Lecture 5 – Engineering cell signaling responses

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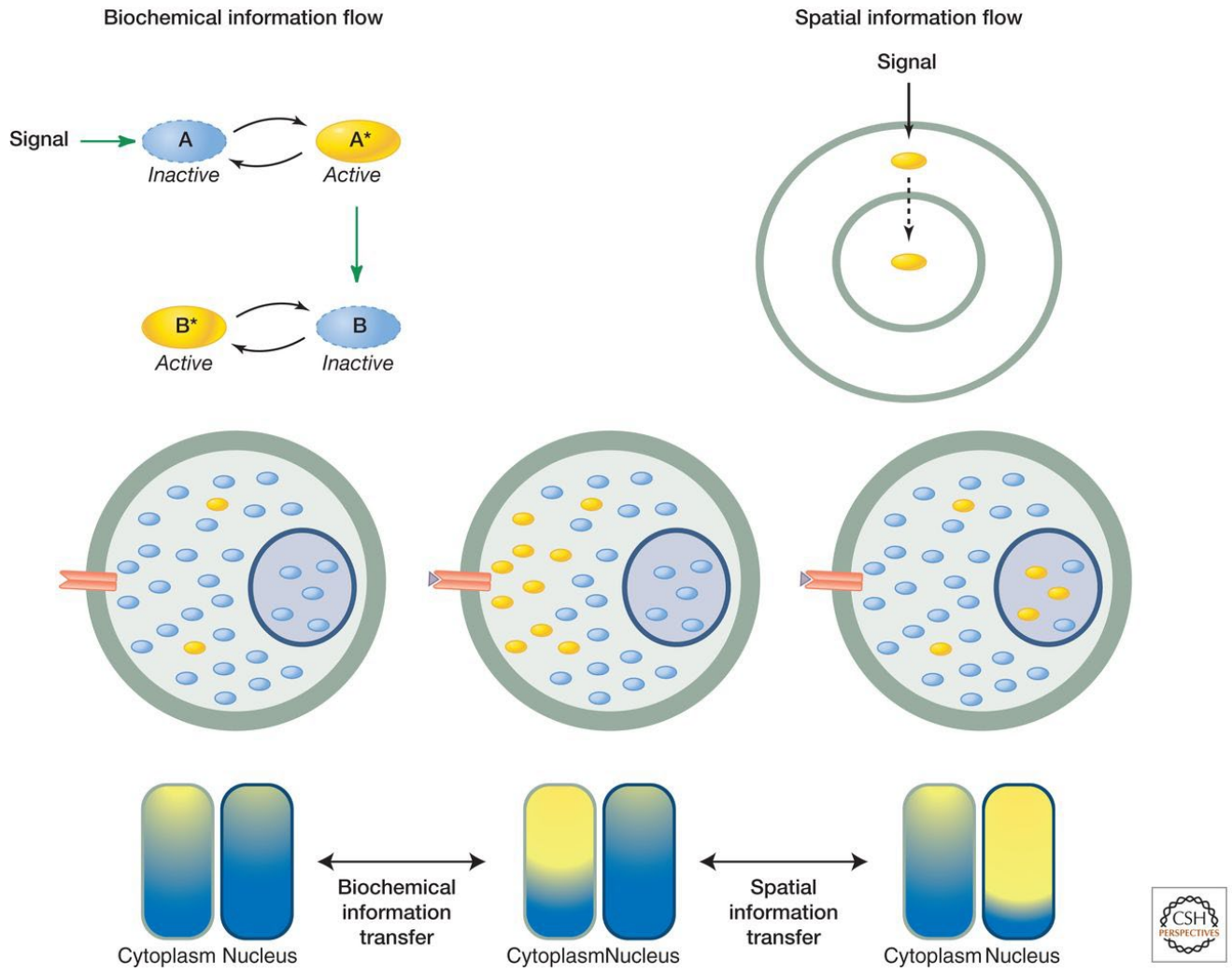
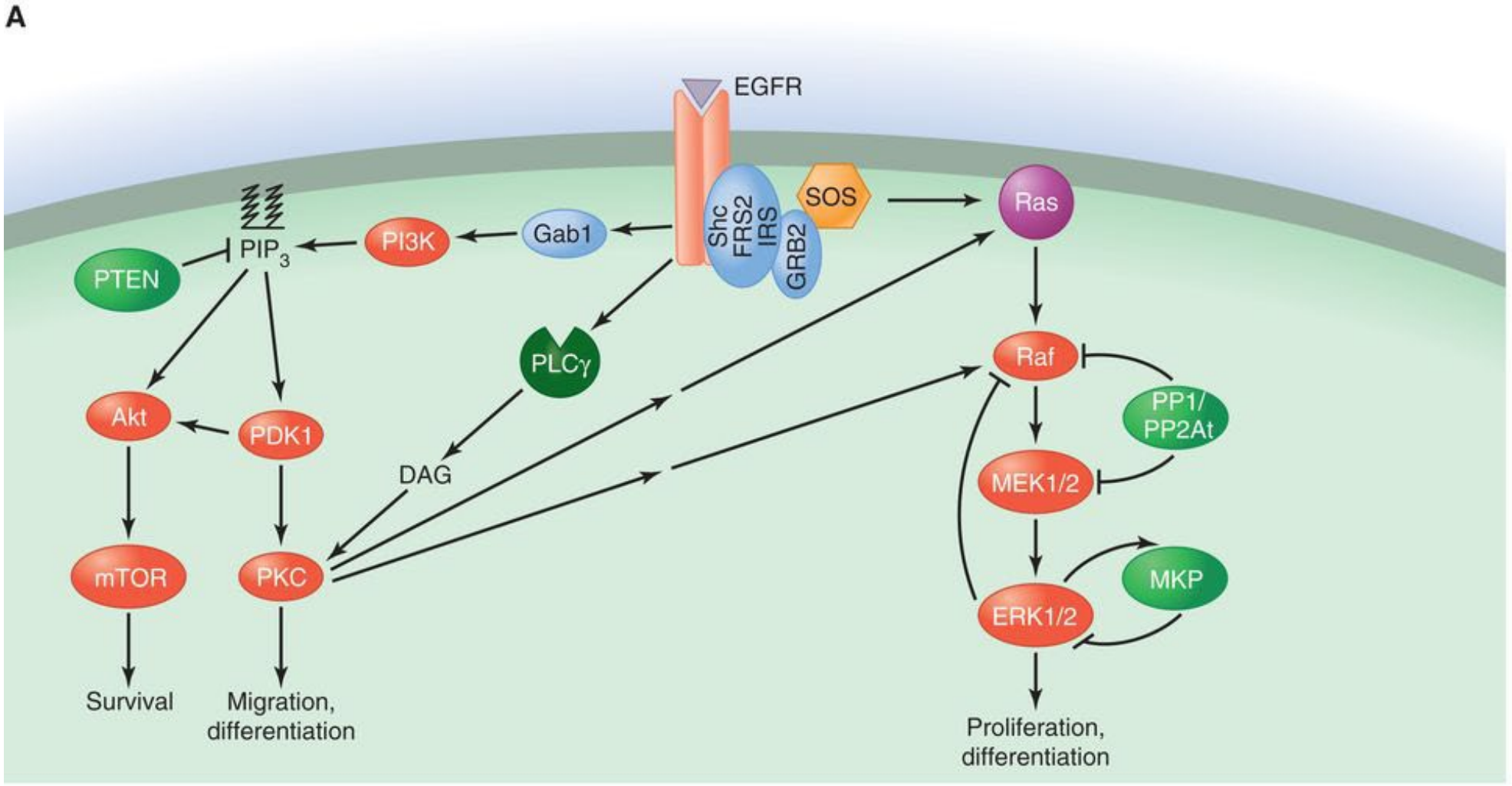
Information flow in cell signaling pathways



Evren U. Azeloglu, and Ravi Iyengar Cold Spring Harb Perspect Biol 2015;7:a005934

Interaction of multiple components with receptors leads to signal flow within multiple signaling pathways.



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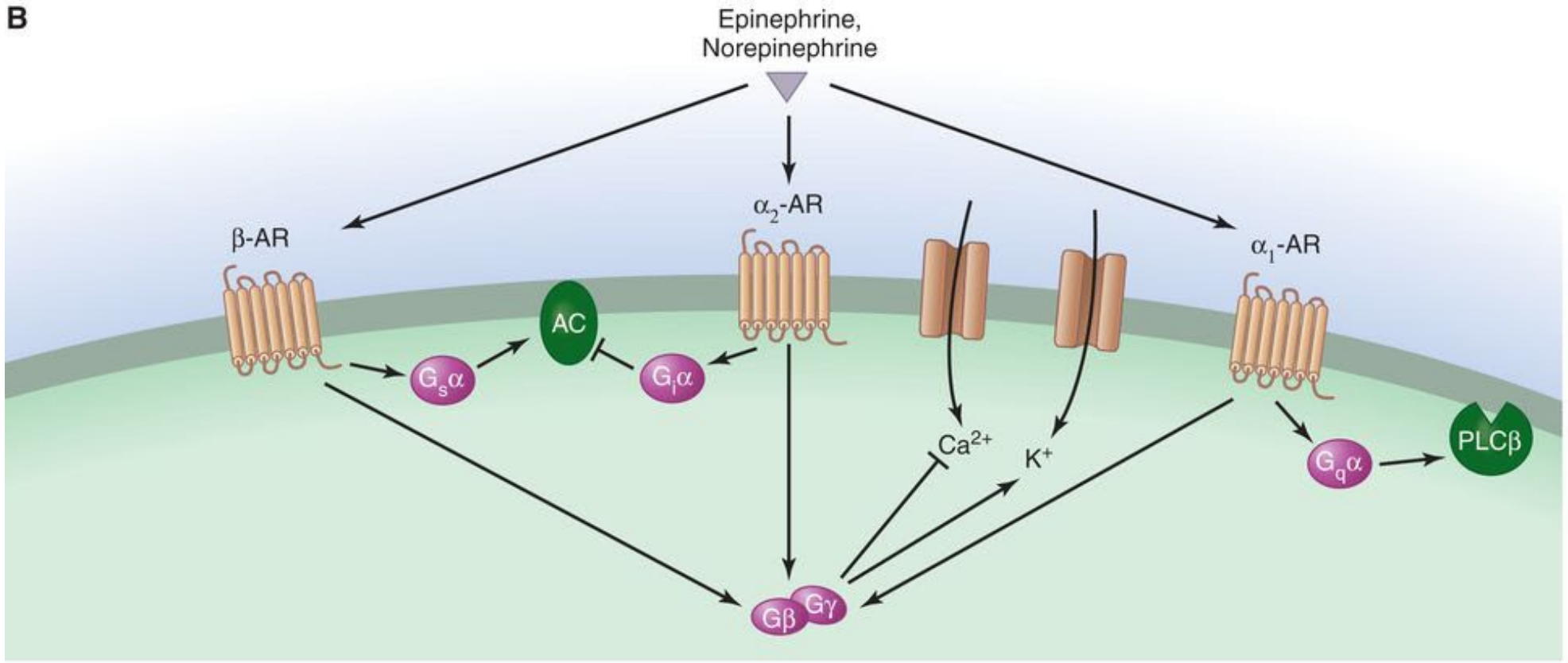
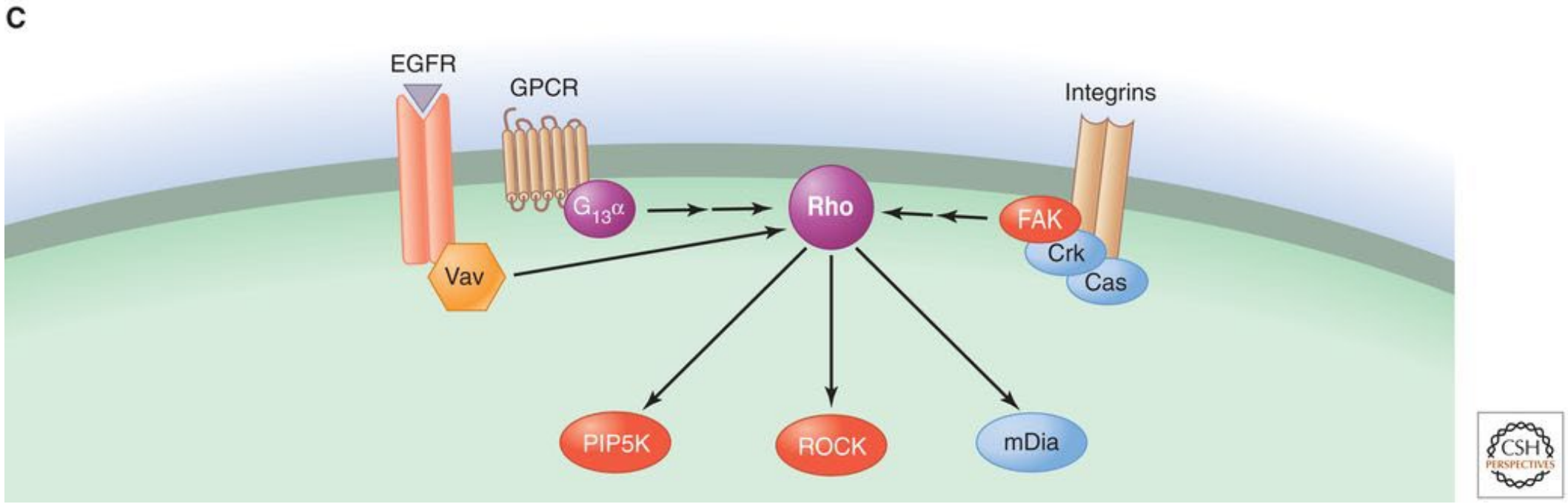


Evren U. Azeloglu, and Ravi Iyengar Cold Spring Harb Perspect Biol 2015;7:a005934

Interaction of multiple components with receptors leads to signal flow within multiple signaling pathways.



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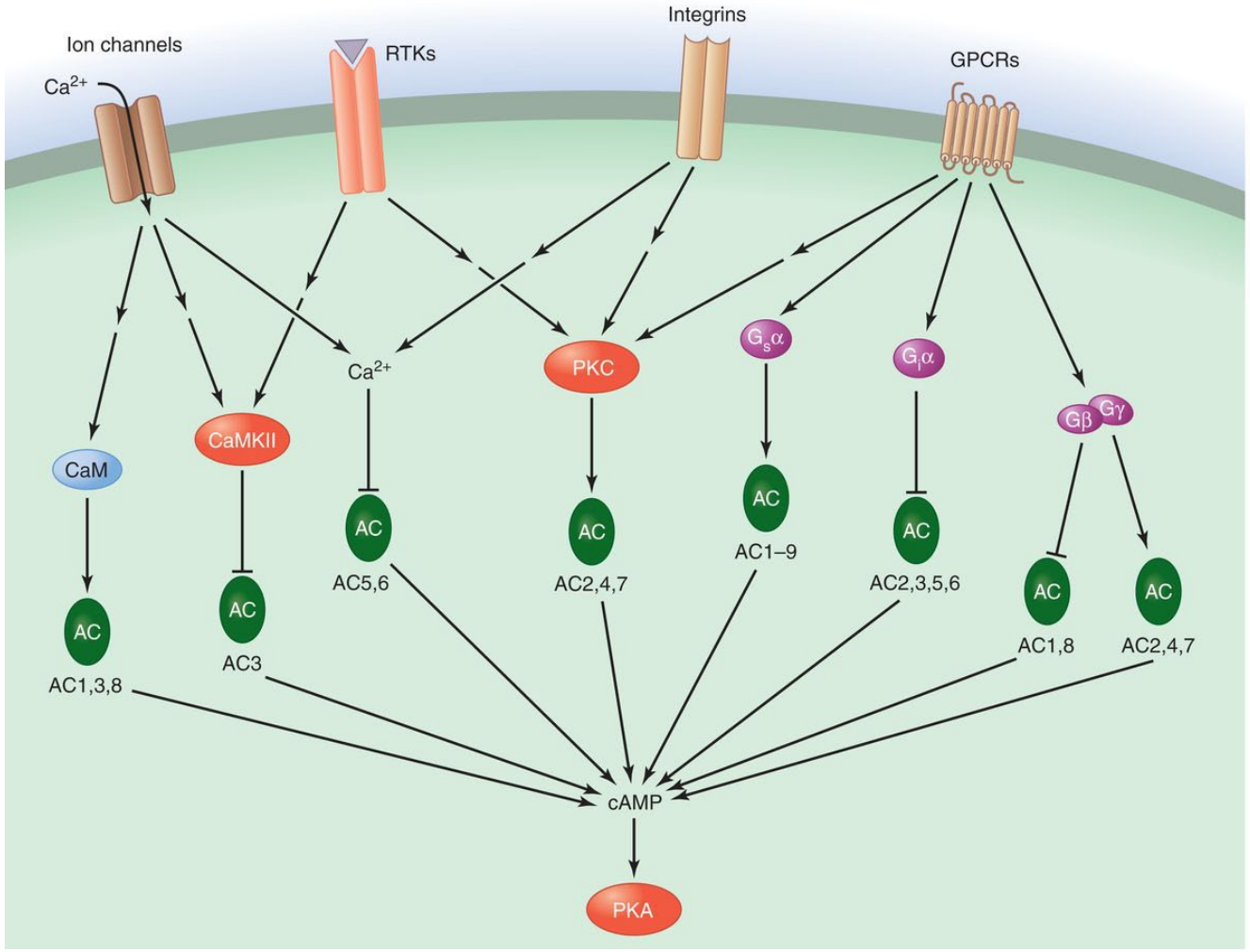
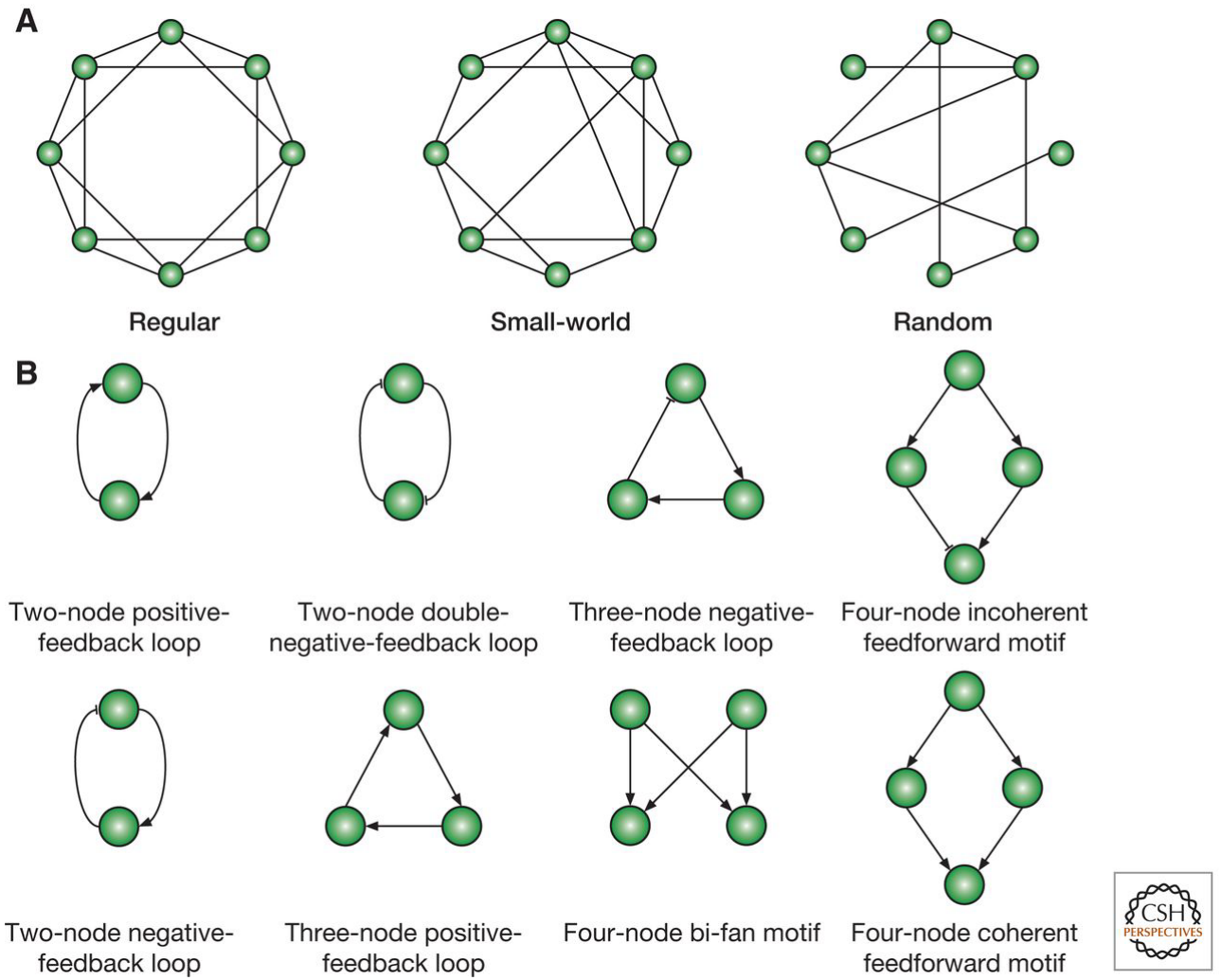
Different adenylyl cyclase (AC) isoforms are activated by multiple different upstream signals.



Evren U. Azeloglu, and Ravi Iyengar Cold Spring Harb Perspect Biol 2015;7:a005934

Network Models

Network Motifs



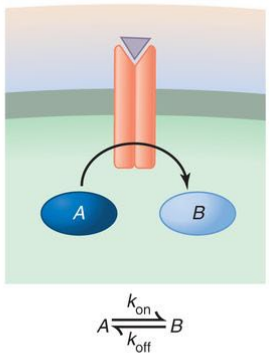
Evren U. Azeloglu, and Ravi Iyengar Cold Spring Harb Perspect Biol 2015;7:a005934

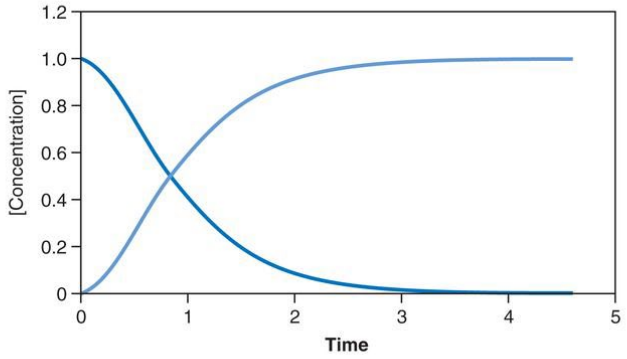
Dynamical Models

Ordinary differential equations (ODEs)

$$\frac{dA}{dt} = k_{off}[B] - k_{on}[A]$$

$$\frac{dB}{dt} = k_{on}[A] - k_{off}[B]$$

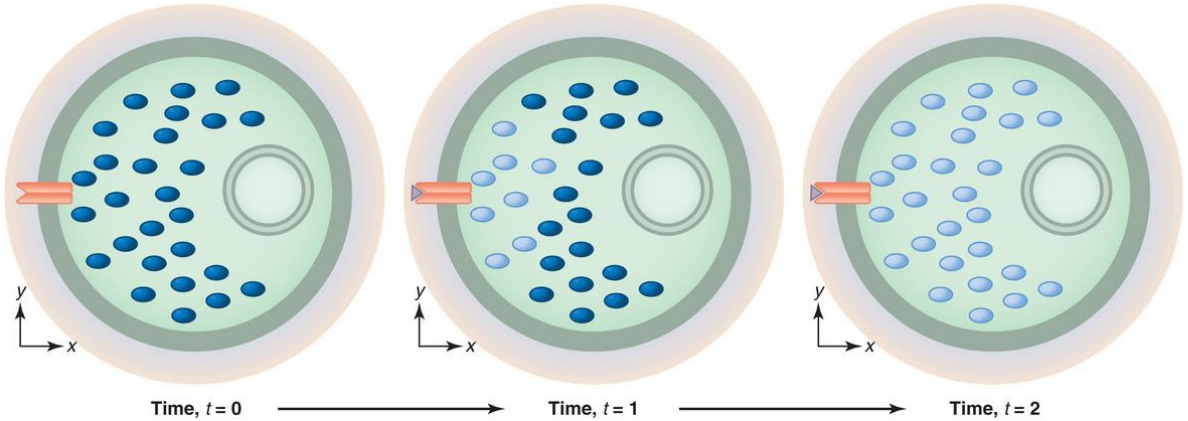




Partial differential equations (PDEs)

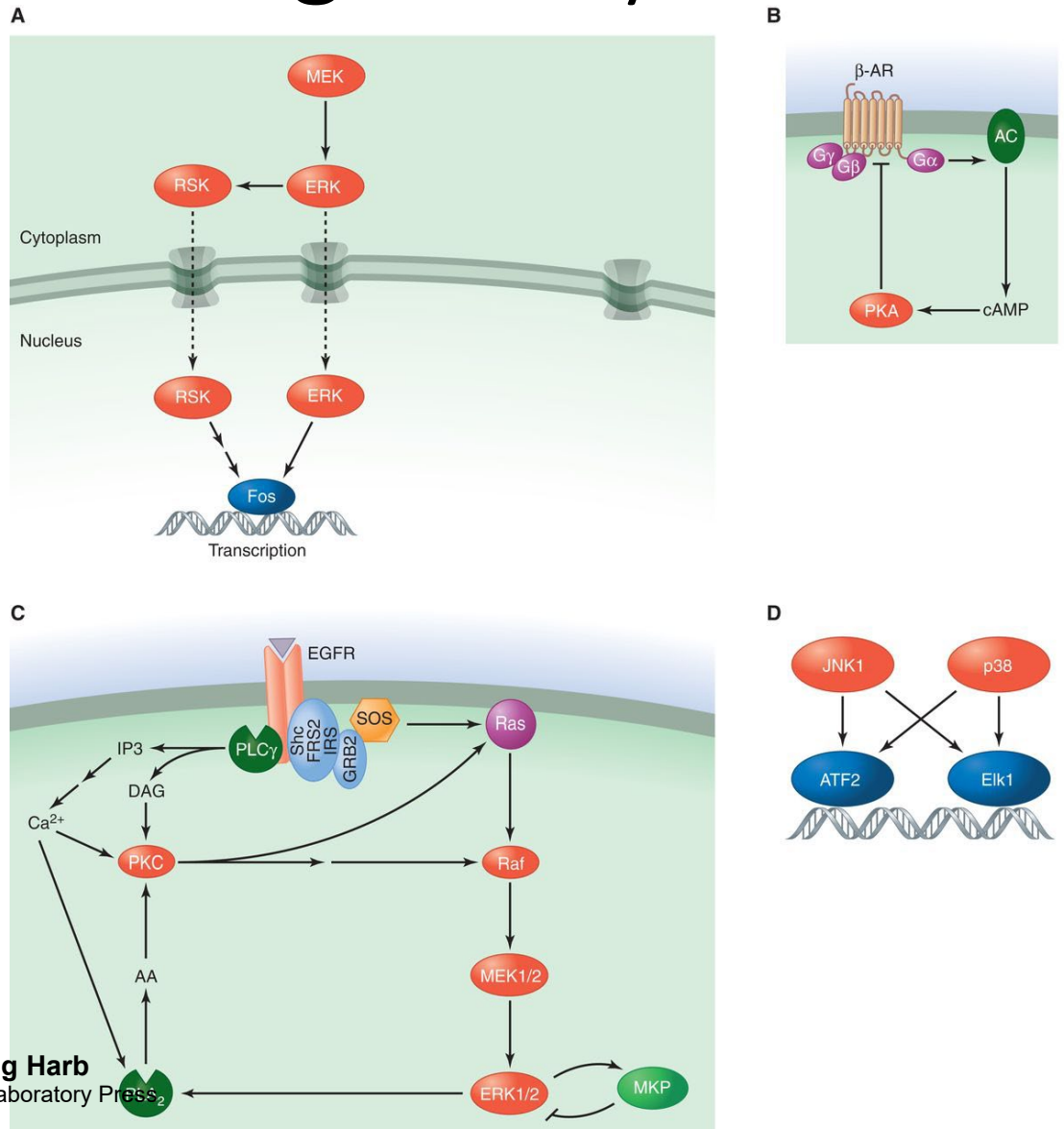
$$\frac{\partial A}{\partial t} = D_A\left(\frac{\partial^2 A}{\partial x^2} + \frac{\partial^2 A}{\partial y^2}\right) - k_{on}[A] + k_{off}[B]$$

$$\frac{\partial B}{\partial t} = D_B\left(\frac{\partial^2 B}{\partial x^2} + \frac{\partial^2 B}{\partial y^2}\right) - k_{off}[B] + k_{on}[A]$$



Evren U. Azeloglu, and Ravi Iyengar Cold Spring Harb Perspect Biol 2015;7:a005934

Regulatory motifs



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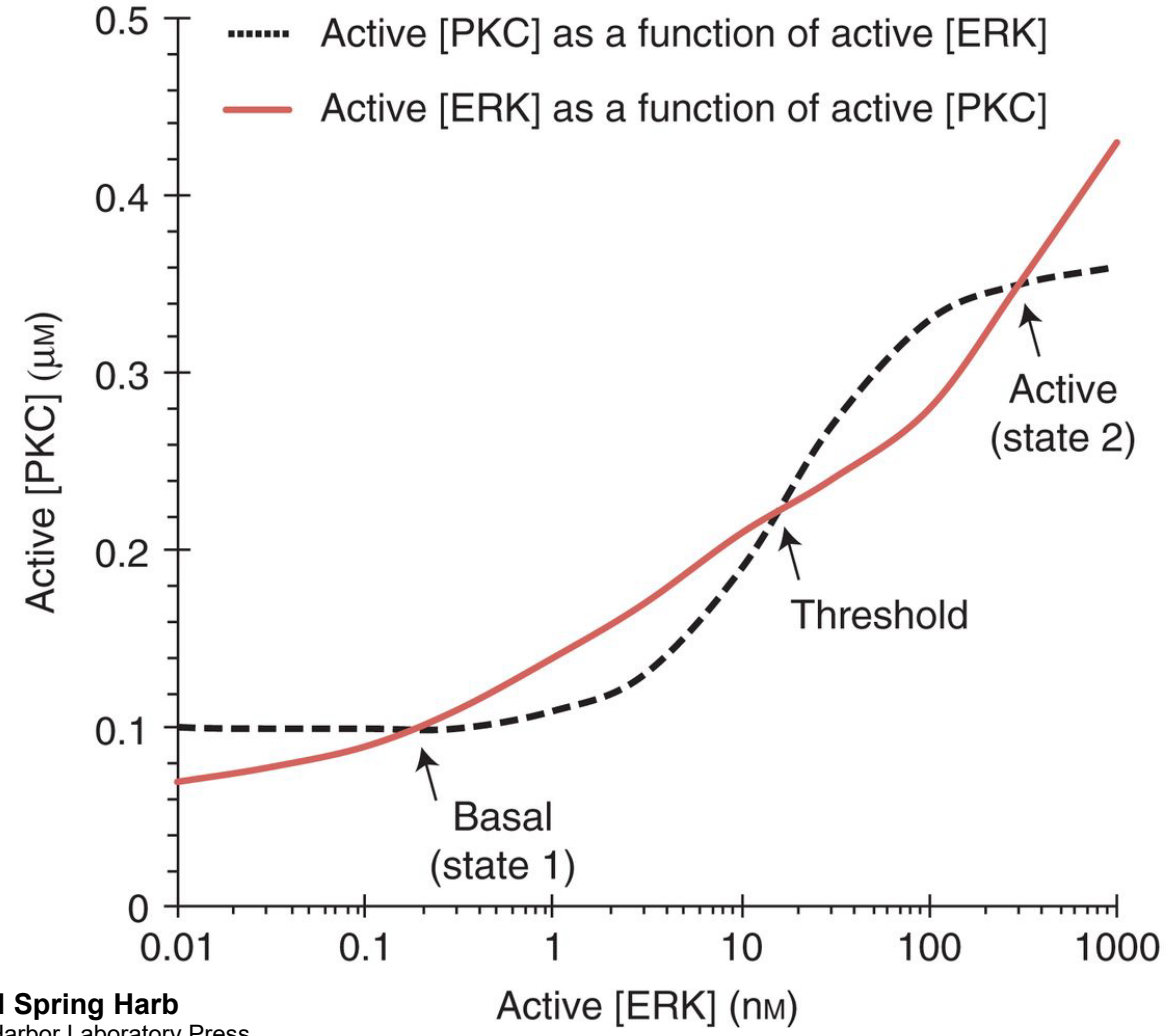
Activity states of components in a positive-feedback loop in a bistable system



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Emergent properties of signaling networks

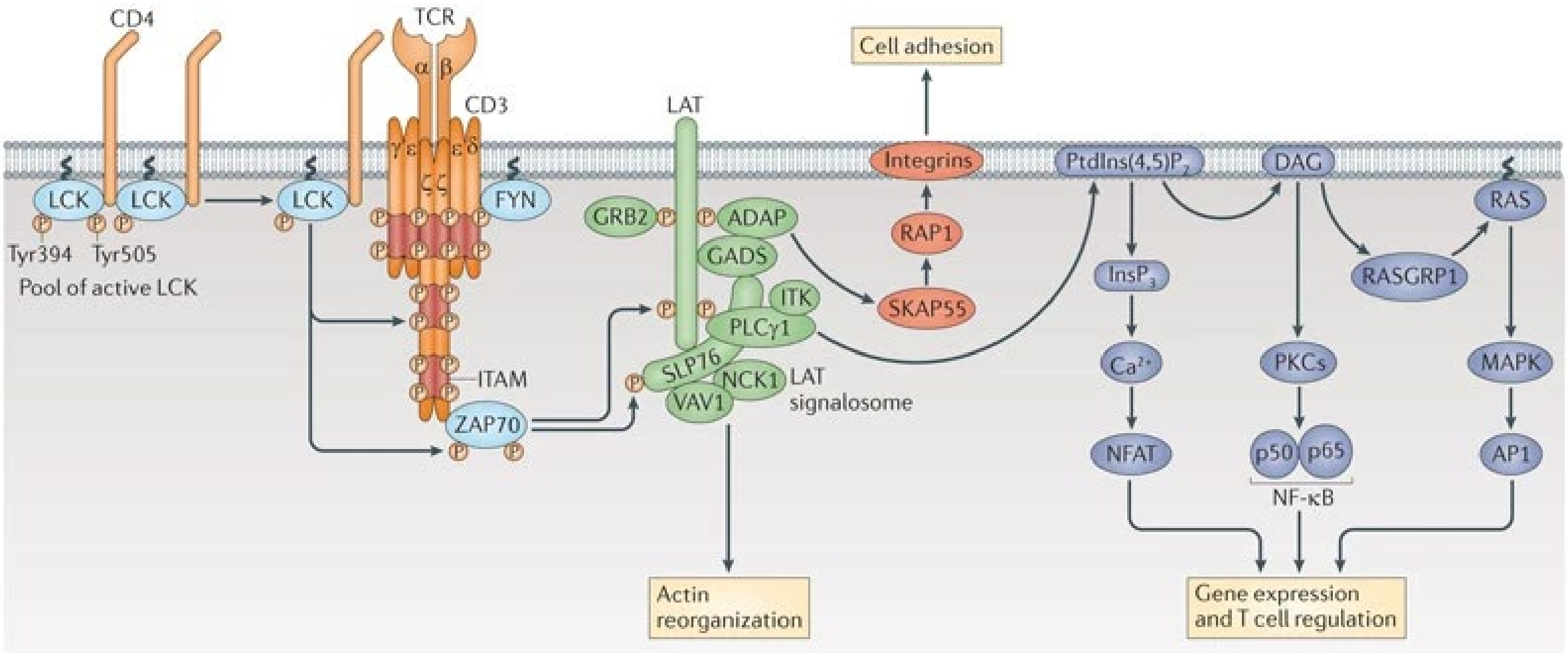
- Bistability
- Ultrasensitivity
  - Small changes in ligand/receptor can cause a large change in activity of a downstream effector.
  - Can be produced by cooperativity, multistep regulation, activator/inhibitor levels
- Redundancy and robustness
  - Multiple inputs into ERK pathway, Coherent feedforward motifs
- Oscillatory Behavior
  - Couple positive- and negative-feedback loops can lead to sustained oscillation

Belousov-Zhabotinsky Reaction

- Reactions that remain far from equilibrium with oscillating behavior
- Due to a system that has a reaction inhibitor and reaction promoter which diffuse across the medium at different rates.

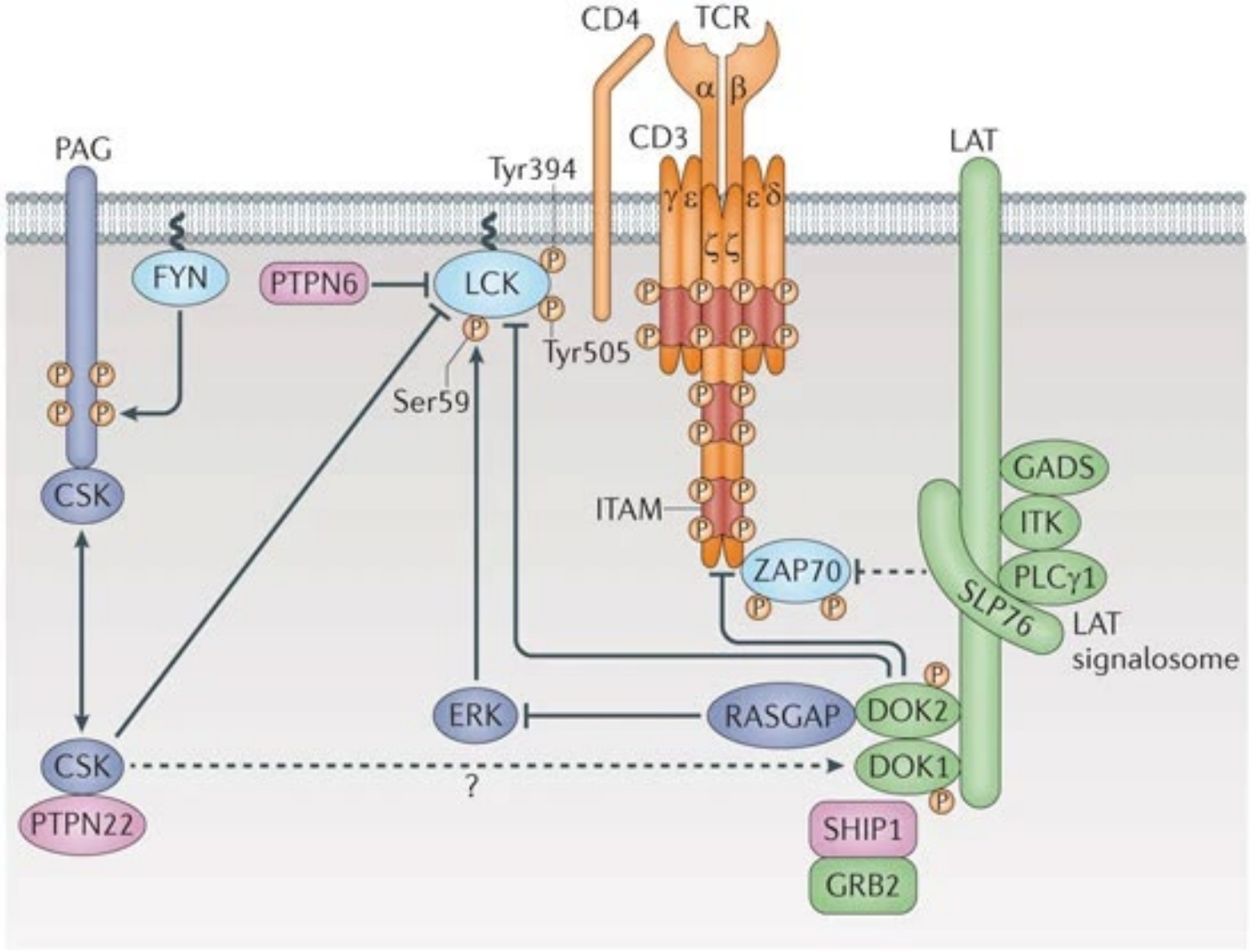
T cell receptor signaling

Overview of TCR signaling



Nature Reviews | Immunology

Negative feedback of TCR signaling



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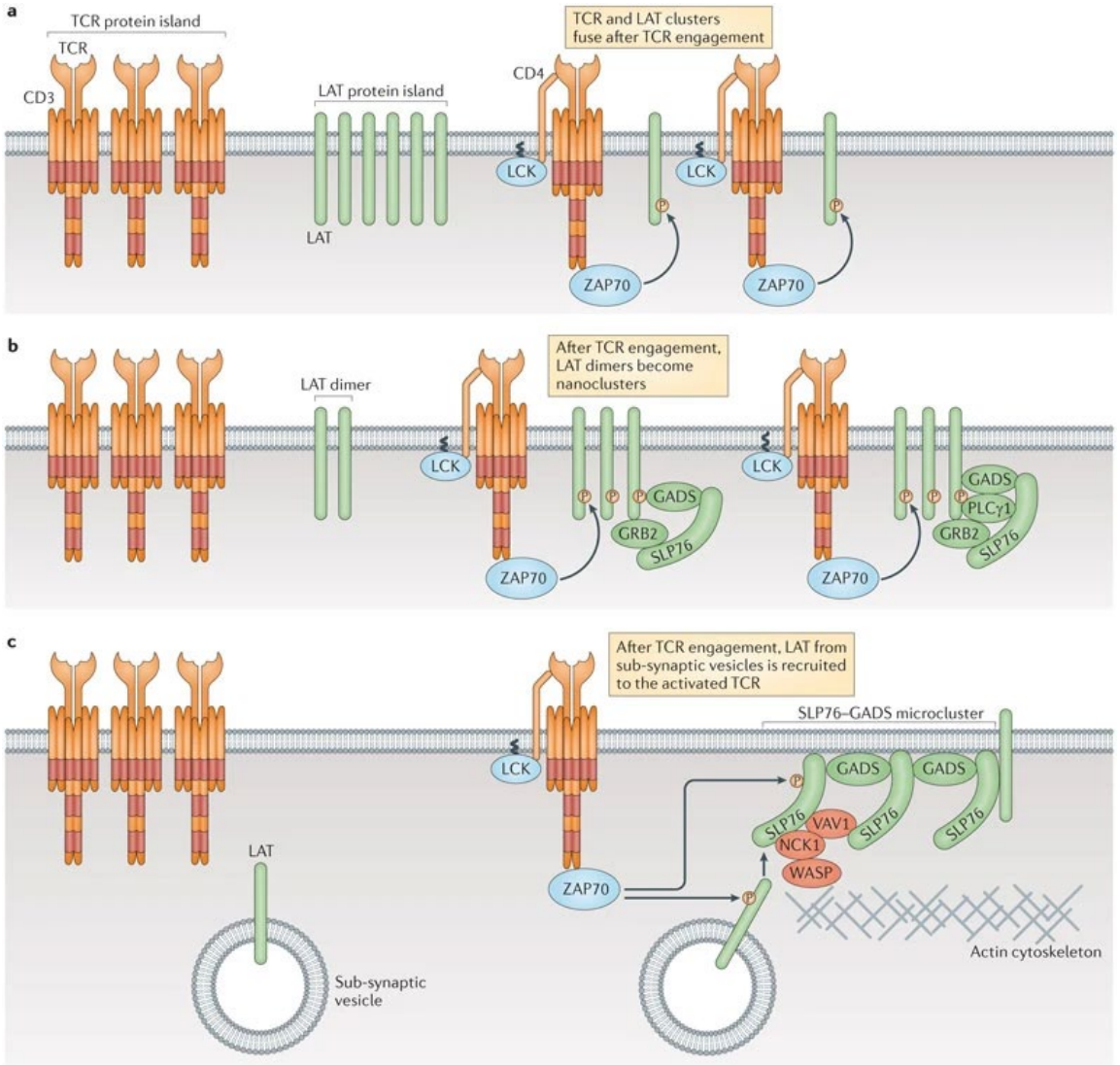
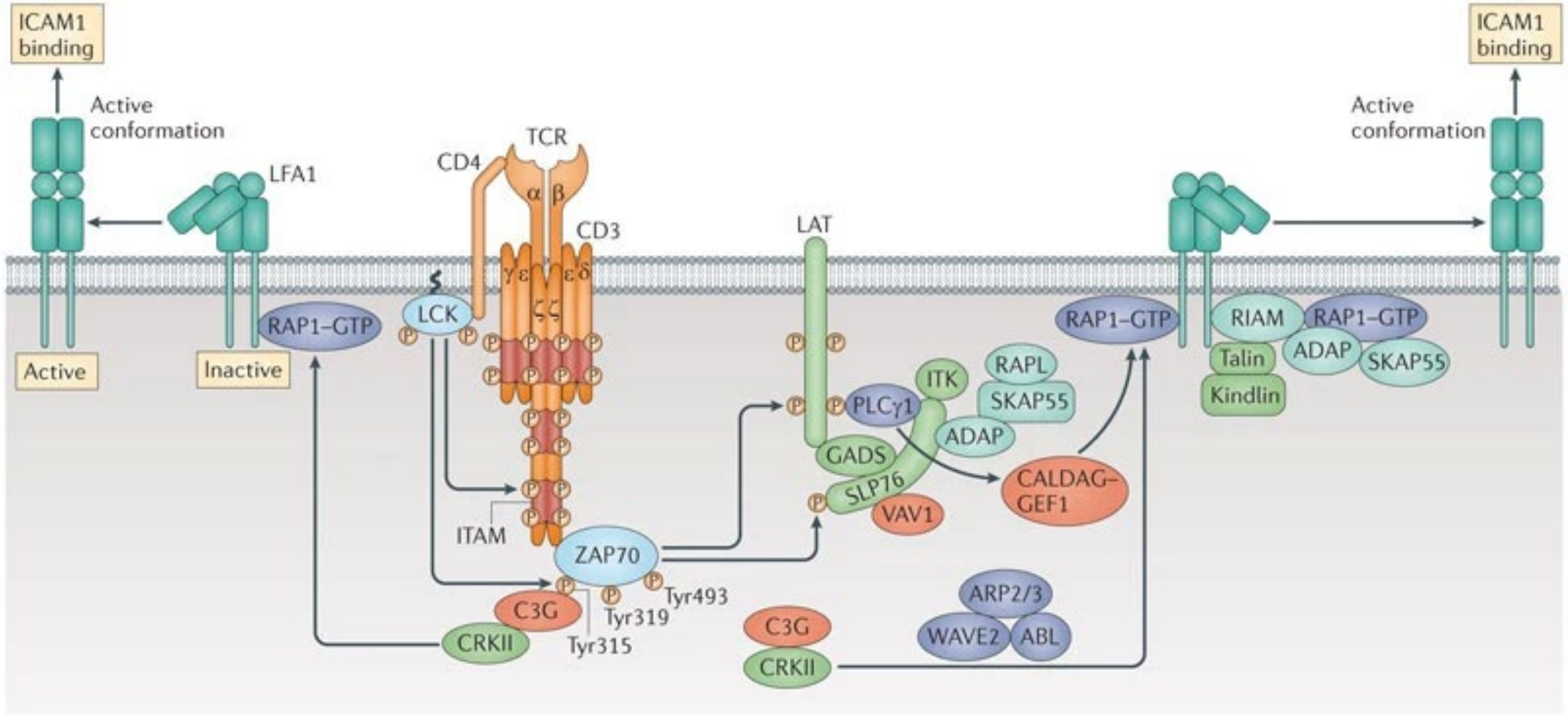
Spatiotemporal control of LAT



NATURE REVIEWS | IMMUNOLOGY VOLUME 13 | APRIL 2013 | 257

Mechanisms of TCR mediated inside-out signaling to integrins



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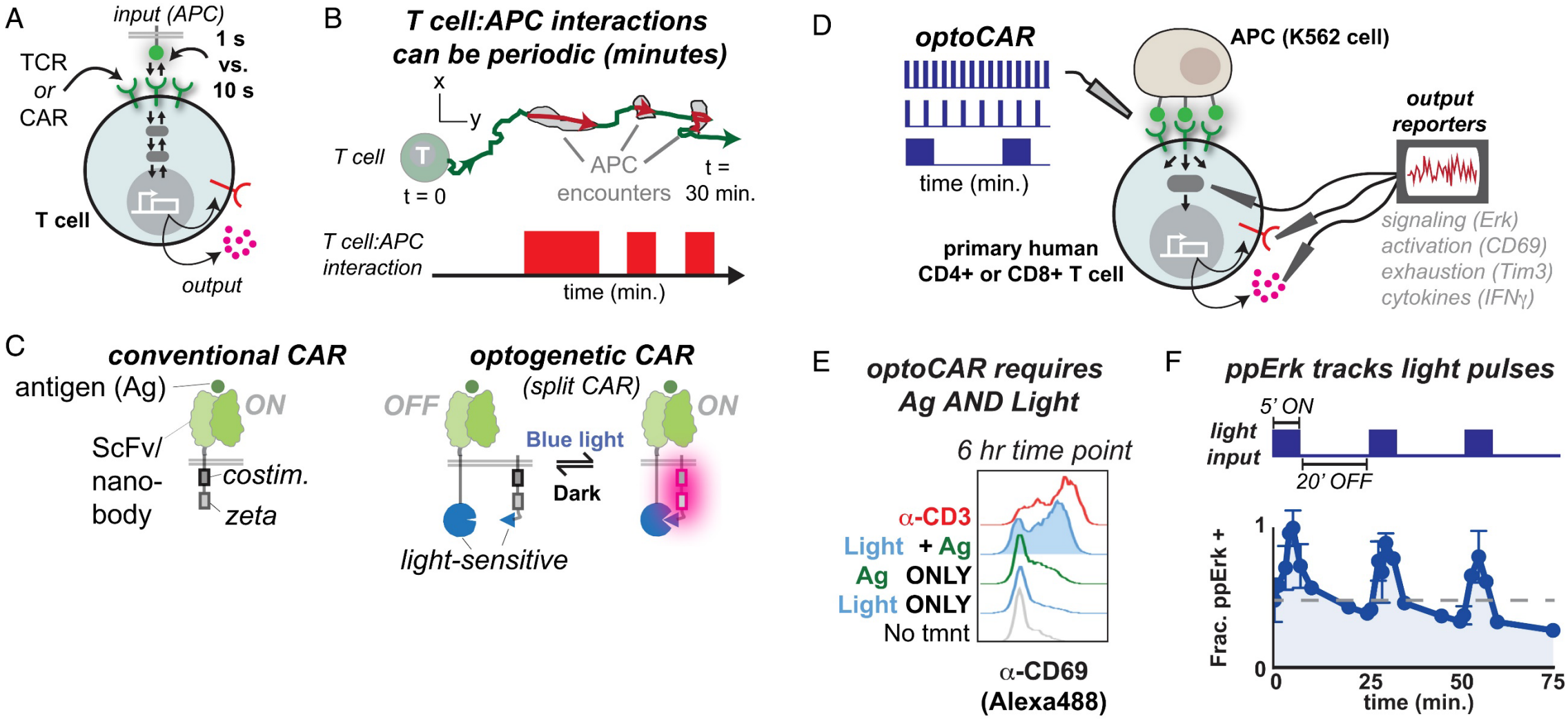
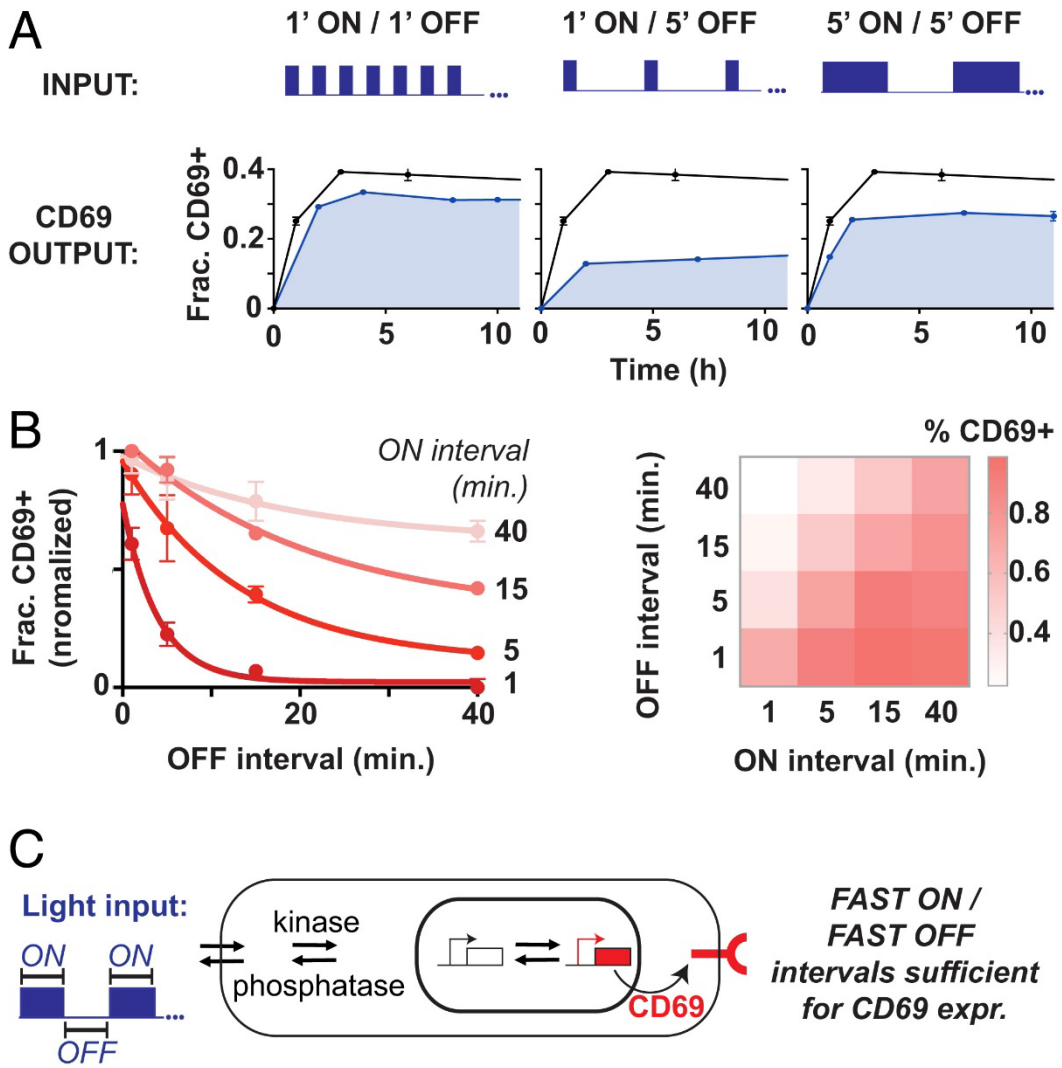
T cells selectively filter oscillatory signals on the minutes timescale

PNAS 2021 Vol. 118 No. 9 e2019285118

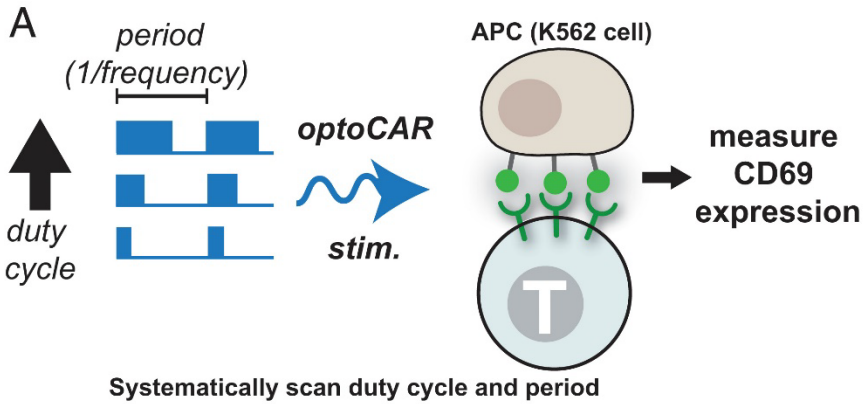
Systematically probing the transmission of periodic signals in T cells using optogenetics

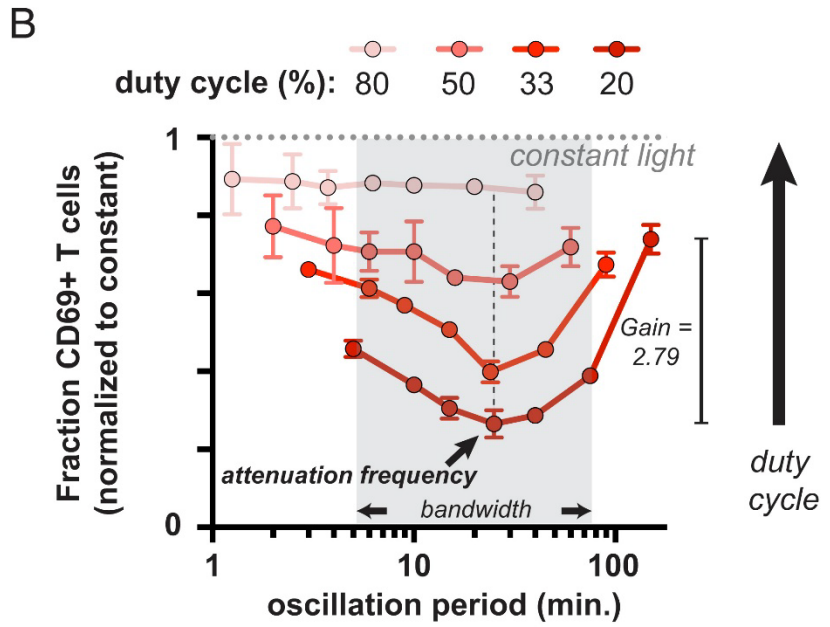


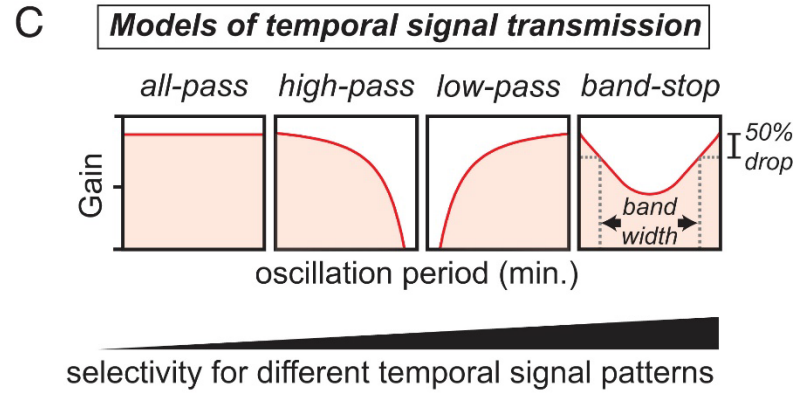
CD69 expression is sensitive to fast, minute-scale oscillations in T cell stimulus

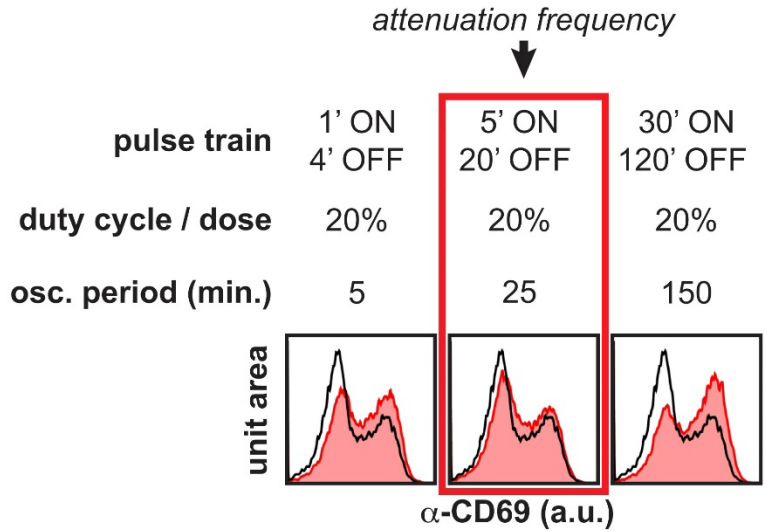


CD69 expression is a band-stop filter that is selectively attenuated at an oscillation period of ~25 min

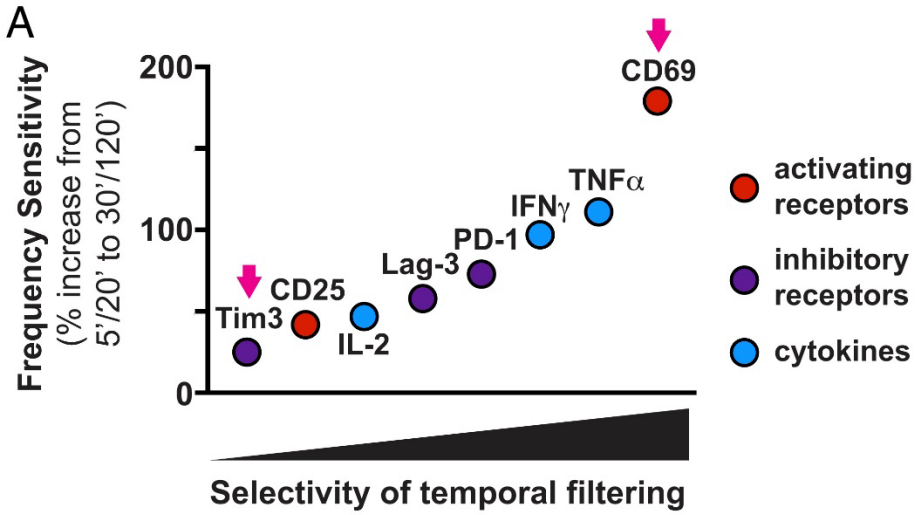


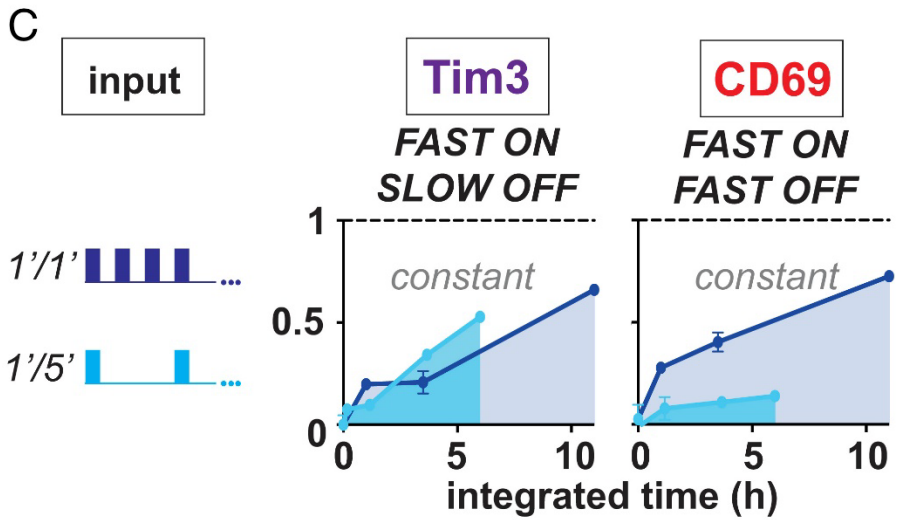


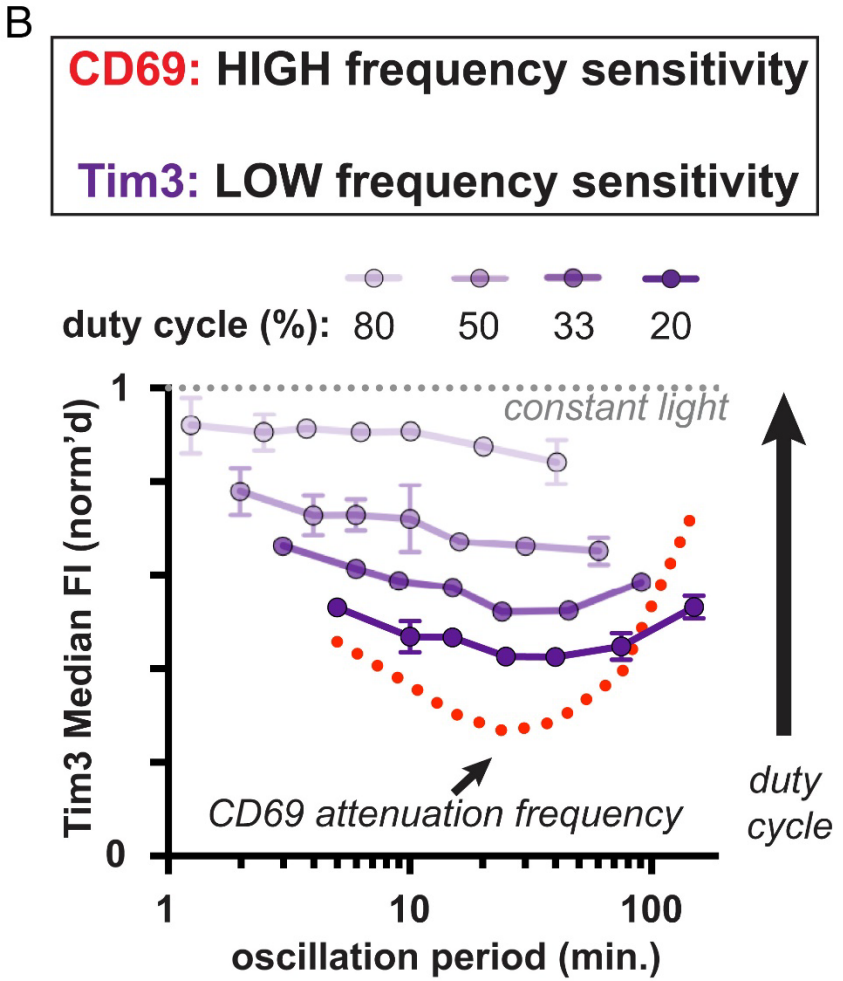




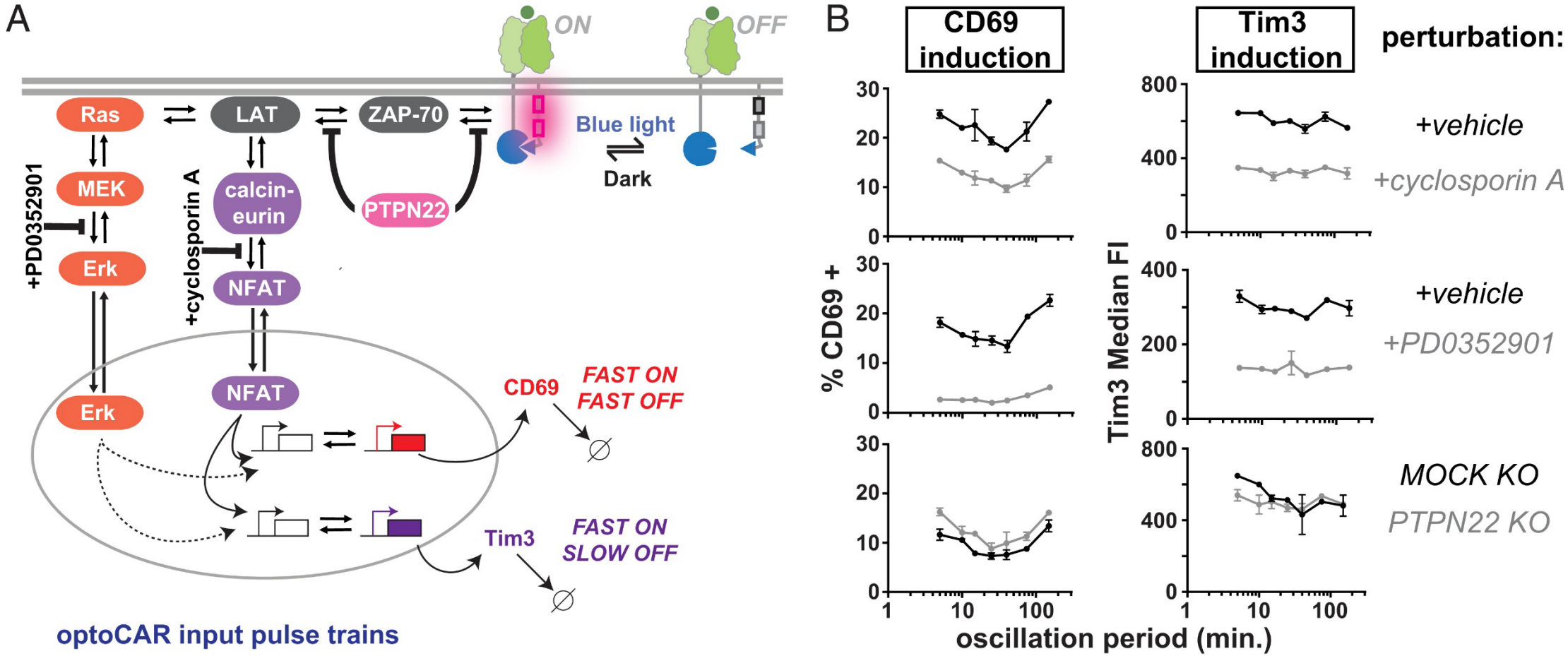
CD69 expression is a more selective temporal filter than other early T cell activation responses







Potential signaling mechanisms that sculpt selectively attenuated CD69 activation in response to specific oscillatory signals



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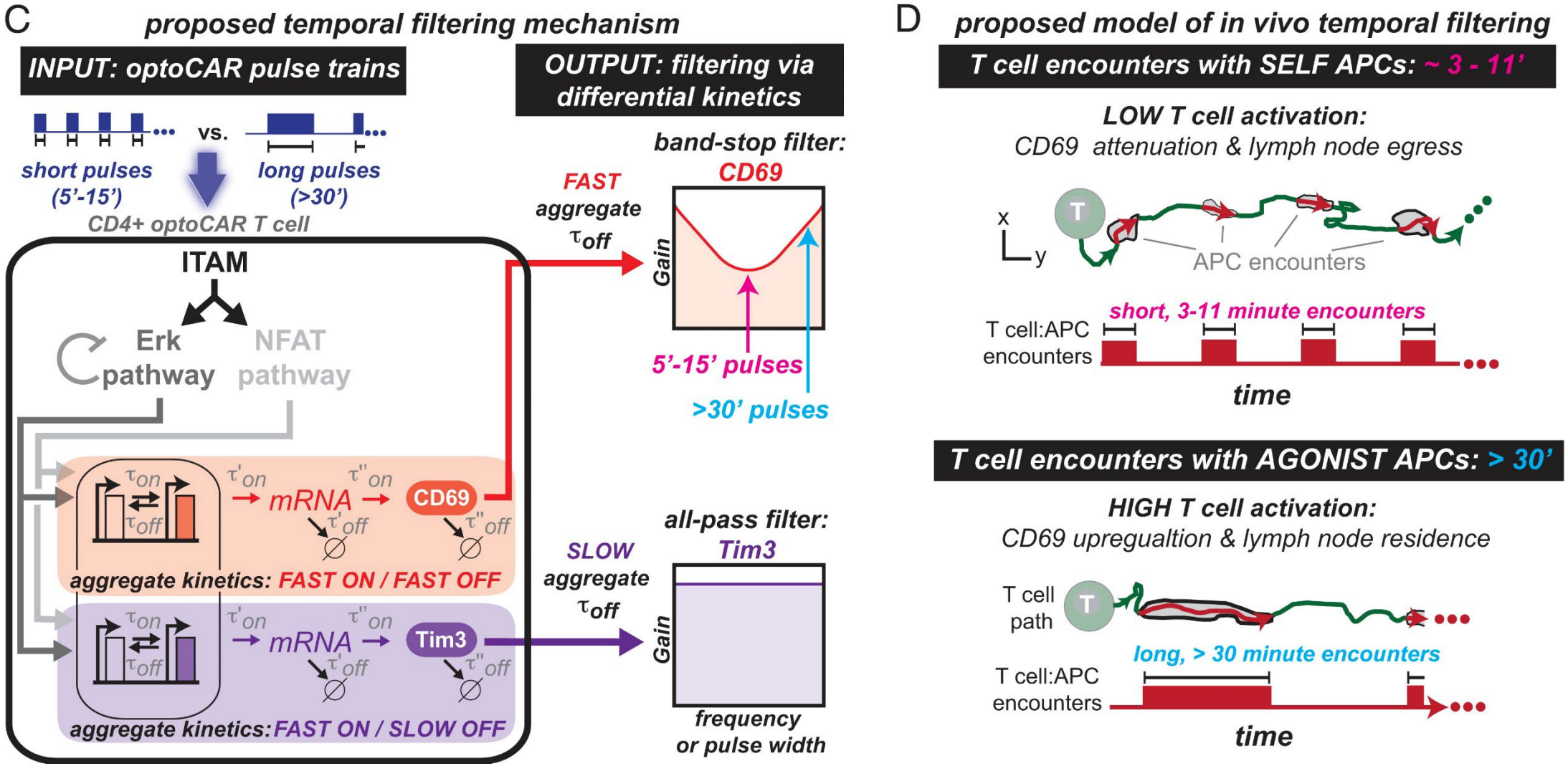
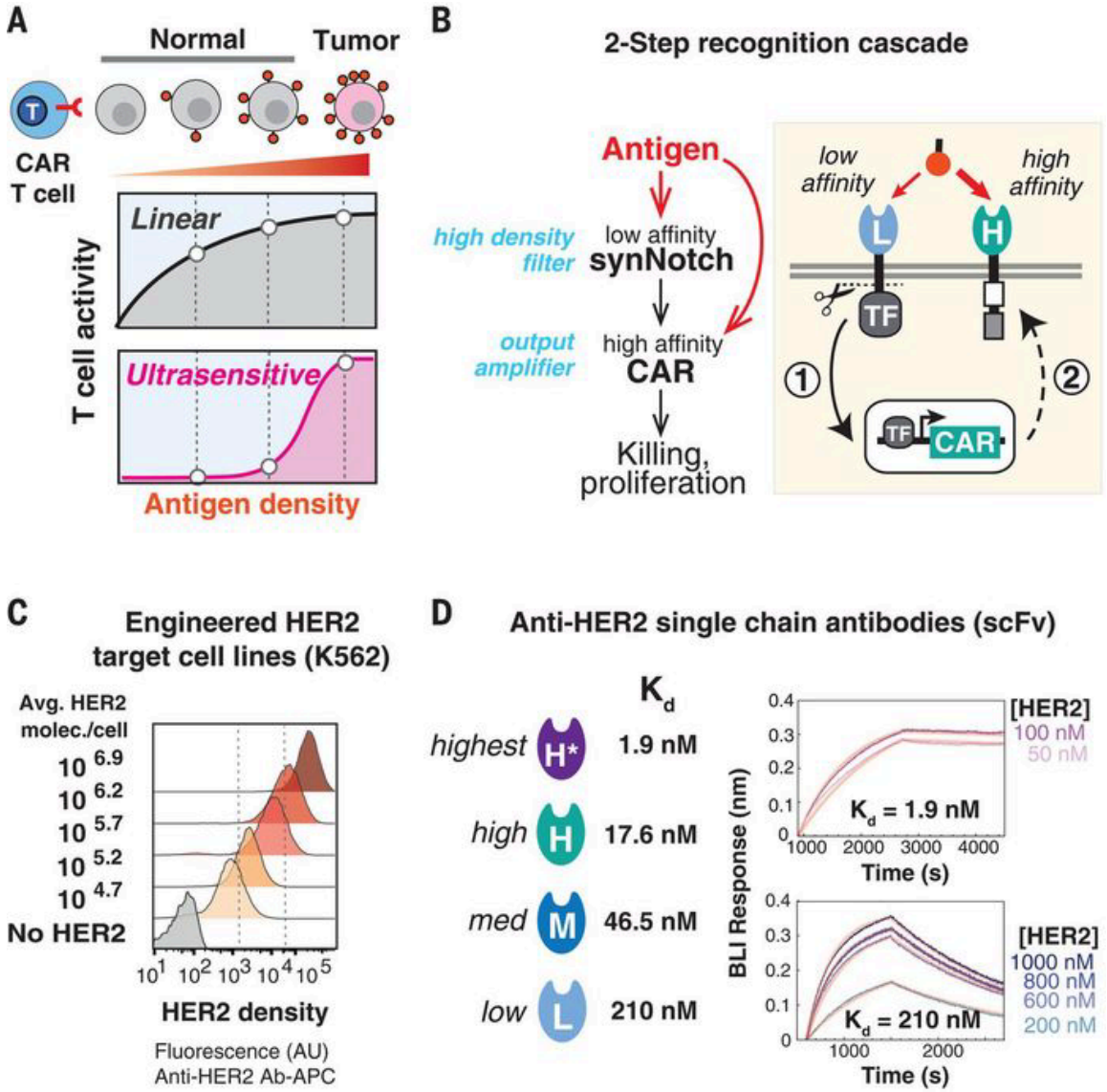


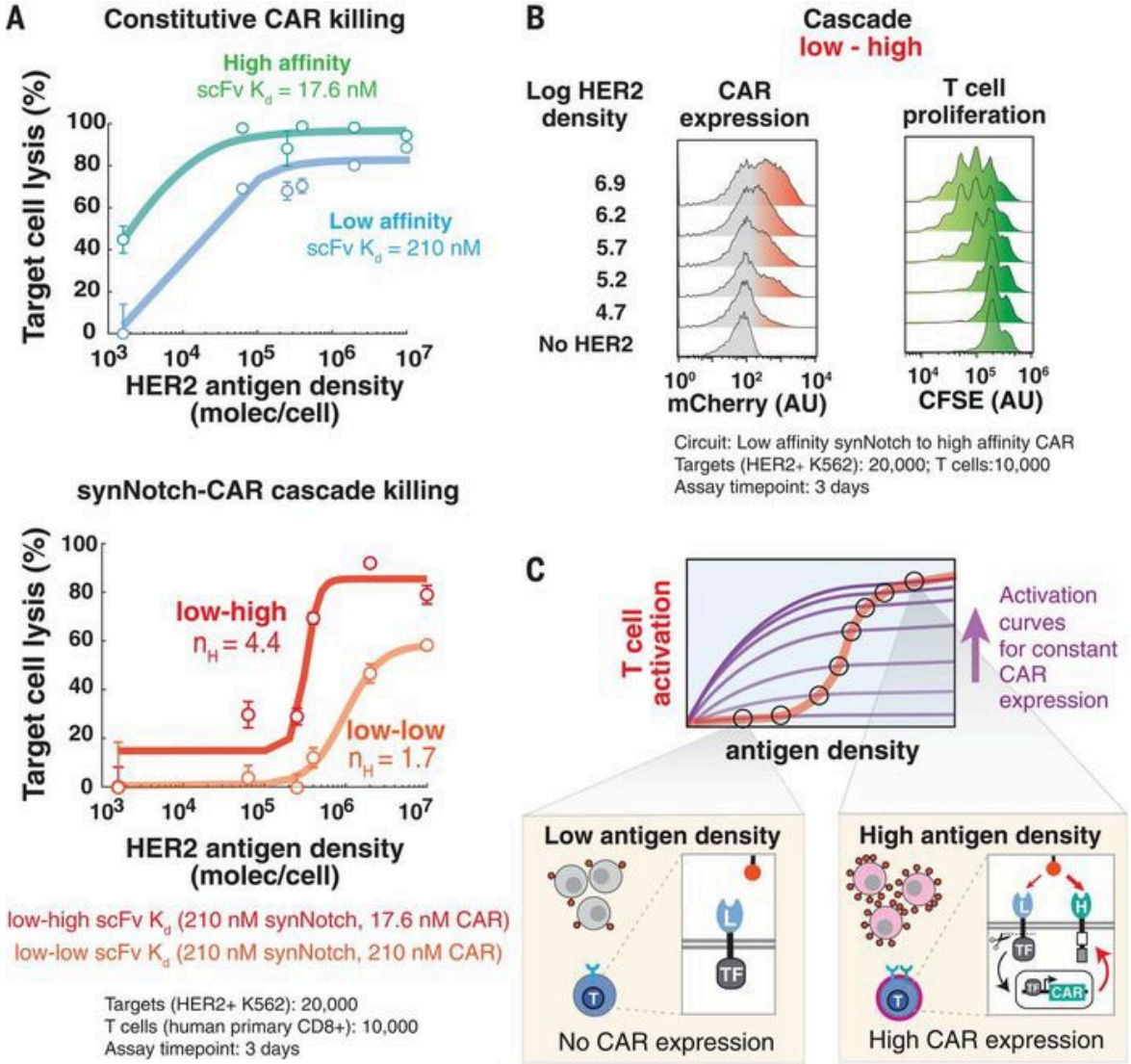
T cell circuits that sense antigen density with an ultrasensitive threshold

Hernandez-Lopez et al., Science 371, 1166–1171 (2021) 12 March 2021

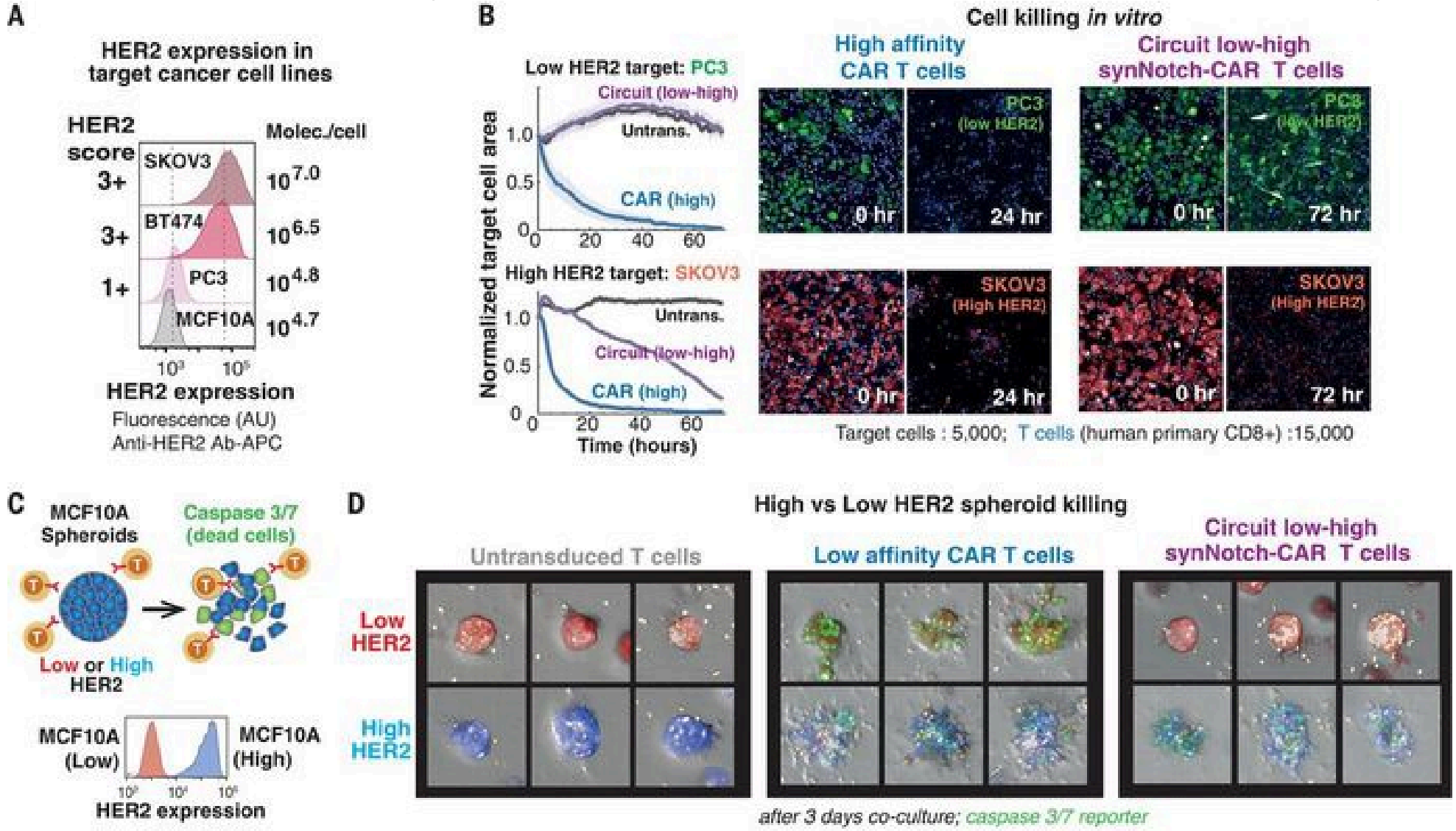
Design of T cells with ultrasensitive antigen density sensing



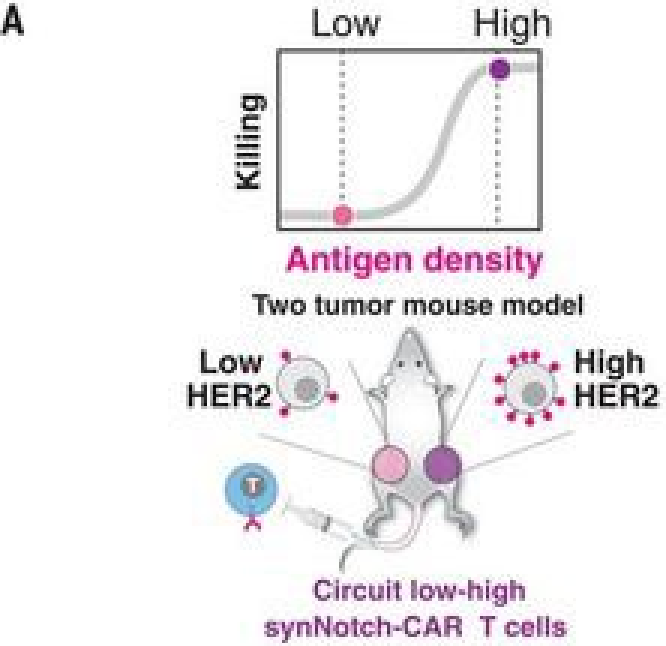
A two-step low- to high-affinity recognition circuit yields ultrasensitive antigen-density sensing

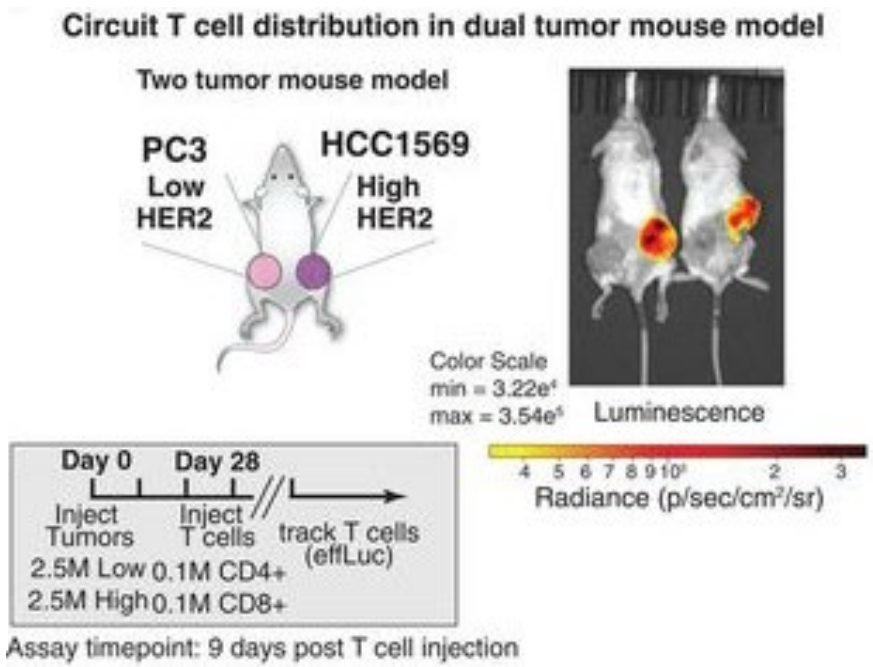


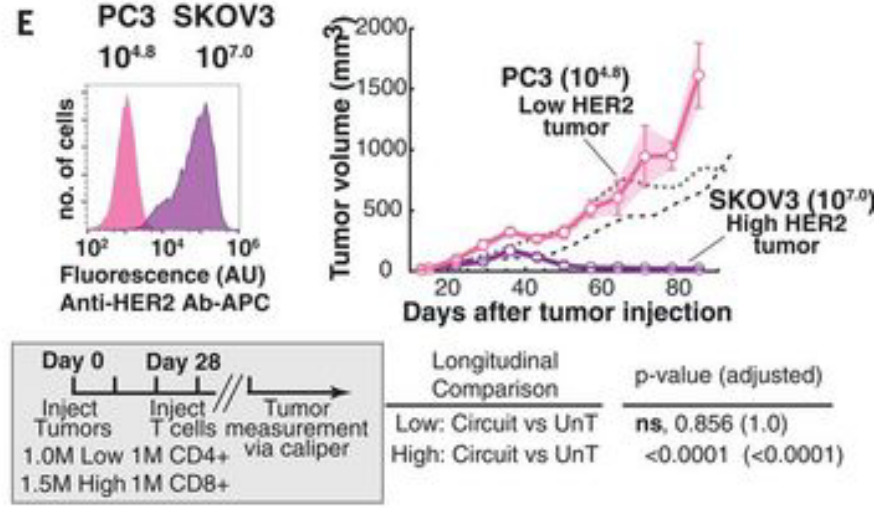
Low-to-high synNotch-to-CAR circuit: Discrimination between high- and low-density tumor cancer cell lines

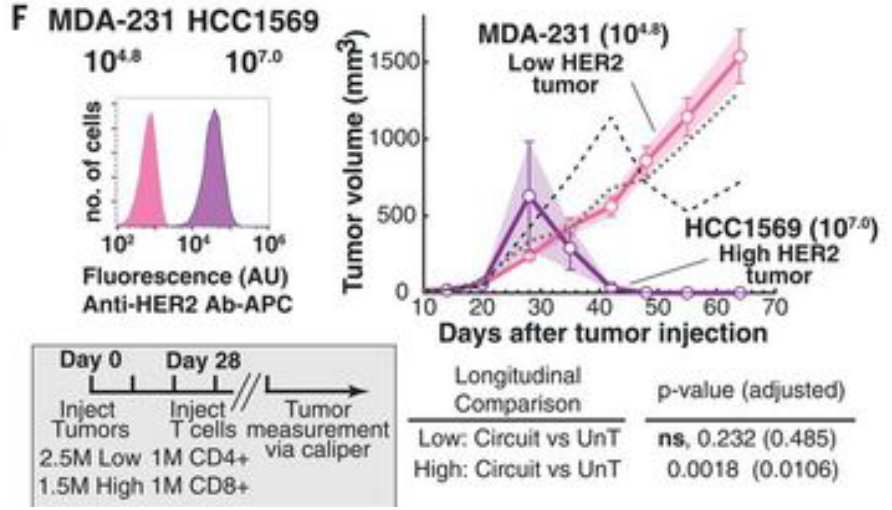


Low-o-high synNotch-to-CAR circuit: Antigen density discrimination in mouse models





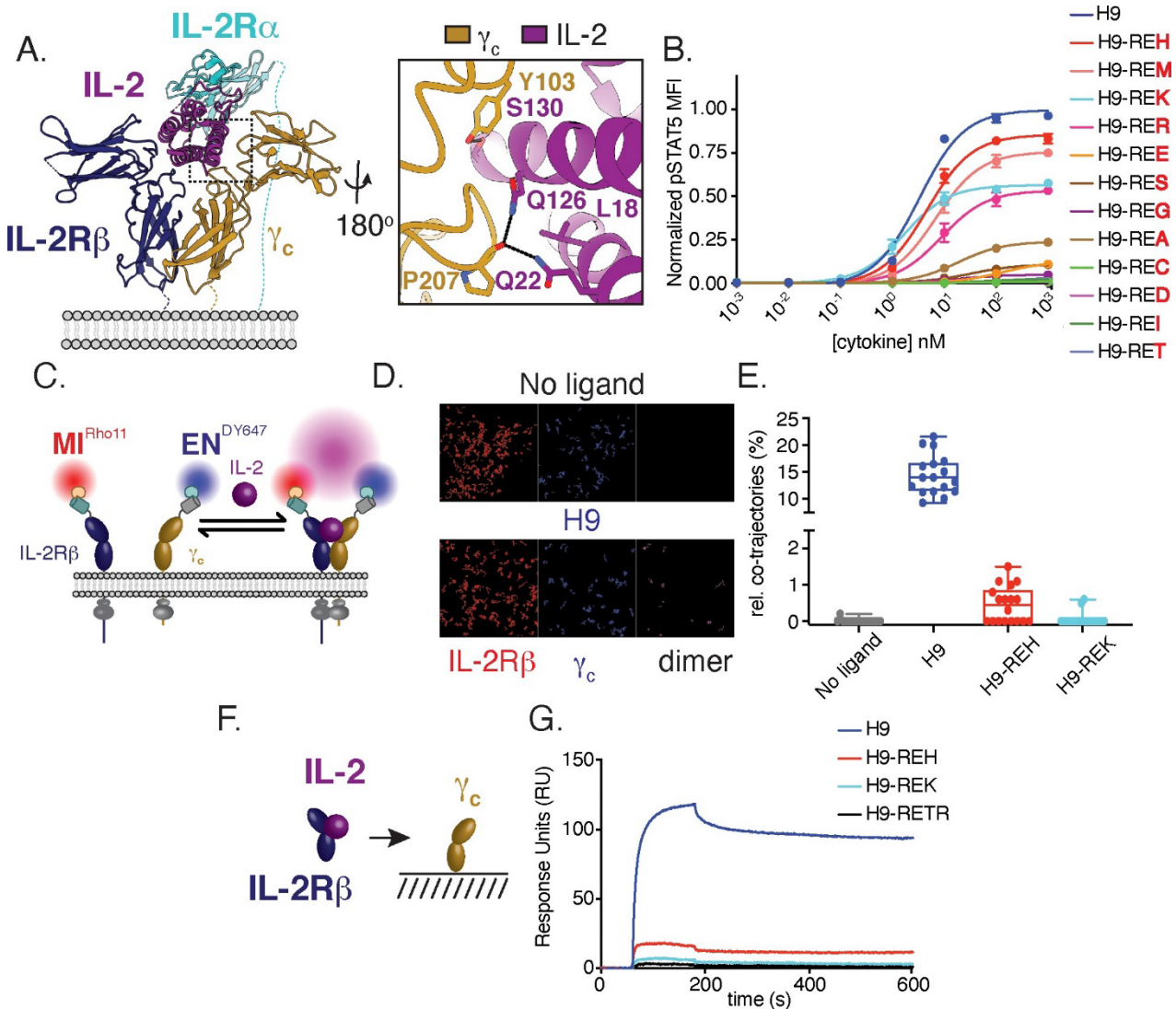




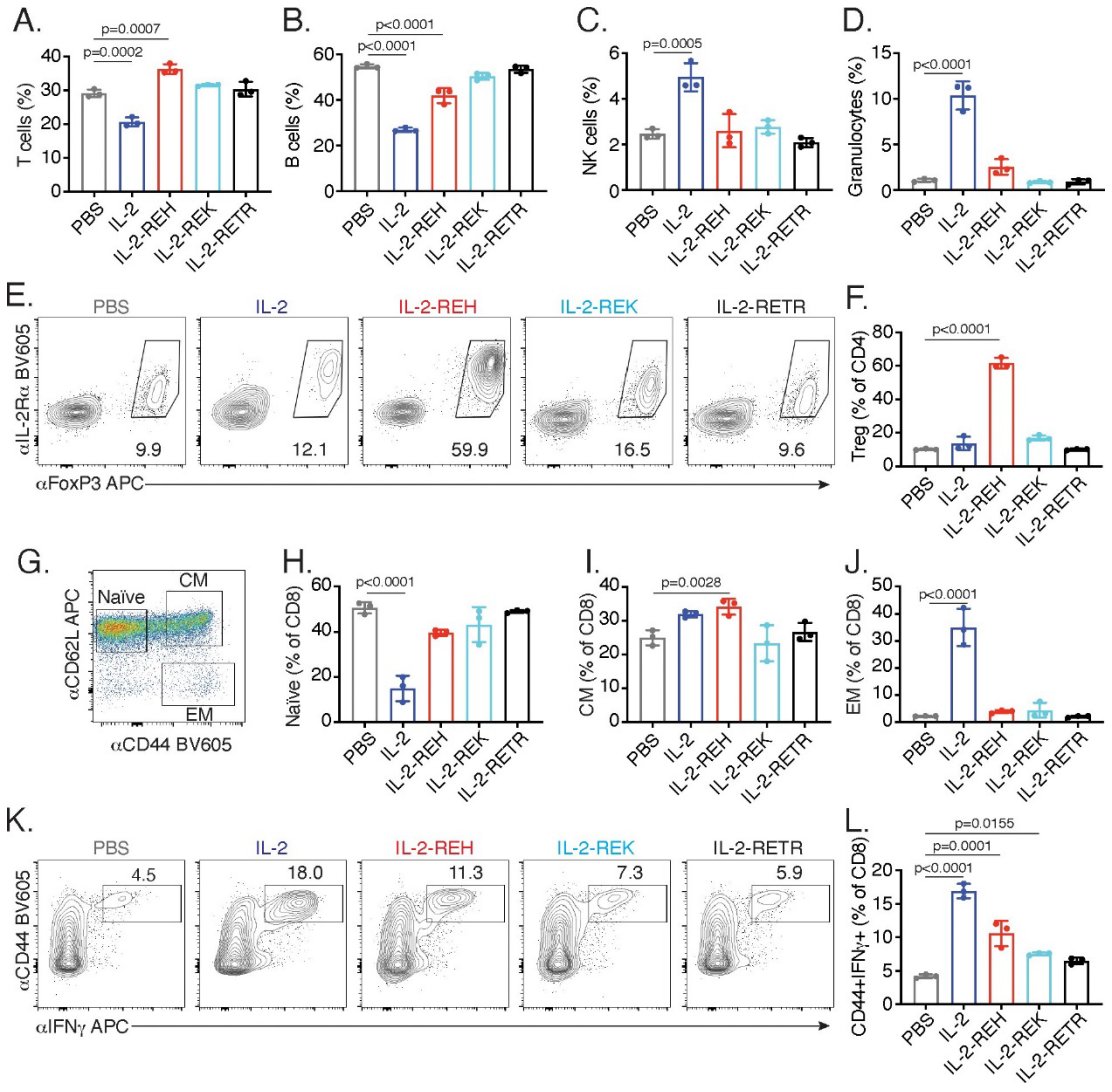
Calibration of cell-intrinsic interleukin-2 response thresholds guides design of a regulatory T cell biased agonist

https://doi.org/10.7554/eLife.65777

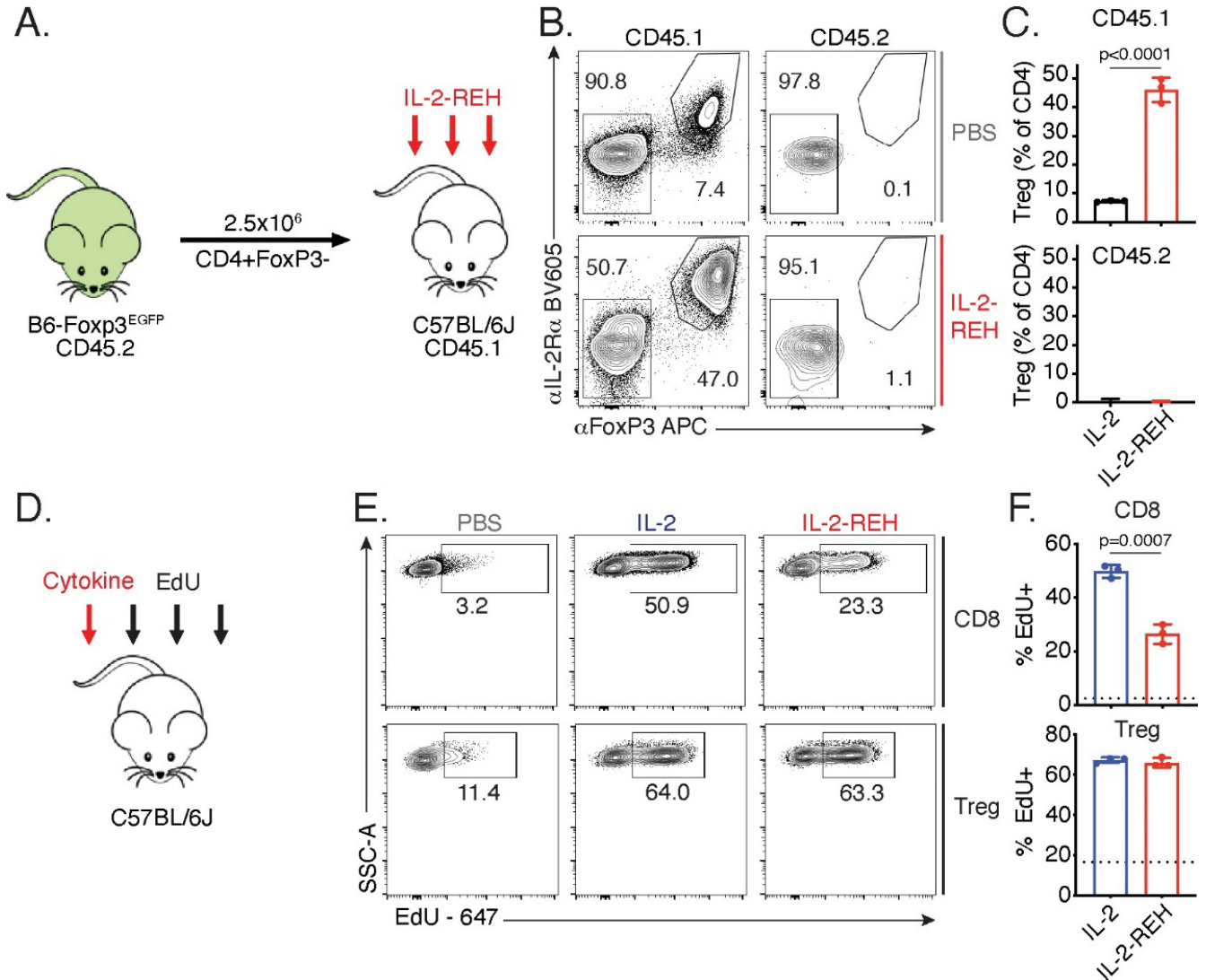
Structure-based design and biophysical characterization of IL-2 receptor partial agonists



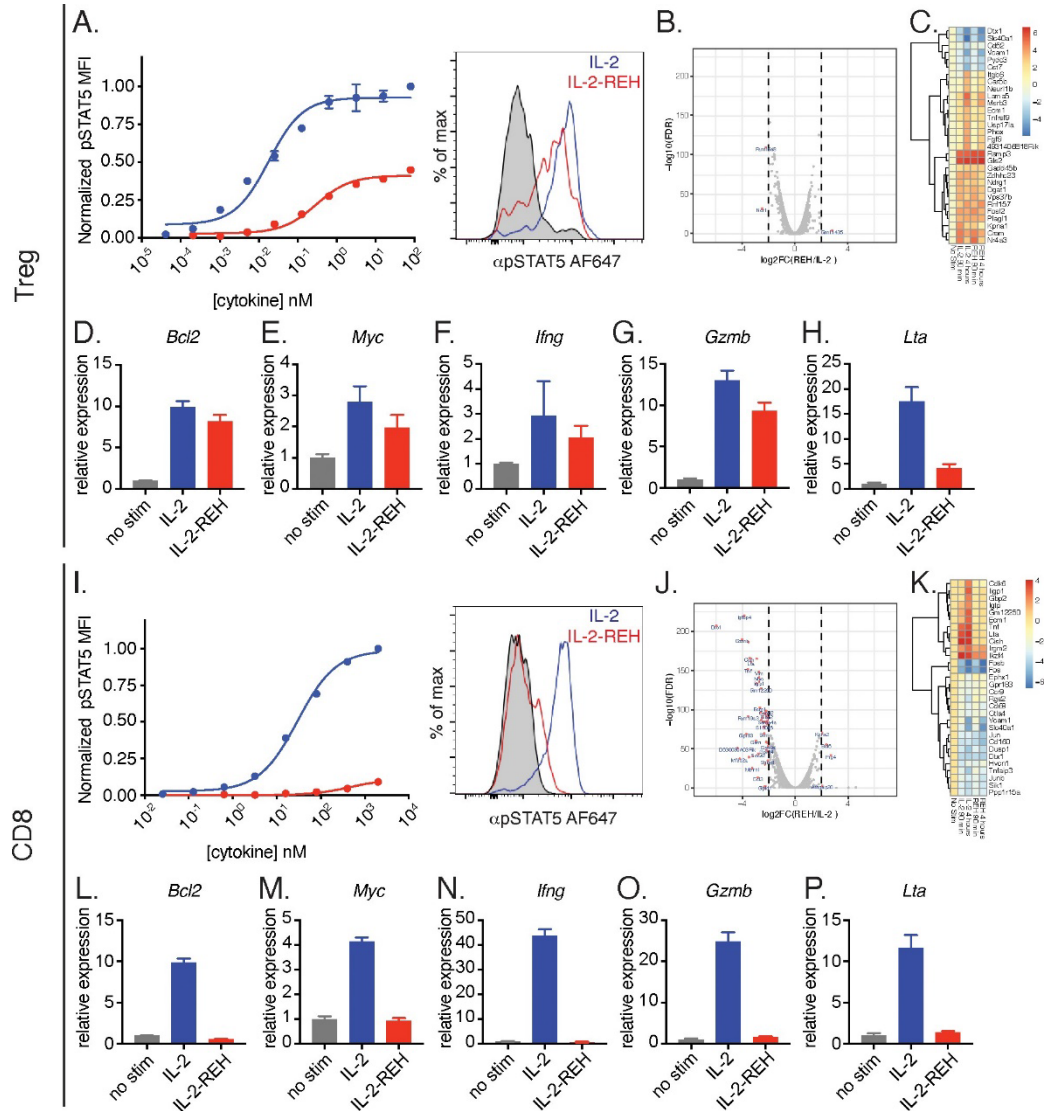
IL-2 receptor partial agonists elicit cell type-specific responses in vivo



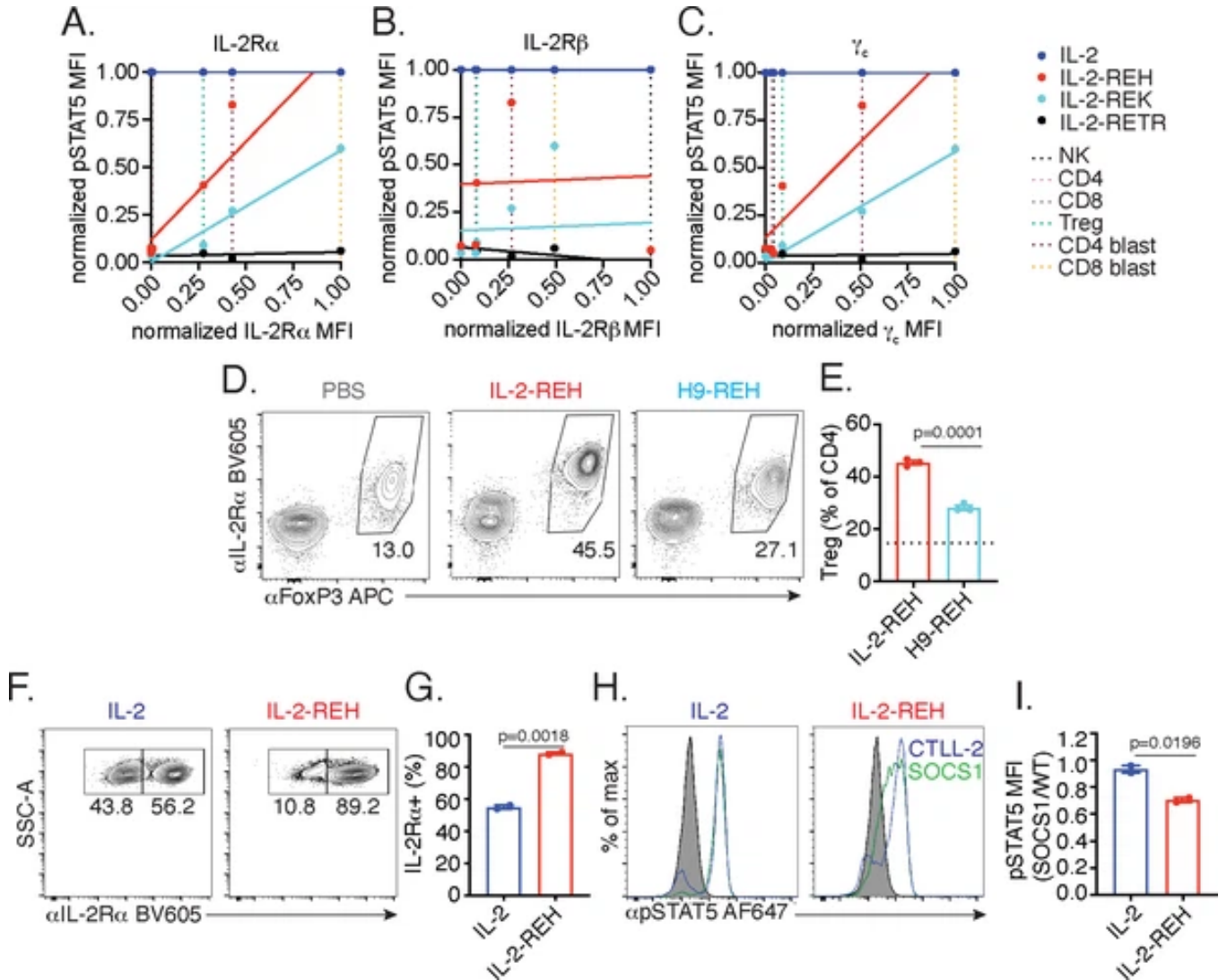
IL-2-REH increases Treg frequency via selective proliferation of Foxp3+ cells



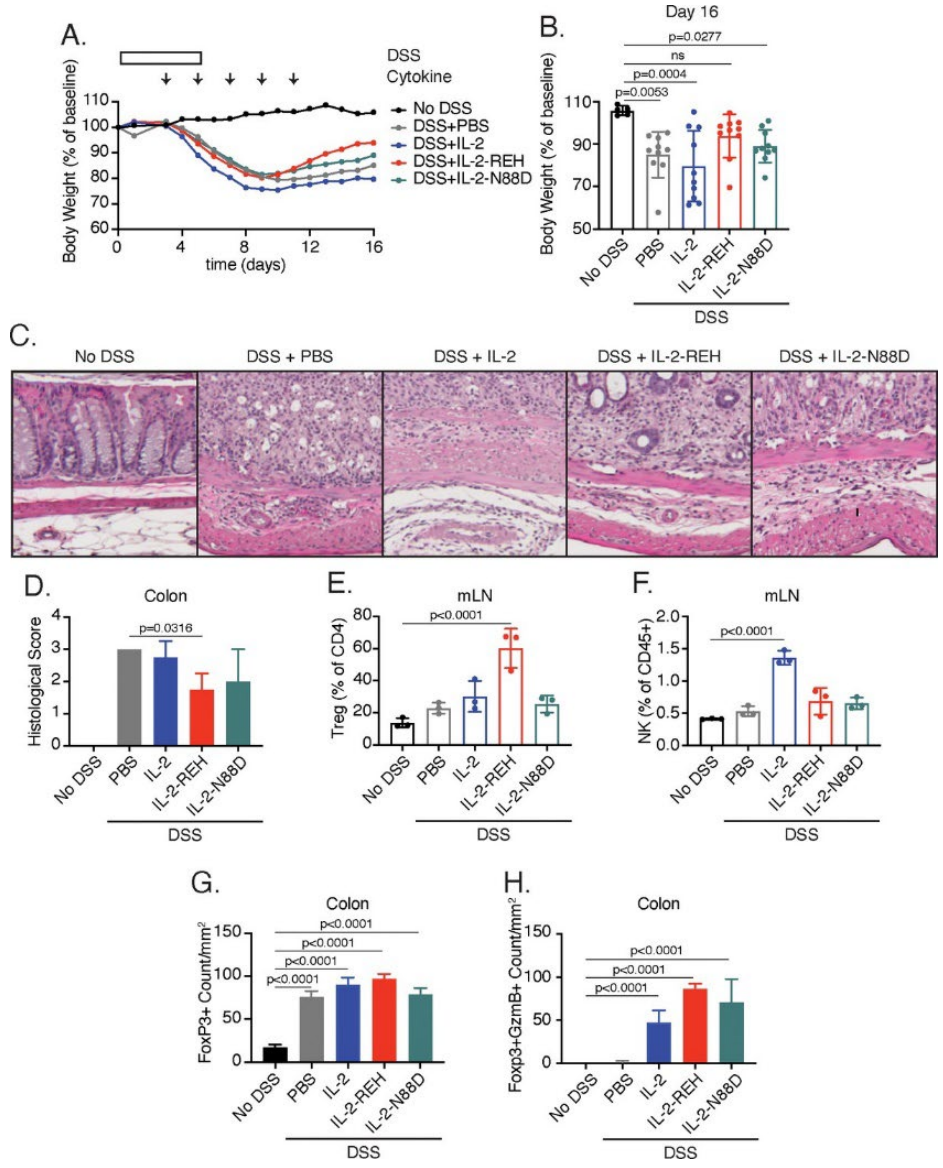
IL-2-REH selectively promotes signaling in Tregs with reduced activity on CD8+ T cells relative to IL-2



IL-2-REH exploits intrinsic differences in IL-2 signaling to elicit cell type-specific activity



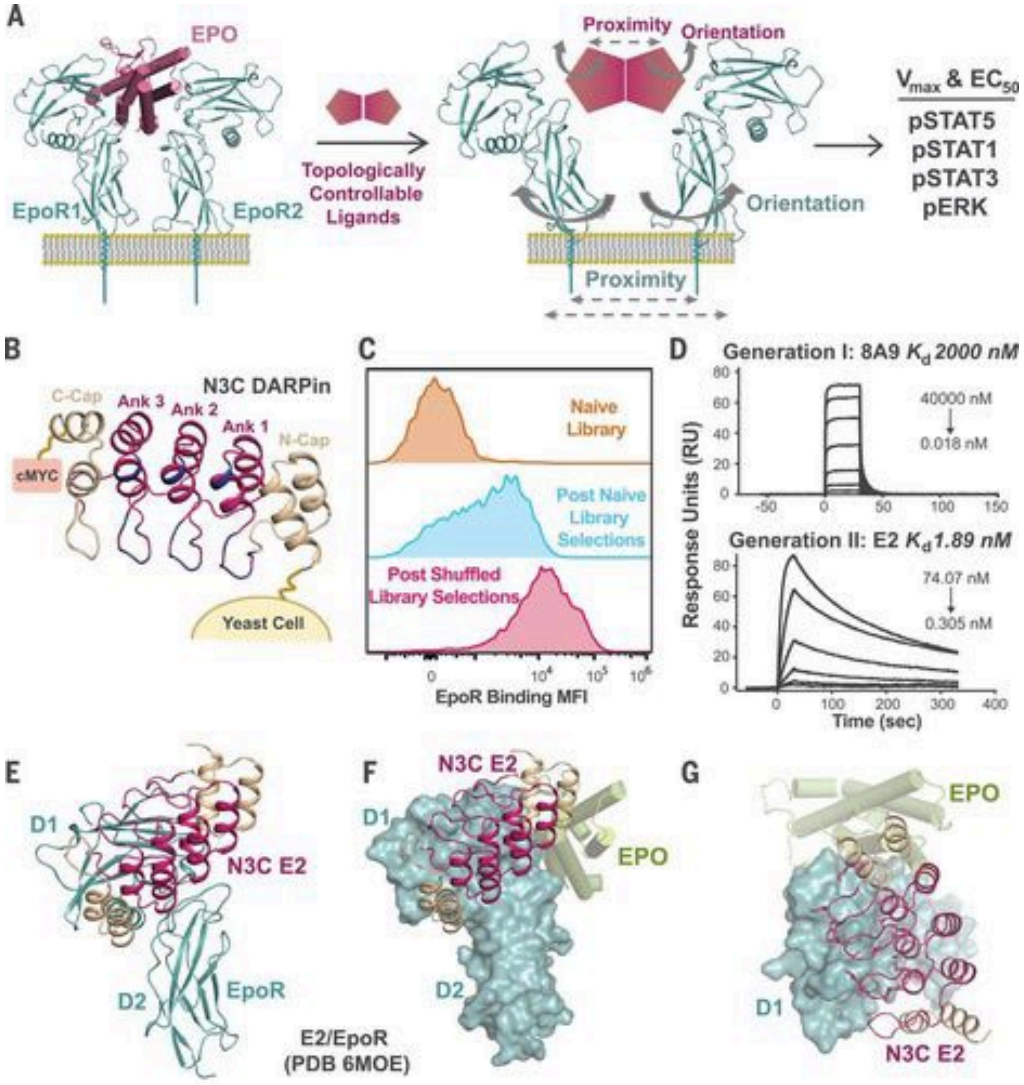
IL-2-REH enhances recovery from DSS-induced colitis



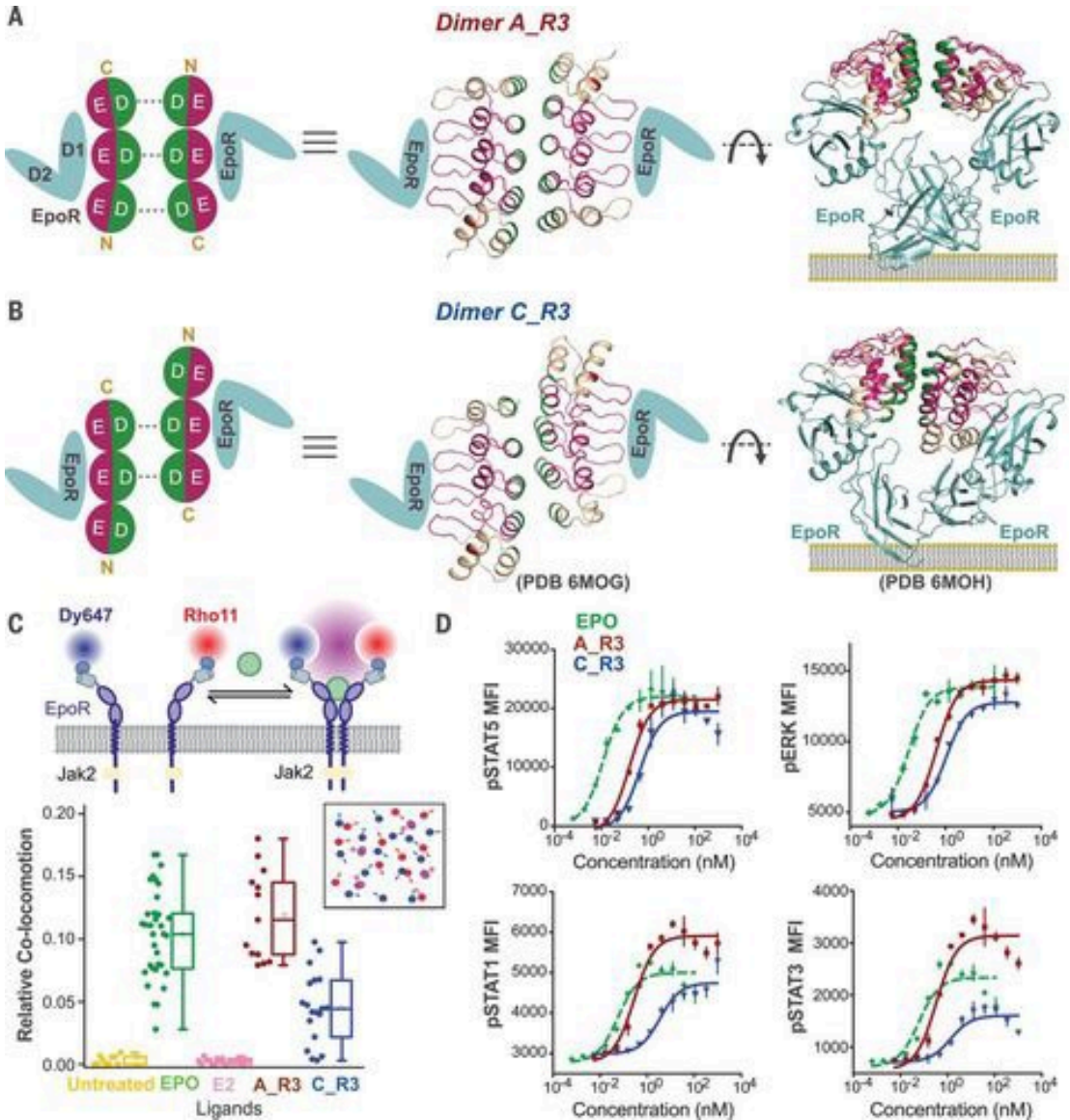
Topological control of cytokine receptor signaling induces differential effects in hematopoiesis

SCIENCE
24 May 2019
Vol 364, Issue 6442
DOI: 10.1126/science.aav7532

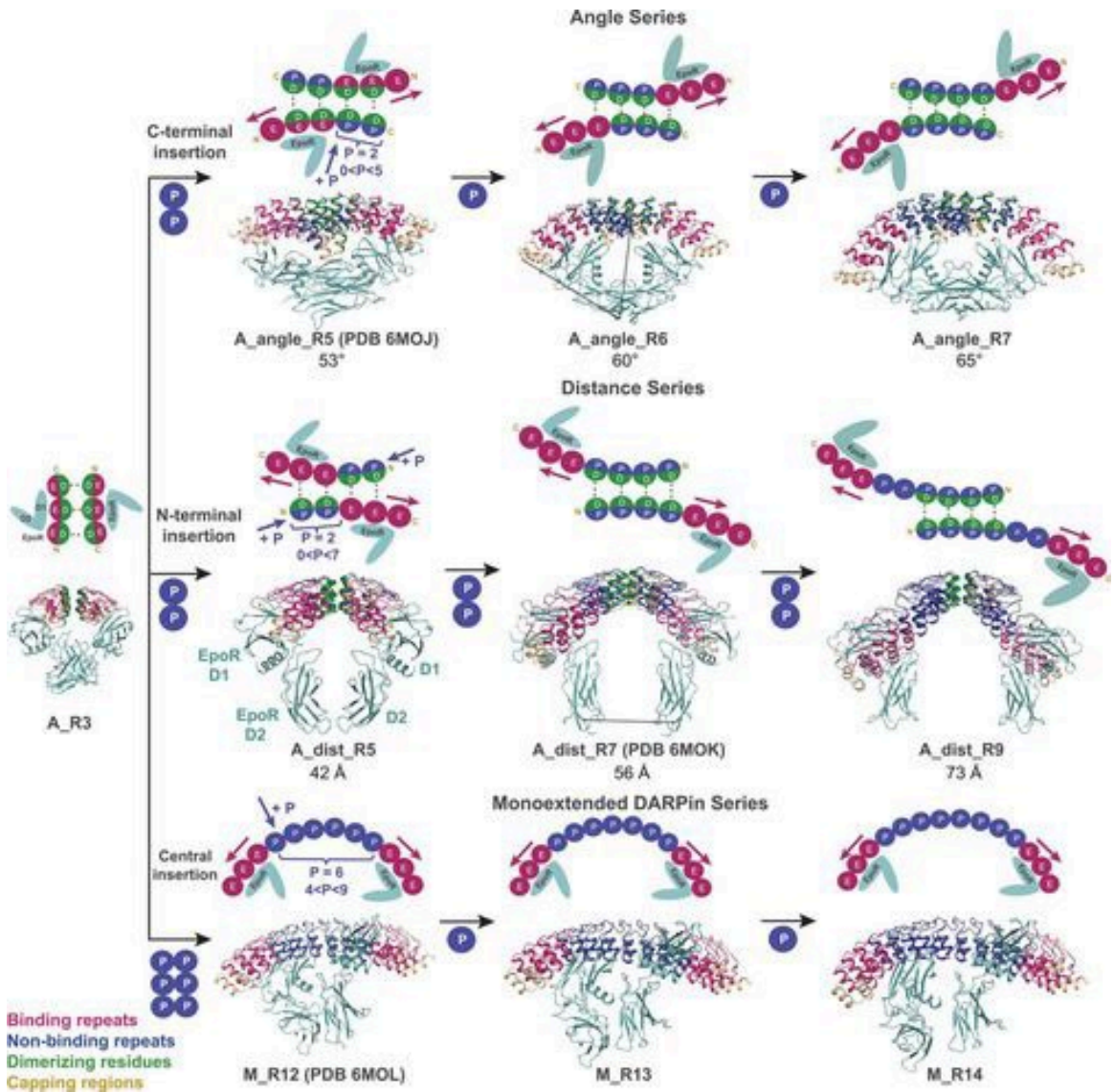
Engineering and characterization of high-affinity DARPin binding to EpoR



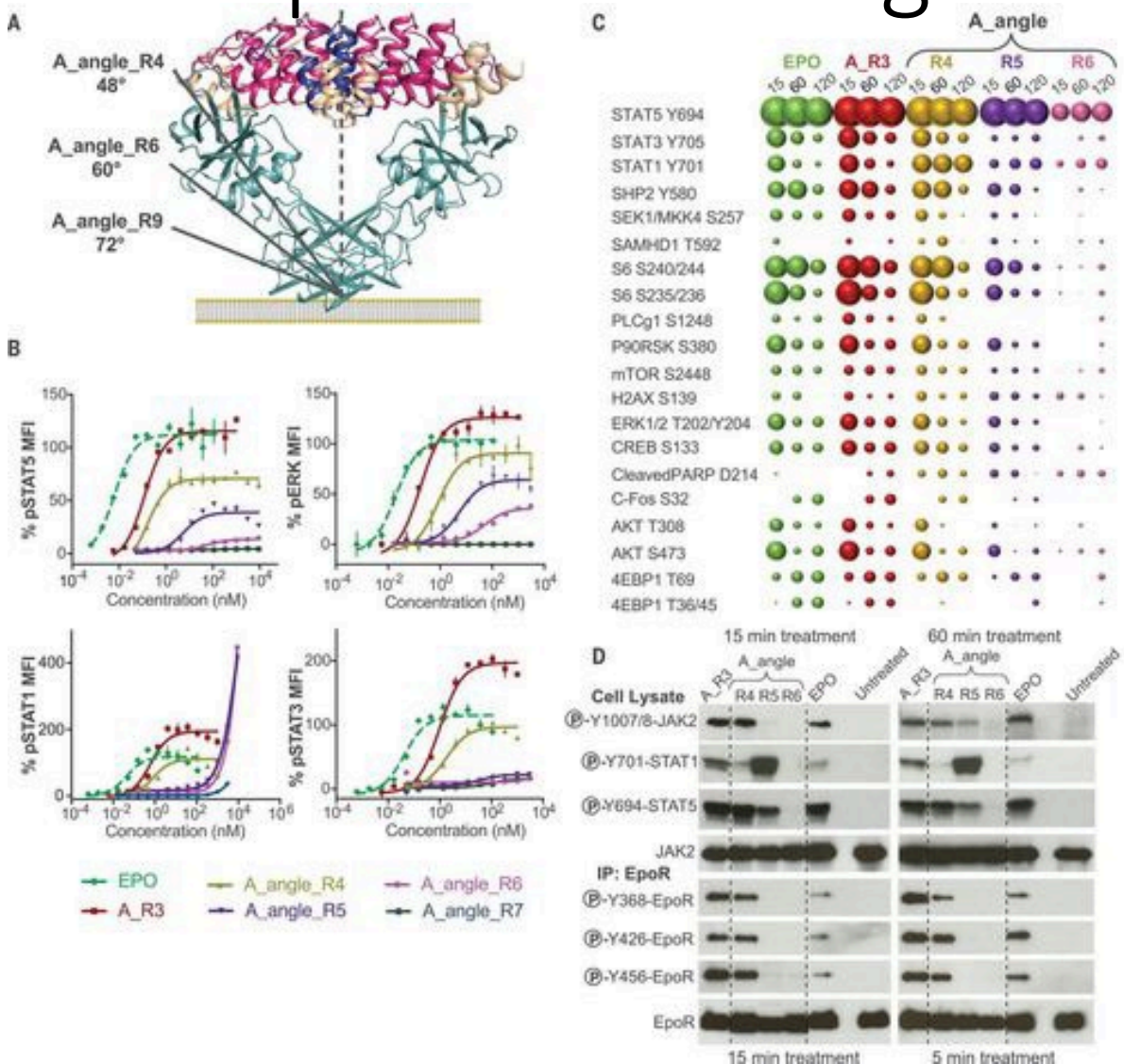
Dimerization scaffolds for E2 resulting in agonism



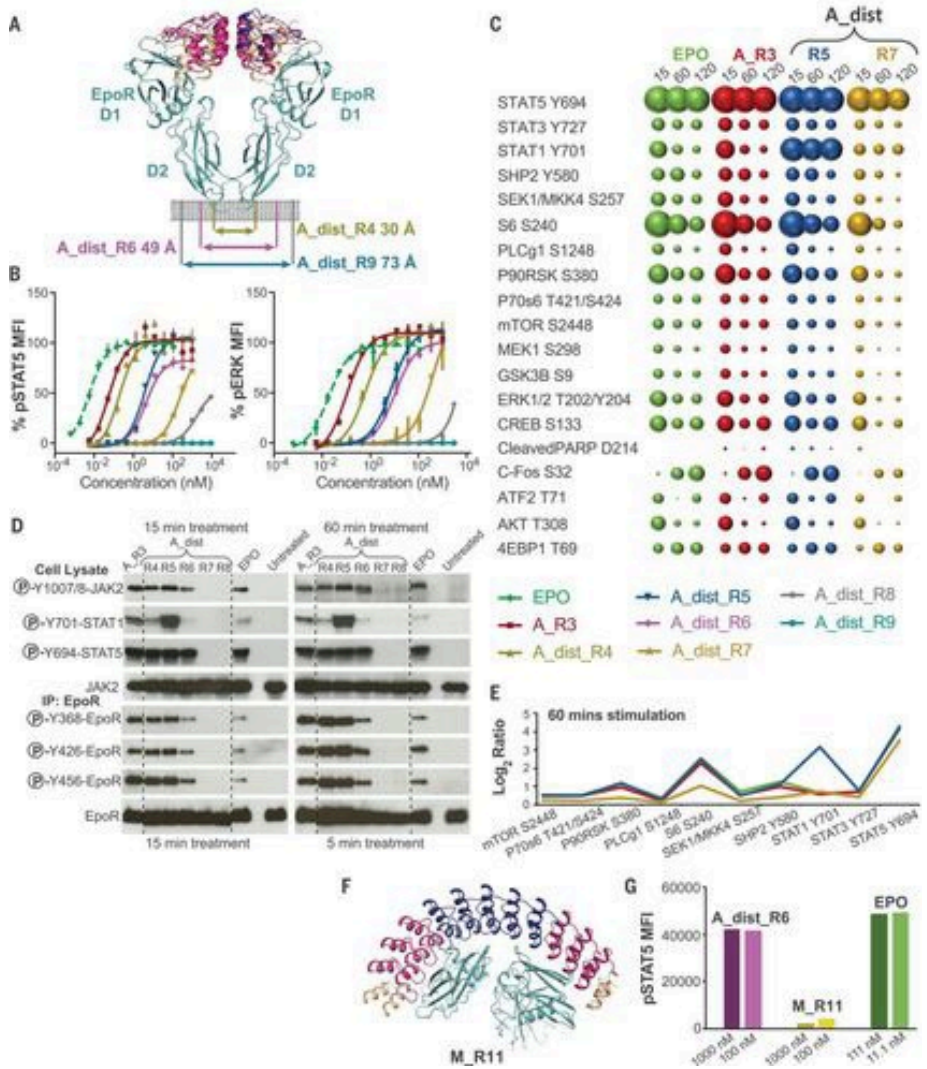
Topological control of EpoR geometry



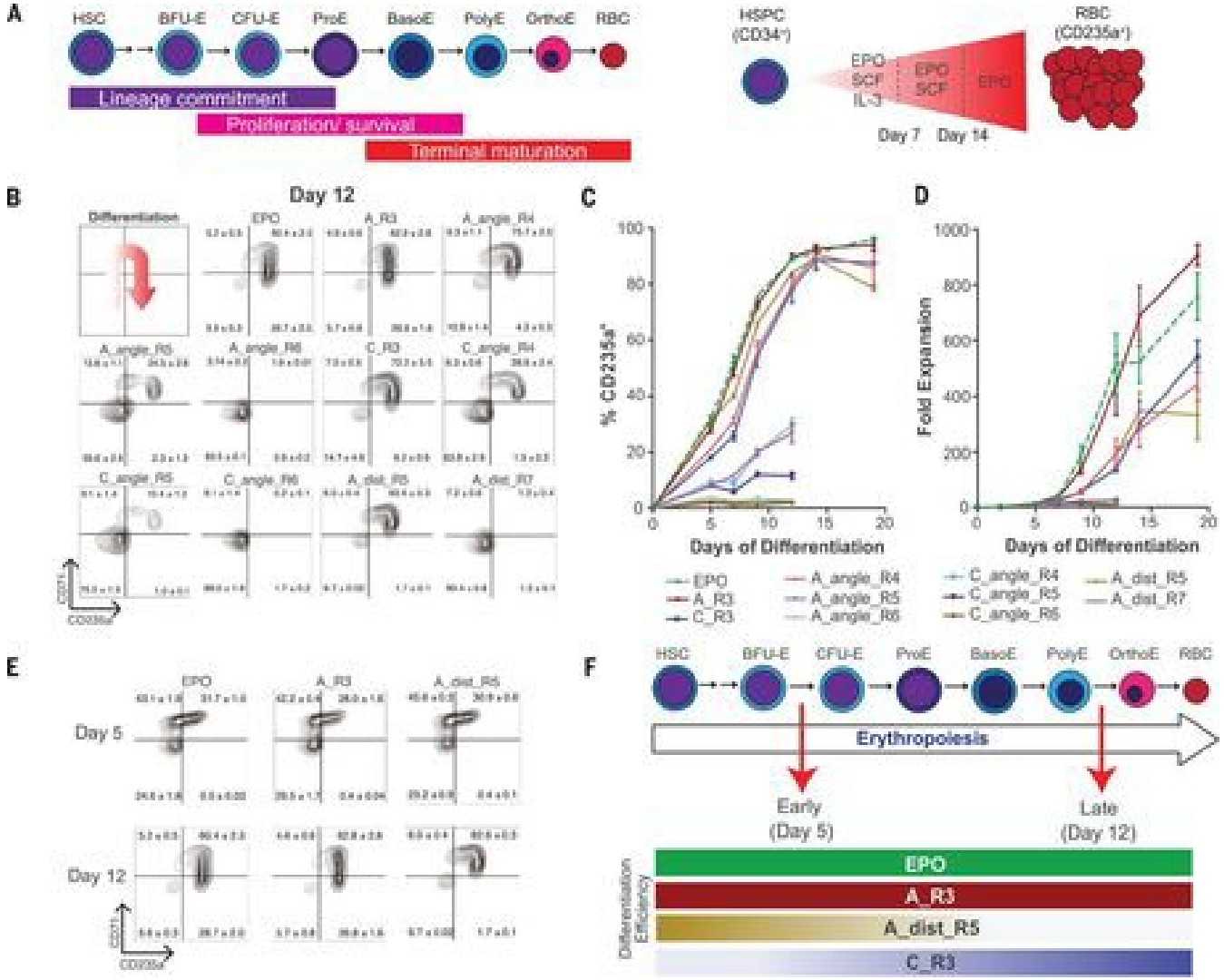
Signaling responses induced through variation in EpoR dimer angle



Signaling responses induced by variation in EpoR ECD proximity



Effects on hematopoiesis of topologically controllable EpoR ligands



Effects on hematopoiesis of topologically controllable EpoR ligands