OMB No. 3145-0279 (Expiration Date 10/31/2026)

NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Skotheim, Jan M.

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0001-8420-6820

Position Title: Professor of the Department of Biology and Department of Chemical and Systems Biology

Organization and Location: Stanford University, Stanford, California, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of Cambridge, Cambridge, England, United Kingdom	Doctor of Philosophy (PHD)	07/2001	10/2004	Applied Mathematics
University of Cambridge, Cambridge, England, United Kingdom	Part III	10/2000	05/2001	Mathematics
Massachusetts Institute of Technology, Cambridge, Massachusetts, United States	Bachelor of Science (BS)	09/1995	06/1999	Physics
Massachusetts Institute of Technology, Cambridge, Massachusetts, United States	Bachelor of Science (BS)	09/1995	06/1999	Mathematics

Appointments and Positions

2020 - present	Professor of the Department of Biology and Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States
2015 - 2019	Associate Professor of the Department of Biology and Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States
2008 - 2015	Assistant Professor of the Department of Biology and Department of Chemical and Systems Biology, Stanford University, Stanford, California, United States
2005 - 2008	Postdoctoral Fellow, The Rockefeller University, New York, New York, United States

Products

Products Closely Related to the Proposed Project

1. Topacio BR, Zatulovskiy E, Cristea S, Xie S, Tambo CS, Rubin SM, Sage J, Kõivomägi M, Skotheim JM. Cyclin D-Cdk4,6 Drives Cell-Cycle Progression via the Retinoblastoma Protein's C-Terminal Helix. Mol Cell. 2019 May 16;74(4):758-770.e4. PubMed Central PMCID: PMC6800134.
2. Zatulovskiy E, Zhang S, Berenson DF, Topacio BR, Skotheim JM. Cell growth dilutes the cell cycle inhibitor Rb to trigger cell division. Science. 2020 Jul 24;369(6502):466-471. PubMed Central PMCID: PMC7489475.
3. Xie S, Zhang S, de Medeiros G, Liberali P, Skotheim JM. The G1/S transition in mammalian stem cells in vivo is autonomously regulated by cell size. Nat Commun. 2025 Oct 13;16(1):9071. PubMed Central PMCID: PMC12518844.
4. Lanz MC, Zhang S, Swaffer MP, Ziv I, Götz LH, Kim J, McCarthy F, Jarosz DF, Elias JE, Skotheim JM. Genome dilution by cell growth drives starvation-like proteome remodeling in mammalian and yeast cells. Nat Struct Mol Biol. 2024 Dec;31(12):1859-1871. PubMed Central PMCID: PMC13015536.
5. Lanz MC, Zatulovskiy E, Swaffer MP, Zhang L, Ilerten I, Zhang S, You DS, Marinov G, McAlpine P, Elias JE, Skotheim JM. Increasing cell size remodels the proteome and promotes senescence. Mol Cell. 2022 Sep 1;82(17):3255-3269.e8. PubMed Central PMCID: PMC9444988.

Other Significant Products Highlighting Contributions to Science

1. Skotheim JM, Di Talia S, Siggia ED, Cross FR. Positive feedback of G1 cyclins ensures coherent cell cycle entry. Nature. 2008 Jul 17;454(7202):291-6. PubMed Central PMCID: PMC2606905.
2. Schmoller KM, Turner JJ, Kõivomägi M, Skotheim JM. Dilution of the cell cycle inhibitor Whi5 controls budding-yeast cell size. Nature. 2015 Oct 8;526(7572):268-72. PubMed Central PMCID: PMC4600446.

3. Swaffer MP, Marinov GK, Zheng H, Fuentes Valenzuela L, Tsui CY, Jones AW, Greenwood J, Kundaje A, Greenleaf WJ, Reyes-Lamothe R, Skotheim JM. RNA polymerase II dynamics and mRNA stability feedback scale mRNA amounts with cell size. Cell. 2023 Nov 22;186(24):5254-5268.e26. PubMed PMID: 37944513.
4. Kõivomägi M, Swaffer MP, Turner JJ, Marinov G, Skotheim JM. G(1) cyclin-Cdk promotes cell cycle entry through localized phosphorylation of RNA polymerase II. Science. 2021 Oct 15;374(6565):347-351. PubMed Central PMCID: PMC8608368.
5. Doncic A, Atay O, Valk E, Grande A, Bush A, Vasen G, Colman-Lerner A, Loog M, Skotheim JM. Compartmentalization of a bistable switch enables memory to cross a feedback-driven transition. Cell. 2015 Mar 12;160(6):1182-95. PubMed Central PMCID: PMC4377233.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

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Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

Certified by Skotheim, Jan M. in SciENcv on 2026-05-19 20:27:17

NIH BIOGRAPHICAL SKETCH SUPPLEMENT

Name: Skotheim, Jan M.

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Personal Statement

Since establishing my laboratory in 2008, I have built an interdisciplinary team that applies advanced quantitative approaches to fundamental questions in cell growth and cell-cycle control, including single-cell imaging, mathematical and statistical modeling, and proteomic methods. This expertise and our prior work on the link between cell growth, cell cycle control, and cellular senescence directly supports the 3 aims of the R01 proposal that seeks to define large cells as a distinct pre-senescent state that can be therapeutically targeted. My lab has extensive experience developing and applying single-cell quantitative assays to understanding cell growth and division, including in vivo (see Xie et al Nature Communications 2025). Our landmark study of growth and division showed how cell growth dilutes inhibitors of cell division in budding yeast (Schmoller et al Nature 2015). We found that the Rb protein in human cells is similarly diluted as cells grow in G1 phase of the cell cycle to provide a novel trigger pathway controlling G1/S (Zatulovskiy et al Science 2020). This work linking growth to division led us to study the effects of when cells became too large. We found that when cells become too large, they remodel their proteomes to continuously approach that of a senescent cell that is incapable of division (Lanz et al. 2024 Nature Structural and Molecular Biology; Lanz et al. 2022 Molecular Cell). Taken together these studies demonstrate our commitment to studying deep questions at the interface of cell growth, division, and senescence.

In addition to research qualifications, I have a strong record of mentoring trainees and preparing them for independent research careers. 8 of 9 postdoctoral scholars from my laboratory have obtained faculty positions as principal investigators at leading institutions, including the University of Cambridge, the NIH National Cancer Institute, the University of Edinburgh, UT Southwestern, the University of Tübingen, the Helmholtz Institute Munich, and UC Santa Cruz. Among my graduate students, 14 of 15 completed their Ph.D. in a timely manner (one required medical leave). Alumni have pursued independent fellow positions and academic postdoctoral training, while others have transitioned into biotechnology; one former trainee founded BillionToOne, a company applying quantitative biological approaches to diagnostics now valued over $5 billion.

I also contribute actively to the broader scientific community through leadership, conference organization, and inclusive training initiatives. I served on Stanford University's Long-Term Planning Committee for the natural sciences and have been a primary organizer of the biennial Cell Cycle Meeting at the Salk Institute since 2015, including the addition of a low-cost online participation option to broaden access. I have also organized meetings on cell size control (2018, 2020, 2023, 2025) and co-hosted more than 150 sessions of the freely accessible online international seminar series "Cell Size and Growth." I was recently named a fellow of AAAS.

For a full list of publications see:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40631145/?sort=date&direction=descending

Honors

2026	Elected Fellow, American Association for the Advancement of Science
2022	Named Investigator, Chan Zuckerberg Biohub
2016	Trends in Cell Biology, Young and Trending, Trends in Cell Biology, Young and Trending
2016	Named Faculty Scholar, HHMI, Gates Foundation & Simons Foundation
2012	Named David Hunington Dean's Faculty Scholar, David Hunington Dean's Faculty Scholar
2011	Recipient of an NSF CAREER Award, National Science Foundation
2009	Member, The Stanford Bio-X Program for interdisciplinary research
2008	Recipient of the Burroughs Wellcome Fund Career Award at the Scientific Interface, Burroughs Wellcome Fund
2008	Member, The Stanford Biophysics Program
2006	The François Naftali Frenkiel Award for a significant contribution to Fluid Mechanics by a researcher under 40., American Physical Society
2006 - 2008	Ruth L. Kirschstein National Research Service Award (Individual Fellowship), National Institutes of Health

2003	Rayleigh-Knight Prize, University of Cambridge
2001	Foundation Scholarship and Bachelor Scholarship, Queens' College, University of Cambridge
2000 - 2003	Graduate Fellowship, National Science Foundation
1999 - 2000	Grant to study in Spain, Fulbright

Contributions to Science

1. How yeast cells control their size:

   Cell size is crucial as it influences a cellular function and the ecological niches a single-celled organism can occupy. Although key regulatory proteins impacting cell size were identified, the molecular mechanisms linking cell size to cell proliferation were not well-understood at the outset of our studies. In budding yeast, cell size control occurs in the G1 phase and is influenced by the level of the G1 cyclin Cln3, which was believed to be the main initiator of cell division. However, the concentration of Cln3 remains nearly constant during G1, making its role in triggering division unclear. Instead, we found that Whi5, a stable inhibitor synthesized outside G1, is diluted as cells grow until its concentration falls below a threshold that triggers the G1/S transition (Schmoller et al., Nature 2015). Thus, cell size promotes division primarily by diluting Whi5, while Cln3 sets the Whi5 threshold required for commitment. We then explained how Whi5 dilution is achieved mechanistically: cells synthesize an approximately size-independent number of Whi5 molecules via transcriptional control, and Whi5 is partitioned equally between mother and daughter because it associates with chromatin that is evenly segregated at mitosis (Swaffer et al., Molecular Cell 2021). We further identified a Forkhead (Fkh) transcription factor binding array in the WHI5 core promoter as a determinant of size-independent synthesis (Kim et al., bioRxiv 2025), and quantified the relative contributions of Whi5 abundance versus phosphorylation to size regulation (Xiao et al., Current Biology 2024).

2. How cell size triggers division in animal cells:

   Our research has advanced understanding of the link between cellular growth and proliferation, initially through identifying the inhibitor dilution mechanism in yeast. We have applied similar methods to mammalian cells, discovering a comparable concentration decrease of the tumor suppressor Rb during the G1 phase, akin to the Whi5 inhibitor in yeast (Zatulovskiy et al., Science 2020). Notably, Rb's reduction is mainly driven by its degradation via the E3 ubiquitin ligase UBR5 (Zhang et al. 2024). However, and importantly, most studies on animal cells are conducted in vitro, raising questions about their relevance in actual tissues. To bridge this gap, we utilized intravital time-lapse imaging to study cell size control in the highly proliferative adult mouse epidermis. Tracking epidermal stem cells over a week revealed a cell-autonomous size control mechanism reliant on the Rb pathway. While the cellular microenvironment influenced cell growth rates, it did not affect the intrinsic cell size control. Our findings challenge established models of cell cycle regulation in complex tissues and underscore cell-autonomous size control as a key mechanism regulating in vivo cell divisions, significantly impacting stem cell heterogeneity (Xie and Skotheim, Current Biology 2020; Xie et al., Nature Communications 2025).

3. Cell size extensively remodels the proteome to drive broad changes in cell physiology:

   The identification of Whi5 and RB as diluted cell cycle inhibitors (see contributions sections #1 and #2 above) raised the question as to whether there are other proteins that are synthesized in a similar size-independent manner. If so, what role do these other proteins play in size control or in coordinating other cellular processes with changes in cell size? To investigate this, we developed a quantitative mass spectrometry technique to analyze how protein concentrations vary with cell size across thousands of proteins simultaneously (Lanz et al., Molecular Cell 2022). Our findings indicate that changes in protein concentration are common as cells enlarge. Indeed, most of the >3000 proteins we were able to accurately measure exhibited significant size-dependent changes in their concentration. Notably, proteins previously identified as markers of cellular senescence also become prominent in larger proliferating cells. This result suggested direct contribution of large cell size to senescence, which was confirmed through cell biological experiments. In a second study, we showed that changes in the proteome that take place in larger cells also take place in cells whose growth is inhibited. This result suggested that the inefficient growth (protein synthesis rate per unit mass) of large cells plays a role in remodeling the proteome (Zatulovskiy et al., Front. in Cell and Dev. Biol. 2022). These changes appear to be driven by genome dilution, which mimics the effects of a limiting nutrient for growth (Lanz et al., Nature Structural and Molecular Biology 2024). Additionally, we have been exploring how transcriptional and feedback mechanisms ensure that mRNA amounts scale with cell size in budding yeast, leading to the discovery of a novel mechanism that stabilizes mRNA in larger cells (Swaffer et al., Cell 2023).

4. Transcriptional mechanisms controlling the G1/S transition into the cell cycle:

The commitment point to the eukaryotic cell cycle is triggered by a transcriptional positive feedback loop in late G1 phase. We found that the positive feedback genes including the G1/S cyclins CLN1/2 in yeast and CCNE in human cells are expressed prior to other genes co-regulated by the SBF and E2F transcription factors, repectively. This feedback-first regulation ensures that the G1/S transition is a two-step process in which a cell first decides its fate by activating positive feedback and then activates the genome-wide transcription program to change its state (Eser et al., Molecular Cell 2011). We also found an unexpected role for the yeast G1 cyclin Cln3, demonstrating that it initiates the G1/S transition by directly phosphorylating and activating RNA Polymerase II (Koivomagi et al., Science 2021). This is a departure from the previously held belief that Cln3 primarily functions by inhibiting the cell cycle inhibitor Whi5. The findings from this research challenge the established view that the cell cycle Cdks are separate from the transcriptional Cdks. Our studies of transcriptional activation in yeast motivated our studies of the G1/S transition in animal cells, which we showed is triggered by a specific threshold of cyclin-dependent kinase activity (Schwarz et al., Molecular Cell 2018). In addition, we showed how Cyclin D recognizes Rb to target it for phosphorylation by Cdk4/6 complexes to drive transcription at the G1/S transition in mammalian cells (Topacio et al., Molecular Cell 2019). Cyclin D docks the C-terminal helix of Rb, which is a novel structural mechanism for cyclin docking because previous docking was only described for linear motifs in unstructured regions of the proteome. Taken together, this series of systems level and mechanistic biochemical studies have given us insight into how cell cycle-dependent transcription is activated at the G1/S transition.

5. Control of cell division by dynamic differentiation signals:

   I have led several studies revealing the importance of single-cell analysis for understanding the G1/S transition, which is where cells make the decision to commit to division. Beyond the G1/S transition, known as the restriction point in mammalian cells and Start in yeast, cells proceed through the division cycle despite loss of mitogenic signaling. Using a combination of microfluidics, quantitative imaging, and single cell analysis, we showed that commitment to cell division in yeast is directly determined by the activation of a positive feedback loop of G1 cyclins (Skotheim et al., Nature 2008, Doncic et al., Molecular Cell 2011). In another study, we show how the decision to commit to cell division in yeast depends not only on current input MAPK pathway activities, but also on its history of activity (Doncic and Skotheim, Molecular Cell 2013). Moreover, we showed that this memory can be enhanced by the compartmentalization of the cell cycle inhibitor Far1 (Doncic et al., Cell 2015). This demonstrates that the proliferation decision in yeast crucially depends on the dynamics of the input signals. Moreover, taken together, this work provides a general framework for how dynamic input signals can be processed by a cell to enable it to make a robust and accurate decisions.

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