intelligence

MULTIPLY



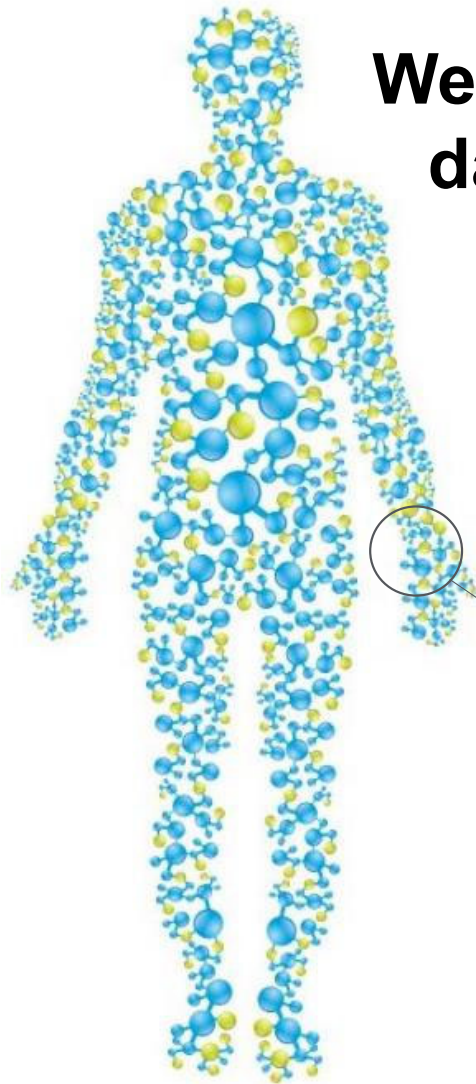
MOVE

DIE



LIVE

We are made up of ~37.2 trillion intelligent data processors, all interconnected for information transfer

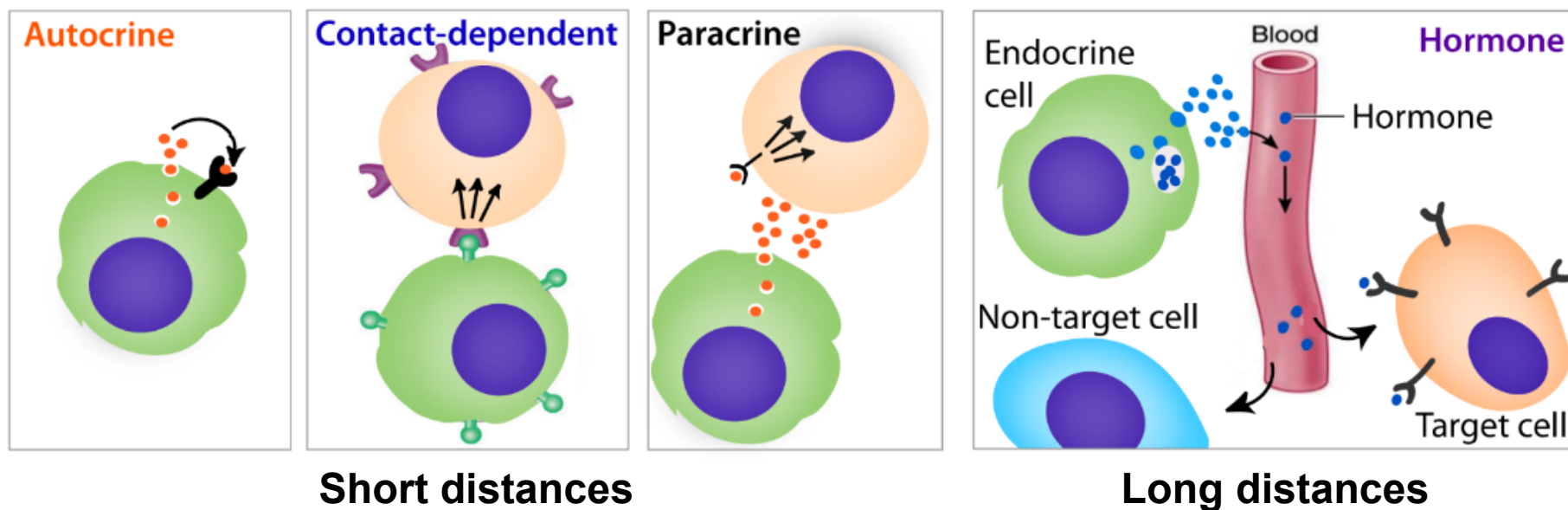


Each cell is
~20 microns dia

18.6 times
around the earth



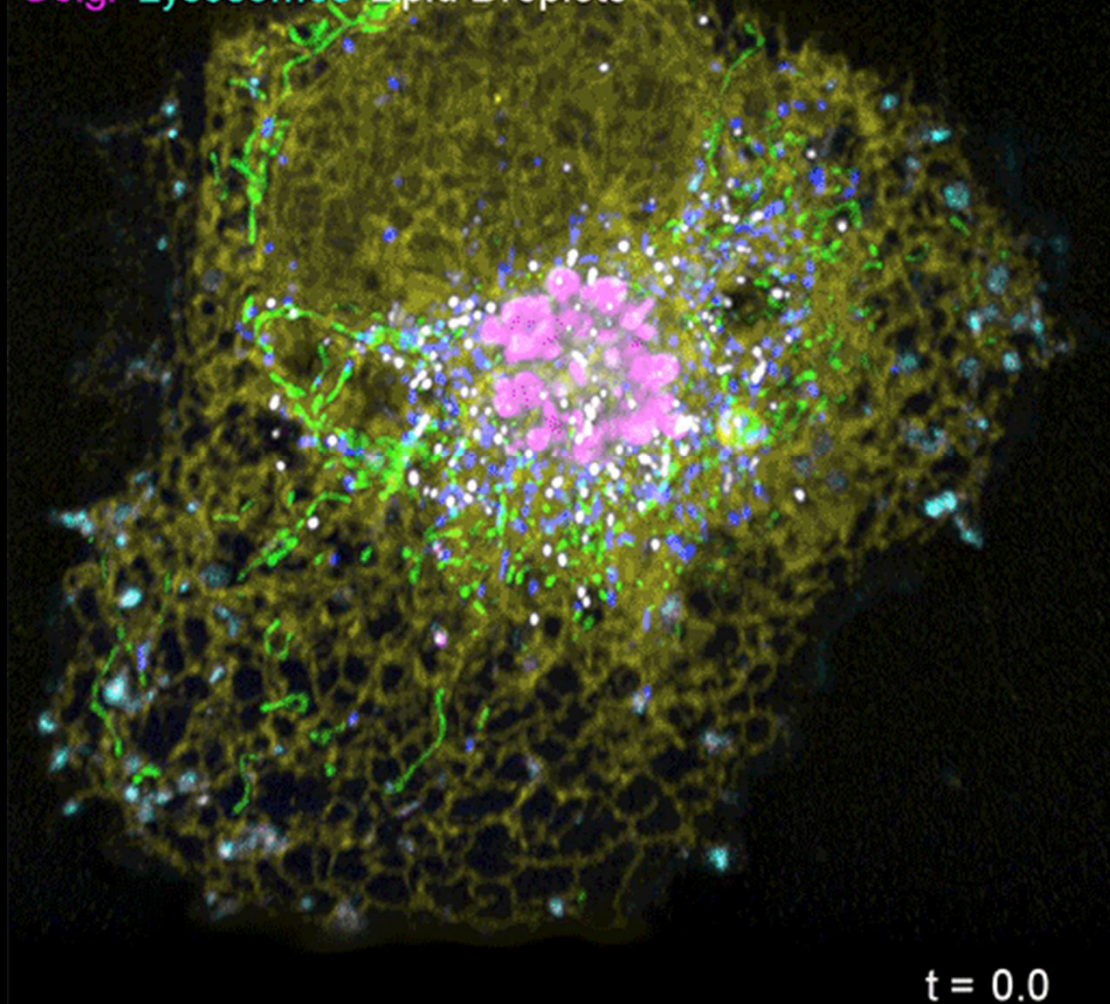
Although we know a lot about how cells communicate with each other...



**...we know very little
about how different
parts within a cell
remain interconnected
for rapid data
processing**

Jennifer Lippincott Schwartz, HHMI
Credit: Sarah Cohen and Alex Valm

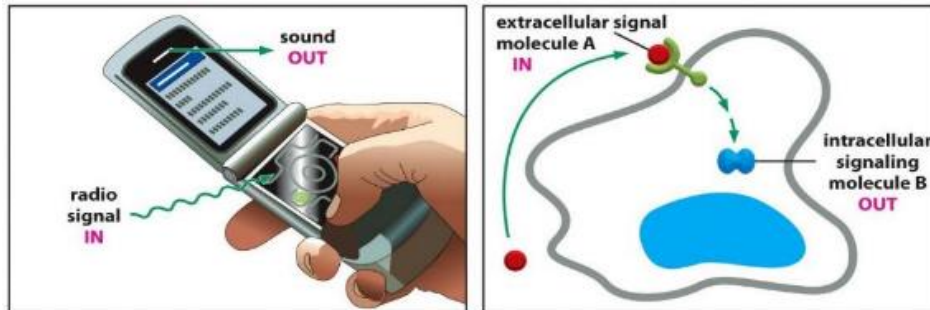
Peroxisomes Mitochondria Endoplasmic Reticulum
Golgi Lysosomes Lipid Droplets



Many analogies have been put forth to describe what the cell's communication grid looks like

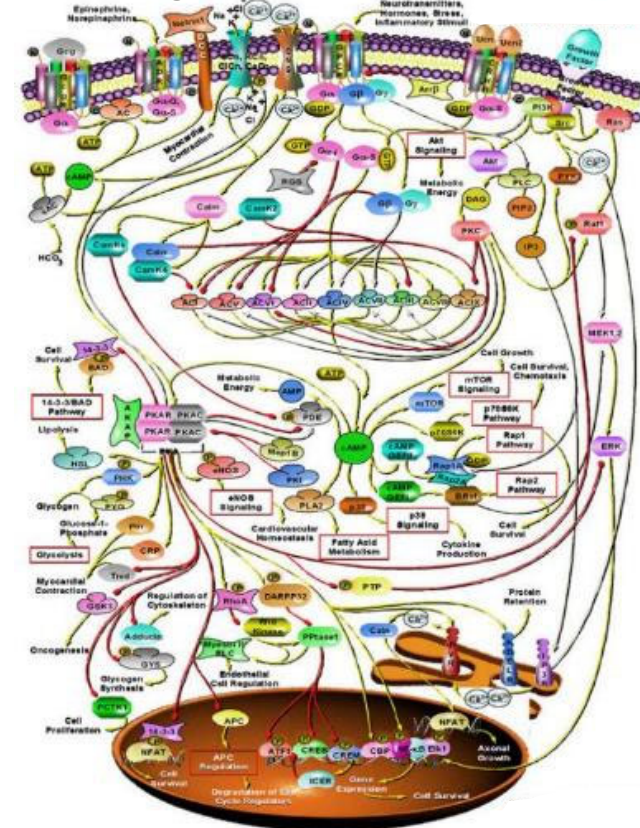
Is it like a phone?

Essentials of Cell Biology; Garland Sciences, 2010

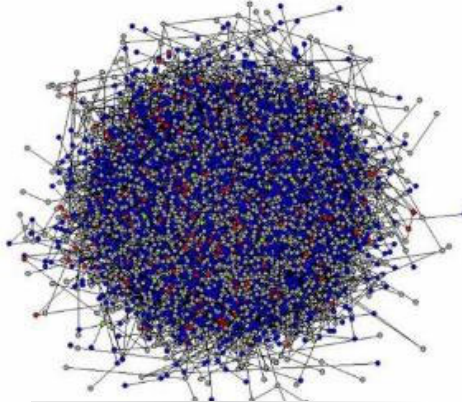


Is it a tangled mess?

e.g., the cAMP pathway



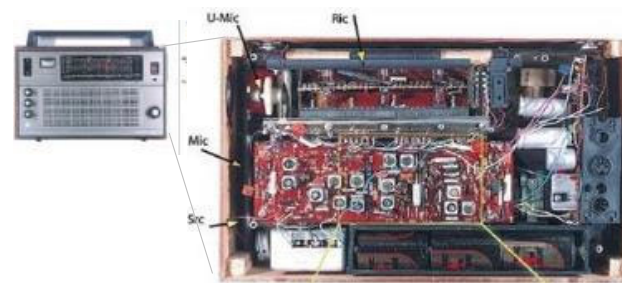
Is it like a cloud?



The Human Protein-protein Interaction network

Is it like a radio?

Lazebnik et al., Cancer Cell 2002



....but we still have no clue how the cell may respond when perturbed



Rewiring of these dynamic networks is the primary reason why a 'cure' has been impossible for so many diseases....

An Inconvenient Truth:

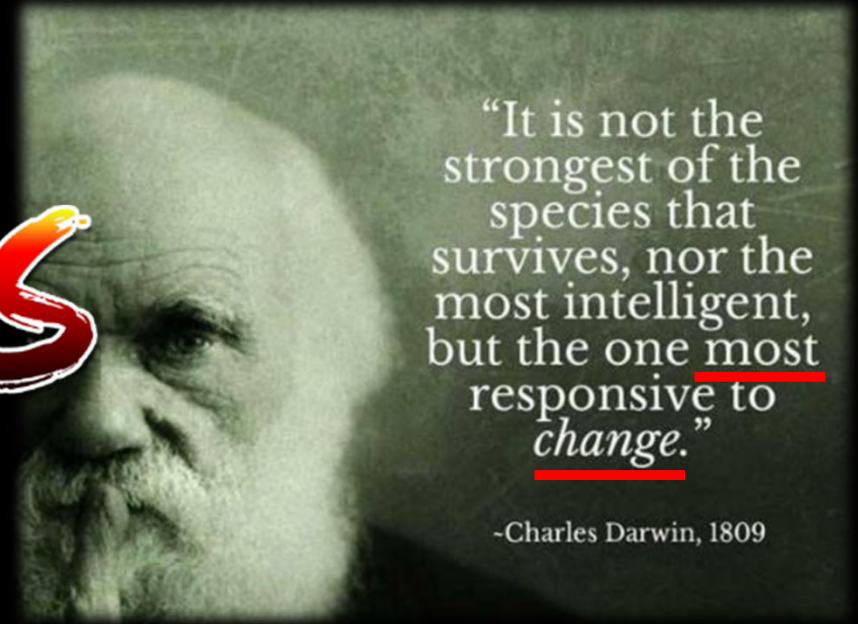
Diseases are unstoppable unless we know what the cell's communication grid looks like, and how it behaves...

Can we cure all diseases
in our children's lifetime?



CHAN ZUCKERBERG |

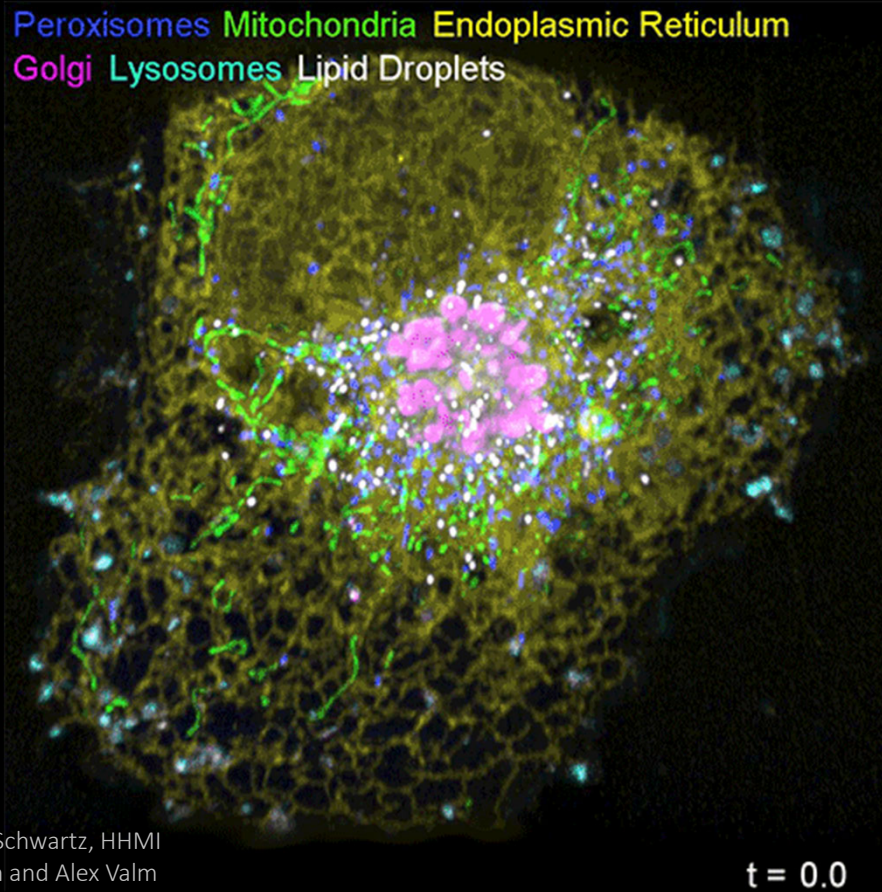
VS



\$\$ + Good Intentions

Darwin's law of evolution

Complex dynamical systems must have architecture, but can operate via simple rules



Rules of life that govern behavior and allow

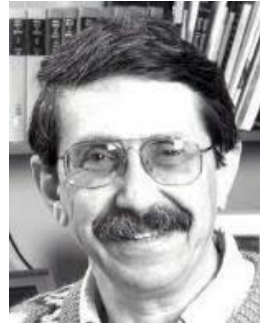
- emergence
- self-organization
- robustness
- flexibility
- vulnerability...

Jennifer Lippincott Schwartz, HHMI
Credit: Sarah Cohen and Alex Valm

Prominent scientists organized to engage in a decade long effort to resolve the network's architecture, behavior and components



Al Gilman



Mel Simon

nature

[Explore content](#) ▾ [About the journal](#) ▾ [Publish with us](#) ▾

[nature](#) > [introduction](#) > article

Introduction | [Published: 12 December 2002](#)

Overview of the Alliance for Cellular Signaling

[Participating investigators and scientists of the Alliance for Cellular Signaling](#)

[Nature](#) 420, 703–706 (2002) | [Cite this article](#)

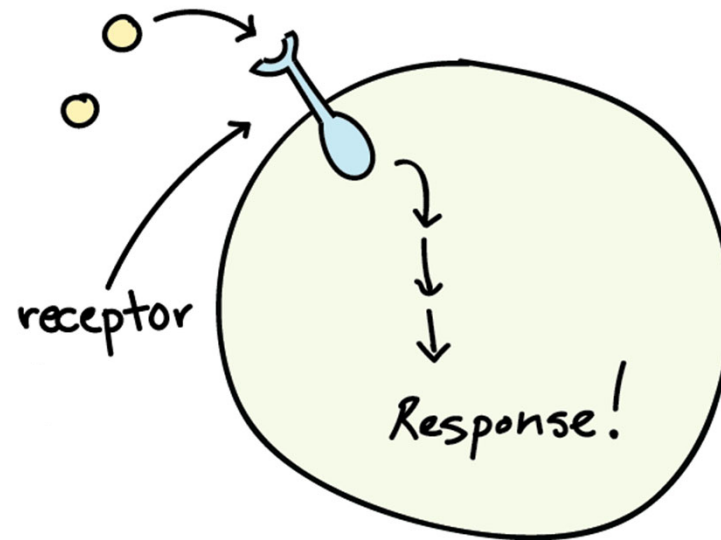
5458 Accesses | 104 Citations | 3 Altmetric | [Metrics](#)

Table 1 Central questions of the AfCS

Question

1. How complex is signal processing in cells ?
2. What is the structure of the whole signaling network?
3. How much does network topology constrain signal processing capability?
4. Can functional modules be abstracted mathematically?
5. What are the dynamics of the signaling network?
6. Why is the network the way it is?

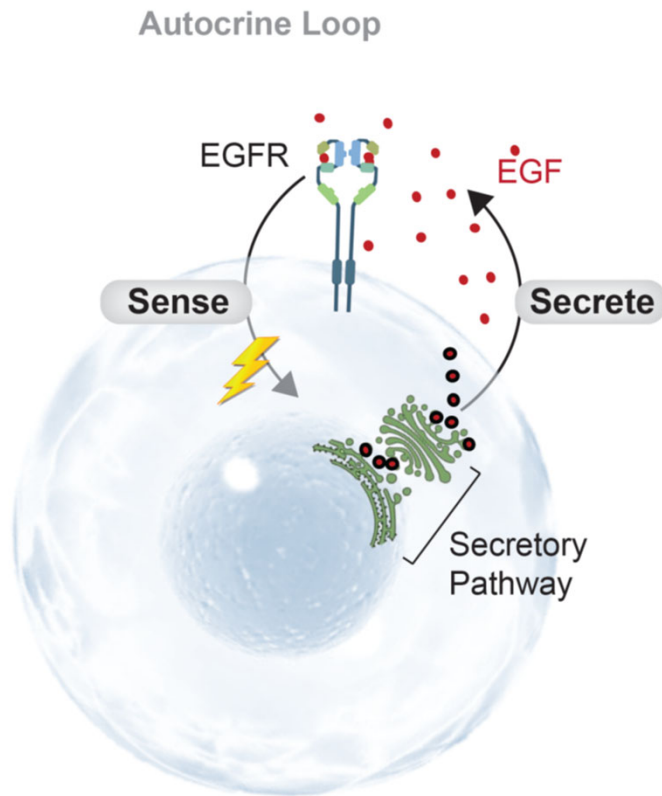
**Although they failed to solve the architecture,
they agree it is not so simple as we draw it today!!!**



**A 'bag of water' model
(likely unreal)**

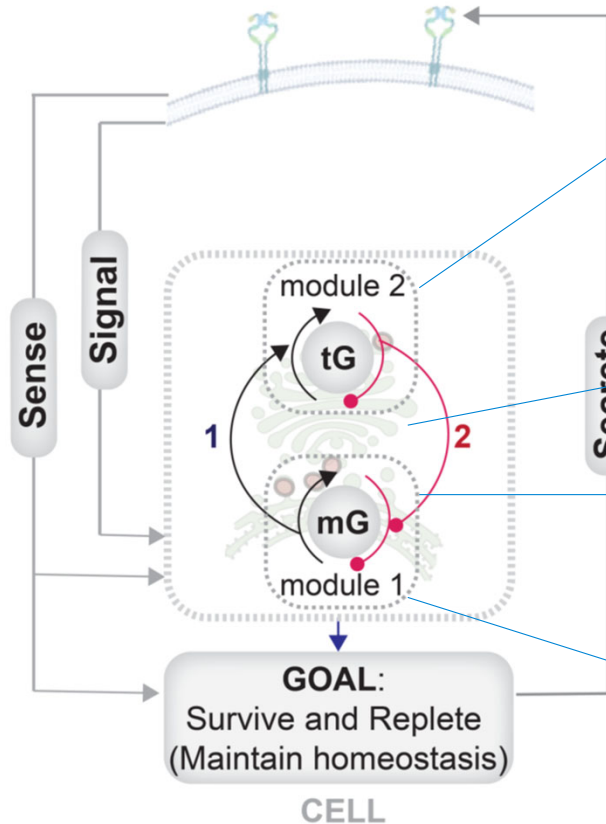
We stumbled upon something unusual.....

Our cells learned how to live amidst scarcity

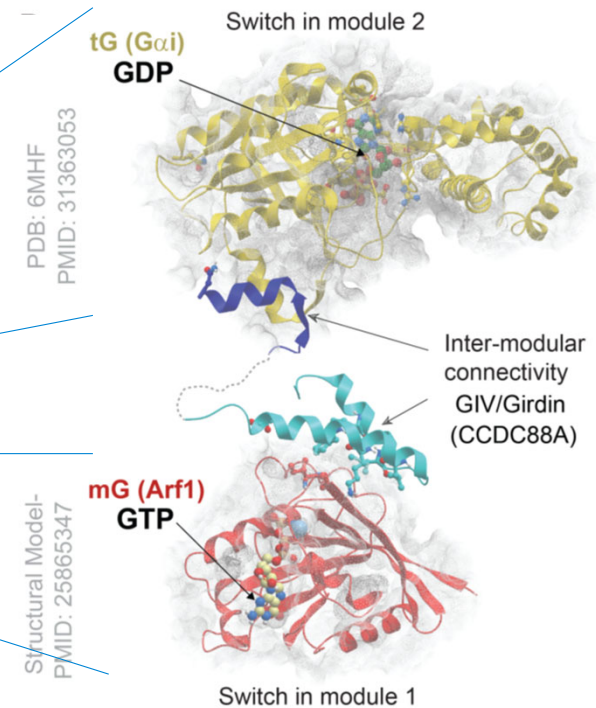


...it began to eat what it killed to live...

EXTRACELLULAR SPACE

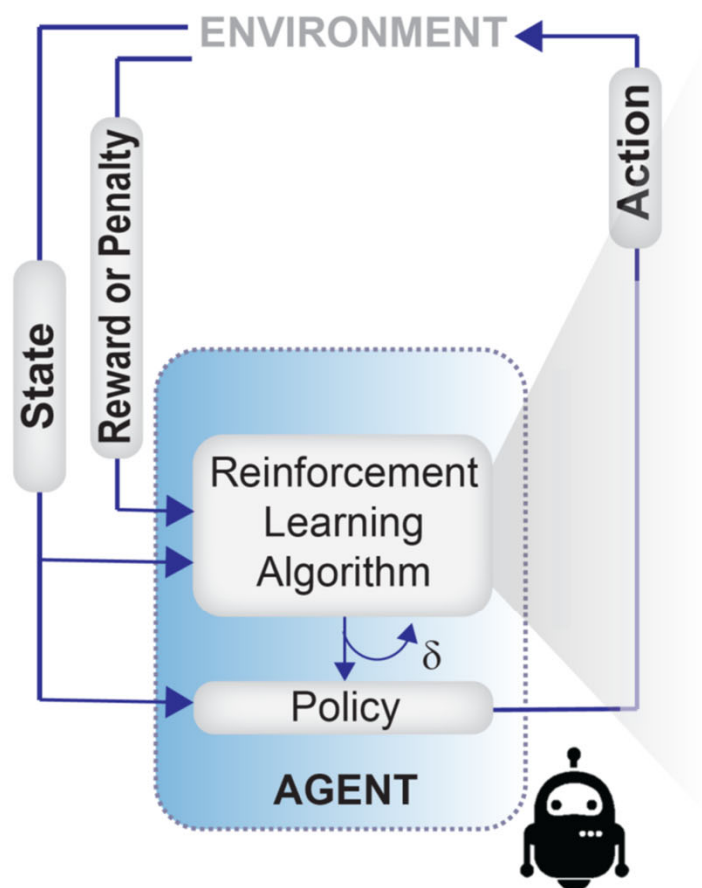


...using a two switch circuitry...



Lo I. et al., Dev Cell 2015
Qiao L and Sinha S et al., Mol Sys Bio, 2023

Reinforcement learning (like ChatGPT)

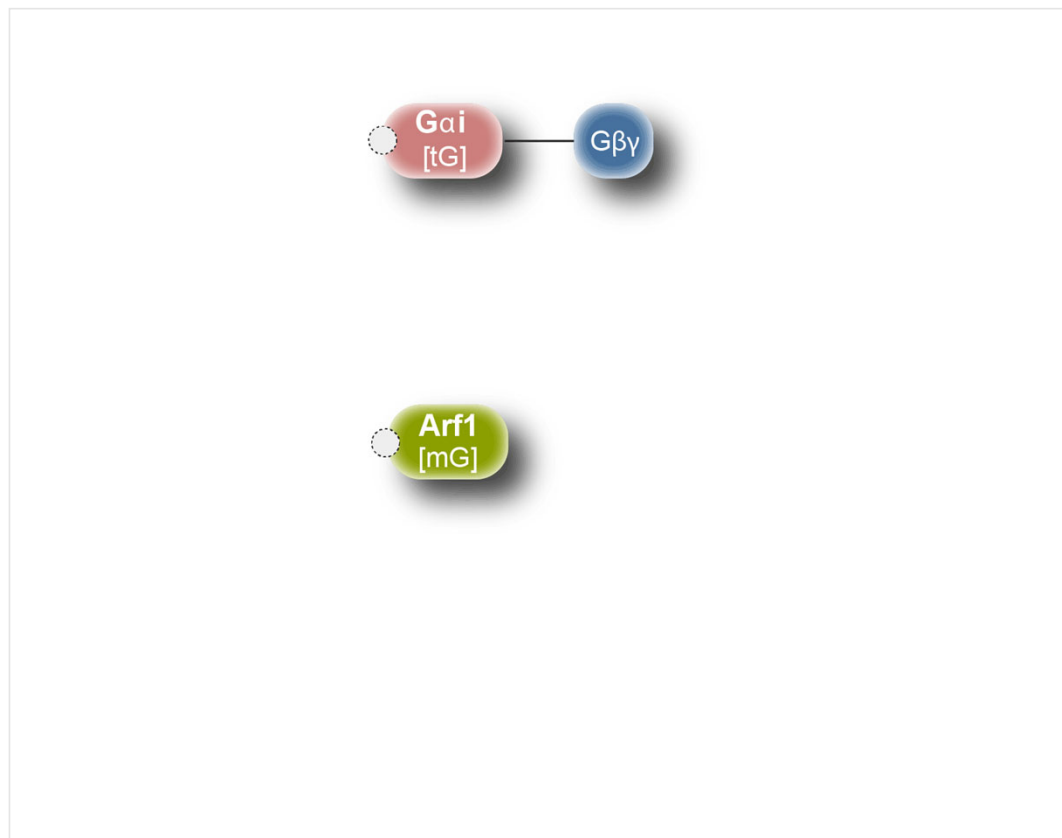


Title

Molecular Circuits of Biological Intelligence

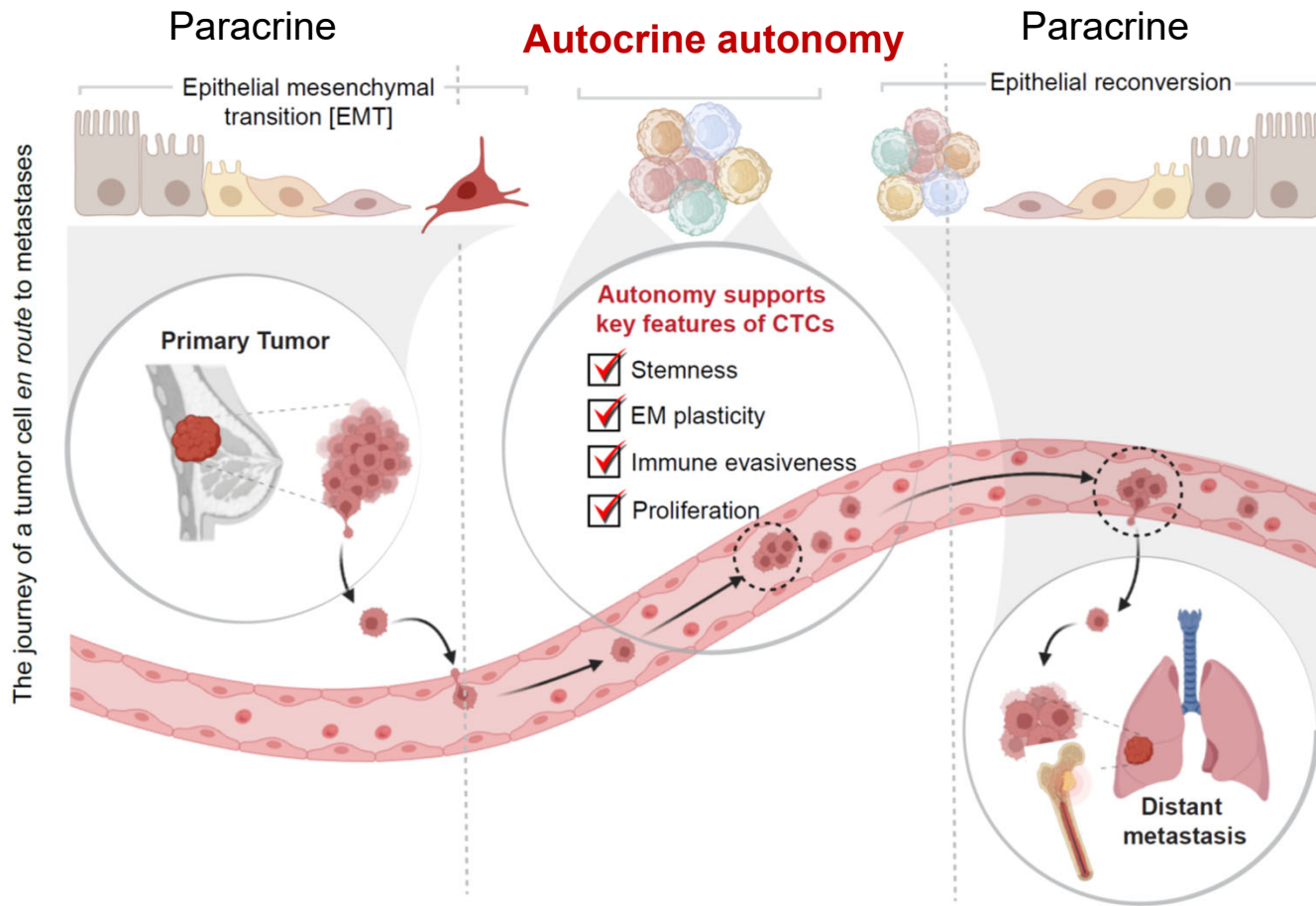
Authorship

Raktim Mukherjee¹, Saptarshi Sinha¹, Gary D. Luker^{3,4,5,6}, Pradipta Ghosh^{1,2}



Mukherjee R et al., Trends in Biochemical Sciences, 2024; PMID: 38341333

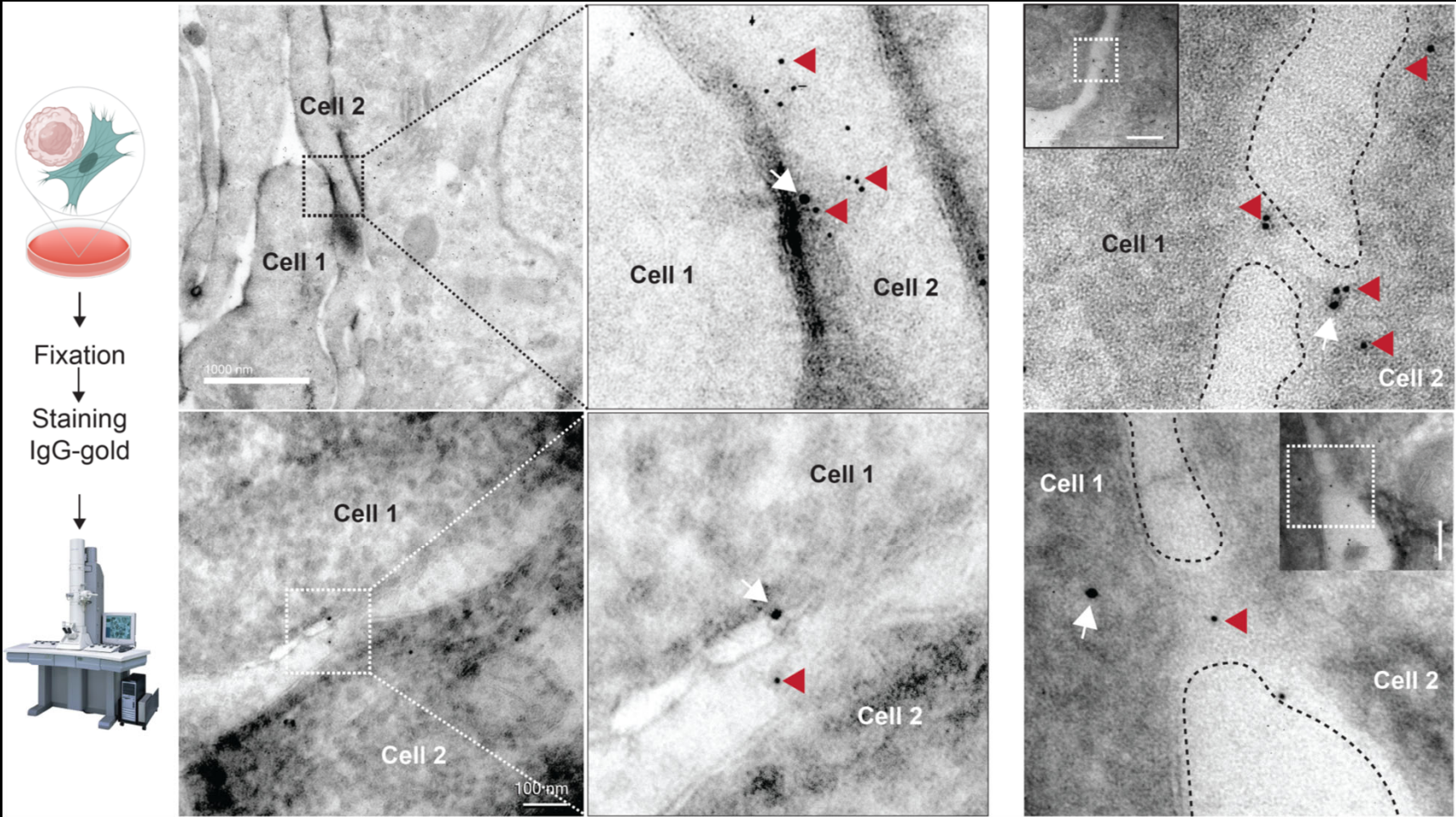
Tumor cells that could turn on their **'learning'** mode were the ones that efficiently seeded metastases



Sinha et al., PNAS nexus 2024; PMID: 38312224

Smuggling components of the 'learning' circuit through tunnels preceded tumor relapse

Sinha S., et al., 2024; PMID: 36993616



~ - # B a f i D < f n f n ; †

. E C C 2 . S # S E
: C C E Y % S 2

Institute for
Network
Medicine

vn+nl1.jfl.nl.#



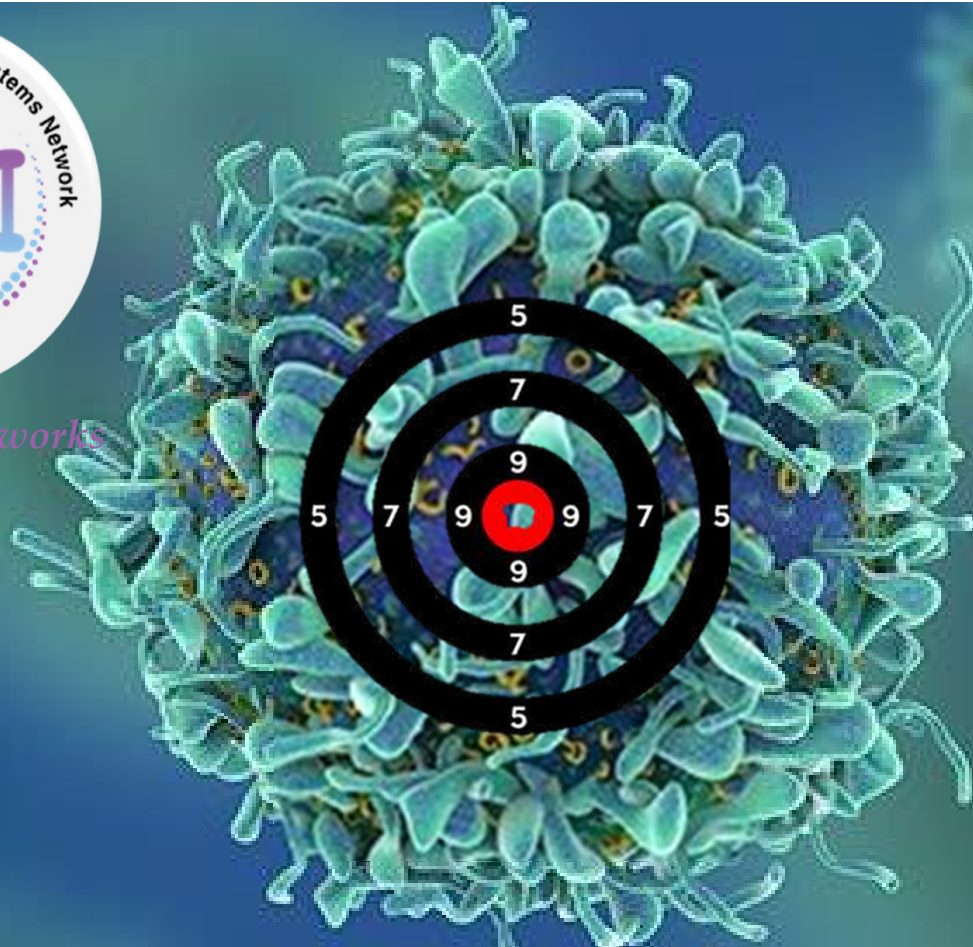
Actionable Networks



Pre-clinical human models



Cellular circuits and networks

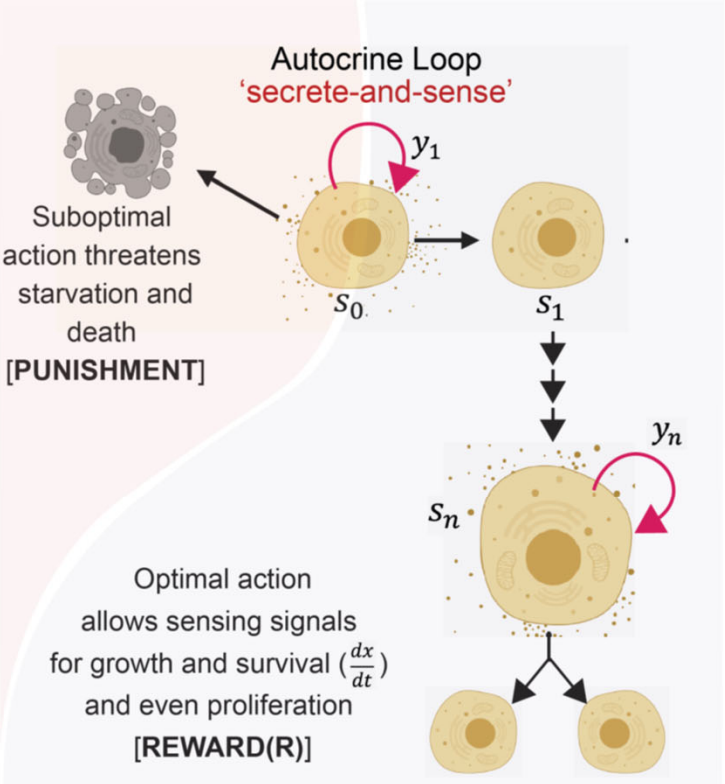


Actionable Networks

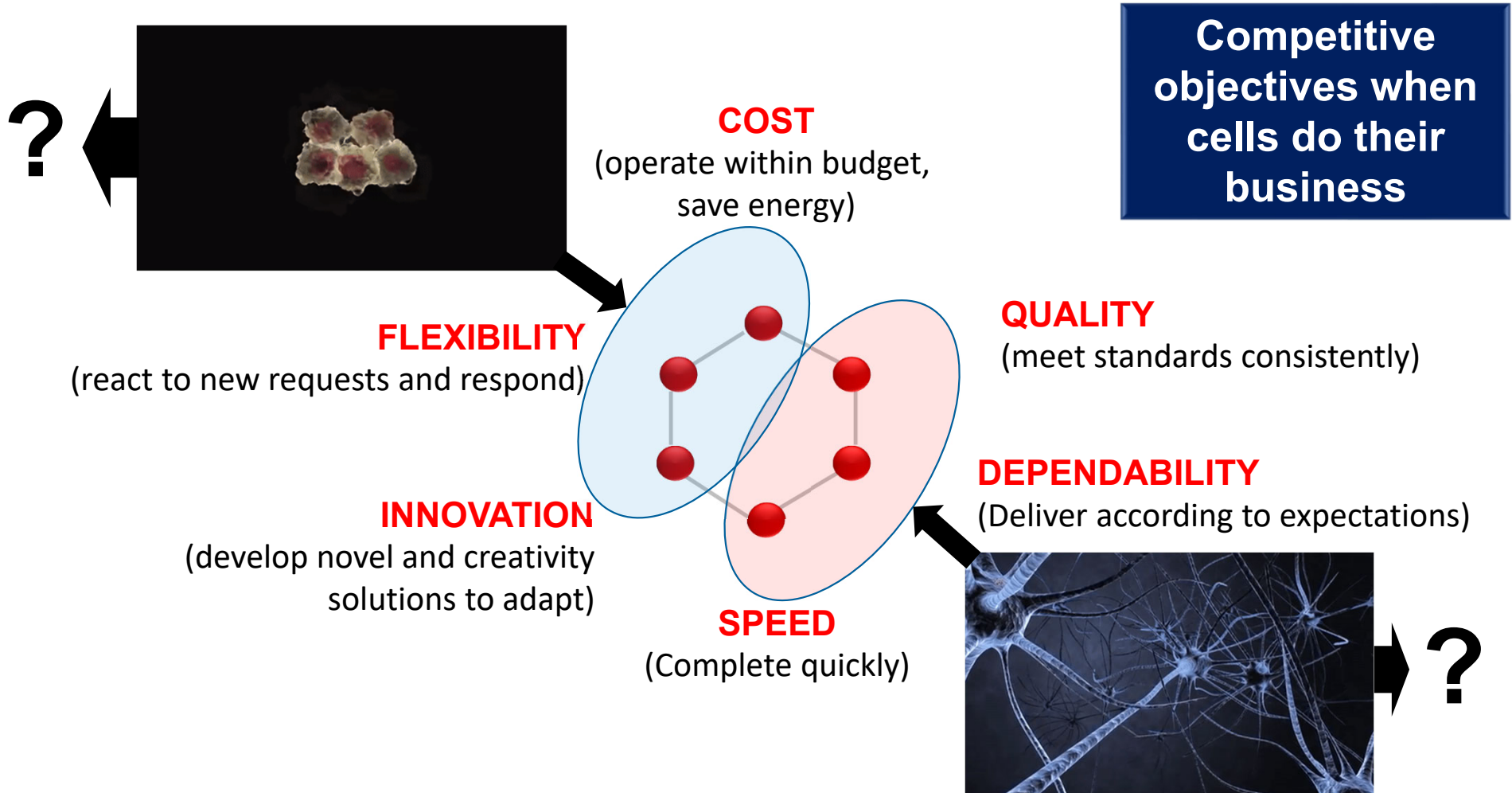
Pre-clinical human models

Precision medicine can be achieved if we can decode cellular intelligence

AI could borrow emergent properties of biological intelligence that have been perfected under evolutionary pressure over billions of years



What kind of network behavior do we care to tweak?



~ - # B a f i D < f n f n ; †

. E C C 2 S # S E #
: C C E Y % S 2

Institute for
Network
Medicine

vnt.nl · jfl.nl · #



Actionable Networks



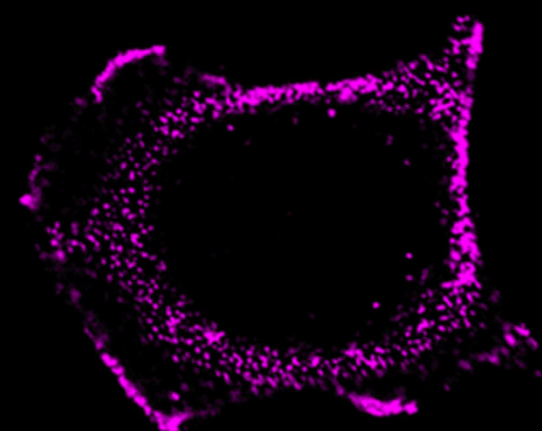
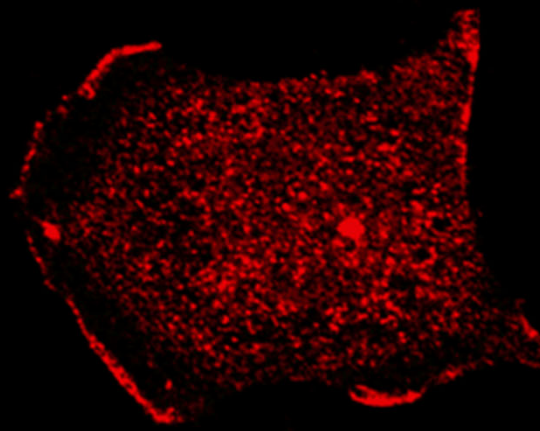
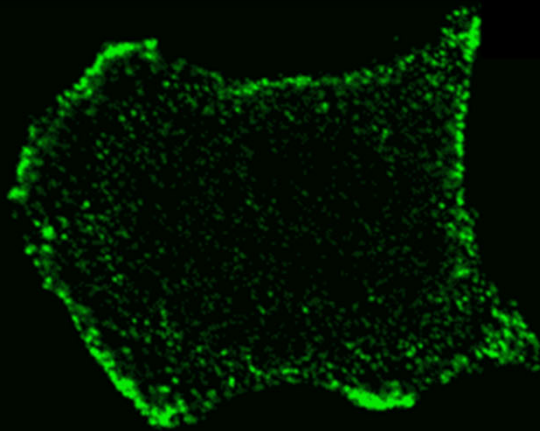
Pre-clinical human models



Measure across scales



Cellular circuits and networks



Lab Website

Ghoshlab.ucsd.edu

Institute for Network Medicine

iNetMed.ucsd.edu

Thank you

UC San Diego

**AGILENT CENTER OF EXCELLENCE
IN CELLULAR INTELLIGENCE**

Todd Christian

Vice President and General Manager,
Cell Analysis Division, Agilent



Technology and Solutions

Agilent provides the technology and solutions researchers need throughout the cancer continuum

UNCOVER

How cancer cells behave and avoid the immune system

DISCOVER

The genetic changes which drive cancer

TRANSLATE

Advance your discoveries from basic to clinical research

ENABLE

The diagnosis with trusted pathology solutions

DELIVER

Precision diagnostics to guide therapeutic decision making

FIGHT

Drive cutting edge molecular and cellular therapies





EVERY DAY COUNTS

Every day Agilent strives to bring forward the moment when cancer can be overcome by providing the solutions and tools scientific and medical professionals need to take time back from cancer and give it to the people who need it most of all.

Q&A



Todd Christian

Vice President and
General Manager,
Cell Analysis Division,
Agilent



Roddy O'Connor

BSc, MS, Ph.D., Research
Assistant Professor of Pathology
and Laboratory Medicine,
Perelman School of Medicine,
University of Pennsylvania



Pradipta Gosh

M.D., Professor,
Medicine and Cellular
and Molecular Medicine,
UC San Diego



Agilent

Trusted Answers