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Special Committee
The Board of Trustees
of the Leland Stanford Junior University
Office of the Board of Trustees
Littlefield Center
365 Lasuen Street
Stanford, CA 94305

Special Committee Chair Lam, Board Chair Yang, and Trustees Coulter and Stone:

In late November 2022, various public allegations of scientific misconduct were raised regarding certain papers on which Stanford University President Dr. Marc Tessier-Lavigne is a co-author. In response, the Stanford University Board of Trustees, the governing body responsible for overseeing the university's president, formed a Special Committee of the Board to examine the facts underlying the allegations. This structure was consistent with what is often seen as best practice from a governance standpoint when allegations have been lodged against the most senior executive officer of an organization so that any review is not led by individuals who ultimately report to the subject of the inquiry.

The Special Committee and the Board thereafter retained me and colleagues at Kirkland & Ellis LLP to lead the review. In January 2023, we engaged a Scientific Panel (also "Panel") to assist in conducting a thorough and impartial evaluation of the facts and scientific issues deemed relevant. The panelists, Hollis Cline, Ph.D., Kafui Dzirasa, M.D., Ph.D., Steven E. Hyman, M.D., Randy Schekman, Ph.D., and Shirley M. Tilghman, Ph.D., were selected for their preeminent academic and scientific backgrounds, as well as their experiences in university leadership, research, and scientific publication.

The work of the Scientific Panel, with the assistance of its forensic consultants,[1] has been thorough, methodical, diligent, and independent. It has included the collection of more than fifty

[1] To assist the Scientific Panel, we engaged as technical consultants Mary Walsh, Ph.D. and Corinna Raimondo, Ph.D., co-founders of Maidstone Consulting, and Hany Farid, Ph.D., University of California, Berkeley, based

thousand documents from journals, institutions, and Dr. Tessier-Lavigne's own digital records, which have been reviewed and, where appropriate, forensically assessed. It has included more than fifty meetings with individuals with knowledge pertaining to one or more aspects of the investigation, including seven meetings with Dr. Tessier-Lavigne. The Panel itself met for internal deliberations generally on a weekly basis since it began its work in early 2023, and it often met multiple times per week. The efforts of counsel at Kirkland & Ellis LLP, the Panel, and its forensic experts have together amounted to thousands of hours of work.

Twelve papers on which Dr. Tessier-Lavigne is a co-author came within the scope of the Panel's review based in substantial part on allegations of research misconduct aired on the website PubPeer, a crowd-sourced platform where members of the scientific community can raise issues or concerns regarding scientific publications. These allegations on PubPeer were sometimes accompanied by parallel press reporting. The Panel was also charged to pursue any significant issues and leads discovered during its review that it determined to be relevant to its work, including those bearing upon the integrity of the scientific process. For that reason, the Panel examined additional topics, including certain allegations about scientific research and papers written when Dr. Tessier-Lavigne was an executive and scientist at Genentech, Dr. Tessier-Lavigne's approach to correcting the scientific record, and his management and oversight of his scientific laboratories.

It should be noted that, while we tried to meet with as many individuals with knowledge pertaining to one or more aspects of the investigation as feasible, it was not always possible to meet with everyone. For example, some individuals with knowledge or potential knowledge of matters pertaining to our work refused to speak with us, often despite multiple overtures. Similarly, some media reporting regarding matters within the scope of our review cited anonymous sources. We believe we were able to locate some of the putative anonymous sources, but certainly not all of them, and the others did not respond to general invitations to the public to speak with us. In addition, while most individuals and institutions—and certainly Dr. Tessier-Lavigne—cooperated with our requests for documents, a small number of them did not cooperate either through direct refusals or indirect conduct amounting to the same.

In addition, for various reasons, certain evidence, including some original research data, was unavailable, including because of the age of the research in question. The conclusions set

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on their expertise and experience, including in scientific research forensics, research integrity matters, and digital imaging forensics. Among their many accomplishments, Dr. Walsh was a leader within the forensics team at Harvard Medical School for many years, Dr. Raimondo held a senior position at Northwestern University's Office of Research Integrity, and Dr. Farid is an eminent professor at the University of California, Berkeley who has been described as the "father" of digital image forensics. Their efforts have substantially contributed to this process and we are grateful for their assistance.

forth in the accompanying report are necessarily based on the evidence and witnesses available to us. The conclusions are limited to the assessment of Dr. Tessier-Lavigne's conduct for the purpose of assisting the Board of Trustees in the exercise of its fiduciary duties, rather than offering judgments as to any other person or satisfying regulatory obligations.

Furthermore, the scope of the Panel's work is limited to the matters described above; it was not feasible to conduct a timely review of the entire body of Dr. Tessier-Lavigne's scientific work with the care required to assess or draw conclusions regarding papers beyond the twelve discussed herein. Practicalities and prudence required a more focused review although, as mentioned above, the review has been rigorous within its defined scope.

Despite these practical limitations, our results are presented with confidence based on the skills, expertise, and experience of the panelists and forensic advisors and the robustness of the process that has been enacted. In performing this task, we have been aware both of Dr. Tessier-Lavigne's distinguished scientific career, including his substantial contributions to neuroscience, as well as his service as president of both Rockefeller and Stanford universities. We have also been aware of the importance of this matter to Stanford, its various stakeholders, and the broader scientific-academic community. The document which follows this letter provides the report of the Scientific Panel, beginning with an Executive Summary, then providing its detailed report, and concluding with a technical Appendix of select forensic issues identified in the course of the review. Immediately below is a brief summary of the key findings and conclusions. I respectfully direct you to the full report for a comprehensive account of these matters.

Brief Summary

The review encompassed three topics: (1) the twelve papers on which Dr. Tessier-Lavigne was a co-author; (2) Dr. Tessier-Lavigne's approach to correcting issues or errors in the scientific record; and (3) Dr. Tessier-Lavigne's management and oversight of his scientific laboratories. The latter two subjects were intertwined with the examination of the twelve papers from early stages of the Panel's review.

Of the twelve papers reviewed, Dr. Tessier-Lavigne was a non-principal author on seven of them and a principal author on the other five. For the seven reviewed papers where Dr. Tessier-Lavigne was a non-principal author, the Scientific Panel has concluded that Dr. Tessier-Lavigne did not have actual knowledge of any manipulation of research data,[2] did not have a material role

[2] The phrase "manipulation of research data" as used here and in the Scientific Panel's report is intended to capture a variety of examples of improper scientific conduct including, for example, splicing of gel panels, digital

in the preparation of the data and/or figures that have been publicly challenged, and was not in a position where a reasonable scientist would be expected to have detected any such misconduct. For the five reviewed papers where Dr. Tessier-Lavigne was a principal author (sometimes referred to as the "primary papers"), the Scientific Panel has concluded that Dr. Tessier-Lavigne did not have actual knowledge of the manipulation of research data that occurred in his lab and was not reckless in failing to identify such manipulation prior to publication. Nonetheless, based on the available research record and other factors, each of the papers has serious flaws in the presentation of research data; in at least four of the five papers, there was apparent manipulation of research data by others.

For one of the five primary papers, published in 2009 in the prominent scientific journal *Nature* (Nature '09), we have also assessed allegations reported in the media that Genentech previously conducted a fraud investigation and made a finding of fraud as to that paper. The paper proposed a model of neurodegeneration which was seen as having great potential for Alzheimer's disease research and therapeutics. The allegations of fraud related to the paper appear to be mistaken, as Genentech also has stated publicly. That said, the Nature '09 paper does have multiple problems. First, the process through which the science of the paper was developed in Dr. Tessier-Lavigne's lab, culminating in its publication in February 2009, lacked the rigor expected for a paper of such potential consequence, although the Panel did not find, based on the evidence available to it, that Dr. Tessier-Lavigne was aware of this lack of rigor. Second, the day-to-day scientific research that went into the paper and its presentation of scientific results contained various errors and shortcomings.

It is our understanding that, regarding these five papers, Dr. Tessier-Lavigne intends to retract at least three of them and, at a minimum, pursue robust corrections as to the other two. The Scientific Panel agrees that significant action is appropriate to correct the scientific record.

As stated above, because the Scientific Panel was charged with pursuing any significant issues and leads discovered during its review that it determined to be relevant to its work, including those bearing upon the integrity of the scientific process, the Panel also examined certain other topics. One of those topics was Dr. Tessier-Lavigne's approach to correcting mistakes in the scientific record. The Scientific Panel has concluded that at various times when concerns with Dr. Tessier-Lavigne's papers emerged—in 2001, the early 2010s, 2015-16, and March 2021—Dr. Tessier-Lavigne failed to decisively and forthrightly correct mistakes in the scientific record.

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manipulation of panel backgrounds, importation of blot results from a research record other than that associated with the paper in question, duplication of bands with or without alteration, and digital alteration of blots.

A second topic which the Scientific Panel examined was Dr. Tessier-Lavigne's management and oversight of his scientific laboratories. Because multiple members of Dr. Tessier-Lavigne's labs over the years appear to have manipulated research data and/or fallen short of accepted scientific practices, resulting in at least five publications in prominent journals now requiring retraction or correction, the culture of the labs in which this conduct occurred was considered. The Scientific Panel has concluded that Dr. Tessier-Lavigne created a laboratory culture with many positive attributes, but the unusual frequency of manipulation of research data and/or substandard scientific practices from different people, at different times, and in labs at different institutions, suggests that there may have been opportunities to improve laboratory oversight and management.

Thank you for the opportunity to assist the Special Committee and the Board in this matter. It was a pleasure to work with the Special Committee, whose members showed great dedication in the discharge of their fiduciary duties to Stanford's many constituencies. I especially thank our panelists who—in addition to holding multiple day jobs as professors, world-class scientists, and academic leaders—worked tirelessly, generously, and amiably on our task. Finally, I thank all the witnesses and other individuals involved in this process for their earnestness, dedication, and hard work, including Dr. Tessier-Lavigne, who was cooperative and professional throughout his interactions with us.

Sincerely,

Mark Filip

Mark Filip, P.C.

KIRKLAND & ELLIS LLP

JULY 17, 2023

Report of the Scientific Panel of the Special Committee of the Stanford University Board of Trustees

Scientific Panelists

Hollis Cline, Ph.D.

Kafui Dzirasa, M.D., Ph.D.

Steven E. Hyman, M.D.

Randy Schekman, Ph.D.

Shirley M. Tilghman, Ph.D.

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Mark Filip, P.C., Kirkland & Ellis LLP

Executive Summary

In January 2023, the Trustees of Stanford University announced that Kirkland & Ellis LLP had convened a panel of distinguished scientists (the "Scientific Panel" or "Panel")[1] to assist in the review of twelve scientific publications on which Stanford University President Dr. Marc Tessier-Lavigne is a co-author.[2] The papers had been the subject of public allegations or concerns about potential research misconduct—primarily, that certain figures in the papers had been inappropriately altered or manipulated. These publications include seven papers[3] where Dr. Tessier-Lavigne is a non-principal author and five papers[4] where he is a principal author.[5]

The Panel was charged with leading the scientific review and analysis of the twelve papers. The Panel was further charged with pursuing any significant issues and leads discovered during its review that it determined to be relevant to its work, including those bearing upon the integrity of the scientific process. In this regard, the Panel examined certain related topics, including allegations about work and papers written when Dr. Tessier-Lavigne was an executive and scientist at Genentech, his approach to correcting the scientific record, and his management and oversight of his scientific laboratories. These additional topics were aspects of the Panel's review insofar as they are intertwined with Dr. Tessier-Lavigne's research and work; they also bear upon the effective functioning of the scientific process, which requires the ability to reproduce and build upon prior results and thereby ensure that science is self-correcting.

Dr. Tessier-Lavigne has enjoyed a distinguished career as a scientist. He arrived at Stanford in 2016 from his presidency of The Rockefeller University, a premier scientific research

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[1] Hollis Cline, Ph.D.; Kafui Dzirasa, M.D., Ph.D.; Steven E. Hyman, M.D.; Randy Schekman, Ph.D.; Shirley M. Tilghman, Ph.D.

[2] Carol Lam, *Update from the Special Committee of the Board of Trustees* (Jan. 13, 2023), https://boardoftrustees.stanford.edu/special-committee/#2023-01-13.

[3] *Journal of Neuroscience* (2012), "Genetic Analysis of DSCAM's Role as a Netrin-1 Receptor in Vertebrates," E. Palmesino *et al.*; *Molecular and Cellular Neuroscience* (2011), "Semaphorin 4C and 4G are ligands of Plexin-B2 required in cerebellar development," V. Maier *et al.*; *Neuron* (2011), "VEGF Mediates Commissural Axon Chemoattraction through Its Receptor Flk1," C. Ruiz de Almodovar *et al.*; *Genesis* (2009), "Generation of an OMgp Allelic Series in Mice," J. Lee *et al.*; *The EMBO Journal* (2008), "FAK–MAPK-dependent adhesion disassembly downstream of L1 contributes to semaphorin3A-induced collapse," A. Bechara *et al.*; *Current Biology* (2004), "Novel Role for Netrins in Regulating Epithelial Behavior during Lung Branching Morphogenesis," Y. Liu *et al.*; *Nature* (2003), "Class 3 semaphorins control vascular morphogenesis by inhibiting integrin function," G. Serini *et al.*

[4] *Nature* (2009), "APP binds DR6 to trigger axon pruning and neuron death via distinct caspases," A. Nikolaev *et al.*; *Nature* (2004), "The netrin receptor UNC5B mediates guidance events controlling morphogenesis of the vascular system," X. Lu *et al.*; *Science* (2001), "Binding of DCC by netrin-1 to mediate axon guidance independent of adenosine A2B receptor activation," E. Stein *et al.*; *Science* (2001), "Hierarchical Organization of Guidance Receptors: Silencing of Netrin Attraction by Slit Through a Robo/DCC Receptor Complex," E. Stein & M. Tessier-Lavigne; *Cell* (1999), "A Ligand-Gated Association between Cytoplasmic Domains of UNC5 and DCC Family Receptors Converts Netrin-Induced Growth Cone Attraction to Repulsion," K. Hong *et al*.

[5] For purposes of this report, "principal author" is defined as: first author or identified as having contributed equally as the first author, last author or identified as having contributed equally as the last author, or a corresponding author. In the case of all five of these papers, Dr. Tessier-Lavigne is identified as a corresponding author.

and education institution. He has been widely recognized for his seminal contributions to the field of neuroscience, including pathbreaking work in the area of axon guidance. Many of the individuals interviewed by the Panel spoke of Dr. Tessier-Lavigne's scientific acumen, his intellect, and the considerable influence that his discoveries have had on the field. Dr. Tessier-Lavigne has built a large body of scientific work amounting to hundreds of papers on which he is a principal or non-principal author.

The Scientific Panel has concluded that Dr. Tessier-Lavigne did not personally engage in research misconduct for any of the twelve papers about which allegations have been raised, based on the evidence currently available to the Scientific Panel. However, several of these papers do exhibit manipulation of research data.[6] The Panel has identified evidence of manipulation of research data in at least four of the five primary papers at issue. The misconduct and/or substandard practices in these papers occurred in Dr. Tessier-Lavigne's lab, but the Panel did not find evidence to conclude that Dr. Tessier-Lavigne engaged in, directed, or knew of the misconduct when it occurred, and the misconduct was of such a nature that a scientist exercising reasonable care could not have been expected to have detected it at the time. The Scientific Panel has also found noteworthy certain aspects of the environment in Dr. Tessier-Lavigne's laboratories and Dr. Tessier-Lavigne's approach to correcting the scientific record.

Methodology of the Panel. The Panel's work to inform its conclusions has been thorough, methodical, diligent, and independent. It has collected more than fifty thousand documents from journals, institutions, and Dr. Tessier-Lavigne's own digital records. These documents have been reviewed and, where appropriate, forensically assessed. In addition, more than fifty meetings were conducted with individuals with knowledge pertaining to one or more aspects of the Panel's review, including seven meetings with Dr. Tessier-Lavigne.[7] The Panel has met for internal deliberations generally on a weekly basis since beginning its work in early 2023, and it often met multiple times per week.

The efforts of the Panel, its third-party forensic consultants, and counsel at Kirkland & Ellis LLP have together amounted to thousands of hours of work, reflecting the seriousness with which everyone involved took the task. The Panel is grateful for the generosity of the many witnesses, most of whom are practicing scientists, with their time and expertise. The conclusions here can be presented with confidence based on the skills, expertise, and experience of the panelists and the robustness of the process that has been enacted. The Panel's conclusions are limited to its assessment of Dr. Tessier-Lavigne's conduct for the purpose of assisting the Board of Trustees in the exercise of its fiduciary duties, rather than offering judgments as to any other person or directly satisfying regulatory obligations. For various reasons, certain evidence, including some original

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[6] The phrase "manipulation of research data" as used throughout this report is intended to capture a variety of examples of improper scientific conduct including, for example, splicing of gel panels, digital manipulation of panel backgrounds, importation of blot results from a research record other than that associated with the paper in question, duplication of bands with or without alteration, and digital alteration of blots. Specific examples of manipulation of research data are discussed throughout this report and an appendix providing forensic detail for certain of these examples and select other instances of manipulation of research data is included with the report. *See* Appendix.

[7] Two of these seven meetings were between Dr. Tessier-Lavigne and the Panel's forensic consultants.

research data, was unavailable to the Panel, including because of the age of the research in question. The Panel's conclusions presented here are necessarily based on the evidence and witnesses available to it. The scope of the Panel's work is limited to the matters described above; it was not feasible to conduct a timely review of the entire body of Dr. Tessier-Lavigne's scientific work with the care required to assess or draw conclusions regarding papers beyond the twelve discussed herein.

Secondary Papers.[8] As to the seven reviewed papers where Dr. Tessier-Lavigne was a non-principal author, the Scientific Panel has concluded that Dr. Tessier-Lavigne did not have actual knowledge of any manipulation of research data, did not have a material role in the preparation of the data and/or figures that have been publicly challenged, and was not in a position where a reasonable scientist would be expected to have detected any such misconduct. For each of these papers, the principal authors have accepted responsibility for the creation of the figure(s) and generation of data at issue and affirmed that Dr. Tessier-Lavigne played no meaningful role in the preparation of the specific data and figures about which questions have arisen in various forums. Furthermore, most of these acceptances of responsibility and affirmations of Dr. Tessier-Lavigne's lack of involvement have also been publicly made.

Primary Papers.[9] As to the five reviewed papers where Dr. Tessier-Lavigne was a principal author, the Scientific Panel has concluded that Dr. Tessier-Lavigne did not have actual knowledge of the manipulation of research data that occurred in his lab and was not reckless in failing to identify such manipulation prior to publication. Nonetheless, based on the available research record and other factors, each of these papers has serious flaws in the presentation of research data; in at least four of the five papers, there was apparent manipulation of research data by others.

Specifically, a group of three papers contain images that are the result of manipulation of research data (Cell '99, Science '01 Binding, Science '01 Silencing). For example, a single blot image was re-used in what were represented to be three separate scientific experiments in Cell '99, and a blot image from Cell '99 was re-used in what was represented to be a different experiment in Science '01 Silencing. Both of these examples have not previously been identified despite years of public scrutiny of the papers.

A fourth primary paper also contains images (which Dr. Tessier-Lavigne did not personally prepare) that indicate manipulation of research data (Nature '04). And a fifth paper includes multiple errors in the work underlying the paper and the presentation of research data and methodology that, at a minimum, fall below customary standards of scientific rigor and process (Nature '09).

With respect to Nature '09, the Scientific Panel investigated allegations reported in the media that Genentech previously conducted a fraud investigation and made a finding of fraud as

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[8] *See supra* n.3.

[9] *See supra* n.4.

to that paper. That allegation appears to be mistaken, as Genentech has stated.[10] Rumors concerning fraud in Nature '09 likely arose from a combination, and potential conflation, of: (1) concerns over the irreproducibility of the research presented in Nature '09, including a central claim of the paper's neurodegeneration model that amyloid-beta precursor protein (APP) binds to death receptor 6 (DR6) at its N-terminus[11] (which was incorrect), and (2) an instance of misconduct committed in Dr. Tessier-Lavigne's laboratory at Genentech (not connected with the Nature '09 paper), the discovery of which led Dr. Tessier-Lavigne to withdraw before publication a different paper on which he was to be a principal author.

The Nature '09 paper has multiple problems. First, the process through which the science of the paper was developed, culminating in its publication in February 2009, lacked the rigor expected for a paper of such potential consequence. Second, the day-to-day scientific research that went into the paper and its presentation of scientific results contained various errors and shortcomings. In that regard, the Panel has identified issues in the paper's underlying calculation of data and presentation of scientific images, along with inadequate disclosures regarding various aspects of the paper's experimental methodologies.

Corrections. The Scientific Panel has concluded that at various times when concerns with Dr. Tessier-Lavigne's papers emerged—in 2001, the early 2010s, 2015-16, and March 2021—Dr. Tessier-Lavigne failed to decisively and forthrightly correct mistakes in the scientific record. These include: (1) failing to correct a duplicated image in Science '01 Silencing, despite the duplication being made known to him within weeks after publication and his providing assurances at that time that he would seek a correction; (2) declining in 2016 to follow up with the journal Science to ensure it published corrections Dr. Tessier-Lavigne had drafted to attempt to address concerns raised in 2015-16 on PubPeer regarding the two Science '01 papers (including the Science '01 Silencing duplication first identified in 2001); (3) deciding again not to pursue the same corrections when concerns arose again on PubPeer in March 2021; and (4) pursuing a strategy of subsequent publication to address the inaccuracies in the model of neurodegeneration presented in Nature '09 without issuing a direct correction or retraction to alert the field in a clear fashion. In addition, the proposed (2015-16) corrections to the Science '01 papers were based in part on an explanation by Dr. Tessier-Lavigne of a "tiling" phenomenon that, while sincerely believed at the time, was not independently forensically assessed. In fact, tiling does not explain the underlying image manipulations in at least some of the figures to which the explanation was intended to apply.

In each of the above cases, timely correction or retraction and/or more forthright and transparent actions toward correcting the scientific record would have better served science and all concerned. In addition, the need for corrective action remains, particularly given several issues newly identified in the Scientific Panel's review of the papers at issue. The Panel understands that Dr. Tessier-Lavigne now intends to retract at least three publications on which he is a principal author and, at a minimum, pursue robust corrections as to the two other publications at issue where

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[10] Genentech, *Findings of 2023 Genentech Review of 2009* Nature *Paper and Related Research* (Apr. 6, 2023), https://www.gene.com/download/pdf/Findings-of-2023-Genentech-Review-of-2009-Nature-Paper-and-Related-Research.pdf.

[11] More technically, that an N-terminal fragment of APP binds to the ectodomain of DR6.

he is a principal author. The Panel agrees that significant action is appropriate to correct the scientific record.

Laboratory Culture. Multiple members of Dr. Tessier-Lavigne's labs over the years appear to have manipulated research data and/or fallen short of accepted scientific practices. As a result, at least five publications in preeminent journals now require retraction or correction. When examining such behavior, the culture of the lab in which it occurred must be considered. The Scientific Panel has concluded that Dr. Tessier-Lavigne created a laboratory culture with many positive attributes, but the unusual frequency of manipulation of research data and/or substandard scientific practices from different people, at different times, and in labs overseen by Dr. Tessier-Lavigne at different institutions, suggests that there may have been opportunities to improve laboratory oversight and management.

I. BACKGROUND

In late-November 2022, various public allegations of scientific misconduct were raised regarding certain papers on which Stanford University President Dr. Marc Tessier-Lavigne is a co-author.[12] In response to those allegations, the Stanford University Board of Trustees, the governing body responsible for overseeing the university president, formed a Special Committee of Trustees to examine the facts underlying the allegations.[13] The Special Committee and Board retained former federal judge and U.S. Deputy Attorney General Mark Filip, now of Kirkland & Ellis LLP, to lead the review. In January 2023, Kirkland & Ellis engaged this Scientific Panel. The Panelists were selected for their preeminent academic and scientific backgrounds, as well as their diverse experiences in university leadership, research and publication, and editorial leadership.

The Panel is comprised of:

- Hollis Cline, Ph.D., Chair of the Department of Neuroscience at the Scripps Research Institute, Director of the Dorris Neuroscience Center at the Scripps Research Institute, Professor of Neuroscience at the Scripps Research Institute, and a Member of the National Academy of Sciences;

- Kafui Dzirasa, M.D., Ph.D., A. Eugene and Marie Washington Presidential Distinguished Professor of Psychiatry and Behavioral Sciences, Biomedical Engineering, Neurobiology, and Neurosurgery at Duke University, Investigator of the Howard Hughes Medical Institute, and a Member of the National Academy of Medicine;

- Steven E. Hyman, M.D., Professor of Stem Cell and Regenerative Biology at Harvard University, Director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard, former Provost of Harvard University, former Director of the U.S. National Institute of Mental Health, and a Member of the National Academy of Medicine;

- Randy Schekman, Ph.D., Professor of Cell and Developmental Biology at the University of California, Berkeley, Investigator of the Howard Hughes Medical Institute, 2013 Nobel Laureate in Physiology/Medicine, a Member of the National Academy of Sciences, and a Member of the National Academy of Medicine; and

- Shirley M. Tilghman, Ph.D., Professor of Molecular Biology and Public Affairs Emerita at Princeton University, former President of Princeton University, an International Member of the National Academy of Sciences, and a Member of the National Academy of Medicine.[14]

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[12] As discussed in detail below in Sections II(B)(1) and III(B)-(C), for certain papers, allegations had been raised at the website PubPeer before 2022.

[13] Jerry Yang, *Statement from Jerry Yang, Chair of the Stanford University Board of Trustees* (Dec. 2, 2022), https://boardoftrustees.stanford.edu/special-committee/#2022-12-02.

[14] The Panel was aided by the scientific forensics research expertise of Maidstone Consulting co-founders Mary Walsh, Ph.D. and Corinna Raimondo, Ph.D. and their team and the digital imaging expertise of Hany Farid, Ph.D. of the University of California, Berkeley. Dr. Walsh was a leader within the forensics team at Harvard Medical

The Panel agreed to conduct a thorough and impartial evaluation of the facts and scientific issues that it determined to be relevant.[15] This document serves as a summary report of the Scientific Panel. It is intended for the Special Committee of the Stanford Board of Trustees. Its scope is necessarily limited to the specific publications described herein.

II. PAPERS AT ISSUE

Twelve papers[16] on which Dr. Tessier-Lavigne is a co-author came within the scope of the Panel's review based in large part on allegations of research misconduct aired on the website PubPeer, a crowd-sourced platform where members of the scientific community can raise issues or concerns regarding published papers. These allegations of research misconduct on PubPeer were often accompanied by parallel reporting in media sources.[17]

For seven of these papers (Nature '03, Current Biology '04, EMBO Journal '08, Genesis '09, Molecular & Cellular Neuroscience '11, Neuron '11, and Journal of Neuroscience '12), Dr. Tessier-Lavigne is not a principal author. This report will sometimes refer to these papers as the "secondary papers." For five of these papers (Cell '99, Science '01 Binding, Science '01 Silencing, Nature '04, and Nature '09), Dr. Tessier-Lavigne is a principal author. This report will sometimes refer to these papers as the "primary papers."

One of the fundamental questions the Panel considered was whether Dr. Tessier-Lavigne engaged in "research misconduct" as that term is defined under the federal Office of Research Integrity ("ORI") regulations.[18] Research misconduct is defined under ORI regulations as

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School for nearly a decade, has served as the co-chair of the Forensics Special Interest Group for the national Association of Research Integrity Officers, and has had appointments as Special Advisor to the Research, Rigor, Reproducibility, and Responsibility Initiative at Harvard Medical School and as a Bioethics Fellow for the Harvard Center for Bioethics. Dr. Raimondo was a Senior Compliance Specialist for the Office of Research Integrity at Northwestern University and has served as the co-chair of the Forensics Special Interest Group for the national Association of Research Integrity Officers. Dr. Farid is a professor at the University of California, Berkeley with joint appointments in electrical engineering and computer sciences and the School of Information. He is a member of the Berkeley Artificial Intelligence Lab, the Berkeley Institute for Data Science, the Center for Innovation in Vision and Optics, and the Development Engineering, Vision Science Program, a senior faculty advisor for the Center for Long-Term Cybersecurity, a recipient of an Alfred P. Sloan Fellowship and a John Simon Guggenheim Fellowship, and a fellow of the National Academy of Inventors; he has been described as the "father" of digital image forensics.

[15] Jerry Yang, *Statement from Jerry Yang, Chair of the Stanford University Board of Trustees* (Dec. 2, 2022), https://boardoftrustees.stanford.edu/special-committee/#2022-12-02.

[16] *See supra* nn.3 & 4.

[17] For example, *The Stanford Daily*, *The Chronicle of Higher Education*, and *Stat News*.

[18] *See generally* 42 CFR Part 93. The Panel has made use of these regulations, and parallel provisions in the Stanford University Research Policy Handbook ("RPH") (*see* RPH § 1.7), as providing the relevant standards to inform its review about whether Dr. Tessier-Lavigne has personally committed research misconduct regarding any of the twelve papers; the applicable evidentiary standard for ORI findings of research misconduct is a preponderance of the evidence. 42 CFR § 93.106(a). However, the Panel's findings in this regard are not a determination pursuant to 42 CFR Part 93 or RPH § 1.7.

"fabrication, falsification or plagiarism in proposing, performing, or reviewing research, or in reporting research results."[19] Research misconduct requires "a significant departure from accepted practices of the relevant research community," and the misconduct must be "committed intentionally, knowingly, or recklessly."[20] Based on the evidence available to it, the Panel does not find that Dr. Tessier-Lavigne engaged in "research misconduct" as to any of the twelve papers at issue. Nor does the Panel find that Dr. Tessier-Lavigne had actual intent or knowledge or was reckless as to any research misconduct in his labs based on the evidence available to it.

A. Secondary Papers (Dr. Tessier-Lavigne Is Not a Principal Author) [Nature '03, Current Biology '04, EMBO Journal '08, Genesis '09, Molecular & Cellular Neuroscience '11, Neuron '11, Journal of Neuroscience '12]

For the seven papers where Dr. Tessier-Lavigne is not a principal author, the Scientific Panel has concluded that Dr. Tessier-Lavigne was not materially involved with the figures that have been challenged or their underlying data. The Scientific Panel has explored the explanations of the authors who were responsible for the challenged figures and data in each paper, and these explanations have not been suggestive of misconduct by Dr. Tessier-Lavigne. Generally, these other authors have publicly stepped forward to acknowledge both their primary role in these papers and Dr. Tessier-Lavigne's lack of involvement in figure and data issues.[21] The Panel has also received corroborating documentation regarding the explanations proffered by the principal authors from either or both those authors and the affiliated journals.

In addition, the Panel does not believe Dr. Tessier-Lavigne was in a position to reasonably detect the alleged errors in these papers to the extent they were present. Dr. Tessier-Lavigne's roles in the secondary papers were often along the lines of contributing a mouse line (an important basis for scientific experimentation), discussing overall scientific approach, and providing drafting input and feedback on the manuscript. These are not atypical roles for a non-principal author, and the realities of modern scientific research, collaboration, and publishing, which often take place with large national and international teams, are such that non-principal authors often are not exposed to the complete underlying research record. Finally, many of the affiliated journals have

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[19] 42 CFR § 93.103.

[20] *Id.* § 93.104. Recklessness is not specifically defined under ORI regulations, but precedent suggests a reasonable definition is "indifference to the truth" or "a lack of proper caution or appropriate care or consideration regarding the risk of fabrication, falsification, or plagiarism." *See, e.g.*, *Off. Rsch. Integrity v. Srivastava*, DAB CR5178 (U.S. Health & Hum. Servs. Sept. 5, 2018) (ALJ's recommended decision), https://www.hhs.gov/about/agencies/dab/decisions/alj-decisions/2018/alj-cr5178/index.html; *Off. Rsch. Integrity v. Kreipke*, DAB CR5109 (U.S. Health & Hum. Servs. May 31, 2018) (ALJ's recommended decision), https://www.hhs.gov/about/agencies/dab/decisions/alj-decisions/2018/alj-cr5109/index.html. Parallel bodies of research integrity regulatory guidance have suggested similar definitions. *See, e.g.*, NAT'L SCI. FOUND., OFF. INSPECTOR GEN., ASSESSING INTENT IN RESEARCH MISCONDUCT INVESTIGATIONS (2021), https://oig.nsf.gov/sites/default/files/document/2021-10/Assessing%20Intent%20in%20RM%20Investigations_4.pdf.

[21] *E.g.*, Binhai Zheng, *Generation of an OMgp Allelic Series in Mice*, PUBPEER (Dec. 2022), https://pubpeer.com/publications/35AFF1942E3E2EA3E009E8441844E4#2.

published corrections that are consistent with both the explanations proffered by the principal authors and the documentation received.[22]

B. Primary Papers (Dr. Tessier-Lavigne Is a Principal Author) [Cell '99, Science '01 Binding, Science '01 Silencing, Nature '04, Nature '09]

For the five papers where Dr. Tessier-Lavigne is a principal author, the Scientific Panel has concluded that Dr. Tessier-Lavigne did not commit research misconduct as that term is defined under ORI regulations. At no point in its work did the Panel encounter evidence to conclude that Dr. Tessier-Lavigne acted inappropriately to manipulate research data within these or any other papers, nor did it encounter evidence to conclude that he knowingly countenanced others doing so. Nonetheless, the five papers are not free of instances of manipulation of research data and other material issues, as described below.

1. Cell '99, Science '01 Binding, Science '01 Silencing

Regarding the group of three papers Cell '99, Science '01 Binding, and Science '01 Silencing, the Panel finds that these papers contain evidence of manipulation of research data. The Panel has found no evidence to suggest that Dr. Tessier-Lavigne knew of these manipulations when they occurred. The issues in these papers are wide-ranging. Some of them have been covered in external comments and others are not publicly known.[23] Prominent examples of manipulation of research data in these papers include: (1) the re-use of a single blot image in three figures in Cell '99 for what are represented to be three separate experiments (Figs. 3C, 7A, and 7B); (2) the re-use of a panel from Cell '99 (Fig. 7D) in what was represented to be a different experiment in Science '01 Silencing (Fig. 4E); (3) extensive manipulations throughout Figure 3 of Science '01 Binding, including the insertion of blots from unknown sources, duplication of and other manipulations to panel backgrounds, the creation of constructed, composite blots not actually associated with the research record for the given experiment, and the reuse with modification of

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[22] *E.g.*, *Neuron* (2023), "Correction: VEGF Mediates Commissural Axon Chemoattraction Through Its Receptor Flk1," C. Ruiz de Almodovar *et al*., https://doi.org/10.1016/j.neuron.2023.03.029.

[23] **Cell '99**: There are public allegations (PubPeer) of issues in seven figures in Cell '99 (3A, 3C, 5A, 5B, 7B, 7C, 7D). The Panel's internal analyses in conjunction with meetings with relevant participants and received scientific documentation substantiate these allegations, to varying degrees of proof, with the exception of the claim regarding Figure 5A. The Panel's internal analyses have also identified additional issues in two figures with existing public allegations and issues in four figures with no prior allegations.

Science '01 Binding: There are public allegations (PubPeer) of issues in four figures in Science '01 Binding (3A, 3B, 3C, 3D). The Panel's internal analyses in conjunction with meetings with relevant participants and received scientific documentation substantiate these allegations, to varying degrees of proof. The Panel's internal analyses have also identified additional issues in two figures with existing public allegations and issues in three figures with no prior allegations.

Science '01 Silencing: There are public allegations (PubPeer) of issues in ten figures in Science '01 Silencing (2D, 4A, 4B, 4C, 4D, 4E, 5C, 5D, 5E, 6C). The Panel's internal analyses in conjunction with meetings with relevant participants and received scientific documentation substantiate these allegations, to varying degrees of proof. The Panel's internal analyses have also identified additional issues in seven figures with existing public allegations and issues in four figures with no prior allegations.

blots between experimental panels (Figs. 3B/3D); (4) extensive manipulations throughout Figures 4 and 5 of Science '01 Silencing, including the insertion—without evidence of connection to the actual research record—of both background and data-containing sections of experimental panels and the duplication—both with and without additional manipulation—of panel backgrounds across what are represented to be separate experiments.[24] There are multiple additional examples of research data manipulation in these three papers beyond the ones cited here as examples.

Some of the publicly challenged conduct in these three papers can be characterized as "beautification" of images in the sense of digital manipulation not affecting data-containing regions of the experimental figure and intended to improve the aesthetics of that figure for presentation. Digital beautification practices were not a norm during the publication period of these papers or the Nature '04 paper, but such practices were not clearly proscribed then, although Dr. Tessier-Lavigne has stated in discussion with the Panel that he has never condoned digital beautification practices in his labs. Standards in the field around digital manipulation began to take shape in the mid-2000s, and beautification is now considered unacceptable. Nonetheless, much of the conduct at issue in these three papers, including the examples given above, would not be fairly characterized as beautification and was clearly impermissible both then and now.

Based on the facts reviewed, it would not be reasonable to expect Dr. Tessier-Lavigne to have identified these instances of research data manipulation prior to or at the time of the respective papers' publications. The Panel has no reason to believe that Dr. Tessier-Lavigne knew about these instances of research data manipulation in the three papers contemporaneous with their occurrence. Indeed, several of these manipulations went undetected by the scientific public even with the use of cutting-edge image analysis tools available fifteen to twenty years after the papers' publications.

In 2015, allegations of research data manipulation concerning the three papers first appeared on PubPeer.[25] Dr. Tessier-Lavigne assessed these issues in the fall of 2015.[26] He stated to the Panel that he initially thought that some of the issues involved "beautification" while others potentially represented more serious instances of manipulation of research data. Over the ensuing

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[24] *See* Appendix for additional forensic detail regarding various examples of research data manipulation within the five primary papers.

[25] *See, e.g.*, Anonymous, *A Ligand-Gated Association Between Cytoplasmic Domains of UNC5 and DCC Family Receptors Converts Netrin-Induced Growth Cone Attraction to Repulsion*, PUBPEER (Oct. 2015), https://pubpeer.com/publications/250D42FBB7D7298E704BFD6CD8B22A#1 (Cell '99); Anonymous, *Binding of DCC by Netrin-1 to Mediate Axon Guidance Independent of Adenosine A2B Receptor Activation*, PUBPEER (Oct. 2015), https://pubpeer.com/publications/59C3359E71EED451E01AF46CFDC0BC#1 (Science '01 Binding); Anonymous, *Hierarchical Organization of Guidance Receptors: Silencing of Netrin Attraction by Slit Through a Robo/DCC Receptor Complex*, PUBPEER (Oct. 2015), https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB#2 (Science '01 Silencing).

[26] The Panel has reviewed an extensive record of correspondence between Dr. Tessier-Lavigne, certain of his co-authors on these papers, and the publishing journals. This is discussed in more detail below in Section III.

months in 2016, based on a discussion Dr. Tessier-Lavigne observed on PubPeer,[27] he came to re-characterize the latter set of issues (in the two Science papers) as attributable to a phenomenon known as "tiling" and caused by Adobe Acrobat software rather than manipulation of research data. The draft corrections he provided to the journal Science in 2016 (which were not published, as discussed further in Section III, below) reflect this view. In late-2022, additional allegations of manipulation of research data regarding two of the three papers began to appear on PubPeer.[28]

Regarding this so-called "tiling" phenomenon, Dr. Tessier-Lavigne and the Scientific Panel along with its forensic experts have had several discussions together both to understand Dr. Tessier-Lavigne's view and to provide him with additional forensic perspectives. The Panel believes that Dr. Tessier-Lavigne sincerely held the belief in 2016 (and through 2023) that: (1) tiling was a valid forensic explanation for certain issues observed in the two Science '01 papers, and (2) by applying that explanation, issues that would otherwise be deemed clearly improper could be properly recharacterized as "beautifications" or as non-issues. Dr. Tessier-Lavigne reached this conclusion based on a description and discussion of the tiling phenomenon in a series of anonymous posts on PubPeer and his own testing of the concept on the two Science '01 papers; it was not independently forensically assessed. As has been conveyed to Dr. Tessier-Lavigne, following a thorough forensic consideration of the topic, the Panel and its forensic experts do not believe that tiling validly explains the underlying image manipulations present in at least some of the relevant figures.

When the Science papers are placed into "Edit" mode within Adobe Acrobat software, the figures in the papers become divided into "tiles," which are movable.[29] These tiles may slightly overlap one another up to the width of a pixel. This overlap can be present for images which have not been altered in any way. When in Edit mode, some of the figures show an orderly division of tiles and others show a disorderly division of tiles (*see* Appendix). For any two tiles that are overlapped, by moving the overlying tile off the underlying tile to remove the overlap, minor additional data will be revealed in the underlying tile. This movement can cause certain of the splices apparent in figures in the Science '01 papers to become smoothed, removing the appearance of the splice, which was Dr. Tessier-Lavigne's understanding of the implications of "tiling" when he developed the explanation.

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[27] *Hierarchical Organization of Guidance Receptors: Silencing of Netrin Attraction by Slit Through a Robo/DCC Receptor Complex*, PUBPEER (May 2016), https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB#20 (comments #20-26).

[28] *See, e.g.*, Elisabeth M. Bik, *A Ligand-Gated Association Between Cytoplasmic Domains of UNC5 and DCC Family Receptors Converts Netrin-Induced Growth Cone Attraction to Repulsion*, PUBPEER (Nov. 2022), https://pubpeer.com/publications/250D42FBB7D7298E704BFD6CD8B22A#9 (Cell '99); Anonymous, *Binding of DCC by Netrin-1 to Mediate Axon Guidance Independent of Adenosine A2B Receptor Activation*, PUBPEER (Oct. 2022), https://pubpeer.com/publications/59C3359E71EED451E01AF46CFDC0BC#16 (Science '01 Binding).

[29] Not all PDF (Portable Document Format) files render images into tiles viewable when Adobe Acrobat software is placed in Edit mode. This variability is likely attributable to variations in how the original PDF was created and whether the associated software at the time partitioned the images in the file into tiles.

However, forensic analysis demonstrates that the presence of disordered sets of tiles for a given figure indicates that manipulation of research data occurred and that the tiles were then used to attempt to reconstitute the panel image following the manipulation. Some of these reconstitution efforts introduced, likely inadvertently, minute overlap between the tiles (thus resembling the overlap which can occur even in the absence of any manipulation). In other words, what Dr. Tessier-Lavigne took to be the implication of tiling, that is, a minor digital overlap generated in Adobe, creating the appearance of a splice, and resolvable through adjusting the tiles, is not a sufficient explanation: When figures show disordered tiles in Edit mode and have accompanying apparent splices, these features are *a result of* underlying manipulations that were performed and then attempted to be obscured. Through forensic analysis, the Panel has observed a record of some of these manipulations involving, for example, the modification of a blot in Figure 3C of Science '01 Binding (this example is included in the Appendix).

To date, all three of these papers (Cell '99, Science '01 Binding, Science '01 Silencing) remain published. Editorial Expressions of Concerns were issued in late-2022 by both Cell and Science, but these notes do not fully address all the issues present in the papers and the Science notes refer to "tiling"[30] in a manner that, as discussed above, is not forensically complete or sound. Given the wide-ranging issues in these three papers, many of which have now been discussed between the Panel and Dr. Tessier-Lavigne, Dr. Tessier-Lavigne has stated to the Panel that he intends to retract all three papers. The Scientific Panel agrees with this proposed action by Dr. Tessier-Lavigne.

2. Nature '04

The Panel finds that the Nature '04 paper reflects evidence of manipulation of research data. The Panel found no evidence that Dr. Tessier-Lavigne knew of these manipulations contemporaneous with their occurrence or that he reasonably should have known. Four figures from the paper have been publicly challenged on PubPeer; Dr. Tessier-Lavigne's laboratory was directly responsible for two of the four challenged figures (Supplementary Figures 2D and 2E, regarding the generation of Unc5b mutant mice).[31]

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[30] *Editorial Expression of Concern*, SCIENCE (Dec. 15, 2022), https://www.science.org/doi/10.1126/science.adg2852 (Science '01 Binding); *Editorial Expression of Concern*, SCIENCE (Dec. 15, 2022), https://www.science.org/doi/10.1126/science.adg2860 (Science '01 Silencing). Science, through its parent organization, the American Association for the Advancement of Science (AAAS), has taken the position in correspondence with the Scientific Panel that the published Editorial Expressions of Concern are not intended to represent endorsements of Dr. Tessier-Lavigne's stated "tiling" explanation but rather signal identifications of apparent problems in both papers that require further explanation or investigation. AAAS has further stated that these Editorial Expressions of Concern were written in collaboration with Dr. Tessier-Lavigne. Based on additional documentation available to the Panel, it is apparent that these Editorial Expressions of Concern, including their reference to the tiling phenomenon, are derived from the 2016 corrections which Dr. Tessier-Lavigne created in consultation with certain of his co-authors on the respective Science '01 papers and the editorial staff of Science.

[31] The Panel's internal analyses in conjunction with meetings with relevant participants and received scientific documentation substantiate these allegations, to varying degrees of proof. The other two figures at issue are Figs. 4A and 4B.

Dr. Tessier-Lavigne has shared with the Panel communications he and others have recently had with the journal Nature on this topic. These communications include proposed explanations for the observed issues in the two supplementary figures and an acknowledgment of certain of the issues raised regarding Figure 4. Other co-authors have also engaged in new experiments intended to show the reproducibility of the results in the challenged figures.

The Panel notes that, even where it is possible to demonstrate a claimed experimental outcome through post-publication experimentation, this does not necessarily dispel a finding of manipulation of research data in the original presentation of results. In addition, regarding the explanations proffered to Nature concerning the challenged figures (for example, that issues observed in Supplementary Figure 2 are attributable to ethidium bromide gel staining and the same membrane being sequentially blotted with the indicated probes), the Panel finds that these explanations are not fully responsive to the range of publicly expressed concerns given the available forensic evidence.

In discussions with the Panel, Dr. Tessier-Lavigne has acknowledged the presence of manipulation of research data in this paper and has pointed to his current engagement with the journal Nature on this topic. It is the view of the Panel that a thorough correction which adequately addresses all issues is required and appropriate for the paper, which it understands Dr. Tessier-Lavigne is seeking.

3. Nature ’09

Beginning in February 2023, allegations emerged regarding the paper Nature ’09, including that Genentech, Dr. Tessier-Lavigne’s employer at the time of its publication, conducted a fraud investigation into the paper[32] and that certain images in the paper reflected manipulation of research data.[33] There has also been reporting[34] regarding Dr. Tessier-Lavigne’s decision to neither retract nor correct Nature ’09 after, by his own acknowledgment, “[w]e were led to revise our initial models[,]” [35] but rather to rely on the publication of follow-on papers (as discussed in more detail below in Section III).

Nature ’09 made claims for a neurodegeneration pathway that, if borne out, could have had significant implications for Alzheimer’s disease research and therapeutics; it was given substantial attention within Genentech and the wider neuroscience field at the time of its publication.

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[32] *E.g.*, *Internal Review Found ‘Falsified Data’ in Stanford President’s Alzheimer’s Research, Colleagues Allege*, THE STANFORD DAILY (Feb. 17, 2023), https://stanforddaily.com/2023/02/17/internal-review-found-falsified-data-in-stanford-presidents-alzheimers-research-colleagues-allege/.

[33] *E.g.*, *id.*

[34] *E.g.*, *‘MTL Knew’: Misconduct Allegations Independently Corroborated in Private Correspondence to Special Committee*, THE STANFORD DAILY (Mar. 6, 2023), https://stanforddaily.com/2023/03/06/mtl-knew-misconduct-allegations-independently-corroborated-in-private-correspondence-to-special-committee/.

[35] *Scientific Context on the 2009 Paper (Nikolaev* et al. Nature *2009) and Subsequent Work* (Feb. 15, 2023), https://tessier-lavigne-lab.stanford.edu/sites/tessier_lavigne_lab/files/media/file/scientific-context6.pdf.

Subsequently, however, elements of the model described in the paper had to be corrected or refined, including:

- One of the model's central claims, regarding where the amyloid-beta precursor protein (APP) bound to death receptor 6 (DR6)—it was claimed that APP bound to DR6 at APP's N-terminus, but it was later shown that the binding in fact occurred in a separate region, the E2 domain;[36]

- The role of particular caspases in axonal degeneration—it was claimed that Caspase-6 but not Caspase-3 was required for axonal degeneration, but it was later shown that Caspase-3 is also required;[37]

- The necessity of beta-secretase (BACE1) enzyme activity for APP-DR6 binding—it was claimed that beta-secretase was necessary to create fragments of APP for binding to DR6, but it was later shown that beta-secretase cleavage is not materially relevant to APP-DR6 binding.[38]

Ultimately, in 2014 and following further *in vivo* work, Dr. Tessier-Lavigne published a paper acknowledging that he did not see evidence for a role of DR6 in the pathophysiology of Alzheimer's disease, although he allowed for the possibility that it could still play a role in axon degeneration associated with the disease.[39]

a. Claims of Fraud

The claim that Genentech conducted a fraud investigation and made a finding of fraud as to Nature '09 appears to be mistaken,[40] as Genentech itself has stated.[41] This includes the erroneous claim made in some media sources that Genentech's Research Review Committee conducted a specific inquiry into the paper, which appears to have confused the ordinary business process of the company with the conduct of an *ad hoc* investigation. The Scientific Panel believes that the mistaken narrative of fraud in certain reporting may stem from a conflation of various

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[36] *Journal of Neuroscience* (2014), "Genetic Analysis Reveals that Amyloid Precursor Protein and Death Receptor 6 Function in the Same Pathway to Control Axonal Pruning Independent of β-Secretase," O. Olsen *et al.*

[37] *Journal of Neuroscience* (2012), "A Caspase Cascade Regulating Developmental Axon Degeneration," D. Simon *et al.*

[38] *Journal of Neuroscience* (2014), "Genetic Analysis Reveals that Amyloid Precursor Protein and Death Receptor 6 Function in the Same Pathway to Control Axonal Pruning Independent of β-Secretase," O. Olsen *et al.*

[39] *Journal of Neuroscience* (2014), "A Death Receptor 6-Amyloid Precursor Protein Pathway Regulates Synapse Density in the Mature CNS But Does Not Contribute to Alzheimer's Disease-Related Pathophysiology in Murine Models," D. Kallop *et al.*

[40] Not every allegation (including recitations of PubPeer comments) that was the subject of outside reporting was incorrect, of course. The Scientific Panel did not undertake to generally assess outside reporting in this matter.

[41] Genentech, *Findings of 2023 Genentech Review of 2009* Nature *Paper and Related Research* (Apr. 6, 2023), https://www.gene.com/download/pdf/Findings-of-2023-Genentech-Review-of-2009-Nature-Paper-and-Related-Research.pdf.

events, including an instance of fraud that did occur in Dr. Tessier-Lavigne's laboratory at this general time but was unrelated to the Nature '09 paper.

In more detail, in 2010 and unconnected with the Nature '09 paper, an individual in Dr. Tessier-Lavigne's lab at Genentech was suspected by other lab members of engaging in research misconduct. A group of postdocs and other personnel in the lab came together to present this concern to Dr. Tessier-Lavigne. Genentech has publicly stated that, in response, it initiated "a formal investigation … resulting in … termination of the postdoc's employment in August 2010."[42] And Dr. Tessier-Lavigne withdrew from upcoming publication an already accepted paper on which he and the individual were co-authors, with Dr. Tessier-Lavigne as the principal author.[43]

The Scientific Panel finds it possible, or perhaps even likely, that this incident, plus a general frustration with the irreproducibility of certain aspects of the Nature '09 paper in subsequent years, have been combined and conflated to produce certain allegations of "fraud," which are not accurate. The Panel also finds that it is possible that accounts on this topic may have been hampered by an incomplete understanding of Genentech's regular business processes (namely, that the Research Review Committee reviews various research at the company as a matter of ordinary course).

b. Scientific Process and Quality Concerns

Although the Panel has concluded that the claims of a Genentech fraud investigation into Nature '09 are unfounded, the Panel has identified multiple problems with the Nature '09 paper. First, the Panel has concerns about the rigor of the process through which the science of the paper was developed, including regarding the degree of critical thinking and rigor applied to experimental design, evaluation, and characterization of reagents and data analysis during the research process. In particular:

- The research for the paper made use of what were, in fact, crude culture supernatant fractions and an insufficiently characterized and insufficiently pure recombinant N-terminal fragment preparation of APP. The Nature '09 paper described the APP as having been "affinity purified" and Dr. Tessier-Lavigne has maintained to the Panel that he regarded the APP as being sufficiently purified to the best of his knowledge at the time. However, although the Nature '09 paper described the APP as having been "affinity purified," in one of the follow-on papers to Nature '09, Dr. Tessier-Lavigne and his co-authors themselves write:

> *The prior study [(Nature '09)] had used N-APP from two sources, commercial (Thermo Fisher) and in-house (Genentech), which gave consistent results. However, both preparations were only partially purified and biochemical analyses revealed them to contain contaminants and aggregated material (data*

[42] Genentech, *Findings of 2023 Genentech Review of 2009* Nature *Paper and Related Research* (Apr. 6, 2023), https://www.gene.com/download/pdf/Findings-of-2023-Genentech-Review-of-2009-Nature-Paper-and-Related-Research.pdf.

[43] Cell '10 (publication halted).

> *not shown). To guard against nonspecific effects, we set out to obtain purer and nonaggregated N-APP. As purification proceeded, we unexpectedly found that the prodegenerative effects of N-APP were lost, as was binding to the DR6 ectodomain (fused to alkaline phosphatase: DR6-AP) observed by ELISA (Fig. 7E). One possibility is that the binding and functional effects seen with earlier material were caused by aggregates that may have accumulated during partial purification; an alternative is that a contaminant in the partially purified material contributed to activity and/or binding.*[44]

- In 2008, both prior to and after the Nature '09 paper was initially submitted to the journal Nature, a Genentech lab conducting certain N-APP-DR6 binding experiments that related to the model presented in the Nature '09 paper[45] was generating inconsistent N-APP-DR6 binding results in mammalian (Chinese hamster ovary (CHO)) derived reagents. This is the cell type that Dr. Tessier-Lavigne has stated to the Panel he found most relevant to his assessment of the validity of Nature '09's model of N-APP-DR6 binding.[46] When Dr. Tessier-Lavigne was shown these data in the course of the Panel's work, he stated that, despite being the Principal Investigator, he had never previously been provided with the full set of inconsistent binding results and, had he known their extent, he would have engaged in additional investigative experimentation. It is very plausible that, if the inconsistent binding had been further explored, findings would have been generated (including the fact that APP does not bind to DR6 at its N-terminus) which would have improved aspects of the model presented in Nature '09 before a decision to publish.[47]

In addition, the quality of the day-to-day scientific research in Dr. Tessier-Lavigne's lab that went into the paper and the presentation of the associated data in the paper, though not performed or generated directly by Dr. Tessier-Lavigne, fell below accepted scientific practices, let alone Dr. Tessier-Lavigne's self-described standard of scientific excellence. This includes:

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[44] *Journal of Neuroscience* (2014), "Genetic Analysis Reveals that Amyloid Precursor Protein and Death Receptor 6 Function in the Same Pathway to Control Axonal Pruning Independent of β-Secretase," O. Olsen *et al.*

[45] The experimental results published in Nature '09 were generated within Dr. Tessier-Lavigne's own lab at Genentech, with two exceptions (Supplementary Figure 8, c & e (ELISA results)).

[46] During the same period of time, the same Genentech lab which generated the CHO-based N-APP-DR6 binding results was also generating baculovirus-based N-APP-DR6 binding results. In October 2008, that lab generated results which showed "much weaker" binding against four different N-APP preparations (full-length NAPP with N- or C-His tags; growth factor domain+Cu binding domain; and growth factor domain alone). Dr. Tessier-Lavigne was aware of these results and has stated to the Panel that he regarded these baculovirus results as significantly less relevant to his assessment of the validity of Nature '09's model of N-APP-DR6 binding because they were insect-based and thus both derived from a different biological context and, in Dr. Tessier-Lavigne's experience, prone to false negatives.

[47] The Panel has also explored with Dr. Tessier-Lavigne his rationale for deciding which experiments he used a DR6 knockout mouse strain available to him in prior to the publication of Nature '09. In particular, the Panel believes it would have been prudent for Dr. Tessier-Lavigne to have conducted a control test on the specificity of the DR6 antibody with the available knockout mice. Dr. Tessier-Lavigne has stated in discussion with the Panel that he agrees this would have been prudent although he has further noted that the results of that experiment would not have gone to the question of the specificity of the APP-DR6 binding site.

- Certain experimental design choices and their associated effects. In two instances in Nature '09, what were originally single experiments were "split" and presented as separate figures in the paper (Figures 1 and 5 and Supplementary Figures 9 and 17). In both cases, control images were re-used, which led to the identification of "duplicate" images on PubPeer.[48] In the case of Figures 1 and 5, a control image was re-used but with re-quantification, resulting in different control quantitation graphs between the two figures. Neither the fact of this re-quantification nor associated methodological details (for example, adequate detail regarding biological and technical replicates) are provided in the paper. In the case of Supplementary Figures 9 and 17, a control image was re-used but with improper labelling (the challenged control image in Supplementary Figure 17 did not follow consistent terminology ("NGF-Deprived" versus "anti-NGF") and omitted reference to the use of Bax inhibitor).

- Basic biostatistical computational errors. From access to portions of the original research record for Nature '09, it has become apparent that certain of the biostatistical calculations underlying the figures in Nature '09 contained errors. Some of these errors relate to rudimentary statistical calculations including, for example, the erroneous inclusion of the sample mean as a data point for the calculation of the sample standard error or standard error of the mean.

- Figure image anomalies. The Nature '09 paper contains instances of figure image anomalies, including a control gel splice (Supplementary Figure 6d) which has been publicly challenged on PubPeer[49] and potential other issues.[50]

The Panel does not find, based on the evidence available to it, that Dr. Tessier-Lavigne knew about the lack of rigor in certain aspects of the scientific process in his laboratory leading up to the publication of Nature '09 or about the lack of quality in certain of the day-to-day scientific work and figure presentation for the paper. Dr. Tessier-Lavigne himself has denied knowledge regarding several of these issues (for example, inconsistent mammalian cell binding results and experimental design choices).

The Panel and Dr. Tessier-Lavigne had several discussions regarding Nature '09, and he is aware of the extent of the Panel's concerns and findings. Dr. Tessier-Lavigne has also provided responses to some of these concerns and findings, as noted above. The Panel's views regarding Dr. Tessier-Lavigne's historical choice to not correct or retract Nature '09 as issues of

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[48] Matthew Schrag, *APP Binds DR6 to Trigger Axon Pruning and Neuron Death via Distinct Caspases*, PUBPEER (Feb. 2023), https://pubpeer.com/publications/B6410F2AF1398E6F379B244E7520A1#2. The Panel's internal analyses in conjunction with meetings with relevant participants and received scientific documentation substantiates these allegations.

[49] Anonymous, *APP Binds DR6 to Trigger Axon Pruning and Neuron Death via Distinct Caspases*, PUBPEER (Mar. 2023), https://pubpeer.com/publications/B6410F2AF1398E6F379B244E7520A1#5. The Panel's internal analysis in conjunction with meetings with relevant participants and received scientific documentation substantiates this allegation.

[50] The Panel's internal analyses have also identified additional potential issues in five figures with no prior allegations.

reproducibility emerged, but instead to rely on the publication of follow-on papers, are discussed in detail in Section III, below. The Panel understands that Dr. Tessier-Lavigne is considering a corrective course regarding the paper given the additional information now known to him. The Panel encourages Dr. Tessier-Lavigne to pursue a robust remedial approach (whether that is a retraction or a comprehensive and robust set of corrections) in the interest of the scientific record and consistent with his own self-described standard of scientific excellence.

III. DR. TESSIER-LAVIGNE'S APPROACH TO CORRECTION

As its work progressed, the Scientific Panel encountered several instances where, when concerns with Dr. Tessier-Lavigne's papers emerged, he took inadequate steps to correct mistakes in the scientific record.

A. Science '01 Silencing Figure 2D Duplication

In 2001, within weeks after the publication of the Science '01 Silencing paper, one of Dr. Tessier-Lavigne's colleagues in the field identified and communicated with Dr. Tessier-Lavigne regarding an obvious error in the paper (a duplication[51] with shifting[52] of a neuronal growth cone image in Figure 2D). Dr. Tessier-Lavigne stated to the colleague in writing that he would take corrective action, including both contacting the journal and attempting to issue a correction.

While Dr. Tessier-Lavigne did confirm that a "correct" image of the neuronal growth cone at the 1-hour mark existed within a responsible postdoc's internal records, he did not contact the journal and he did not attempt to issue an erratum, which is inadequate. In discussion with the Scientific Panel, Dr. Tessier-Lavigne has expressed regret about this incident but has not been able to provide an explanation for his inaction beyond forgetting. The Panel has noted that personally confirming that an accurate image exists does not address the need to publicly remediate the scientific record, and Dr. Tessier-Lavigne agrees with this.

B. 2015-2016 Corrections Sequence with the Journals Science and Cell

As described above, beginning in 2015, allegations of research data manipulation concerning the group of three papers Cell '99, Science '01 Binding, and Science '01 Silencing appeared on PubPeer. This prompted Dr. Tessier-Lavigne to begin to correspond both with the publishing journals Cell and Science and certain of his co-authors to understand the allegations and prepare responses in the form of corrections. Dr. Tessier-Lavigne did an able job of initially pursuing corrective efforts with the journals Cell and Science between 2015-16, despite the uncooperativeness of another co-author during this time.

After sustained discussions with Dr. Tessier-Lavigne, the journal Cell concluded that a correction was not necessary given the nature of the alleged issues and the passage of time. However, after similar discussions with the journal Science, that journal concluded that a

[51] At a technical forensics level, it is likely that the image in question is an additional capture of the growth cone taken at the same 0-hour timepoint (rather than the represented 1-hour timepoint).

[52] The shifting in the image is plausibly attributable to image cropping.

correction was appropriate for both Science ’01 papers. Dr. Tessier-Lavigne prepared drafts of these corrections[53] and coordinated with the journal from the fall of 2015 through the summer of 2016 to a point where he reasonably believed the corrections were going into pre-print. But the corrections were never published and, following a final inquiry on June 22, 2016, Dr. Tessier-Lavigne ceased to follow up. In late-2022, as more recent events were unfolding, Science issued a statement indicating that the failure to publish the corrections was due to an error on its part.[54]

However, as Dr. Tessier-Lavigne has acknowledged in discussions with the Panel, he was also independently responsible for ensuring that the corrections were made, despite the journal also failing to discharge its own responsibility in this regard. Dr. Tessier-Lavigne has not been able to provide an adequate explanation to the Panel for why he ceased pursuing the publication of the two corrections beyond his busy schedule with his transition into the Stanford presidency at the time and his inference that, because Cell had deemed it unnecessary to issue a correction, perhaps the issue was not of enduring concern to Science. To date, the scientific record remains uncorrected. Dr. Tessier-Lavigne’s planned forthcoming retraction of the papers will remedy that.

C. 2021 Correction Sequence with the Journal Science

In March 2021, concerns were again raised on PubPeer about the Science ’01 Binding paper regarding the lack of corrective activity in the approximately five years since the original issues had been identified on PubPeer.[55] This prompted Dr. Tessier-Lavigne, in consultation with others regarding the language, to draft an e-mail to Science’s editorial staff inquiring about the status of the unpublished corrections to both Science ’01 papers, but he did not transmit the e-mail. In discussion with the Panel, Dr. Tessier-Lavigne did not have an explanation for deciding to not follow up on the corrections beyond that he has a practice of drafting many e-mails to see how they read but only sends a portion of them and that he concluded the communication was unnecessary. That decision to not follow up on the Science ’01 corrections was insufficiently attentive to the continuing need to correct the scientific record.

D. Nature ’09 “Correction” Conduct

As described above, following the publication of Nature ’09, elements of the model described in the paper had to be corrected or refined including, critically, the claim of where APP

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[53] Among the issues raised on PubPeer during this time and discussed in Dr. Tessier-Lavigne’s unpublished corrections was the Science ’01 Silencing Fig. 2D duplication.

[54] @ScienceMagazine, TWITTER (Nov. 30, 2022, 12:00 PM), https://twitter.com/ScienceMagazine/status/1597999050997043201; *see also Editorial Expression of Concern*, SCIENCE (Dec. 15, 2022), https://www.science.org/doi/10.1126/science.adg2852 & *Editorial Expression of Concern*, SCIENCE (Dec. 15, 2022), https://www.science.org/doi/10.1126/science.adg2860 (recent Science ’01 Editorial Expressions of Concern, noting the “error[s] on our part” regarding the failure to publish corrections in 2016). It appears likely, based on correspondence between AAAS and the Scientific Panel, that the error originated following handoff of the corrections from the Science editorial team over to its production / copyediting staff.

[55] Elisabeth M. Bik, *Binding of DCC by Netrin-1 to Mediate Axon Guidance Independent of Adenosine A2B Receptor Activation*, PUBPEER (Mar. 2021), https://pubpeer.com/publications/59C3359E71EED451E01AF46CFDC0BC#14.

bound to DR6, along with claims that Caspase 3 was not involved in axon degeneration and about the role of beta-secretase in APP-DR6 binding. Some evidence of problems in the claim of N-APP-DR6 binding clearly existed prior to Nature '09's publication (inconsistent N-APP-DR6 binding results within Genentech), although Dr. Tessier-Lavigne states that he was not informed of this evidence. Other evidence of reproducibility[56] issues by postdocs in Dr. Tessier-Lavigne's lab tasked with reproducing key aspects of Nature '09 appears to have begun to be generated in that lab as early as late-2008, also before Nature '09's publication. At least regarding the misidentification of the APP binding site, Dr. Tessier-Lavigne stated in discussions with the Panel that he did not have scientific confidence regarding that misidentification until the summer of 2012 and that reaching that conclusion required several years of additional experimentation and assessment of results.

The Panel has heard from many witnesses regarding this sequence and has the further understanding that, in the years after the publication of Nature '09, there were at times vigorous discussions involving Dr. Tessier-Lavigne and others about what would be the appropriate corrective course for Nature '09. Dr. Tessier-Lavigne's response to the need to correct and refine the model of neurodegeneration proposed in Nature '09 was to issue a series of follow-on papers in 2012, 2014, and 2015.[57] Dr. Tessier-Lavigne opted neither to retract the Nature '09 paper nor to issue a direct correction to the paper.

Dr. Tessier-Lavigne's decision to use further publishing for the correction of the scientific record is, in the Panel's view, within the boundaries of normal scientific practice, but his decision to neither retract nor directly correct the Nature '09 paper was suboptimal, particularly given the attention the paper originally received. A transparent and affirmative attitude toward correction is fundamental to the proper functioning of the scientific process. If Principal Investigators fail to demonstrate an appropriate appetite for correcting instances of error, mistake, or misconduct, then the often-claimed self-correcting nature of the scientific process will not occur.

As stated above, the Panel understands that Dr. Tessier-Lavigne is considering a corrective course regarding the Nature '09 paper given the additional information now known to him. The Panel encourages Dr. Tessier-Lavigne to pursue a robust remedial approach (whether that is a

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[56] The Scientific Panel uses the term "reproducibility" and like terms as they are commonly understood within the scientific field, that is, as involving the ability to: (1) generate the results of a given paper in independent labs based on the disclosed methods alone, and/or (2) extend the results of a given paper into further scientific applications. At times, in discussion with the Scientific Panel, Dr. Tessier-Lavigne has used the term instead in the sense of "if one takes the same scientific inputs and is able to produce the same scientific outputs, then it is reproducible" and noted that, in that sense, the results of Nature '09 were reproducible. The Panel regards this latter, narrower concept as falling short of what is needed for the scientific process to be robust and self-correcting.

[57] *Genes & Development* (2015), "The crystal structure of DR6 in complex with the amyloid precursor protein provides insight into death receptor activation," K. Xu *et al.*; *Journal of Neuroscience* (2014), "A Death Receptor 6-Amyloid Precursor Protein Pathway Regulates Synapse Density in the Mature CNS But Does Not Contribute to Alzheimer's Disease-Related Pathophysiology in Murine Models," D. Kallop *et al.*; *Journal of Neuroscience* (2014), "Genetic Analysis Reveals that Amyloid Precursor Protein and Death Receptor 6 Function in the Same Pathway to Control Axonal Pruning Independent of β-Secretase," O. Olsen *et al.*; *Journal of Neuroscience* (2012), "A Caspase Cascade Regulating Developmental Axon Degeneration," D. Simon *et al.*

retraction or a comprehensive and robust set of corrections) in the interest of the scientific record and consistent with his own self-described standard of scientific excellence.

IV. LAB CULTURE AND MANAGEMENT

Many of the issues discussed above potentially implicate concerns about the culture of Dr. Tessier-Lavigne's labs. As discussed above, multiple members of labs overseen by Dr. Tessier-Lavigne over the years either engaged in manipulation of research data[58] or, at a minimum, engaged in deficient scientific practices.[59] This affected papers published, or about to be published, in leading scientific journals, and the conduct spanned labs at three separate institutions (UCSF, Stanford, and Genentech).

To consider the role that lab culture played in these events, the Scientific Panel spoke with many postdocs from Dr. Tessier-Lavigne's labs at UCSF, Stanford, Genentech, and Rockefeller.[60] Through those discussions, two themes emerged. First, many of the interviewees spoke of a positive laboratory culture which fostered scientific excellence. These interviewees spoke of their high regard for Dr. Tessier-Lavigne's commitment to scientific mentoring and rigor, particularly during the earlier years of Dr. Tessier-Lavigne's career in his UCSF and original Stanford labs.

However, a second theme emerged among some of the interviewees that the same lab culture also tended to reward the "winners" (that is, postdocs who could generate favorable results) and marginalize or diminish the "losers" (that is, postdocs who were unable or struggled to generate such data). Of course, in any sufficiently large organization, there is likely to be a range of views regarding organizational culture, and some individuals will be happier than others. The Scientific Panel did not find evidence to conclude that Dr. Tessier-Lavigne desired this second dynamic. Perhaps science in general could benefit from a deeper recognition by senior scientists that they need to be mindful to defuse any putative pressure to please a Principal Investigator beyond the significant, ordinary pressure that postdocs already experience in a competitive scientific field.

In any event, there were repeated instances of manipulation of research data and/or subpar scientific practices from different people and in labs run by Dr. Tessier-Lavigne at different institutions. This is unusual and suggests there may have been opportunities to improve laboratory oversight and management.

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[58] Group I: Cell '99, Science '01 Binding, Science '01 Silencing; Group II: Nature '04; Group III: Cell '10 (publication halted).

[59] Nature '09.

[60] The Panel interviewed numerous postdocs and others who either worked in or were otherwise closely connected with one or more of Dr. Tessier-Lavigne's labs at UCSF, Stanford, Genentech, or Rockefeller. Some of these interviews were for multiple purposes (that is, lab culture and one or more additional topics).

V. CONCLUSION

The Scientific Panel thanks the many individuals, institutions, and journals that participated in this process, including the many scientists in academia and industry who took substantial time from their schedules to meet with us. Not only did these journals, institutions, and individuals engage with the Panel, but they did so with significant preparation, enabling our discussions to be informed and productive. Science is strengthened when the scientific community embraces a spirit of collaboration, transparency, and earnest commitment to the truth, all of which were demonstrated these past seven months.

The Panel expresses its appreciation to the Special Committee, the Stanford University Board of Trustees, and the wider Stanford community for their unequivocal support for the Panel's independence and process. The Panel also thanks Mark Filip and his colleagues at Kirkland & Ellis, who worked tirelessly to aid the Panel in the conduct of its review. And the Panel thanks its technical consultants, including Drs. Mary Walsh and Corinna Raimondo and their team at Maidstone Consulting, and Dr. Hany Farid at the University of California, Berkeley for their acumen and insights.

Finally, the Panel expresses its appreciation to Stanford University President Dr. Marc Tessier-Lavigne. He was open, cooperative, and professional throughout these proceedings.

APPENDIX

SELECT FORENSIC ISSUES

Cell ’99

https://pubpeer.com/publications/250D42FBB7D7298E704BFD6CD8B22A

Figure 3C

Initial Issue as represented on PubPeer October 2015

DOI: http://dx.doi.org/10.1016/S0092-8674(00)80804-1

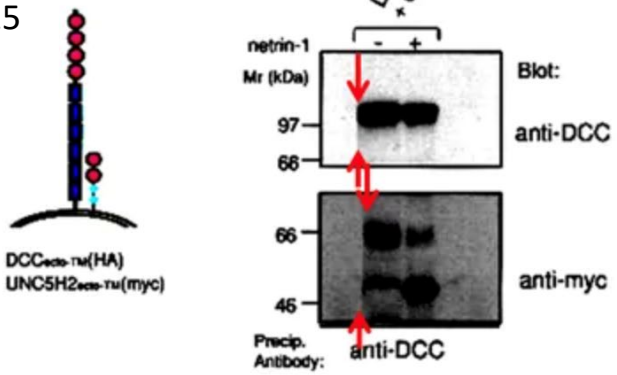
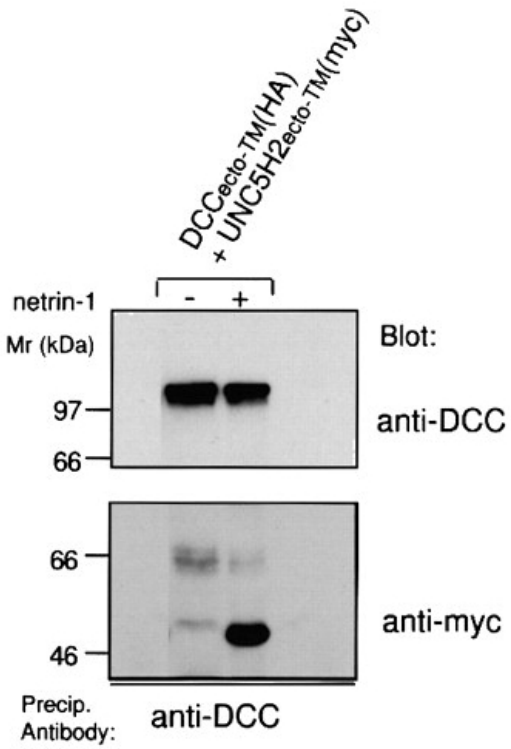


Figure 3C, Research Record Analysis

anti-DCC/anti-myc panel
anti-DCC/anti-DCC panel

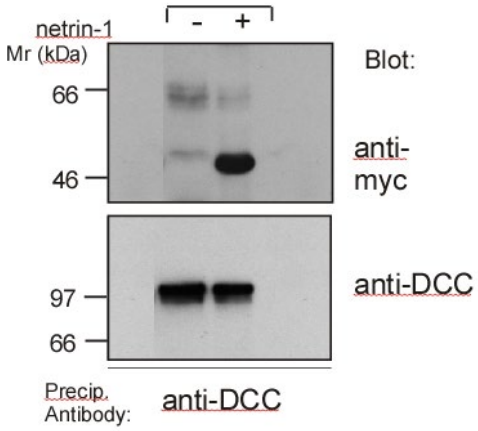
Published Figure 3C



Images are similar ≈ But not identical

Research Record Figure 3C

- A series of Canvas (.CV5) figure preparation files were identified by searching the provided data record
- In this example (file for Figure 3C), the data appear similar but not identical
  - anti-DCC/anti-myc and anti-DCC/anti-DCC panels are swapped in the represented figure
  - Research record appears to be different in terms of visual representation of data (darker, higher resolution)

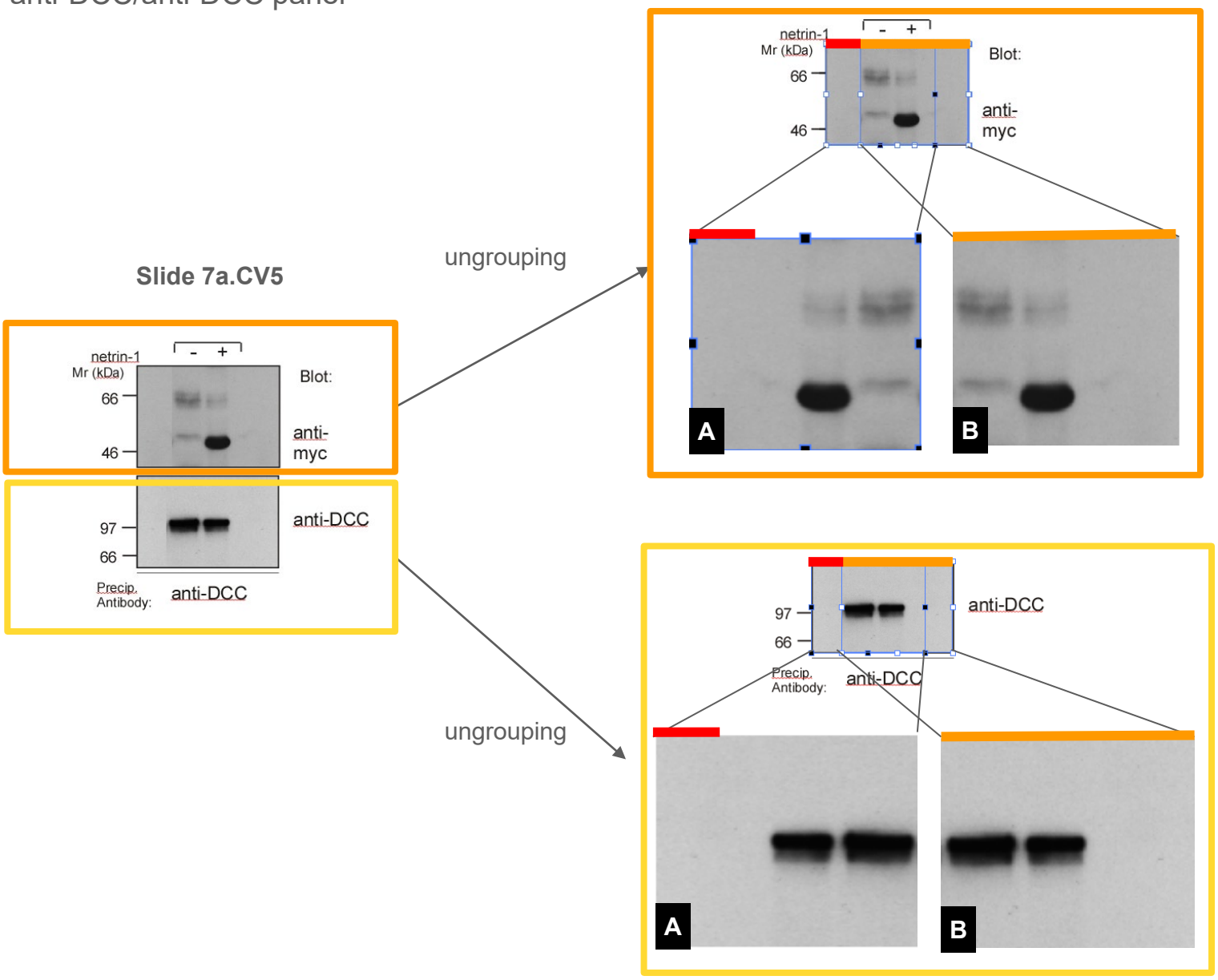


Slide 7a.CV5

Figure 3C preparation file received from MTL data distribution

Figure 3C, Research Record Analysis continued

anti-DCC/anti-myc panel
anti-DCC/anti-DCC panel



Method:

- select image in .CV5 file and “Ungroup”
- move and enlarge ungrouped layers for better visualization

Color coding: **RED** and **ORANGE** demonstrate the resulting representation of the underlying data in Figure form.

Observations:

The images identified by the **ORANGE** and **YELLOW** **BOXES** ☐ appear to have been obtained by superimposition of a duplicate of the same portion of an image mirrored. Layer **A** appears to have been positioned below layer **B**. These superimpositions create the splice features first described on PubPeer.

https://pubpeer.com/publications/250D42FBB7D7298E704BFD6CD8B22A

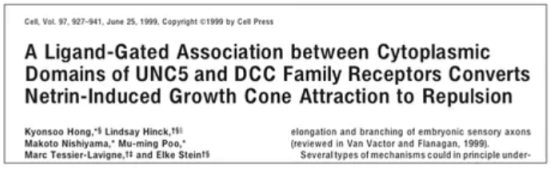
Figures 3C and 7B
Additional Issues as represented on PubPeer December 2022

#14 ***Condylocarpon amazonicum*** commented December 2022

Has anyone else noticed, as I have, the intriguing similarities between some immunoblot bands in Fig. 3C and Fig. 7B?

Resolution is not great but I do wonder if these gellish slices might be very closely related, perhaps even sharing common ancestry? The left-most lane vertical splice is rather noteworthy.

There might be differences in exposure and stretching, for which adjustments can be made. Perhaps even a small rotation. In addition, the labelling is entirely not the same, for reasons that only the figure creator could know.


Cell, Vol. 97, 927–941, June 25, 1999, Copyright ©1999 by Cell Press

A Ligand-Gated Association between Cytoplasmic Domains of UNC5 and DCC Family Receptors Converts Netrin-Induced Growth Cone Attraction to Repulsion

Kyonsoo Hong,*§ Lindsay Hinck,†§ Makoto Nishiyama,* Mu-ming Poo,* Marc Tessier-Lavigne,†‖ and Elke Stein†§

elongation and branching of embryonic sensory axons (reviewed in Van Vactor and Flanagan, 1999). Several types of mechanisms could in principle under-

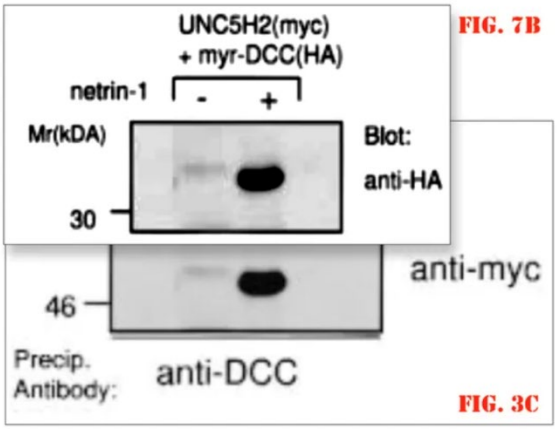


FIG. 7B

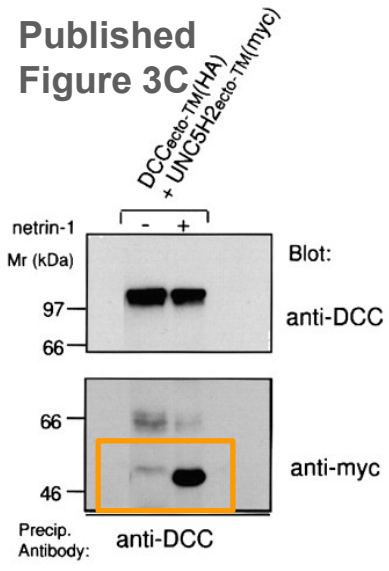
FIG. 3C

FIGS 3C, 7B IMMUNOBLOTS. VERY SIMILAR BANDS BUT DIFFERENTLY LABELLED. NOTE GREY SCALE ADJUSTMENT AND MINOR STRETCHING HAS BEEN APPLIED. A SMALL ROTATION HAS NOT BEEN CORRECTED.

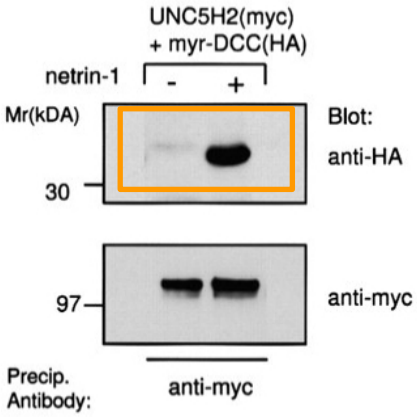
Figure 3C and 7B Research Record Analysis

3C: anti-DCC/anti-myc panel
7B: anti-myc/anti-HA panel

Published Figure 3C

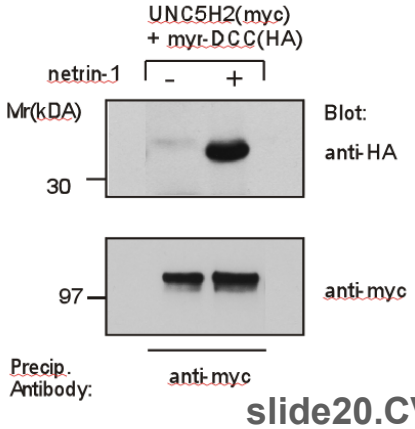


Published Figure 7B



Research record identified for 7B ≈

Research Record Figure 7B



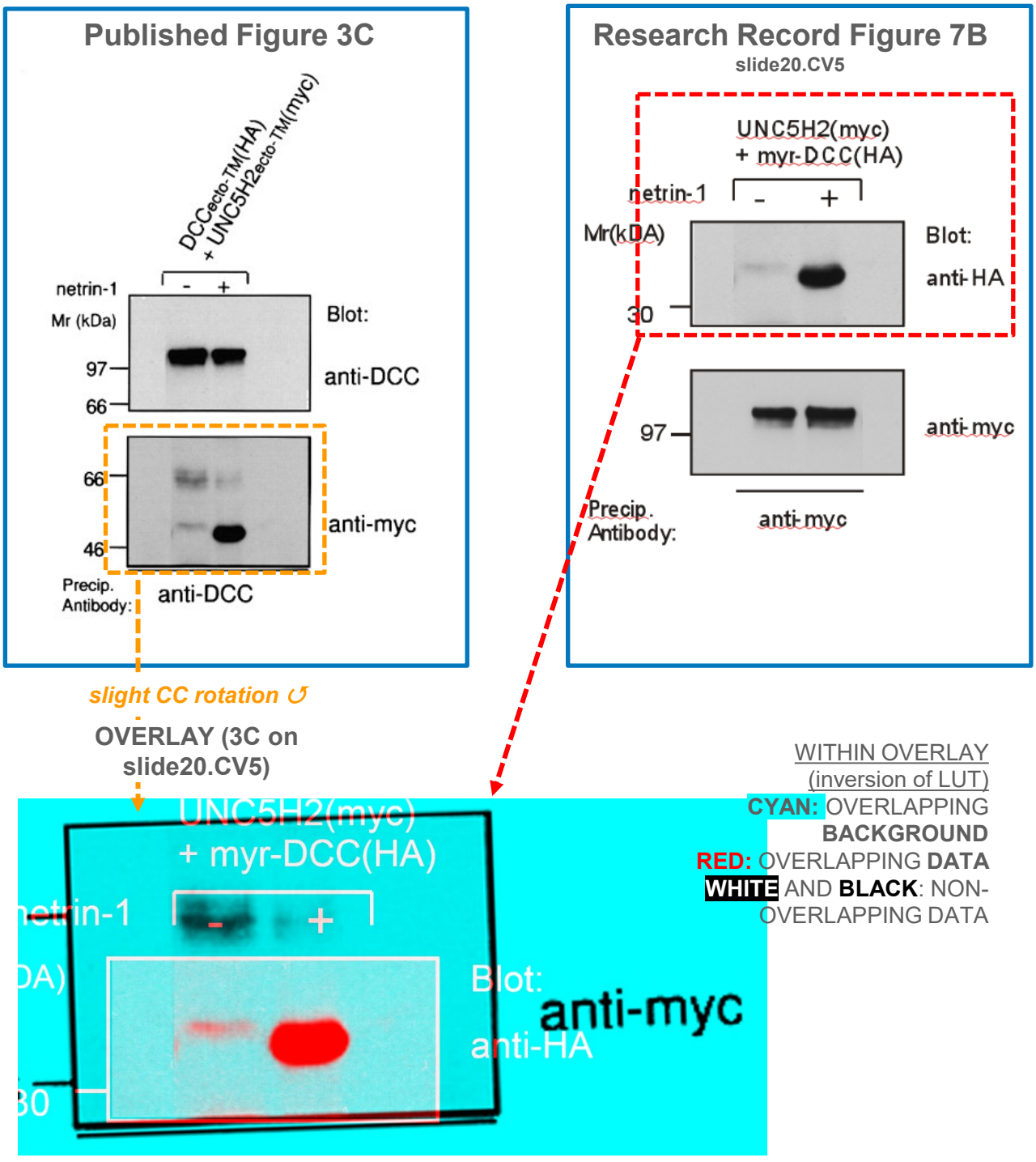
slide20.CV5

Observations:
The sections of the images identified by the **ORANGE BOXES** ☐ appear similar.

Figure 3C and 7B Research Record and Overlay Analysis

3C: anti-DCC/anti-myc panel

7B: anti-myc/anti-HA panel



Method:

Overlay performed by tuning Red/Black gradient by shifting the Red portion of **slide20.CV5** to 60 and performing free transform (resizing) to align images as needed.

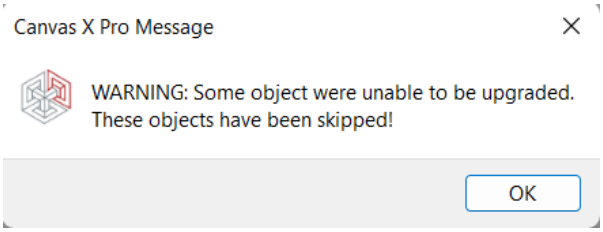
Observations:

Blot image data appear to be duplicated and used to report two different experimental outcomes in Figures 3C and 7B.

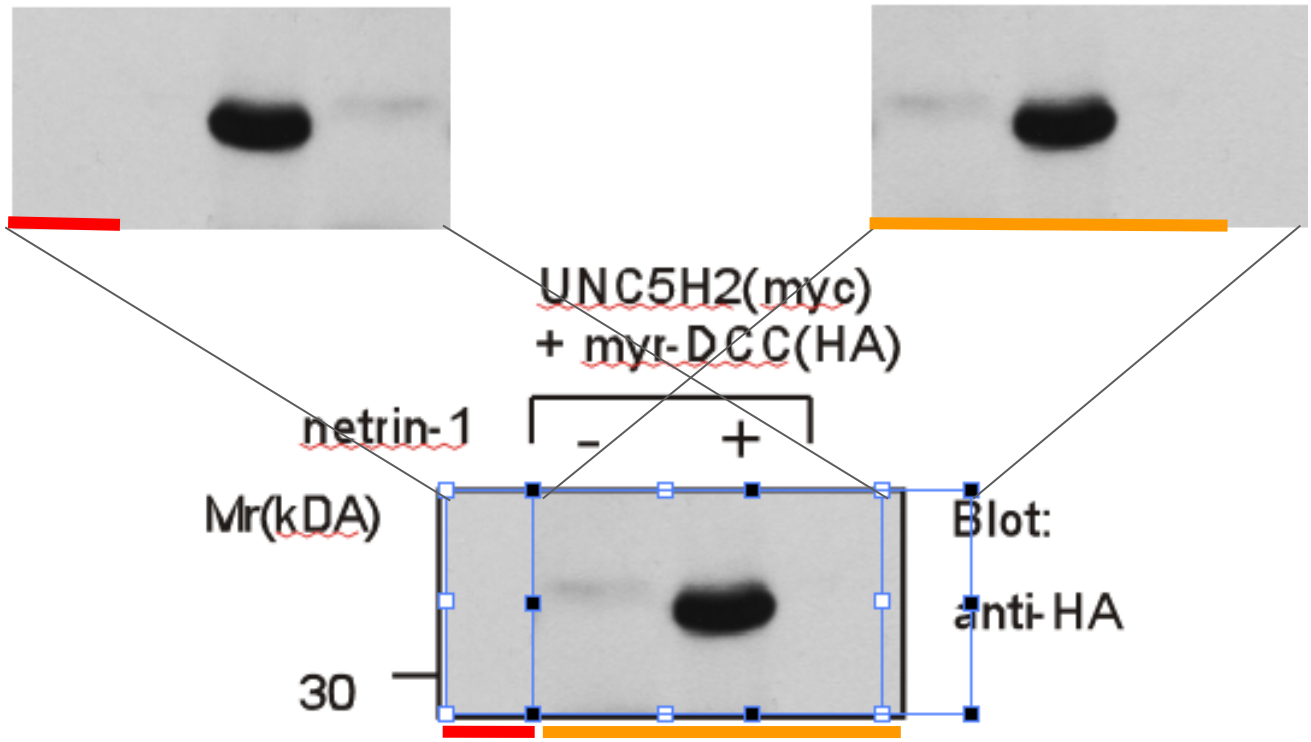
Figure 7B, Research Record Analysis continued

anti-myc/anti-HA panel

1



2



Method:

Inspection, “ungrouping” and enlargement of **slide20.CV5** data.

Color coding: **RED** and **ORANGE** demonstrate the resulting representation of the underlying data in Figure form.

Observations:

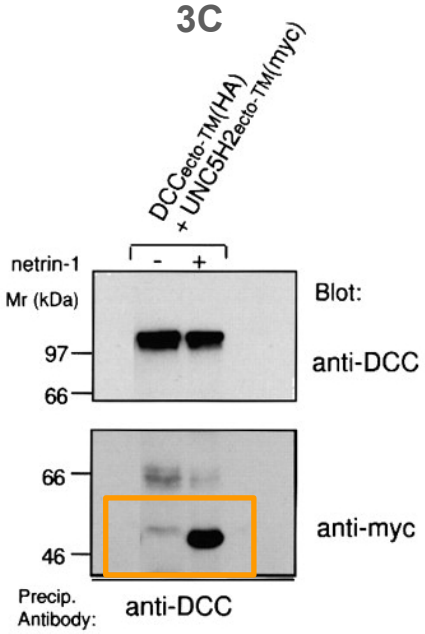
When opening the file a warning stated that additional objects were present in the original file but could not be updated and have been skipped (see **1**). The inspection of the source file for Figure 7B (see **2**) shows that the anti-HA and anti-myc blots were obtained by superimposition of two different layers. Anti-HA source data of Figure 7B appears similar to sections of Figure 3C source data.

Figure 3C and 7A Research Record Analysis

3C: anti-DCC/anti-myc panel

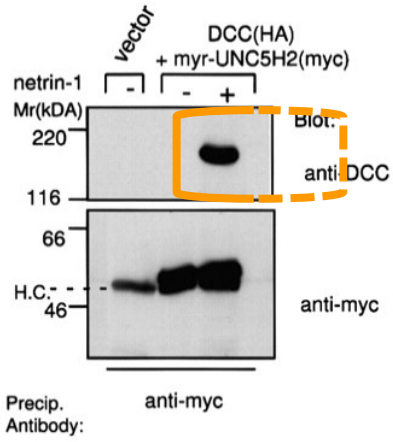
7B: anti-myc/anti-DCC panel

Published Figure 3C



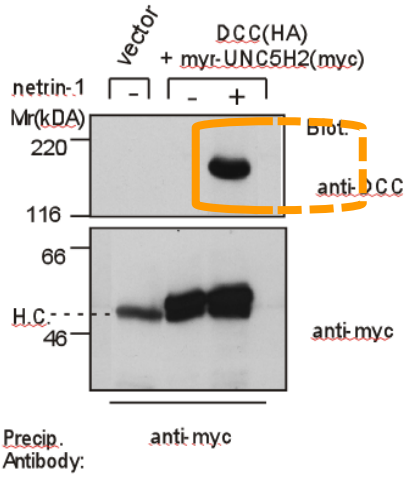
Published Figure 7A

horizontal rotation ⮌ required for alignment with 3C



Research record identified for 7A ≈

Research Record Figure 7A



slide18.CV5

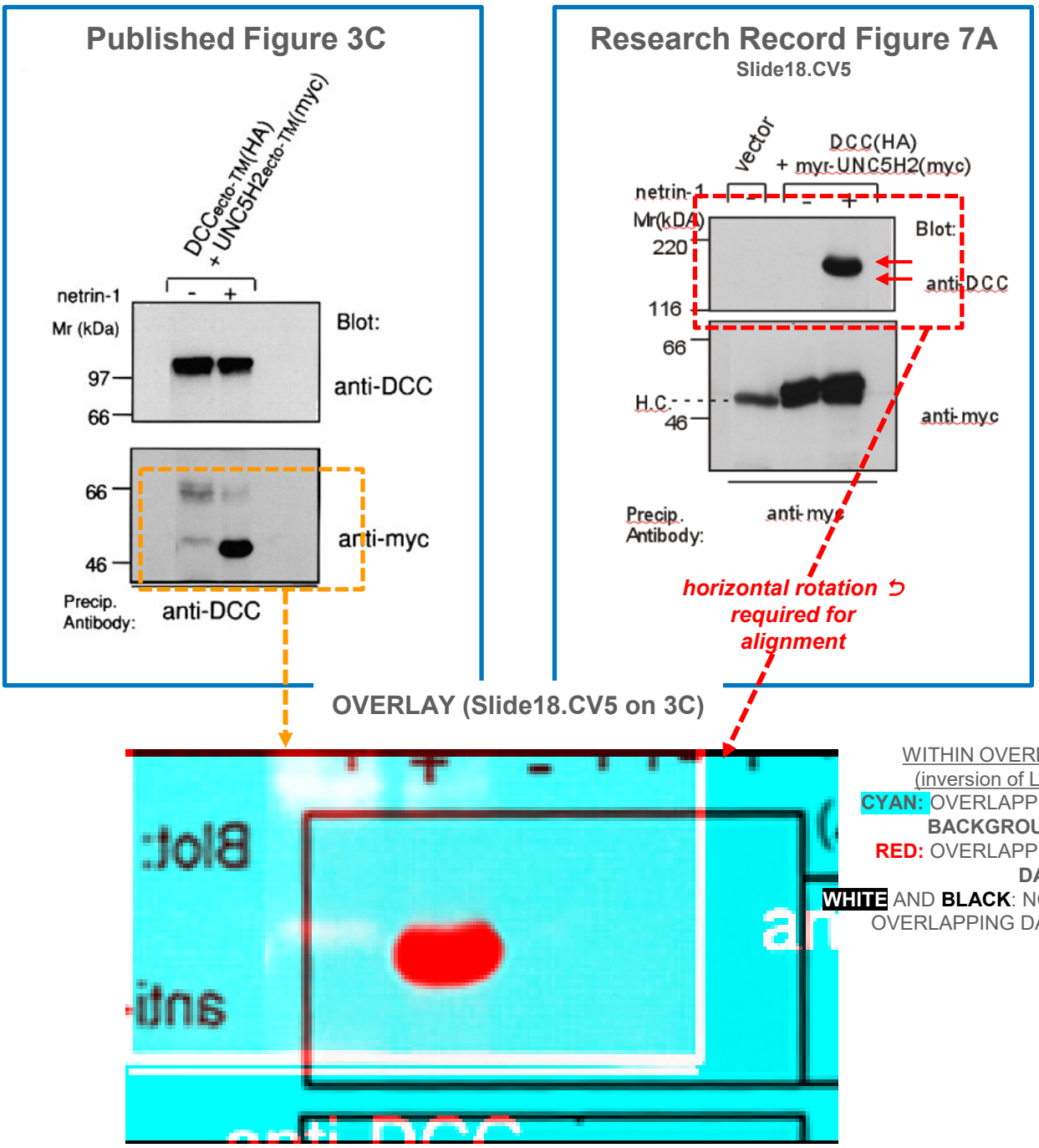
Observations:

The sections of the images identified by the **ORANGE BOXES** ☐ appear similar; note the **DASHED ORANGE BOXES** ☐ in Figure 7A denote where the accompanying data of Figure 3C would appear if the image were extended

Figure 3C and 7A Research Record and Overlay Analysis

3C: anti-DCC/anti-myc panel

7A: anti-myc/anti-DCC panel



Method:

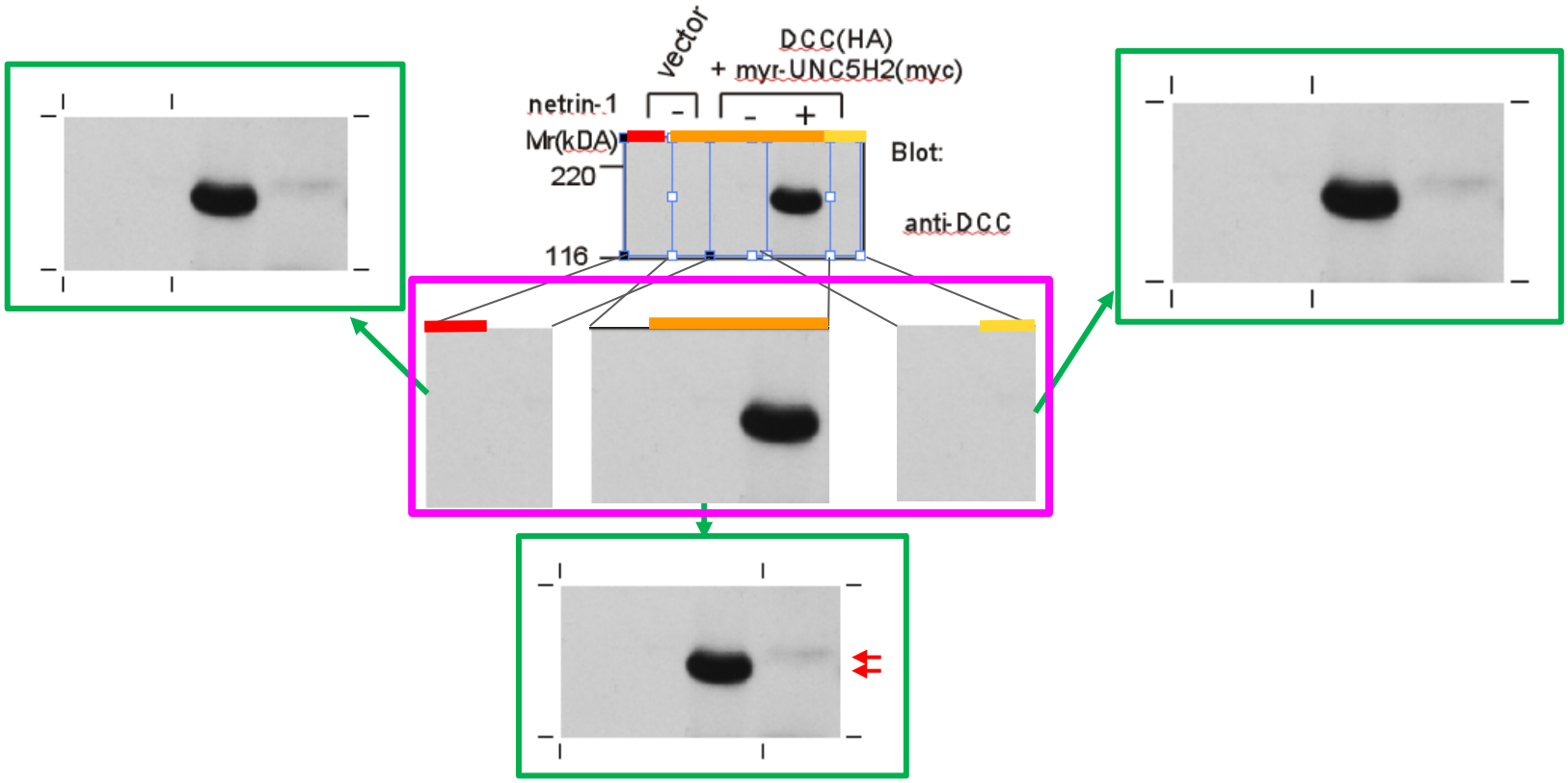
Overlay performed using free transform (resizing) to align images as needed.

Observations:

Blot image data appear to be duplicated and used to report two different experimental outcomes in Figures 3C and 7A. Note the accompanying netrin (-) lane of 3C is not present in “final” 7A as there is splicing/construction in Figure 7A (see **small red arrows ← ←** and research record analysis in the next slide).

Figure 7A, Research Record Analysis

anti-myc/anti-DCC panel



Method:

Ungrouping and enlargement of **Slide18.CV5** (see **MAGENTA BOX**). After double-clicking on obtained images, see **GREEN ARROWS** to visualize the source image used to produce the final figure **before** cropping (see **GREEN BOXES**).

Color coding: **RED** and **ORANGE** demonstrate the resulting representation of the underlying data in Figure form.

Observations:

Review of the source file for Figure 7A shows that the blot in question was obtained by superimposition of three different layers.

As noted, the additional aligning data of Figure 7A that was not visible in the final figure are now apparent with ungrouping of the source data. This is represented in the image by the **small red arrows ←←**.

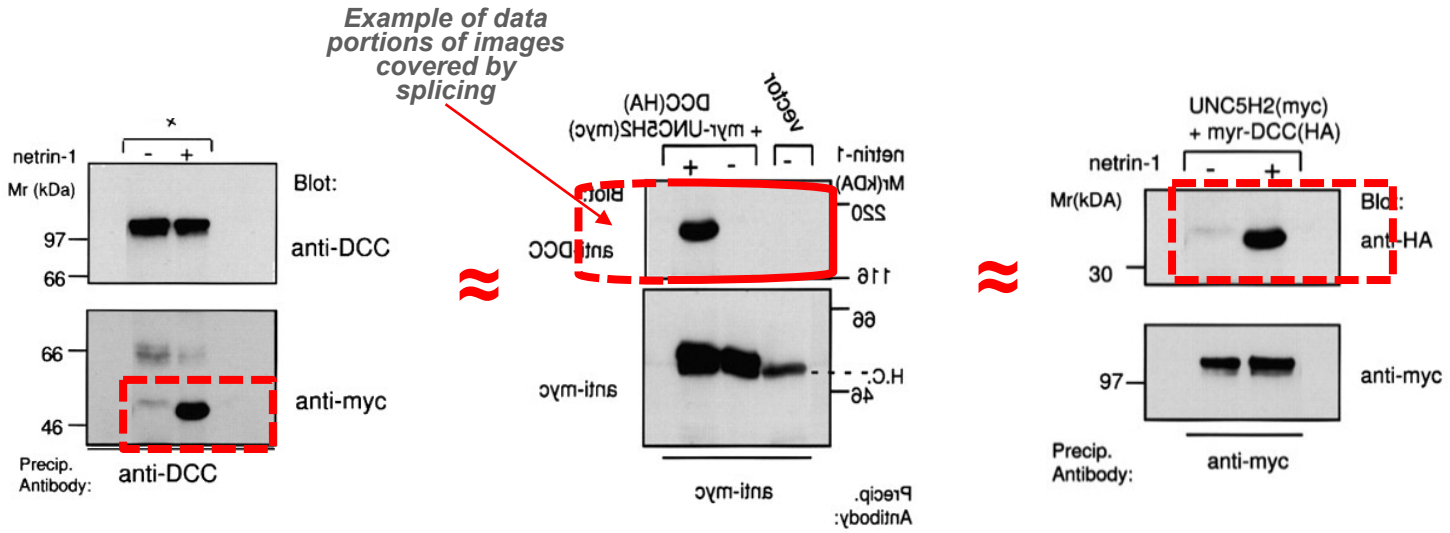
These features appear to be similar to those present in Figure 3C, and thus, Figure 7B as well.

Summary Evaluation, Figures 3C, 7A and 7B: apparent duplication and re-use as the outcome of three distinct experiments

Slide 7a.CV5
CONSTRUCTED/CHIMERIC SPLICED IMAGE

Slide18.CV5
CONSTRUCTED/CHIMERIC SPLICED IMAGE

slide20.CV5
CONSTRUCTED/CHIMERIC SPLICED IMAGE

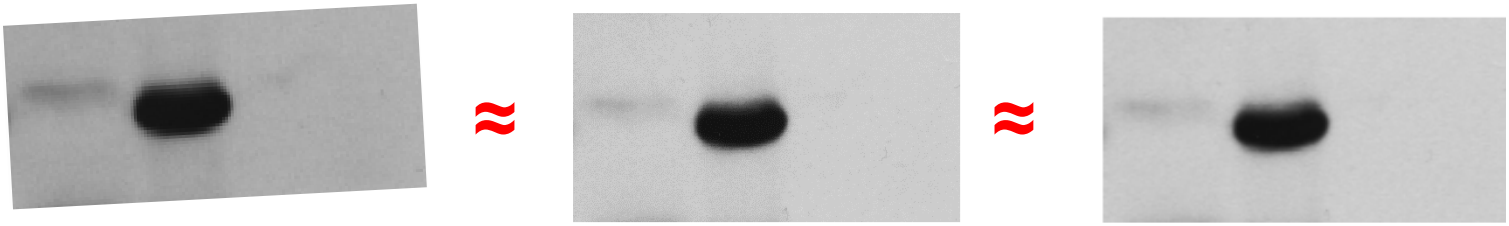


Published Figure 3C

Published Figure 7A horizontally flipped ⮌

Published Figure 7B

Extracted underlying images from Canvas files identified as potential sources for the published images (reported as the outcome of three distinct experiments)



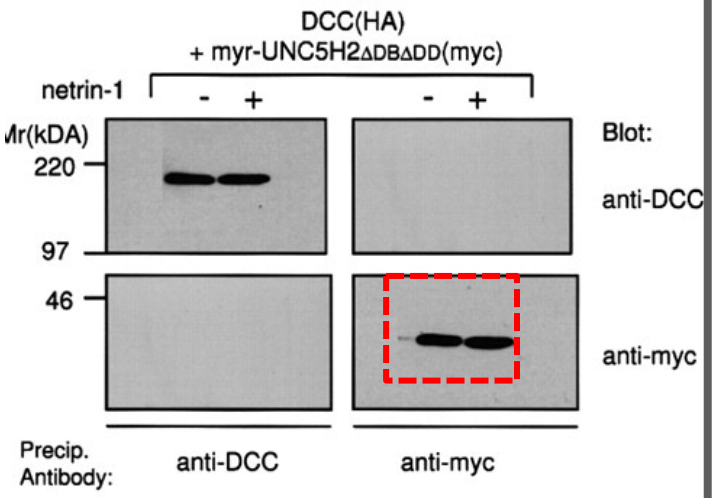
In comparison to other source data, this may be a later-exposure image, or alterations of contrast/brightness of the same image, or some combination of processes leading to the resultant image.

Figure 7C Research Record Analysis

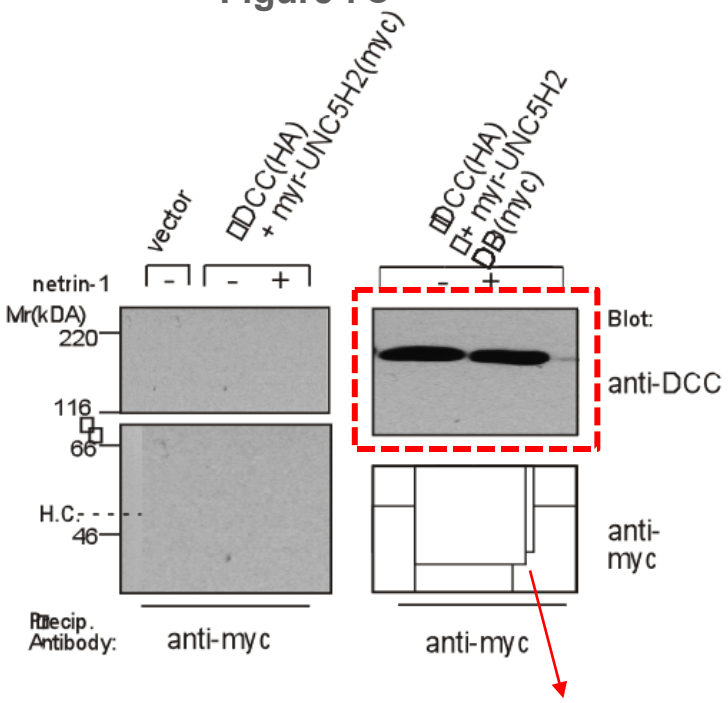
anti-myc/anti-myc panel

The research record data (at right) demonstrate a version of the figure which is not the final figure that appears in publication

Published Figure 7C



Research Record Figure 7C



not all images appear to render correctly (likely due to available technology and age of available data)

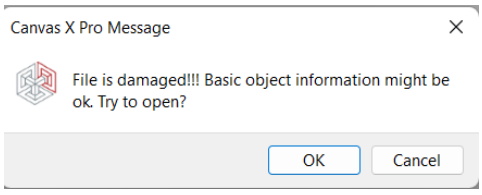
slide19.CV5

RED DASHED BOXES ☐

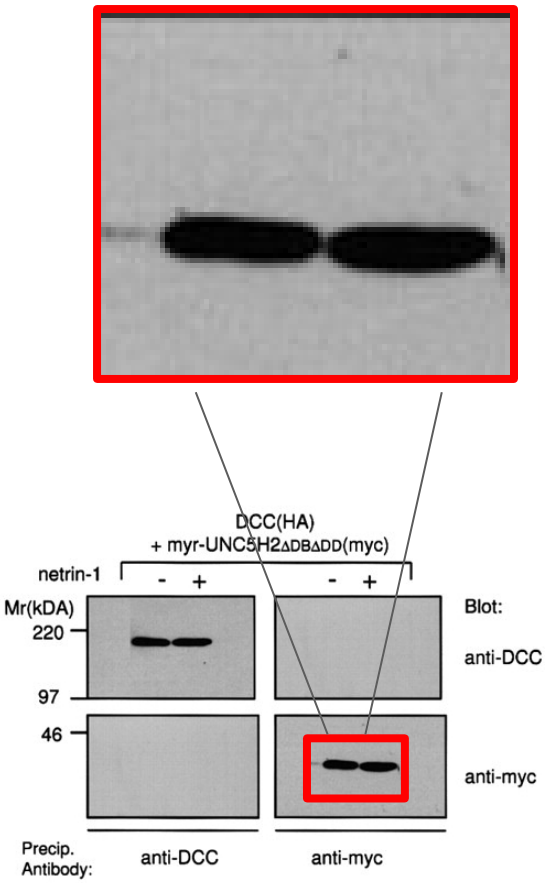
However, images have apparently similar data vertically flipped in different panels ↶

Figure 7C Research Record Analysis continued

anti-myc/anti-myc panel



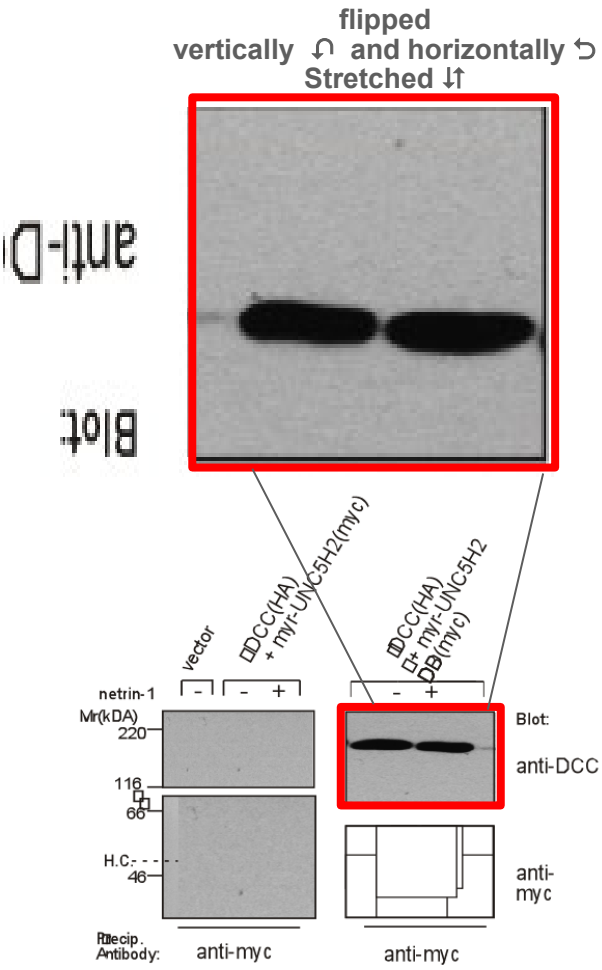
Published Figure 7C



≈

Research Record Figure 7C

flipped vertically ↶ and horizontally ↻ Stretched ⇵



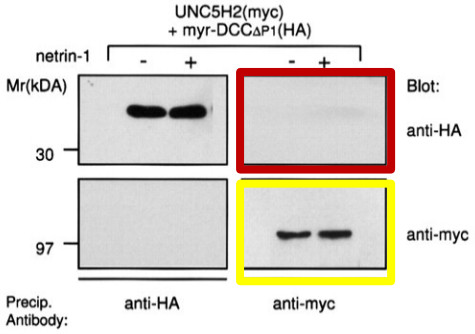
Observations:

While the file is damaged (see screenshot of warning message from Canvas X Pro) it contains portions of the published Figure 7C. All data visible in these files, despite the message above, remain in their original format as used for the figure.

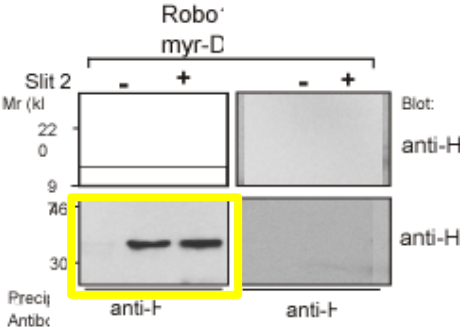
The mirror image of the **anti-myc/anti-DCC** research record, when flipped and resized, appears to contain the same image as the published Figure 7C, but reported as **anti-myc/anti-myc** and the data reported for apparent Netrin-1 outcomes (+/-) are reversed ↻

Figure 7D Research Record Analysis

Published Figure 7D

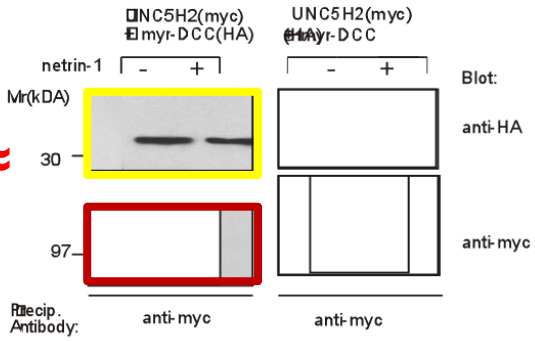


Research Record Figure 4e Science (Silencing) 2001



cshQ2.CV5

Research Record Figure 7D (and 7B)*



Slide 21.CV5

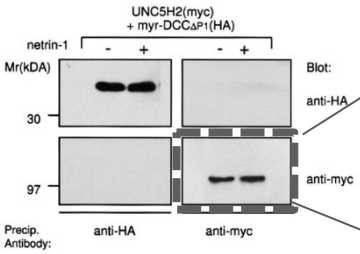
* This figure preparation file (Slide 21.CV5) appears to be a hybrid reporting on two different constructs. Please review the construct images in Slide 21.CV5 for alignment because blot sample titles are challenging to read. Slide 21 "construct" at left aligns with "Figure 7B" myr-DCC(HA)+UNC5H2(myc) and Slide 21 "construct" at right aligns with "Figure 7D" myr-DCC_{DP1}(HA)_UNC5H2(myc) .

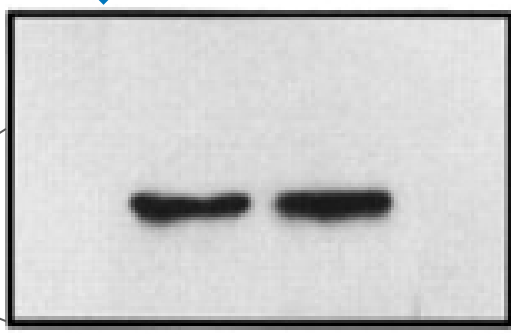
Observations: The research record shows potential iterations of the image, not the final version for publication. The files appear to render incorrectly (they may be damaged), but: a) they appear to contain portions of the published Figure 7D, and b) at least one of these examples has been reused in another paper (Science (Silencing) 2001).

Figure 7D Research Record Analysis continued

anti-myc/anti-myc panel

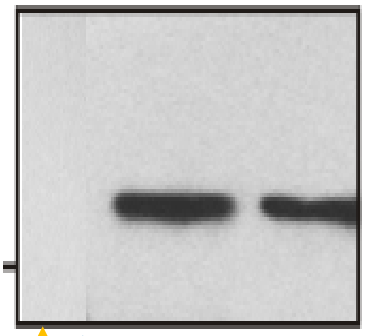
Published Figure 7D



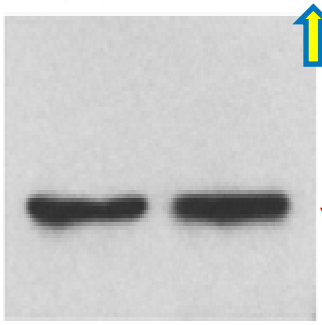


Appear to be partial "mirror" images ≈

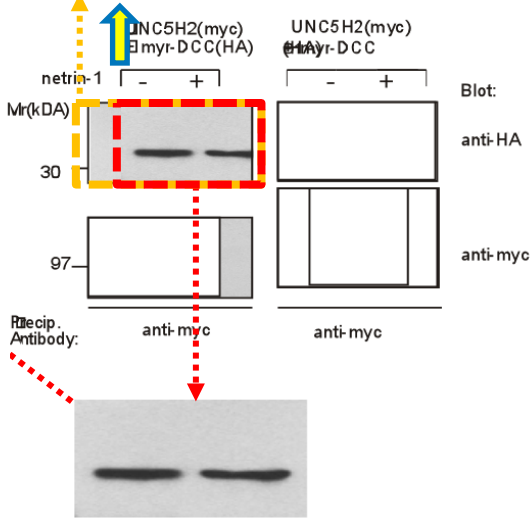
slide21.CV5
Research Record ("7B side")



resized ↕



Extracted the inserted/ spliced panel from the research record, resized, and flipped horizontal ↩

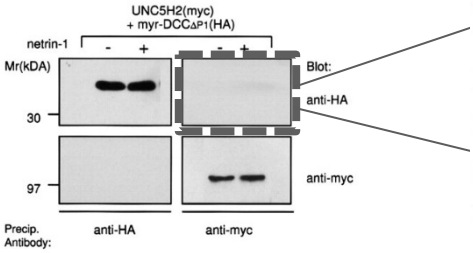


Observations:
There are subtle linear interfaces within the anti-myc/anti-myc panel of Figure 7D **YELLOW ARROWS ↓↑** that appear to align with the cropped panel identified in the .CV5 source file. This demonstrates that Figure 7B/7D figure preparation data may have additional iterations of processing (similar to that seen in **slide21.CV5**) to arrive at the results in the final published figure.

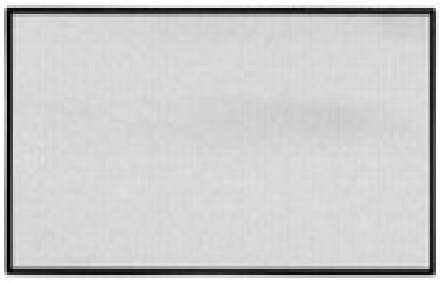
Figure 7D Research Record Analysis continued

anti-myc/anti-HA panel

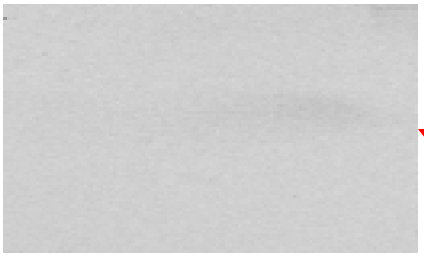
Published Figure 7D



Published Figure 7D
anti-myc/anti-HA panel



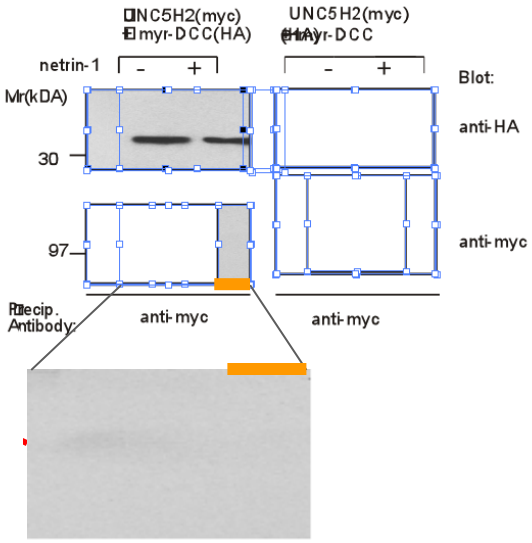
≈ ≠



Resized flipped horizontal

Research Record ("7B" side)
anti-myc/anti-myc

slide21.CV5
Research Record Figure 7D (and 7B)



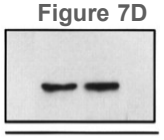
Observations:

Images appear to align ≈ but reported experimental outcomes differ (≠)

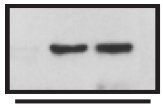
Duplication and Reuse of data across Publications

Figure 7D, Cell 1999 and
Figure 4E Science (Silencing) 2001

Published Figure 7D



Published Figure 4E

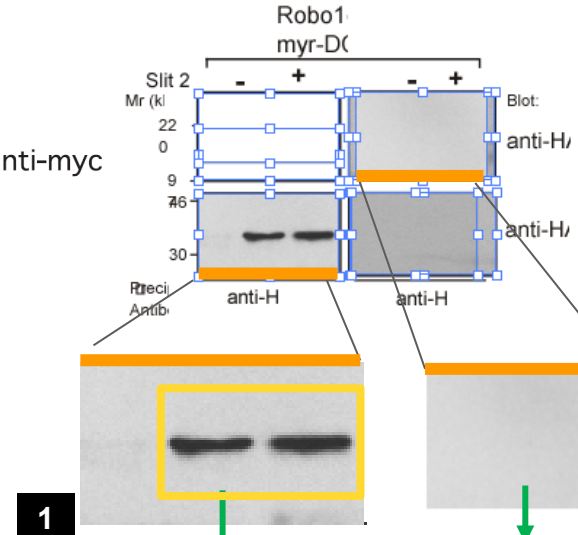


anti-myc

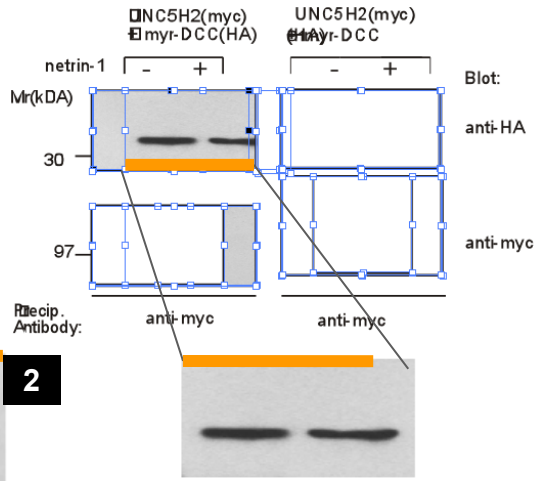
Method: Ungrouping, enlarging, and double-clicking to show uncropped original images.

Observations:
Both the **cshQ2.CV5** image and the **slide21.CV5** image feature the bands shown in Figure 7D (see ORANGE BOXES ☐). **cshQ2.CV5**, however, features a **1** larger portion of image that displays additional bands and features in the background. And, **2** "blank space" in this blot is reported as the outcome.

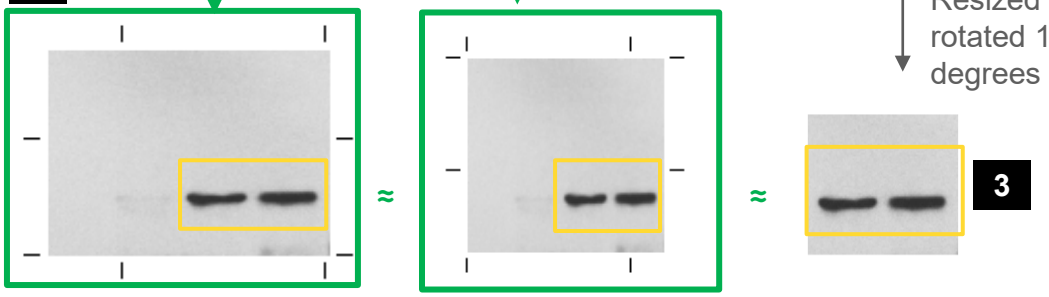
cshQ2.CV5 (4E)



slide21.CV5 (7D Source file)



Resized and rotated 180 degrees



3 **Slide 21.CV5** features a smaller portion of the image containing bands and an additional background portion derived from another image.

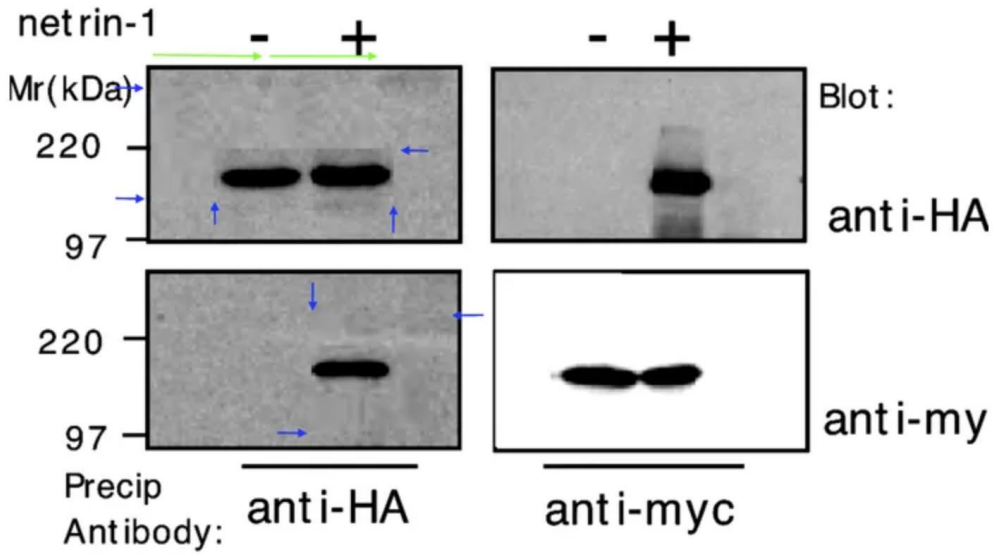
Science ’01 Binding

https://pubpeer.com/publications/59C3359E71EED451E01AF46CFDC0BC

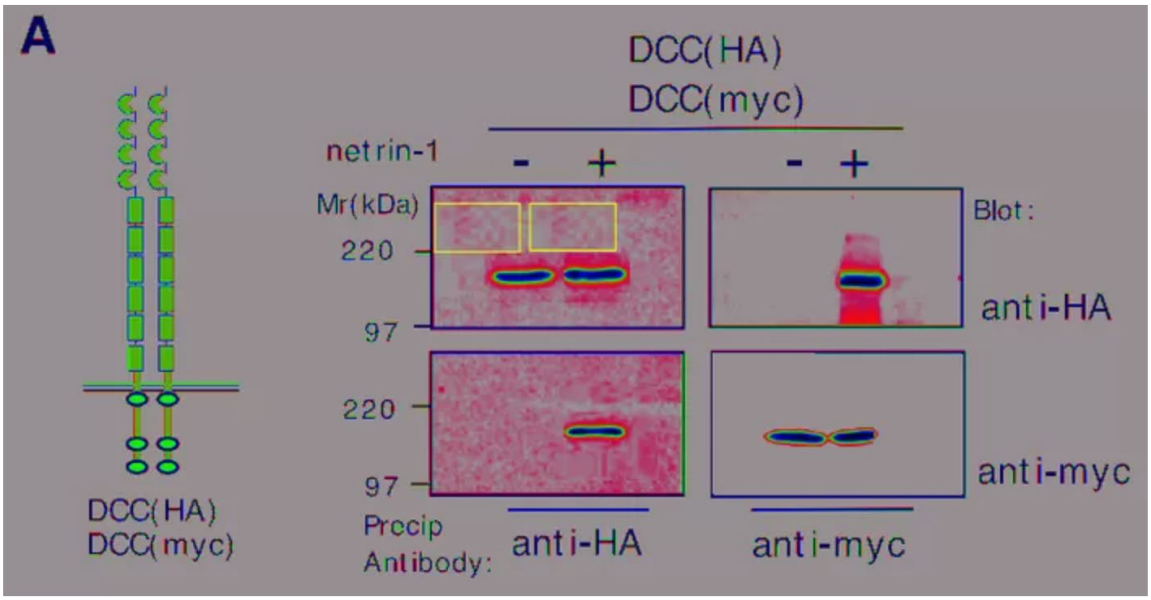
Figure 3A
Initial Issue(s) reported on
PubPeer October 2015

#1 Unregistered Submission commented October 2015

Some of the blots show sudden changes in background:



#4 *Peer 3* commented October 2015



More repeating background regions (yellow squares indicated), and multiple different resolution patches within a single blot.

https://pubpeer.com/publications/59C3359E71EED451E01AF46CFDC0BC

#14 **Elisabeth M Bik** commented March 2021

It has been five years, and there still has not been any action by the journal. The paper keeps on being cited, so it is still relevant and it would be great if these concerns could be looked into.

I agree with the concerns raised above, and will recap them here and add my own findings.

Figure 3A (contrast enhanced)

- Bands are surrounded by sharp transitions that might not be compression artifacts (see comment #1)
- Yellow boxes: A background area in the top left panel appears to be visible two times within the same photo (see comments #1 and #4)
- Green boxes: A background area in the bottom left panel appears to be visible two times within the same photo (a new finding).

Figure 3A

Elke Stein et al. Science (2001)
DOI: 10.1126/science.1059391

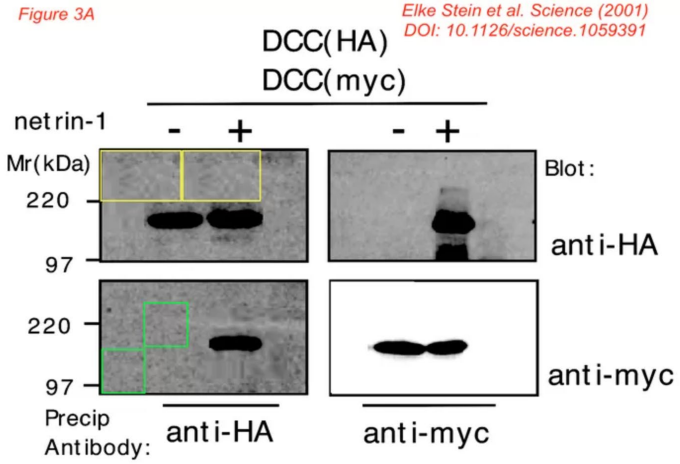


Figure 3A
Initial Issue(s) reported on
PubPeer March 2021

These findings are supported by Forensically (default settings):

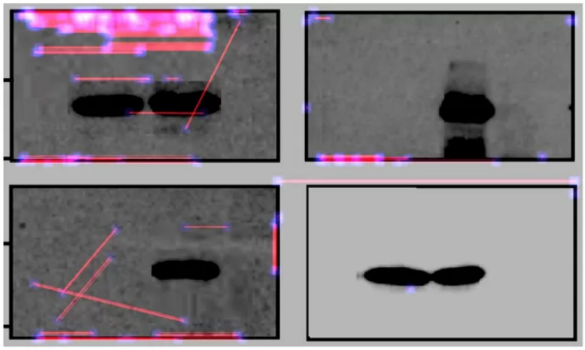


Figure used in
Analysis – Figure 3A
(image from website)

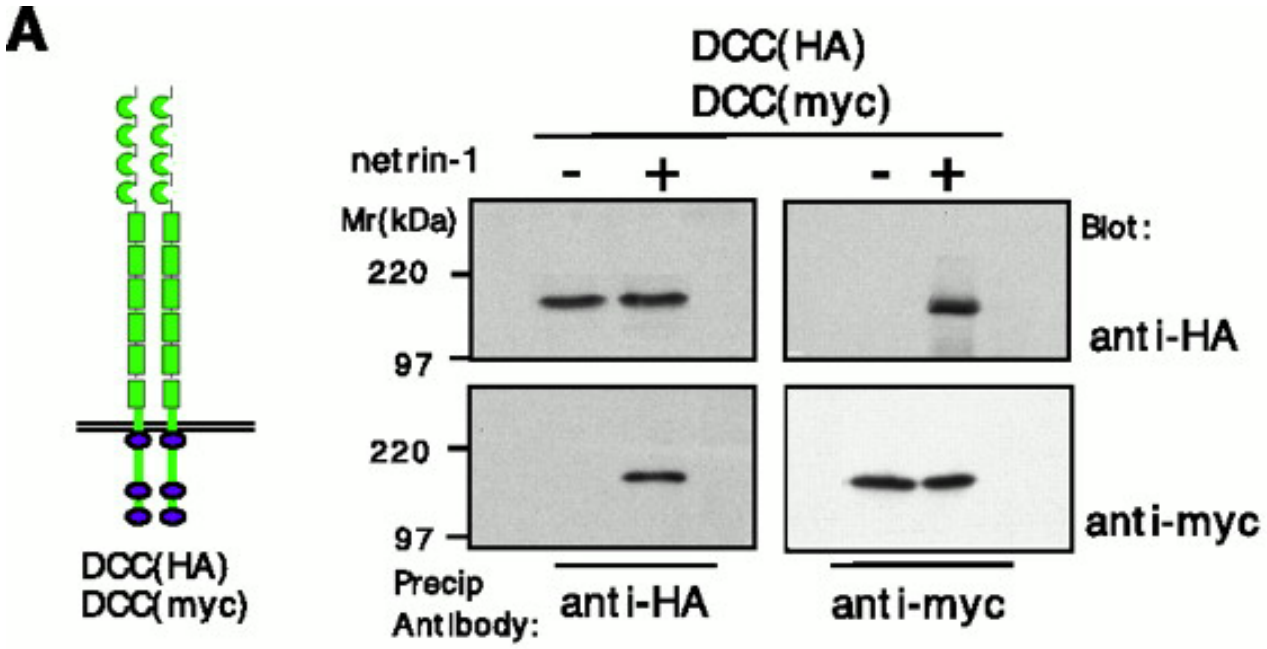
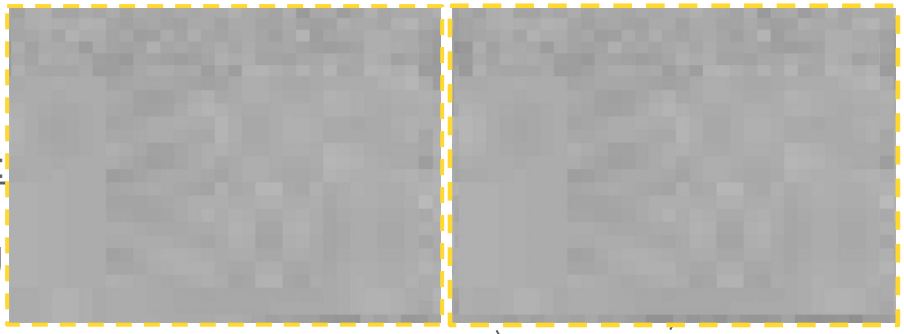
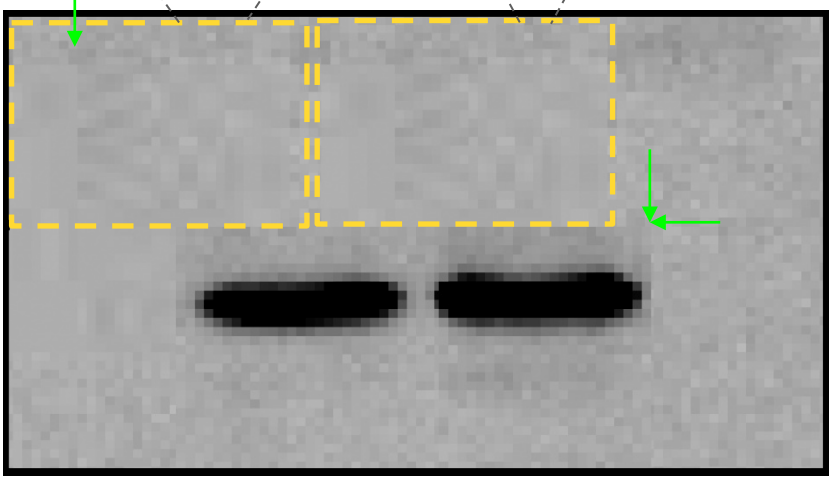


Figure 3A, Image Analysis

anti-HA/anti-HA panel
anti-HA/anti-myc panel



Legacy application
Brightness: - 20
Contrast: + 50

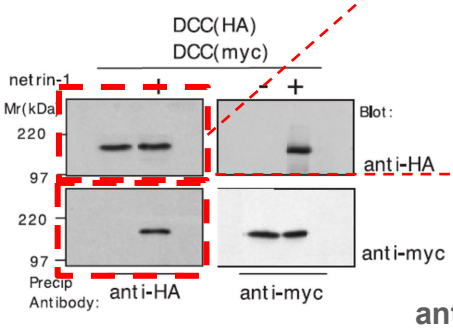


Observations anti-HA/anti-HA panel:

SMALL GREEN ARROWS ↓ → ↓ sections of the image demonstrating distinct data resolution features and different background data signals along distinct linear interfaces, suggesting data insertion, deletion, and/or a combination of both processes, within the published image.

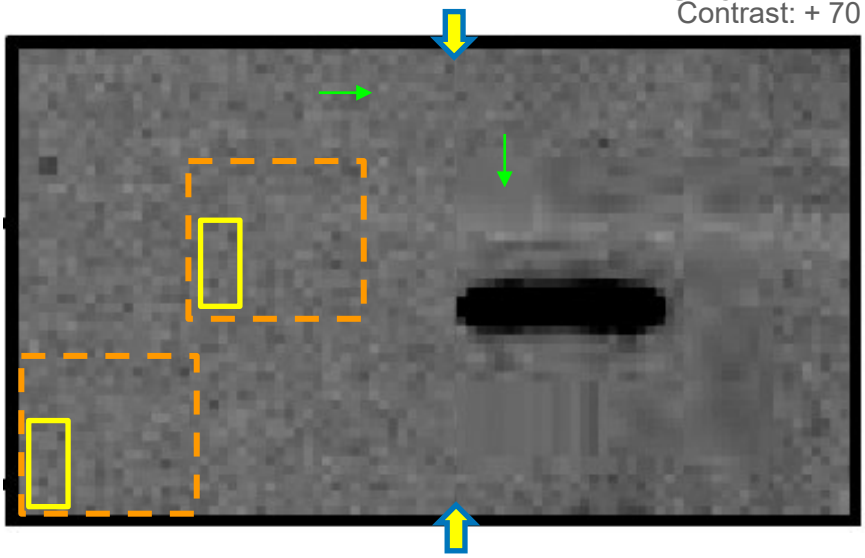
ORANGE DASHED BOXES ☐ ☐ areas enlarged for side-by-side comparison of pixels show that the two regions just above the linear interfaces appear almost identical, suggesting duplication and re-use of data within the image.

Image used:
Published Figure 3A, journal website



anti-HA/anti-HA panel

Legacy application
Contrast: + 70



anti-HA/anti-myc panel

Observations anti-HA/anti-myc panel:

SMALL GREEN ARROWS → ↓ show differences in resolution and **YELLOW ARROWS ↓ ↑** show accompanying indications of splicing, both suggestive of alteration of image data.

ORANGE DASHED BOXES ☐ ☐, with accompanying **YELLOW RECTANGLE ▯ ▯** insets show additional comparisons of the two areas reported as identical (PubPeer). Analysis shows smaller areas that appear identical **YELLOW RECTANGLE ▯ ▯**, and other, larger areas within the **ORANGE DASHED BOXES ☐ ☐** that are similar, but not identical. Inspection of the original image files and experimental data (and metadata) would provide additional insight as to the nature of these features.

Taken together, the analysis suggests data insertion, deletion, and/or a combination of both processes, within the published image.

https://pubpeer.com/publications/59C3359E71EED451E01AF46CF

Figures 3B and 3D

Initial Issue(s) reported on PubPeer October 2022

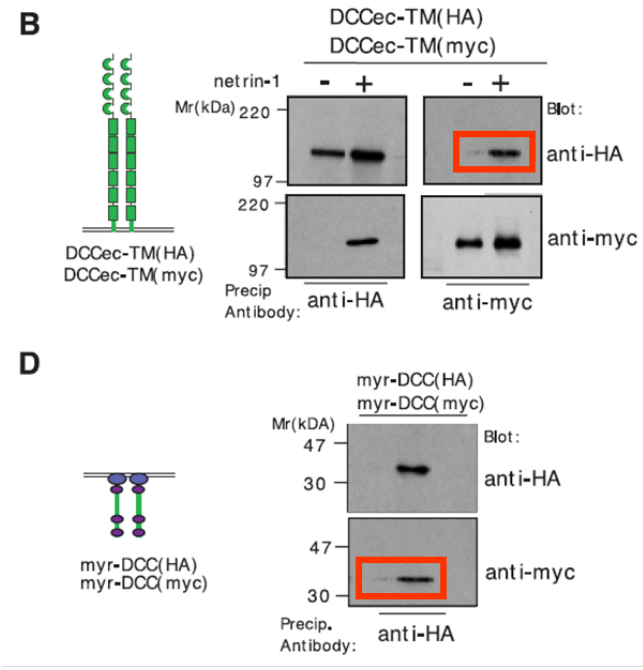


Figure 3B and Figure 3D
Science (2001)
doi: 10.1126/science.1059391

Figure(s) used in Analysis – Figures 3B and 3D

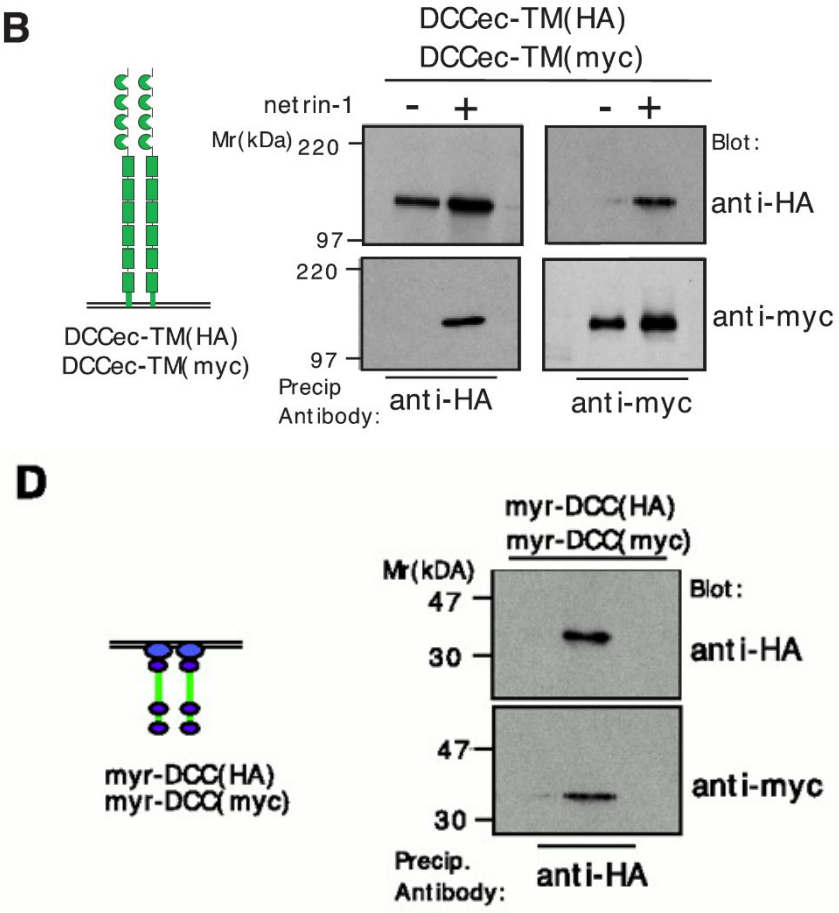
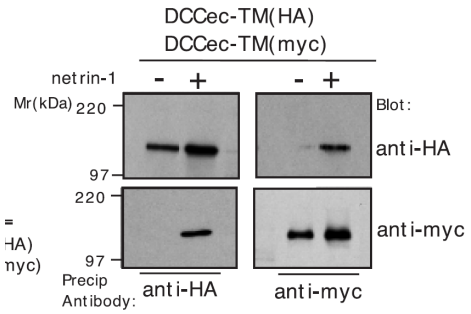
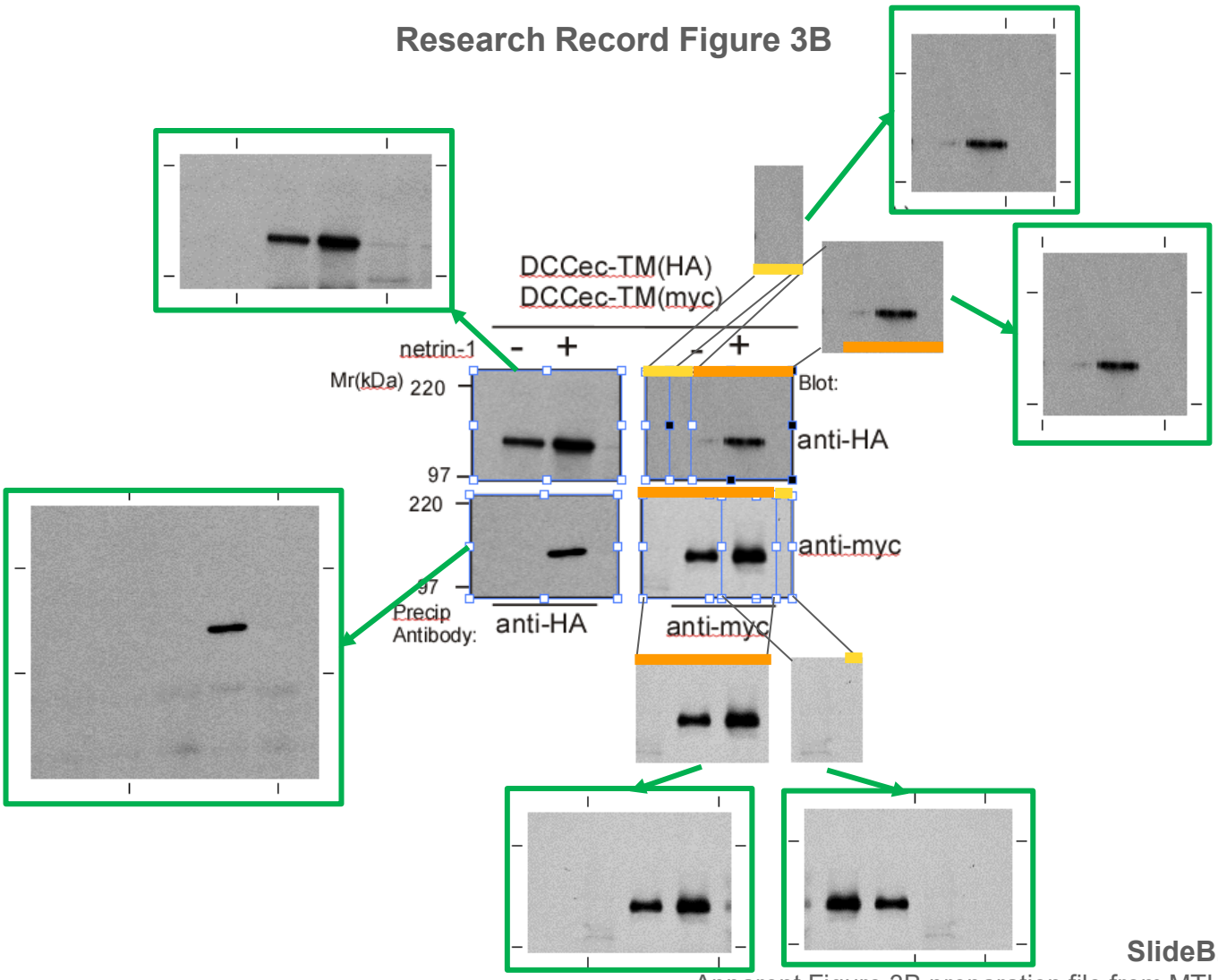


Figure 3B, Research Record Analysis

Published Figure 3B



Research Record Figure 3B



SlideB.CV5
Apparent Figure 3B preparation file from MTL data distribution

Inspection, ungrouping and enlargement of **SlideB.CV5.**
After double-clicking on the obtained images, the **GREEN ARROWS** show the source image that was used to produce the final figure *before* it was cropped (see **GREEN BOXES**).

Color coding: **ORANGE** demonstrates the resulting representation of the underlying data in Figure form.

There are multiple intra-image duplications and reuse of images to create the chimeric image. The initial blot images are taken from various sections of different blot images that do not accurately represent the research record.

Figure 3B, Research Record Analysis
anti-myc/anti-myc panel – example of splicing

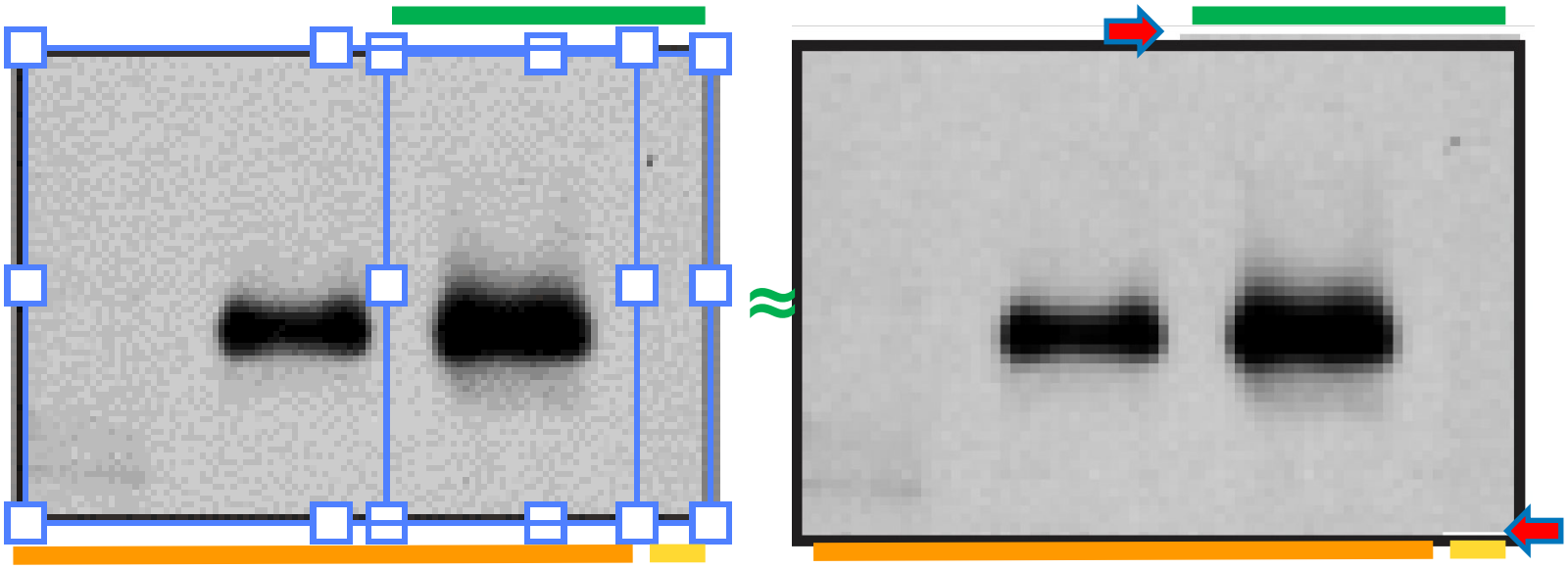


Figure 3B, Research Record Analysis file SlideB.CV5
anti-myc/anti-myc panel enlarged

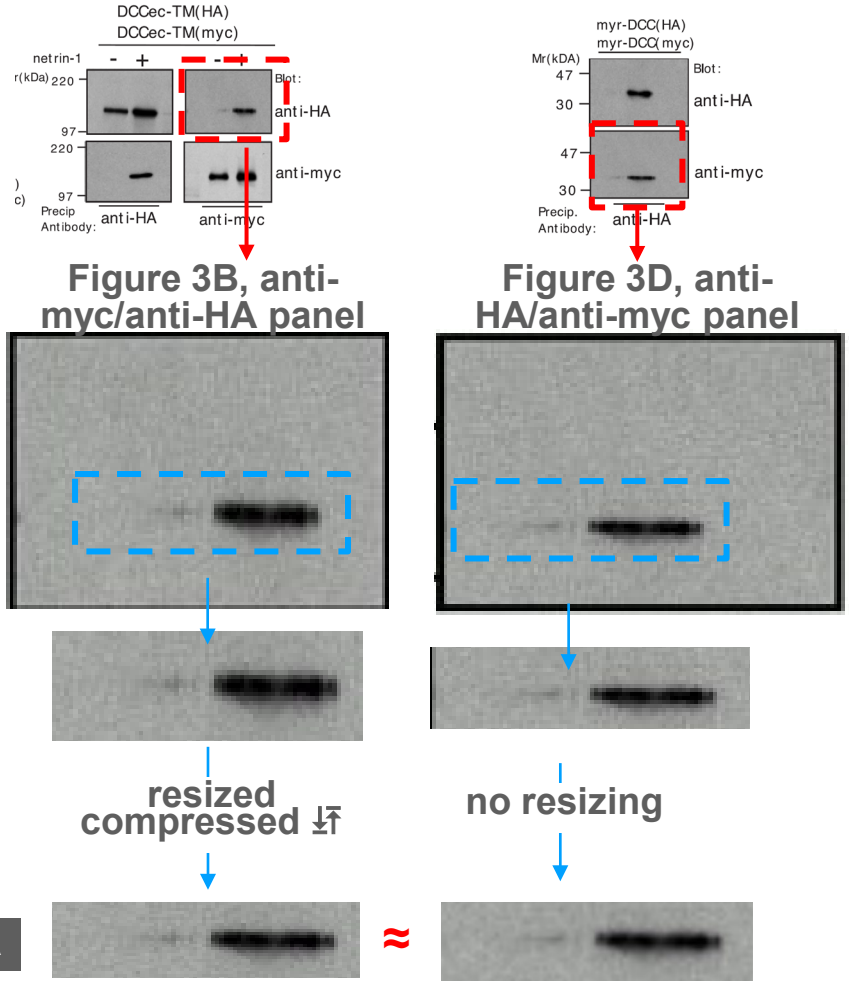
Published Figure 3B
anti-myc/anti-myc panel enlarged

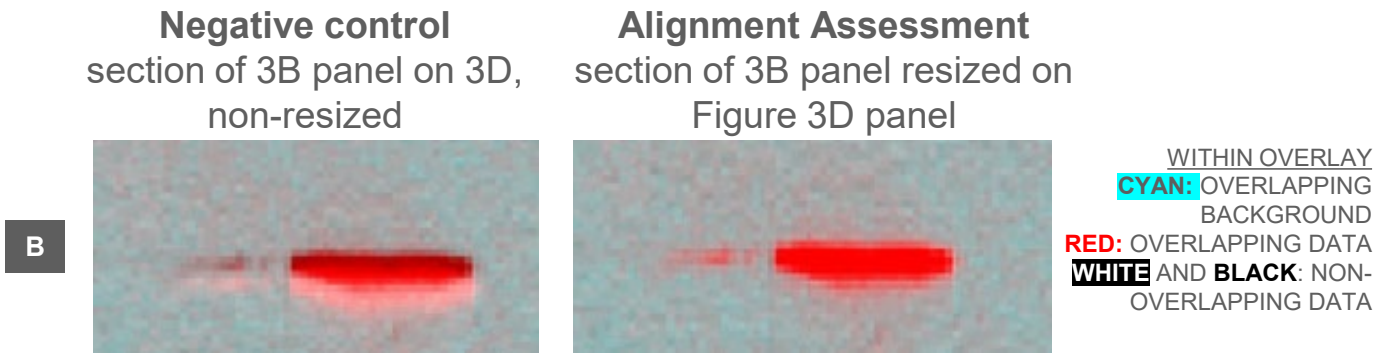
Observations:

RED ARROWS → ← show the seam of overlapping images in the published figure within the reported final figure frame ◘.

GREEN LINES ▬▬ indicate the visible published data panel which aligns with the spliced image in the research record.

Figure 3B and 3D, Image and Overlay Analysis





Observations:

A After resizing the anti-myc/anti-HA blot of Figure 3B, the blot data appear to align with the anti-HA/anti-myc blot data for Figure 3D.

B This alignment is further supported by the overlay assessment of the resized anti-myc/anti-HA blot section of Figure 3B onto the anti-HA/anti-myc blot panel of Figure 3D.

Blot image data appear to be duplicated and used to report two different experimental outcomes in Figures 3B and 3D. The resolution of the available data impacts the overall representation of the features for comparison. Access to original / source data for Figure preparation would provide additional insights as to the origin of the apparent single image used in both Figures.

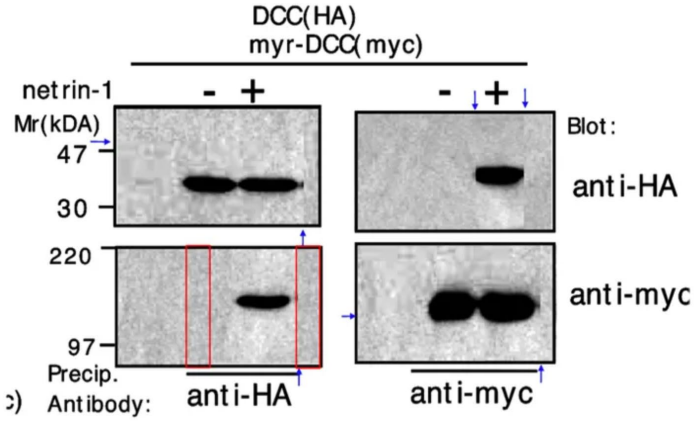
https://pubpeer.com/publications/59C3359E71EED451E01AF46CFDC0BC

Figure 3C
Initial Issue as represented
on PubPeer October 2015

#3 *Peer 2* commented October 2015

#1

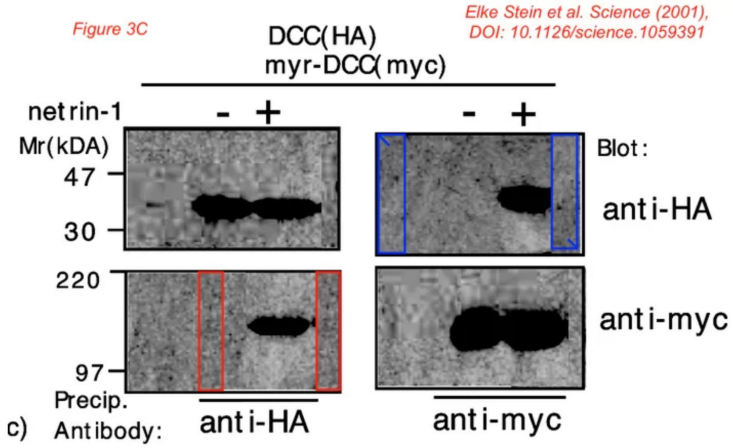
You might also add that the background is the same, e.g.:



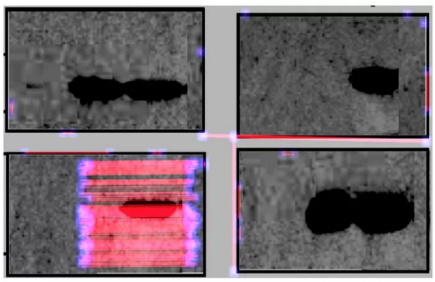
Initial Issue as represented
on PubPeer March 2021

Figure 3C.

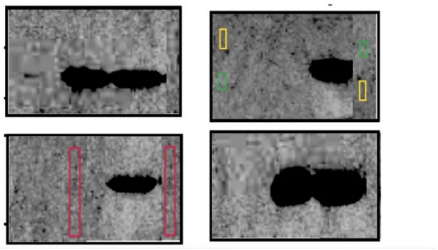
- Bands are surrounded by sharp transitions that might not be compression artifacts (see comment #1)
- Red boxes: the bottom left panel appears to show the same background area twice (see comment #3)
- Blue boxes: the top right panel appears to show the same background area twice, but 180 degrees rotated (a new finding)



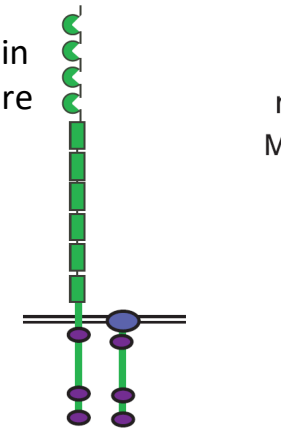
The red-boxed findings are supported by Forensically (which cannot detect rotated duplications):



Both blue- and red-boxed findings are picked up by ImageTwin:



Figures used in
Analysis, Figure
3C



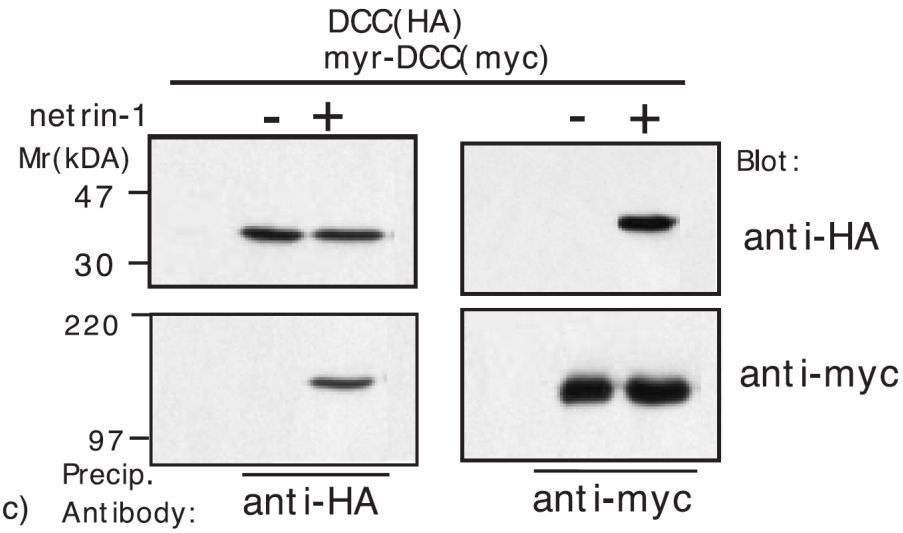
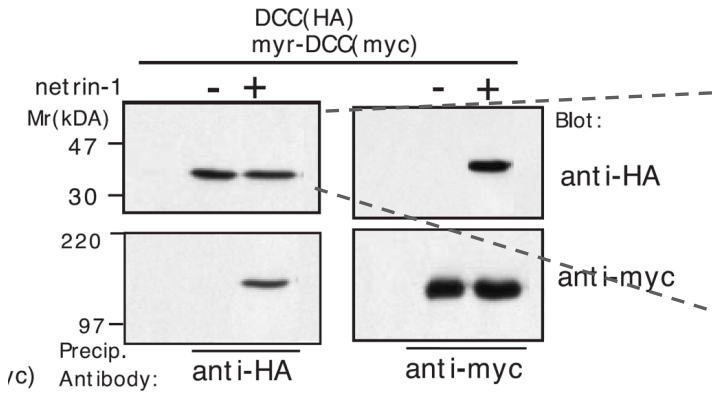


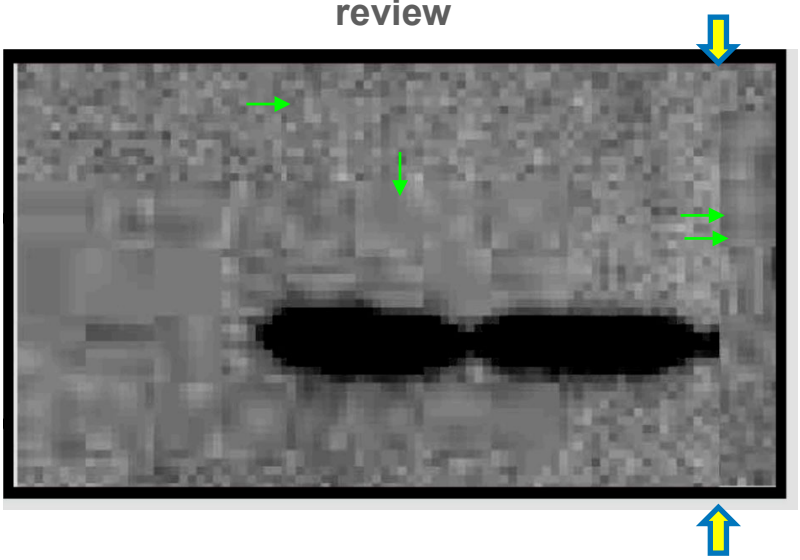
Figure 3C, Image Analysis

anti-HA/anti-HA panel



Published Figure 3C reviewed with level adjustment (brightness -34 and contrast +83).

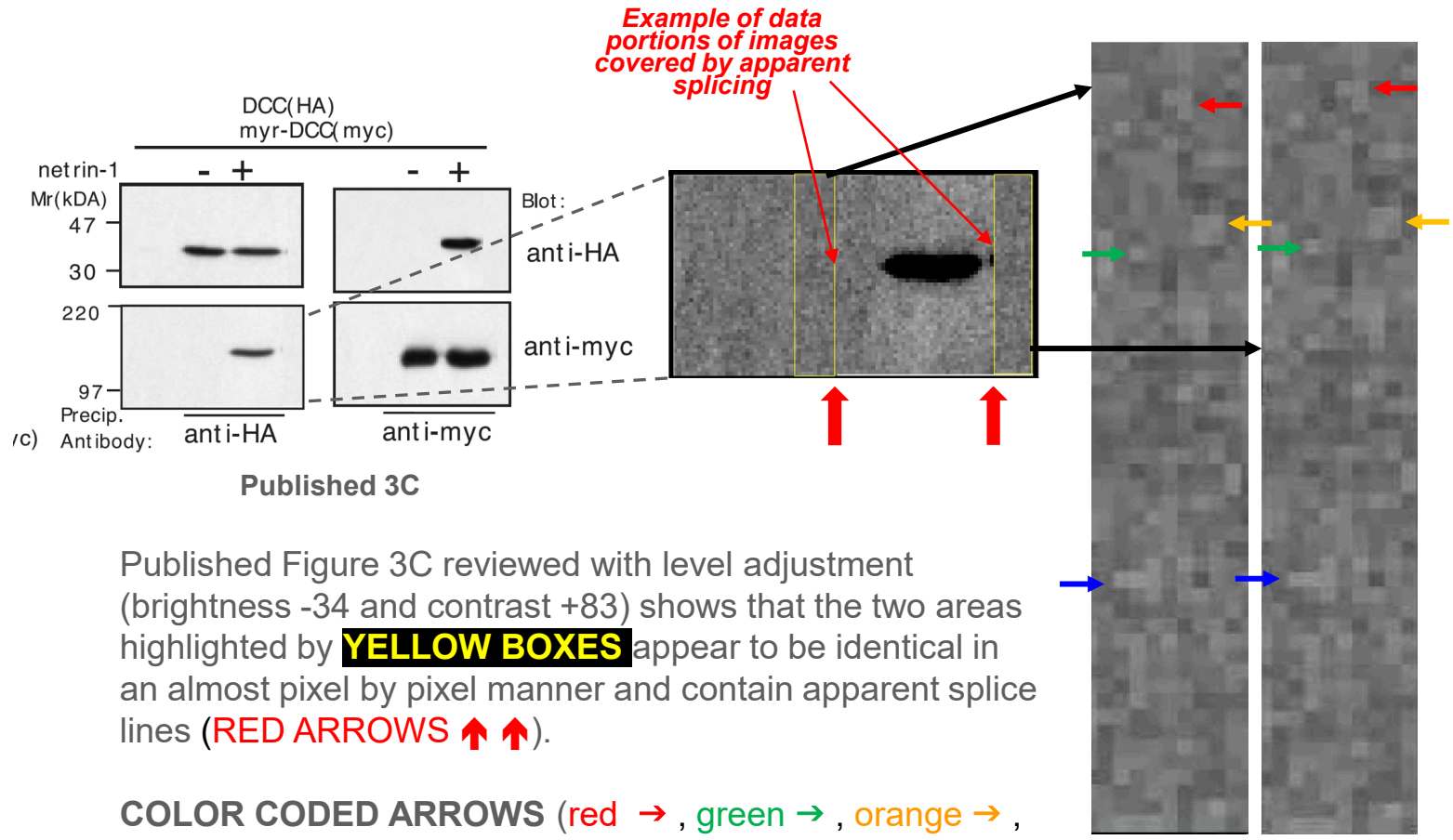
IP: anti-HA, Blot: anti-HA panel enlarged for analysis and review



Observations:

YELLOW ARROWS ↓ ↑ suggest splicing and alteration of the image data.

SMALL GREEN ARROWS → ↓ → → demonstrate differences in resolution, some of which → → accompany the indications of splicing.



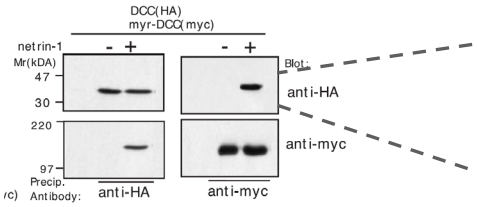
Published 3C

Published Figure 3C reviewed with level adjustment (brightness -34 and contrast +83) shows that the two areas highlighted by **YELLOW BOXES** appear to be identical in an almost pixel by pixel manner and contain apparent splice lines (RED ARROWS ↑ ↑).

COLOR CODED ARROWS (red →, green →, orange →, blue →) show almost identical features between the two sections of the image.

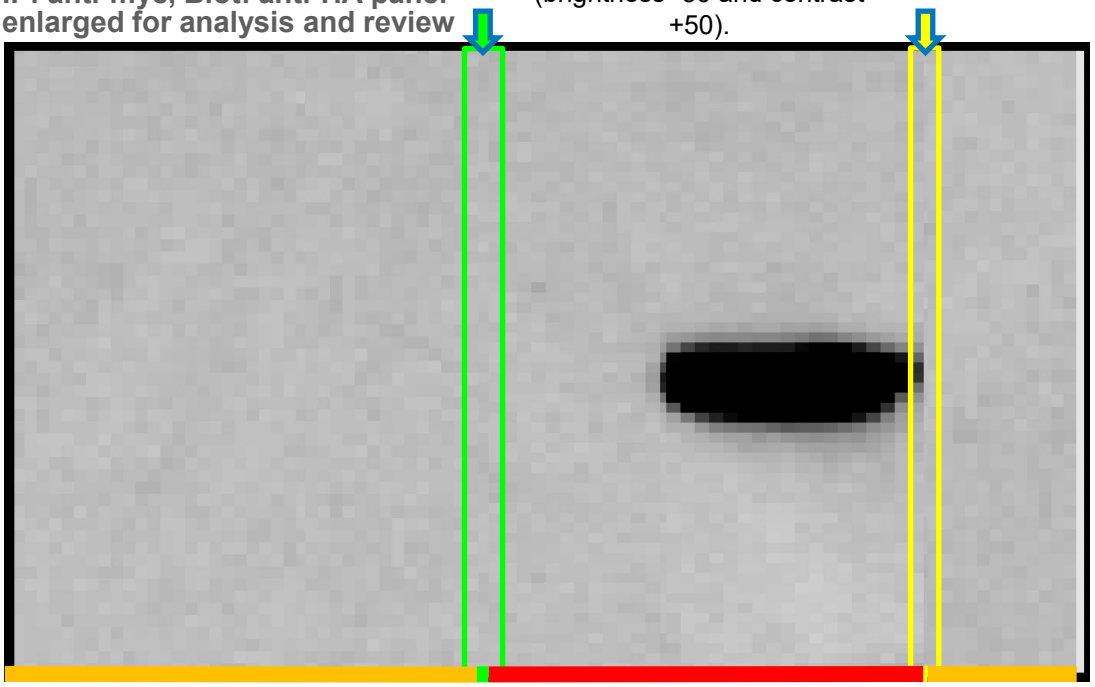
Figure 3C, Image Analysis

anti-myc/anti-HA panel



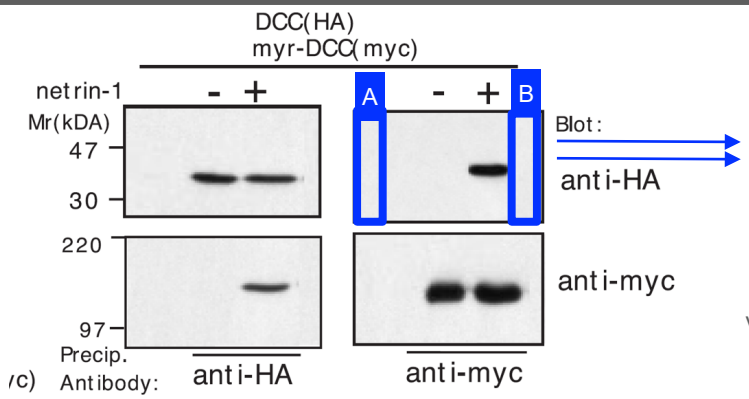
IP: anti-myc, Blot: anti-HA panel enlarged for analysis and review

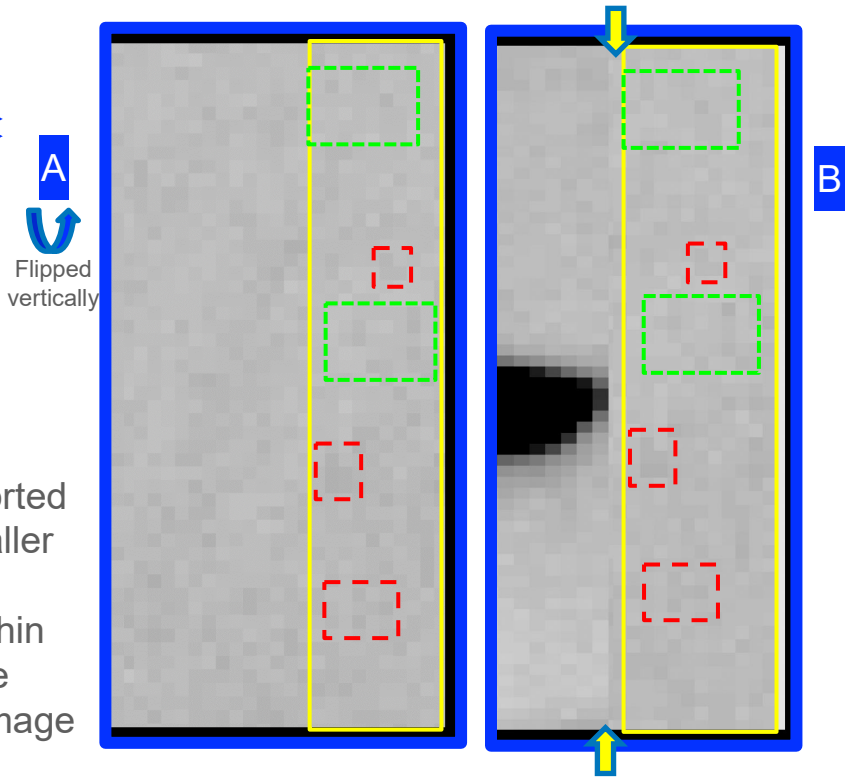
Published Figure 3C reviewed with level adjustments (brightness -30 and contrast +50).



Observations: there are multiple areas of different data resolutions. **ORANGE LINES:** one area of data resolution (square pixels). **RED LINE:** a different area of data resolution (rectangular pixels) with width ≈ to the orange level pixels, but lower height.

GREEN & **YELLOW** area pixels have the same height as the pixels to their immediate right → side, but have significantly lower width. These regions also demonstrate apparent splice interfaces (↓ and ↓). This appears to be a spliced/constructed/chimeric image composed of three different data sources. Inspection of the original image files and experimental data (and metadata) and figure preparation files may provide additional insights into the origin of these features.





Published Figure 3C reviewed with level adjustment (brightness -30 and contrast +50).

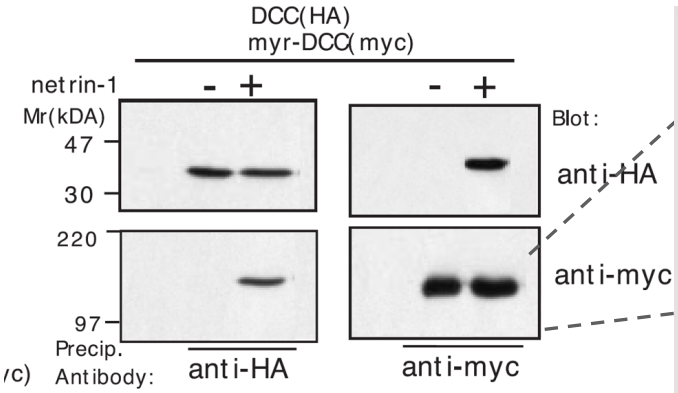
Regions **A** and **B** compared for similarities.

YELLOW RECTANGLE insets show additional comparison of the two areas reported as identical (PubPeer). Analysis shows smaller areas that appear identical **RED DASHED BOXES** ☐ ☐ ☐, and other, larger areas within the **GREEN DASHED BOXES** ☐ ☐ that are slightly different. Inspection of the original image files and experimental data (and metadata) notebooks would be necessary to further evaluate the described features. **YELLOW ARROWS** ↓ ↑ demonstrate an apparent splice.

Combined, these features suggest data insertion, deletion, and/or a combination of both processes, within the published image.

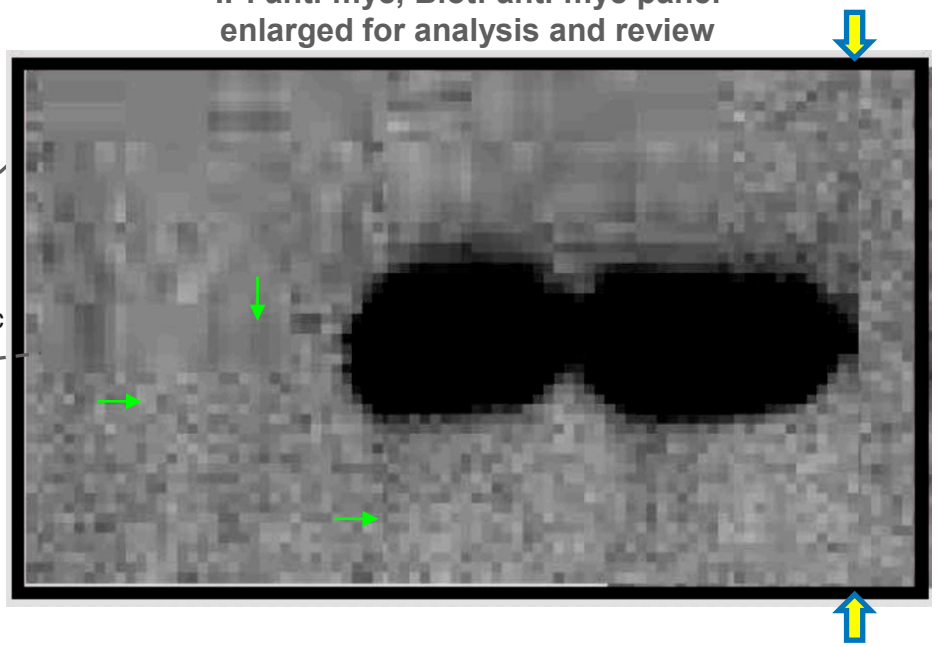
Figure 3C, Image Analysis

anti-myc/anti-myc panel



Published Figure 3C reviewed with level adjustment (brightness -34 and contrast +83).

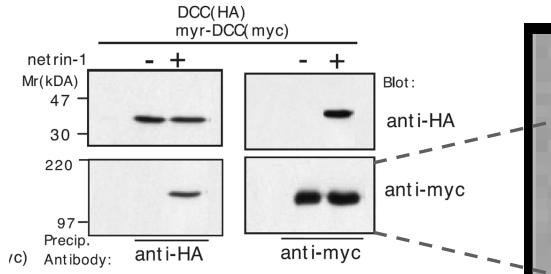
IP: anti-myc, Blot: anti-myc panel enlarged for analysis and review



Observations:

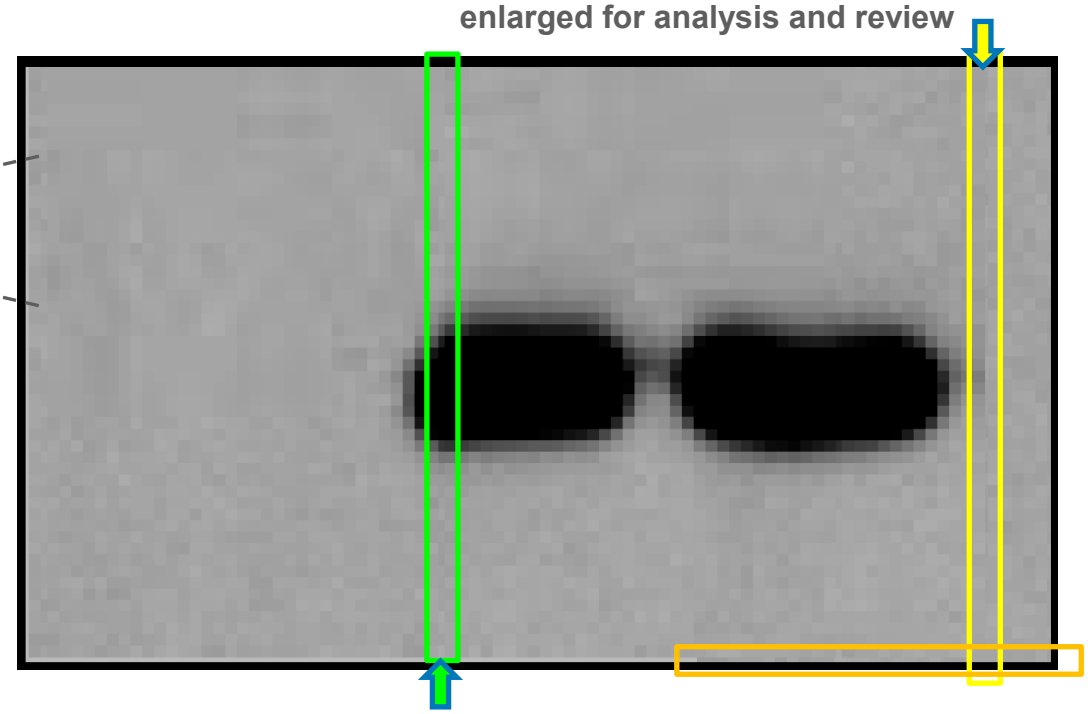
YELLOW ARROWS ↓ ↑ suggest splicing and alteration of the image data.

SMALL GREEN ARROWS → ↓ → demonstrate regions of the image with different resolutions.



Published Figure 3C reviewed with level adjustment (brightness -65 and contrast +20).

IP: anti-myc, Blot: anti-myc panel enlarged for analysis and review



Observations:

GREEN ▯ **YELLOW ▯** and **ORANGE ▯** areas demonstrate multiple areas of different resolution data (pixel shape/size).

At least one of the regions also demonstrates a clear splice interface (↓). Given the overall structure of the image, there appears to have been at least three different panels combined to create the final image. Interestingly, one of insertions appears to traverse the left blot band, ↑ which may suggest manipulation of the band itself.

Science ’01 Silencing

https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB

Figure 4A
Initial Issue as represented
on PubPeer October 2015

Some contrast breaks in Fig 4A and 4E as well:

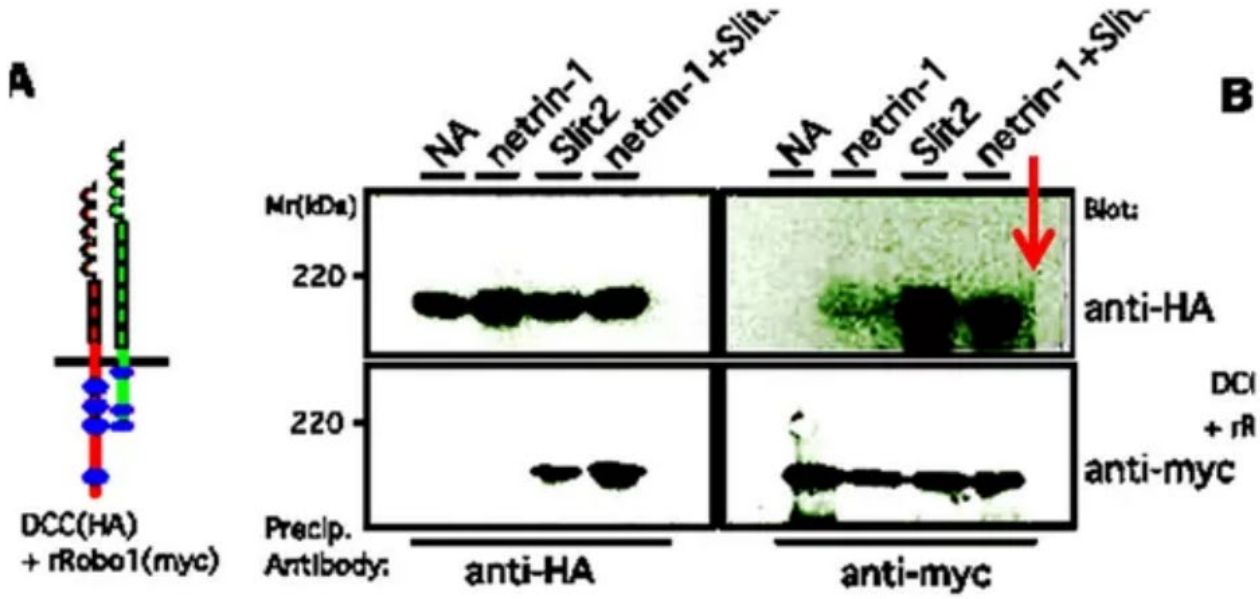


Figure used in
Analysis – Figure 4A
(image from website)

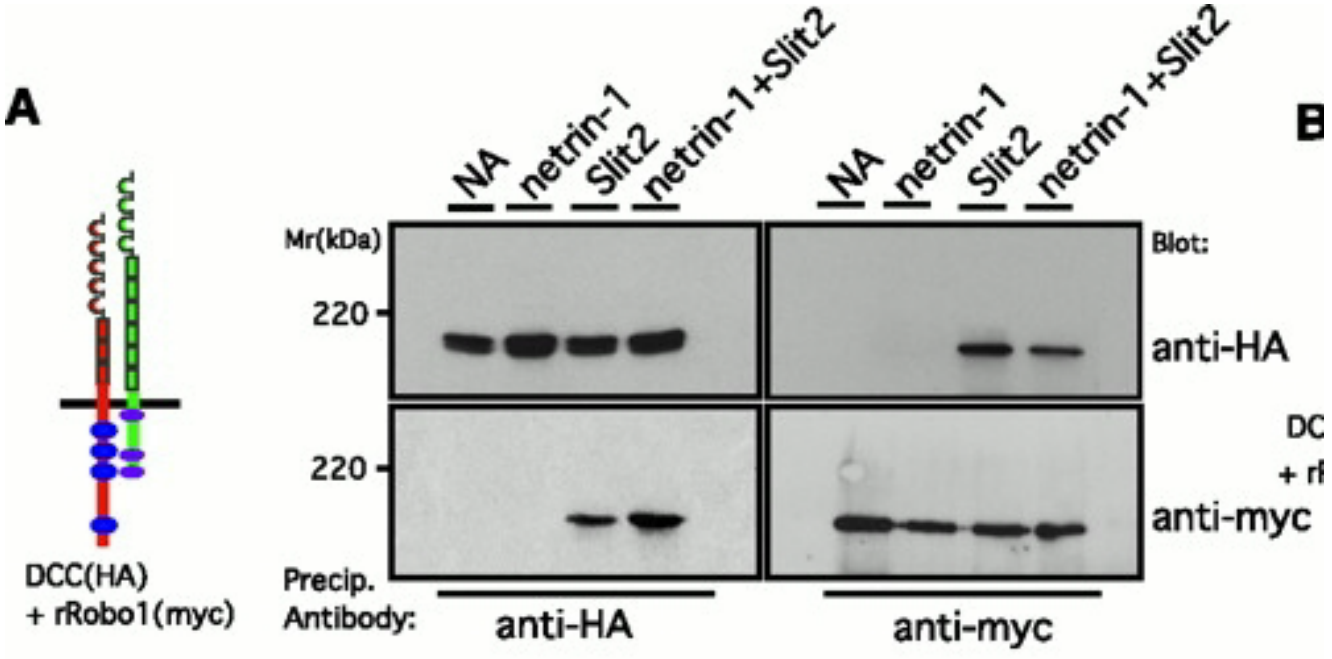
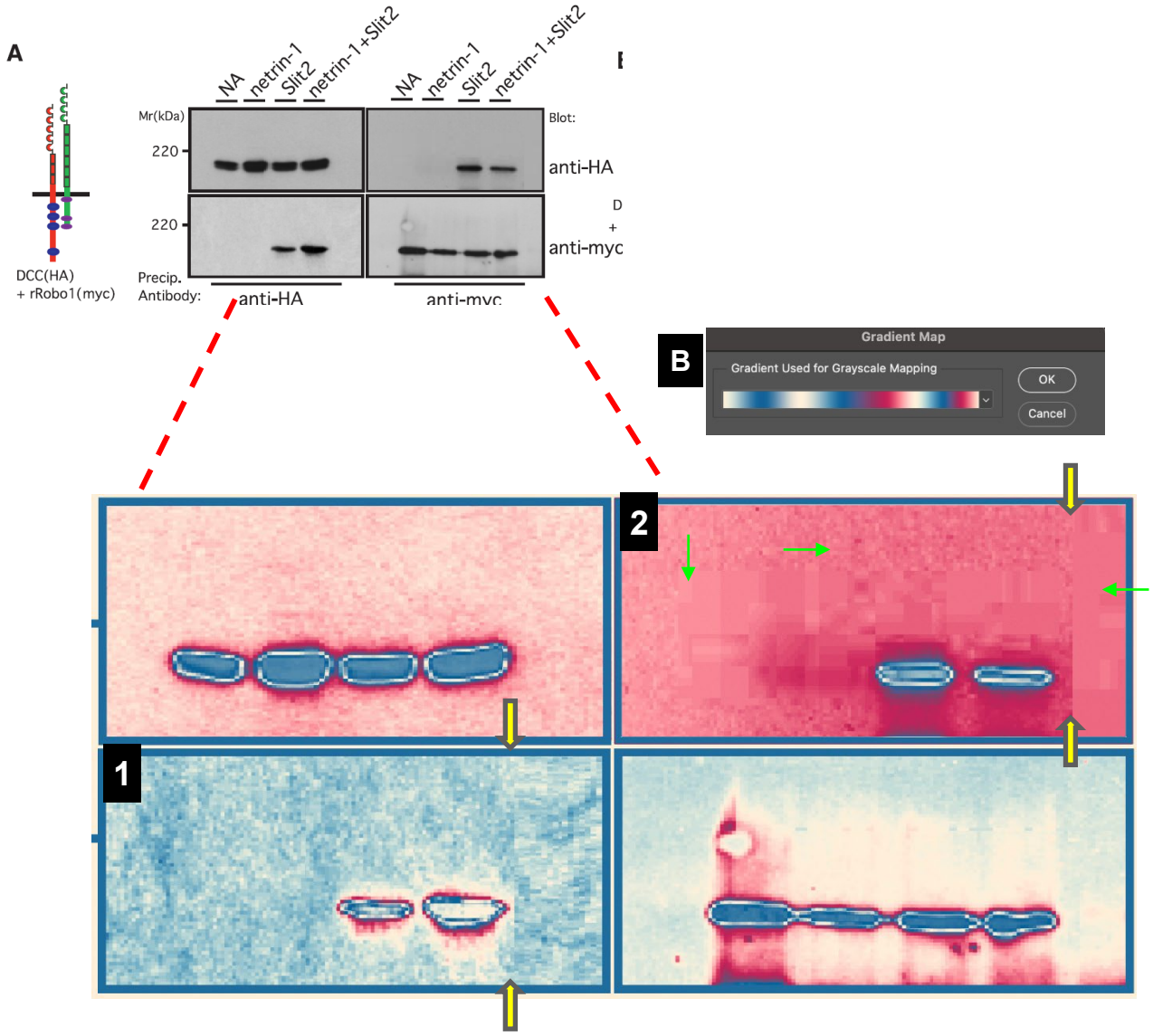


Figure 4A, Gradient Map Analysis

anti-myc/anti-HA panel
anti-HA/anti-myc (added)

A Image used: Screenshot of Published Figure 4A, journal website



Observations:

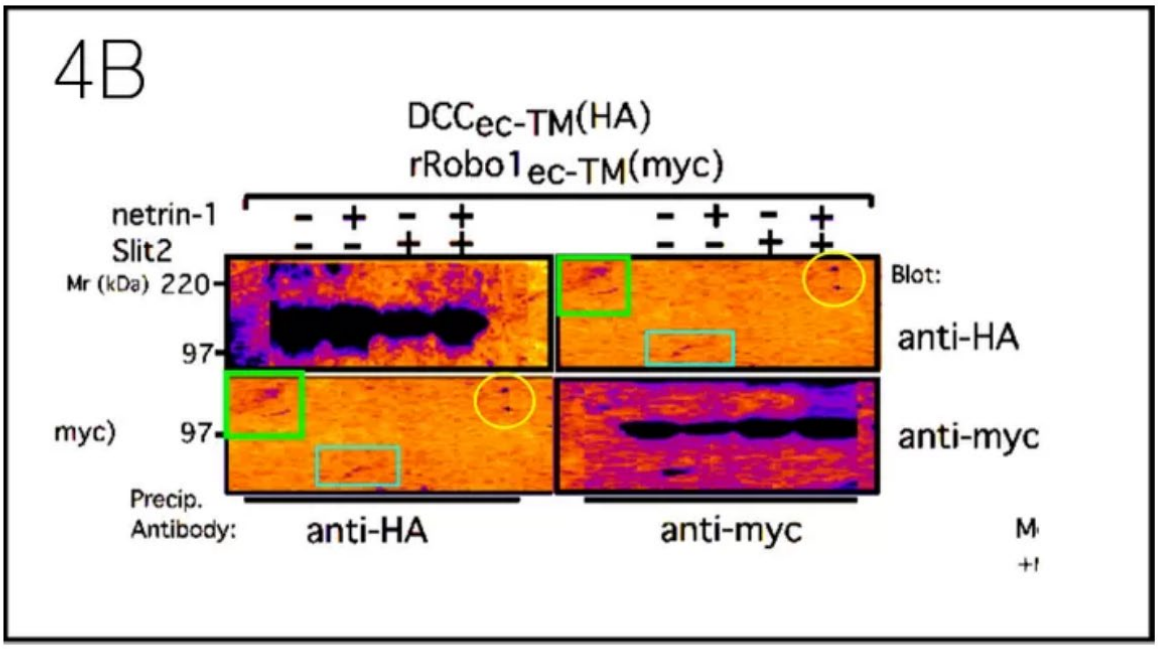
A Published Figure 4A reviewed with Gradient Map (Red, Blue, White) B reveals multiple instances of linear interfaces suggesting splicing YELLOW ARROWS ↑↓ in 1 and 2.

SMALL GREEN ARROWS ↓ → ↓ sections of the image data demonstrate distinct resolution features, further suggesting potential image alteration.

https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB

Figure 4B

Initial Issue as represented on PubPeer October 2015



(https://pubpeer.com/storage/imgur-jlkUTNU.png.jpg) Note apparently repeating features.

Figure used in Analysis – Figure 4B (snapshot from pdf)

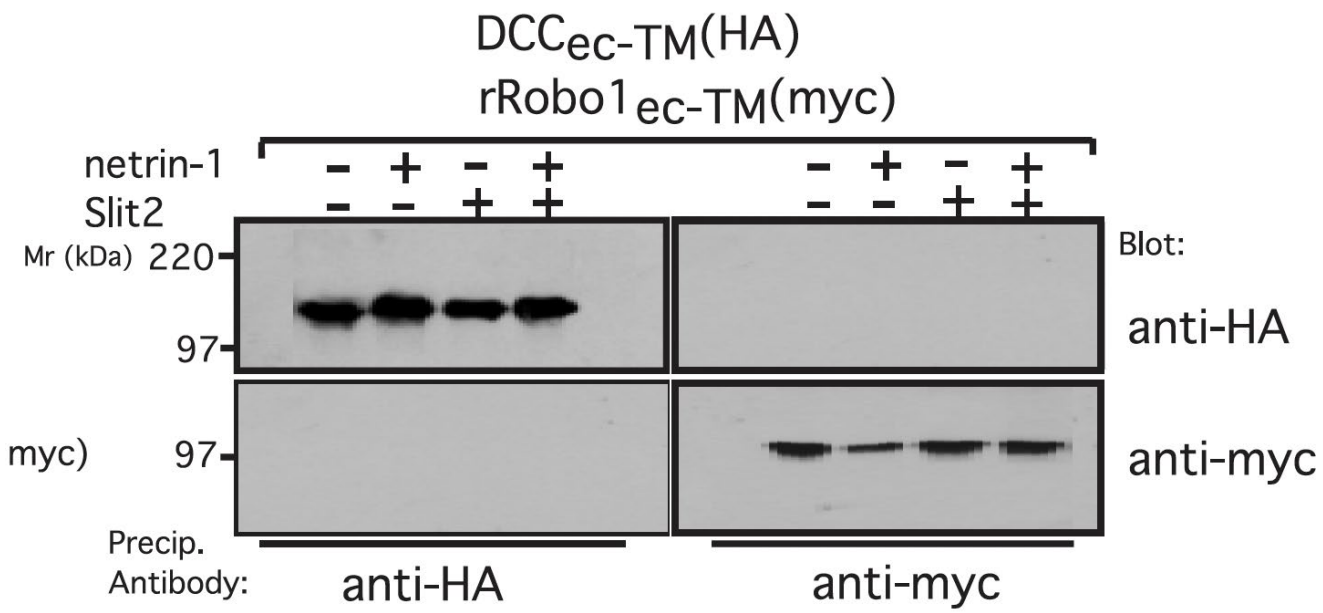
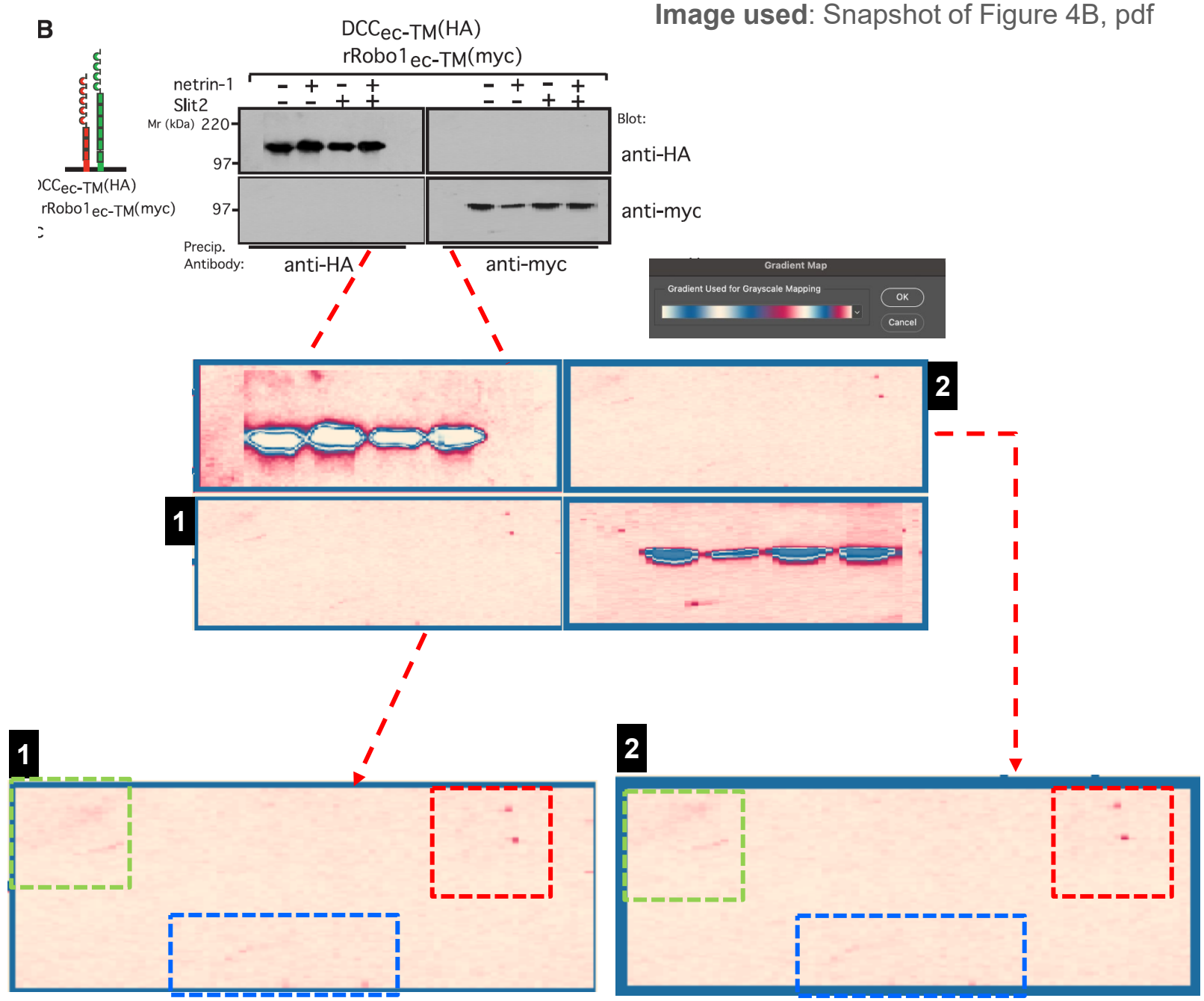


Figure 4B, Gradient Map Analysis

anti-HA/anti-myc and anti-myc/anti-HA panels

Image used: Snapshot of Figure 4B, pdf

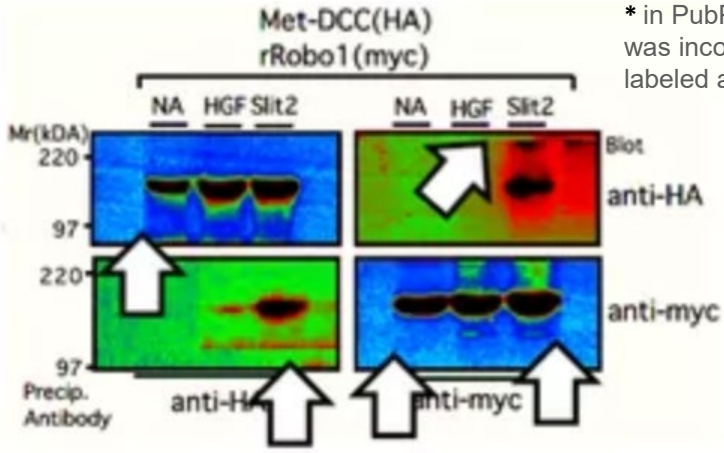


Observations: Published Figure 4B reviewed by Gradient Map. Similarities (**COLOR CODED DASHED BOXES** □□□) between blot panels **1 and 2** described (not exhaustive), demonstrate that the same western blot image is used to represent anti-HA/anti-myc and anti-myc/anti-HA panels.

https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB

Figure 4*C

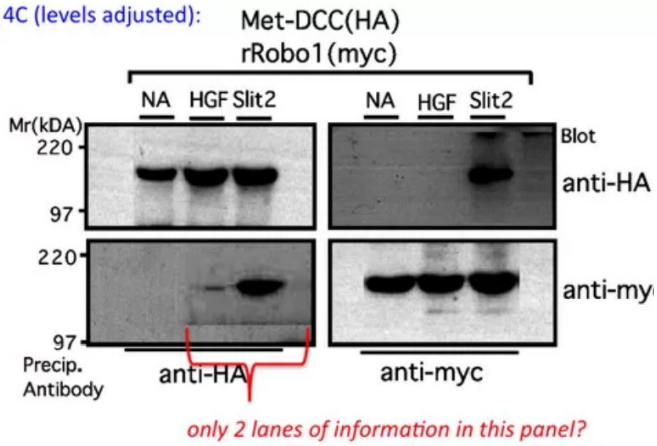
Initial Issue(s) as represented on PubPeer October 2015



* in PubPeer this was incorrectly labeled as Figure 5

Many unexpected apparent edits appear in almost all western blot figures- a small sample is presented here (I got tired). The apparent introduction of regions of background and lane splicing may undermine confidence.

Fig 4C (levels adjusted):



only 2 lanes of information in this panel?

cases where the data has been pasted onto a background, presumably in an attempt to make the panels fit a uniform size, so that the figure is "prettier". This is certainly not best practice, but it does not obscure or misrepresent the results that are shown. Instead, it represents suboptimal presentation practice that, again, should be discouraged (and probably is less common in the current era).

(The only case in Peer 2's examples that seems to suggest between-lane splicing is the three upward-pointing arrows, but I do not agree that the middle arrow points to a splice.)

That said, there are some strange features in a couple of other figures that I have illustrated in a link below.

Figure used in Analysis – Figure 4C (snapshot from pdf)

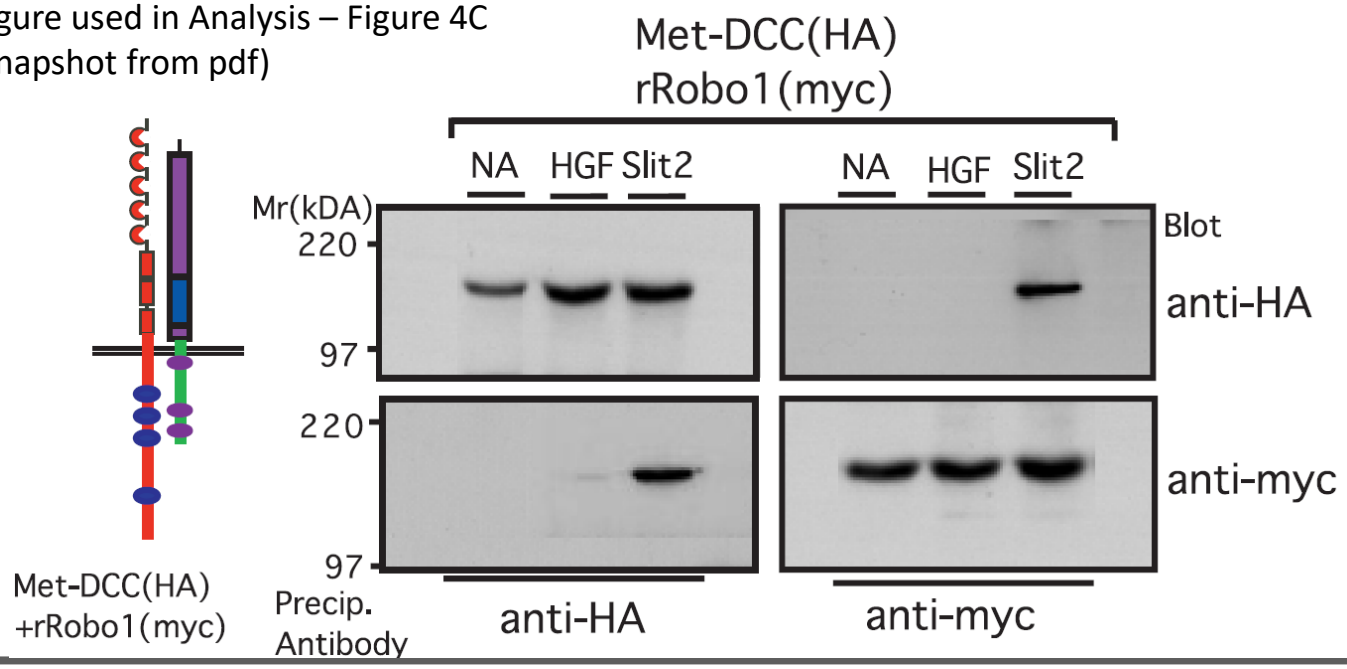
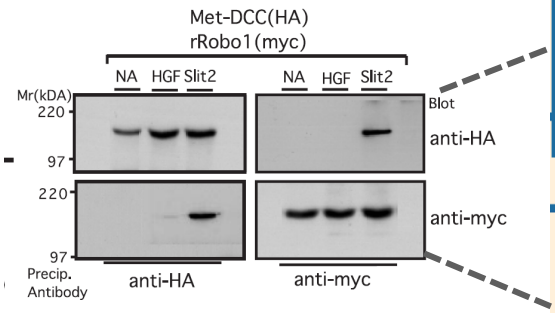
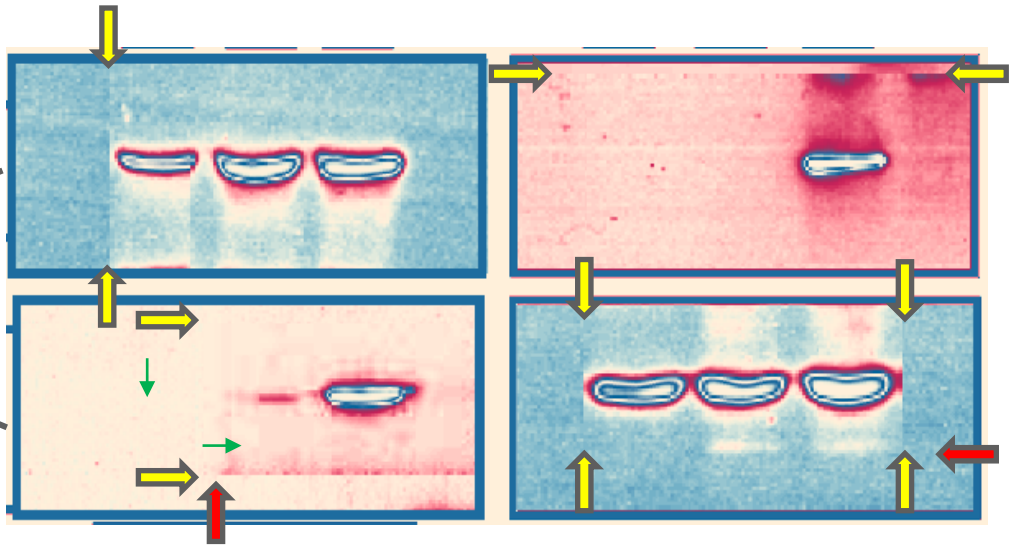


Figure 4C, Gradient Map Analysis

anti-HA/anti-HA
anti-HA/anti-myc
anti-myc/anti-HA
anti-myc/anti-myc

Image used: Snapshot **of** Figure 4C, pdf





Observations:

Published Figure 4C reviewed with Gradient Map (Red, Blue, White) reveals multiple instances of linear interfaces, suggesting splicing in all panels reported. **YELLOW ARROWS ↑↓** **SMALL GREEN ARROWS ↓ →** Sections of the image data show distinct data resolution features, further suggesting potential image alteration.

RED ARROWS ↑ ← Demonstration of different background data signals along interfaces, although not as apparent as other splice features. As described, these data transition along an interface that does not appear to have a distinct splice, but the resolution of the data transitions distinctly along the plane. This suggests that additional data modification (in addition to splicing) may have occurred.

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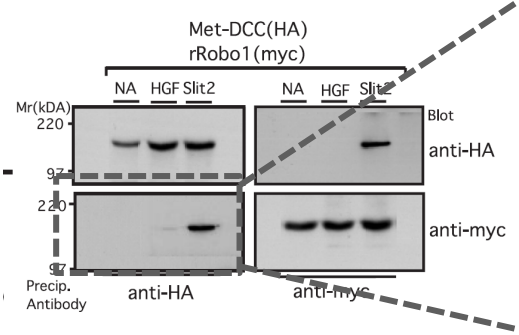
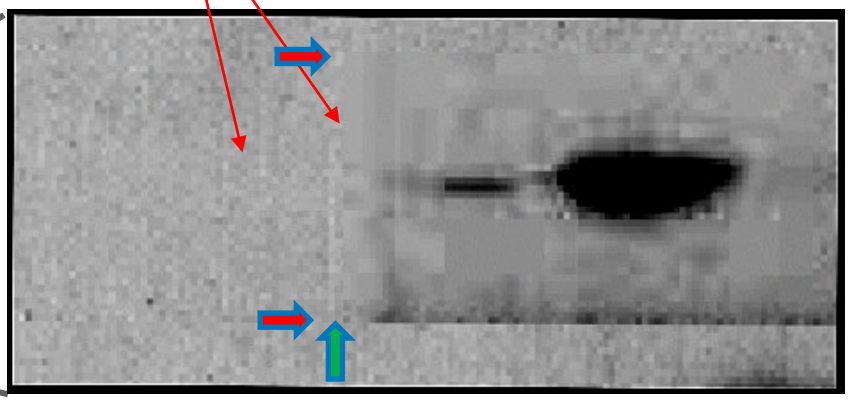
anti-HA/anti-myc additional discussion

Example of data portions of image (e.g., NA lane) removed or altered





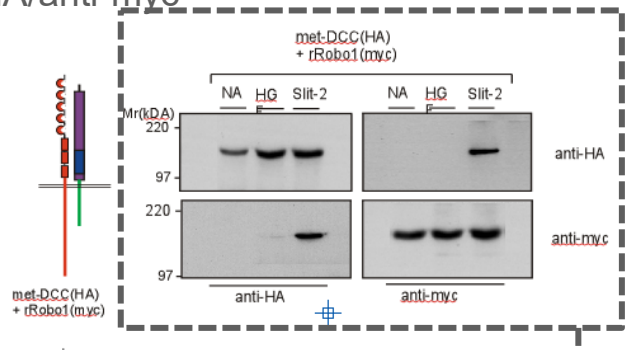
Observations: Published Figure 4C reviewed by adjusting brightness to +20 and contrast to +85 (legacy).

(RED ARROWS ➔➔) indications of splicing, suggesting either insertion, removal (or a combination of both) of data within the reported image.

As described, these data transition along an interface ↑ that does not appear to have a distinct splice, but the resolution of the data transitions along the plane. This suggests that data modification (in addition to splicing) may have occurred.

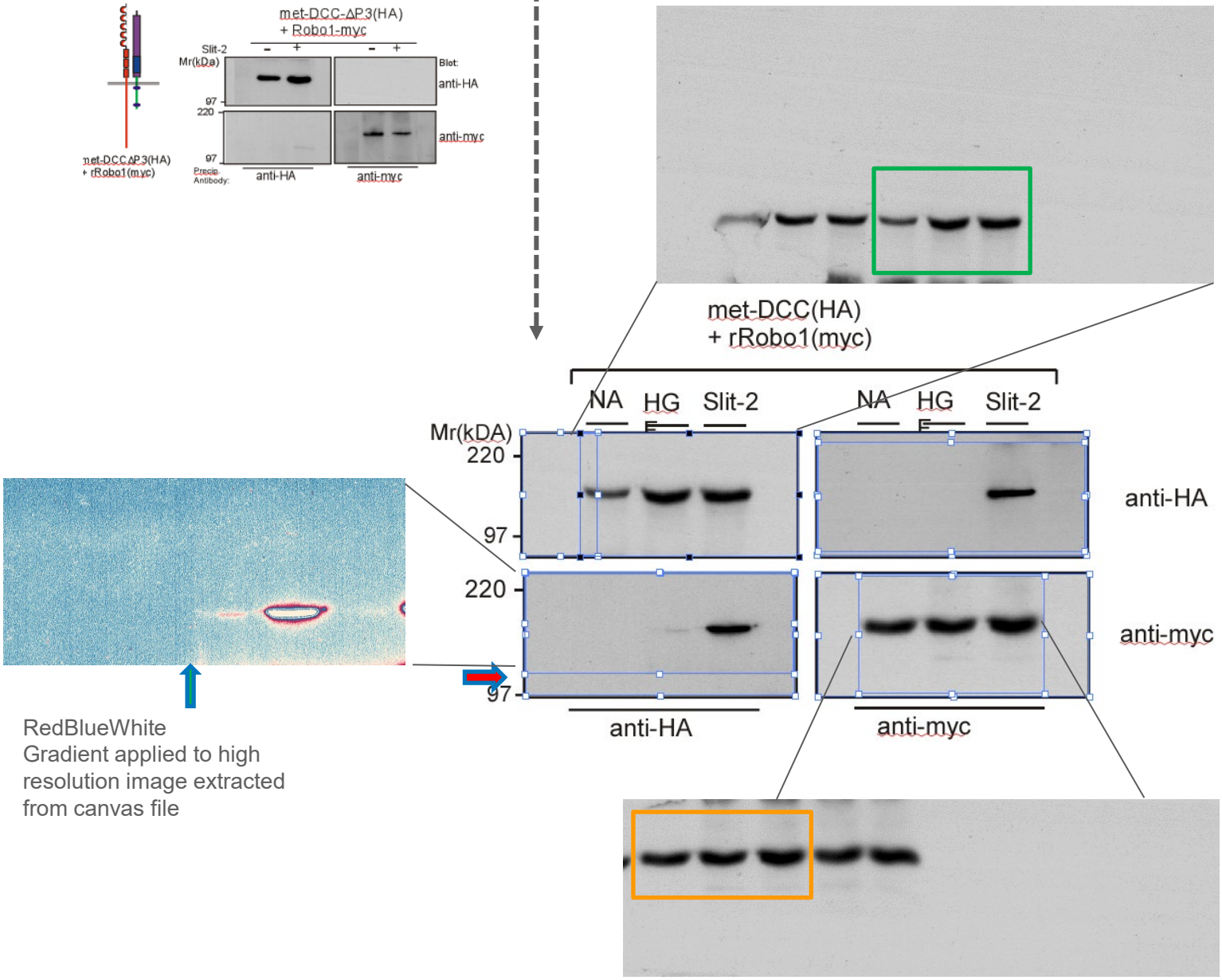
Figure 4C, Research Record Analysis

anti-HA/anti-myc



csh12b.cv5

Apparent Figure 4C preparation file located from MTL data distribution



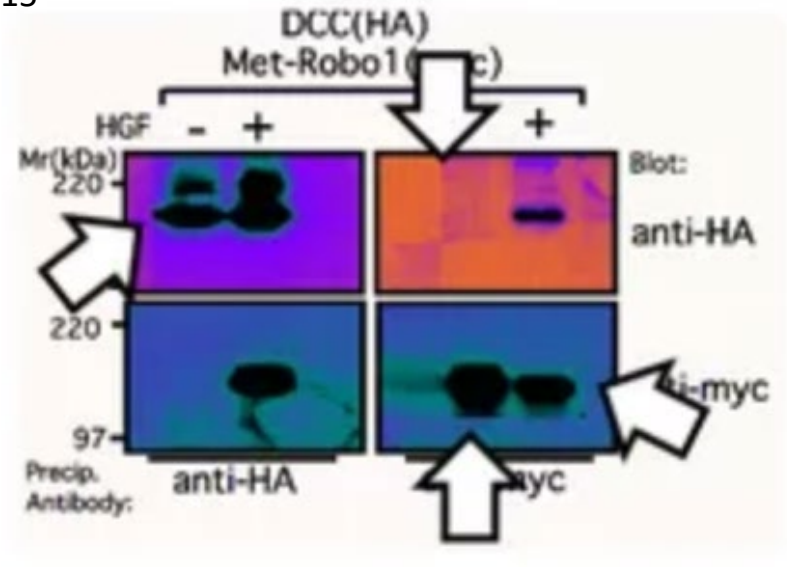
RedBlueWhite Gradient applied to high resolution image extracted from canvas file

Observations: Inspection of the research record shows that all panels in the figure were created by splicing. The high-resolution layer embedded in the research record associated with the bottom left quadrant demonstrates hallmarks of data modification.

https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB

Figure 4*D
Initial Issue(s) as represented on PubPeer October 2015

* in PubPeer this was incorrectly labeled as Figure 5



Many unexpected apparent edits appear in almost all western blot figures- a small sample is presented here (I got tired). The apparent introduction of regions of background and lane splicing may undermine confidence.

Figure used in Analysis – **Figure 4D** (snapshot from pdf)

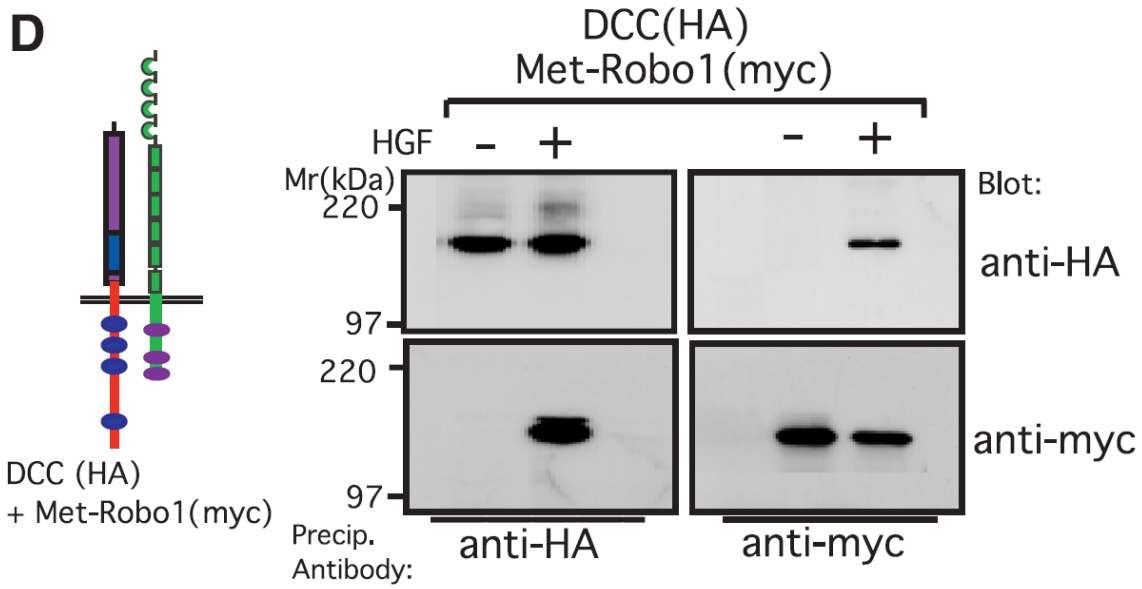
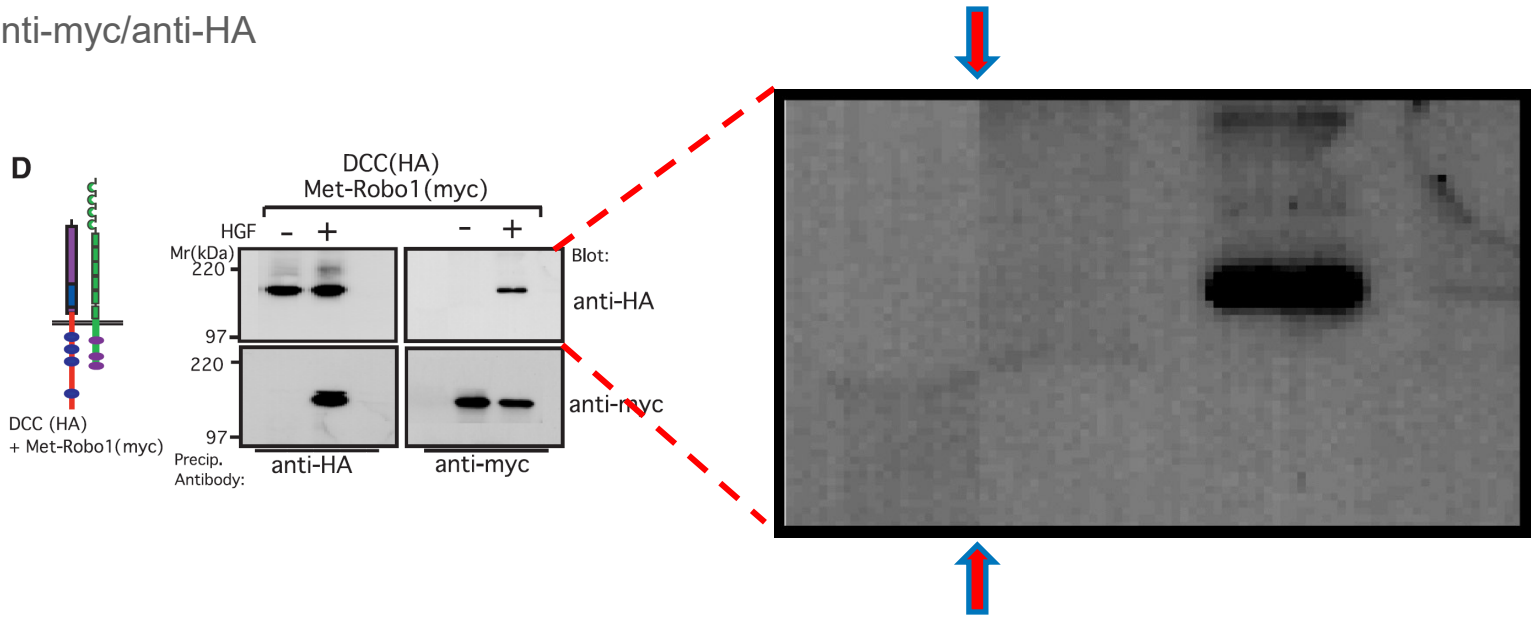
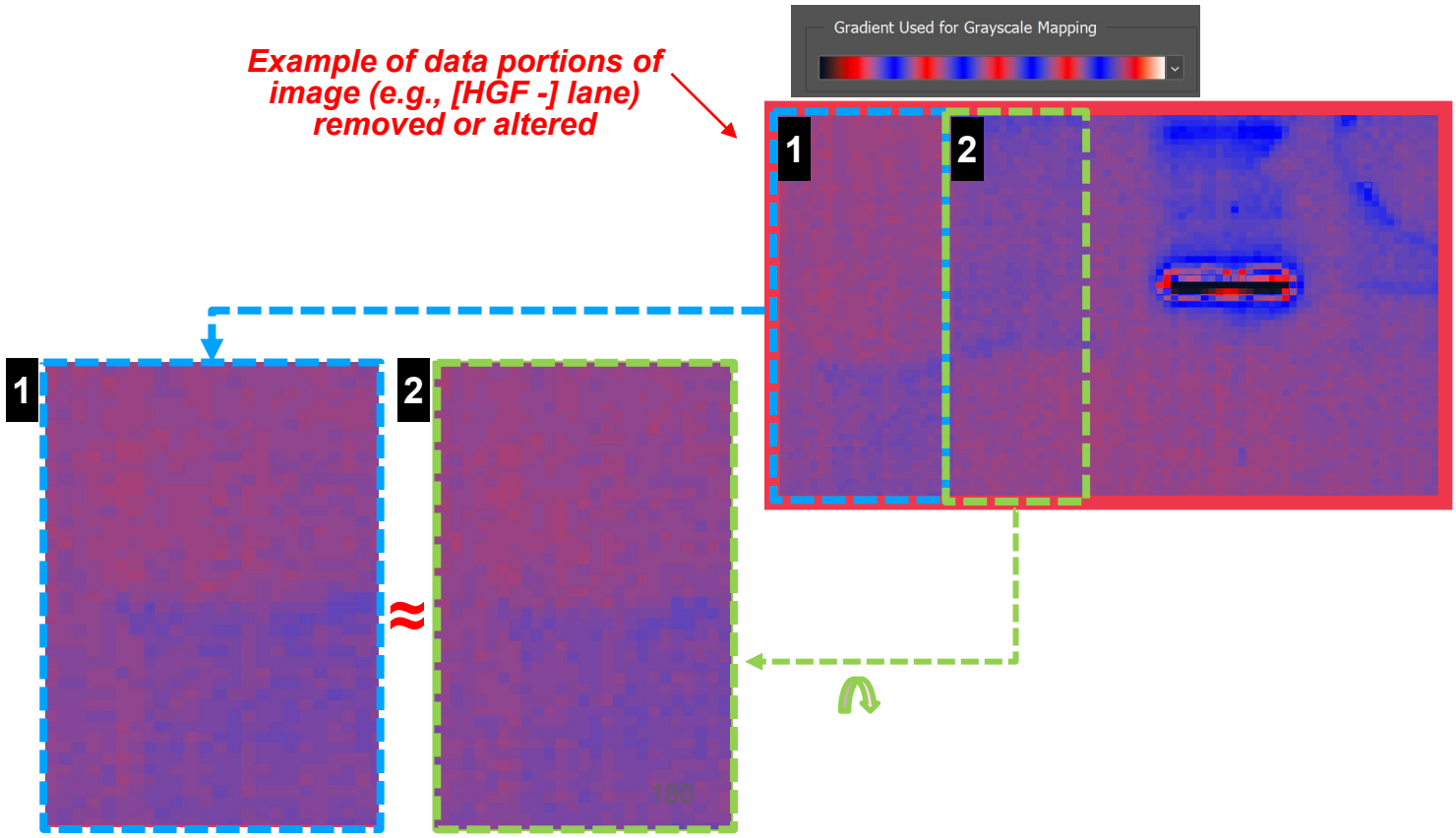


Figure 4D, Image Analysis continued

anti-myc/anti-HA



Observations: Published Figure 4D reviewed by adjusting brightness and contrast (legacy).
(RED ARROWS ↓ ↑) indications of splicing, suggesting either insertion, removal (or a combination of both) of data within the reported image.

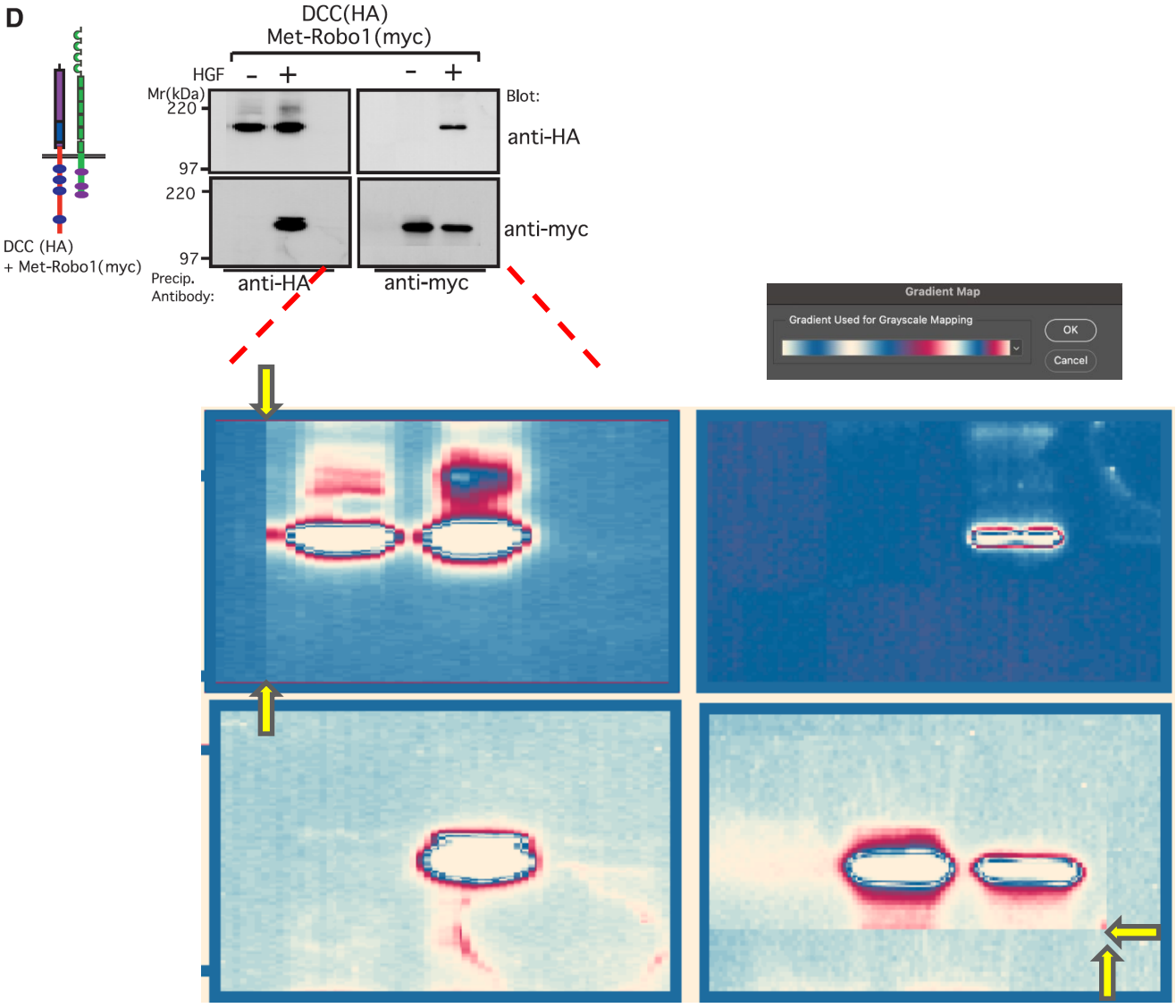


Published Figure 4D reviewed by Gradient Map shows similarities in the background after 180 degree rotation. This suggests that the HGF- lane is constructed from a mirror image of duplicated areas of background data.

Figure 4D, Image Analysis continued

anti-HA/anti-HA

anti-myc/anti-myc

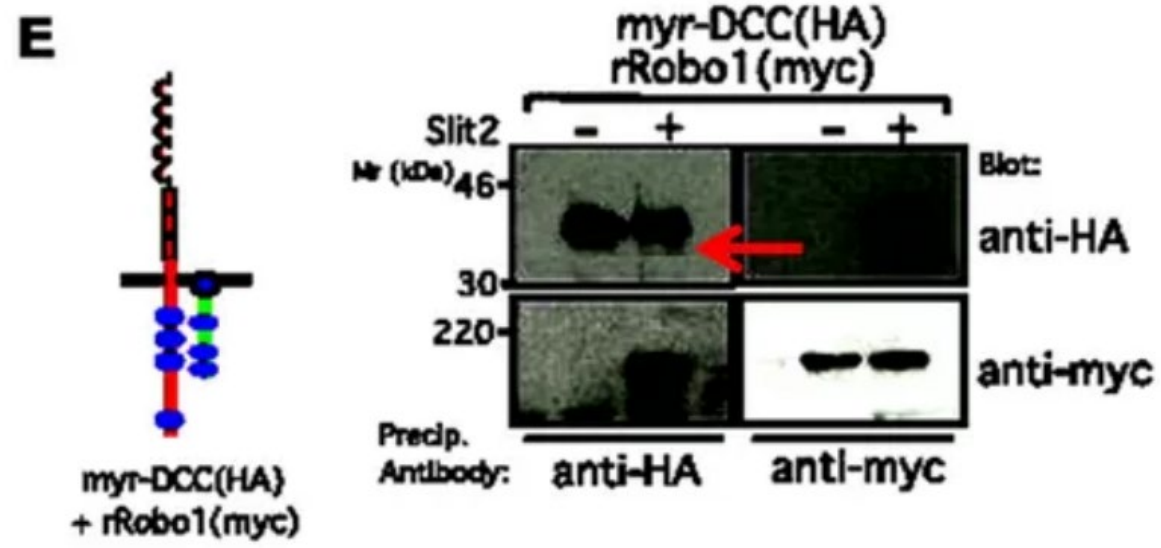


Observations:

Published Figure 4D reviewed with Gradient Map (Red, Blue, White) reveals multiple instances of linear interfaces suggesting splicing in multiple panels as identified by YELLOW ARROWS ↑↓ ↑←

https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB

Figure 4E
Initial Issue(s) as represented on PubPeer October 2015



(https://pubpeer.com/storage/imgur-GS2r1Bf.png.jpg)

Figure used in Analysis –
Figure 4E (snapshot from pdf)

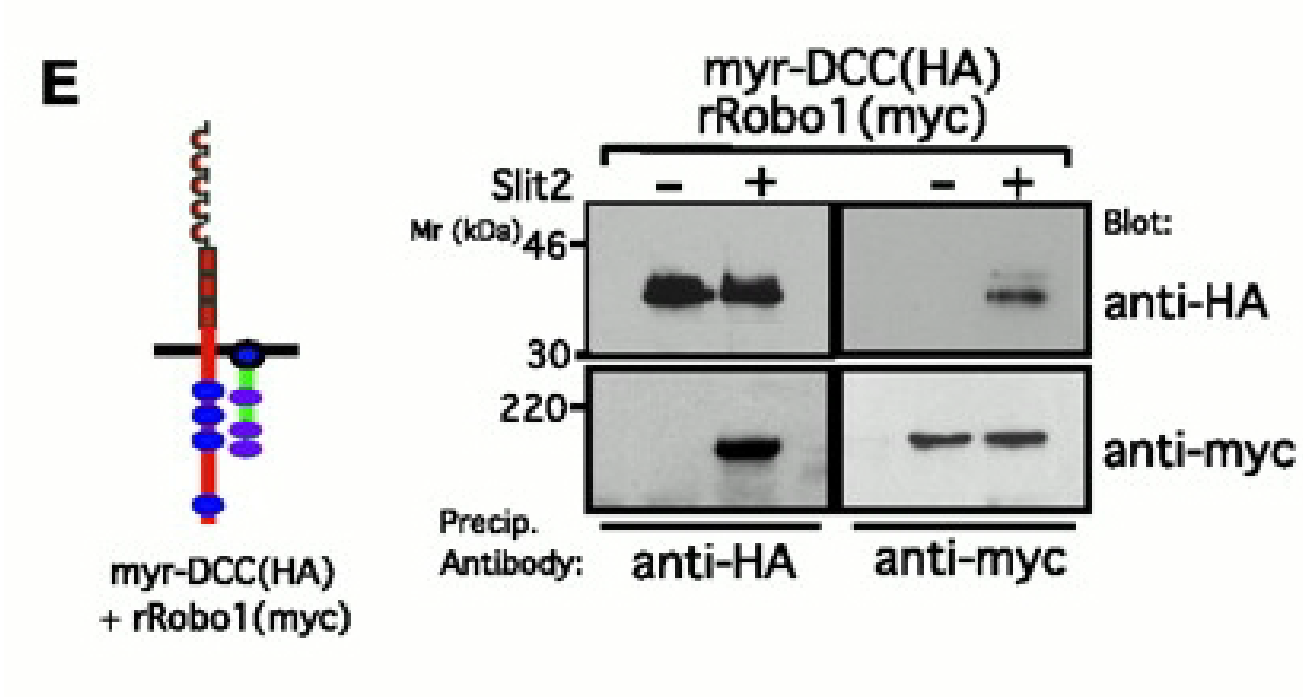
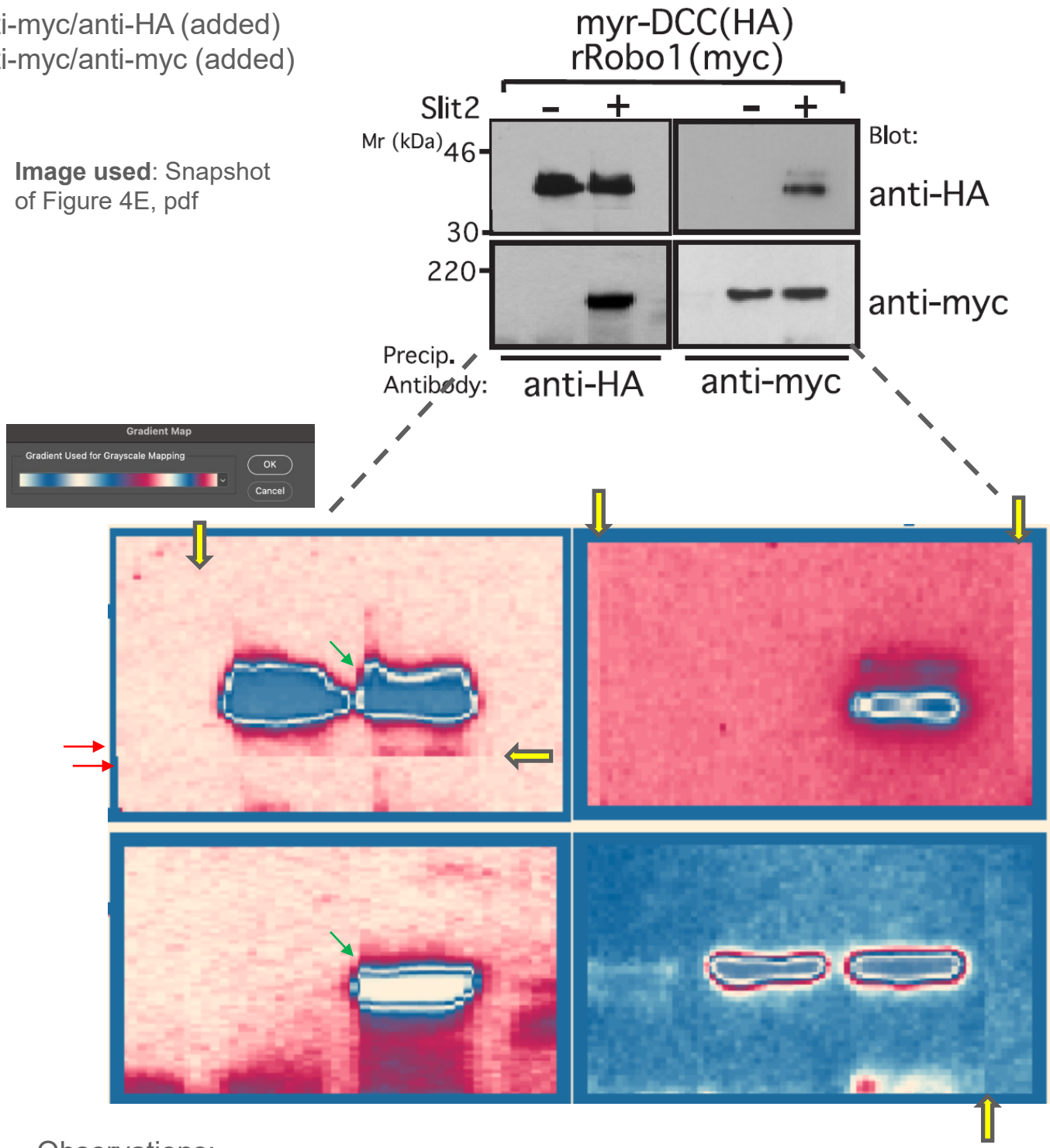


Figure 4E, Gradient Map Analysis

anti-HA/anti-HA
anti-myc/anti-HA (added)
anti-myc/anti-myc (added)

Image used: Snapshot of Figure 4E, pdf



Observations:

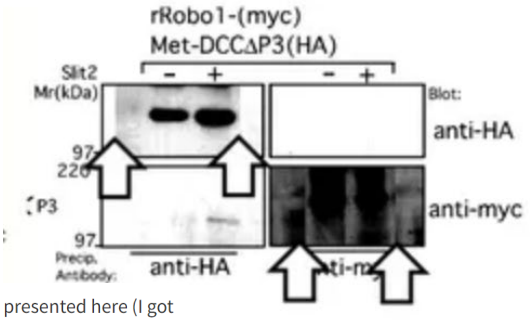
YELLOW ARROWS ↑↓ ← Published Figure 4E reviewed with Gradient Map (Red, Blue, White) reveal multiple instances of linear interfaces suggesting splicing.

SMALL GREEN ARROWS ↘ ↘ Unusual features of bands. The resolution of the data is low, and there are accompanying compression artifacts. It is unclear if the features are representative of image alteration or the processes of figure preparation and publication.

RED ARROWS →→ Demonstration of apparent misalignment of the image data along the linear interface within the image, with ← further demonstrating the apparent splicing of image data.

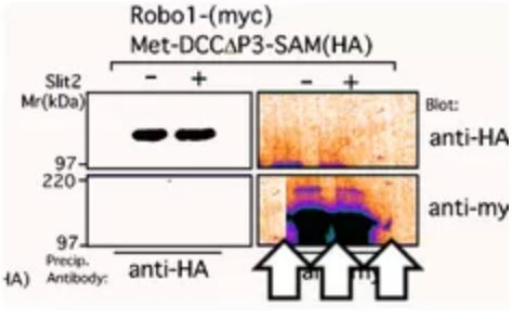
https://pubpeer.com/publications/BFCF07AC5A957DB7E8950B448CB6CB

Figure 5*
C, D and E
Initial Issue(s) as represented on
PubPeer October 2015



Many unexpected apparent edits appear in almost all western blot figures- a small sample is presented here (I got tired). The apparent introduction of regions of background and lane splicing may undermine confidence.

***** in PubPeer this was incorrectly labeled as Figure 6



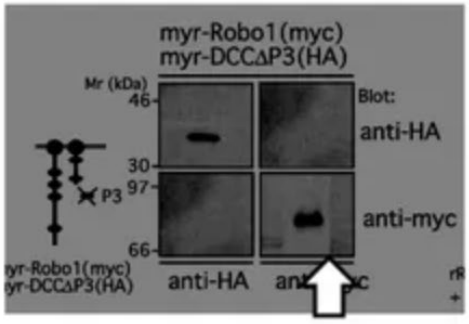


Figure 5E
Initial Issue(s) as represented on
PubPeer December 2015

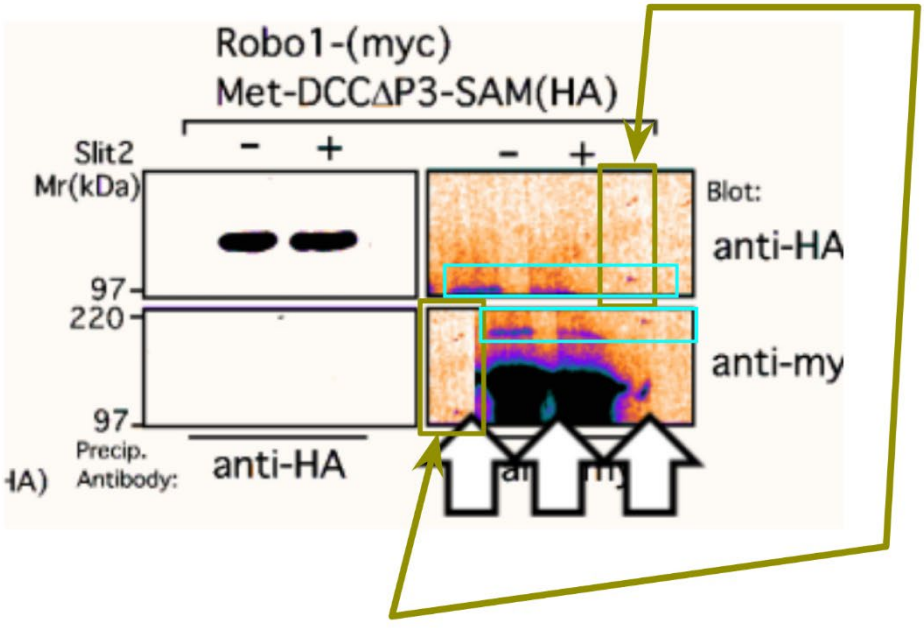


Figure used in Analysis – Figure 5
(snapshots from pdf)

Figure 5C rt panel

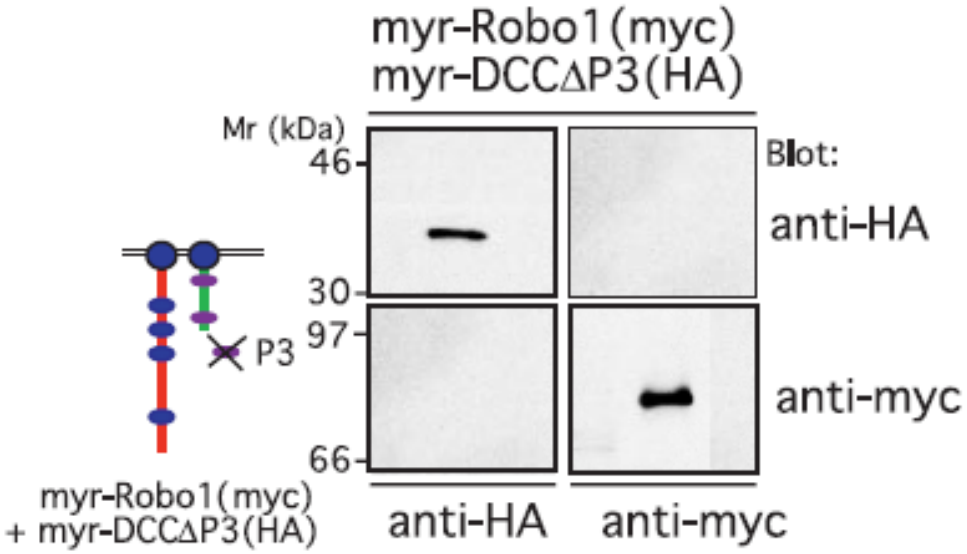


Figure 5D

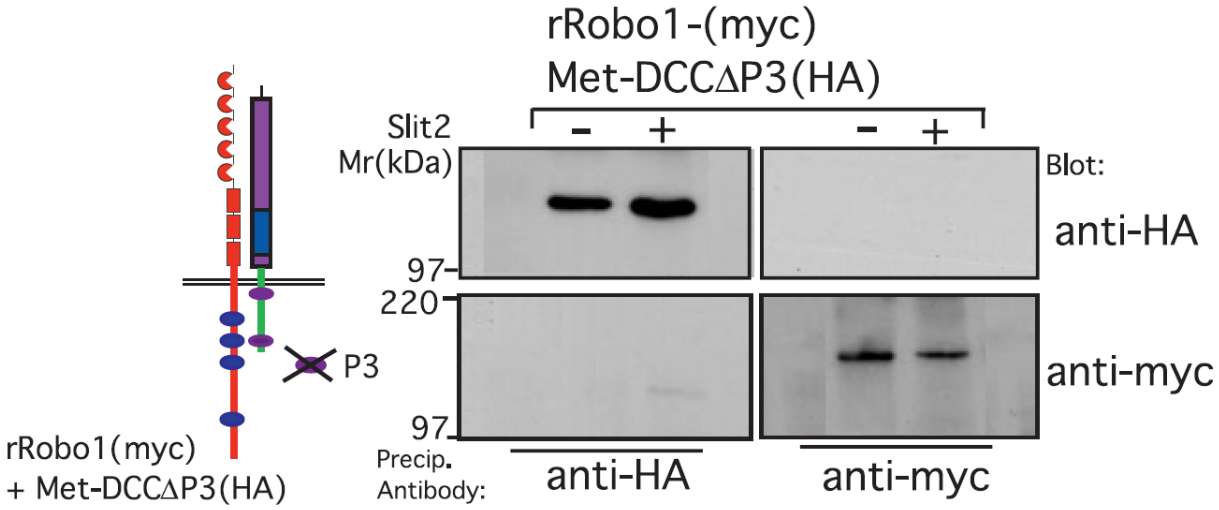


Figure 5E

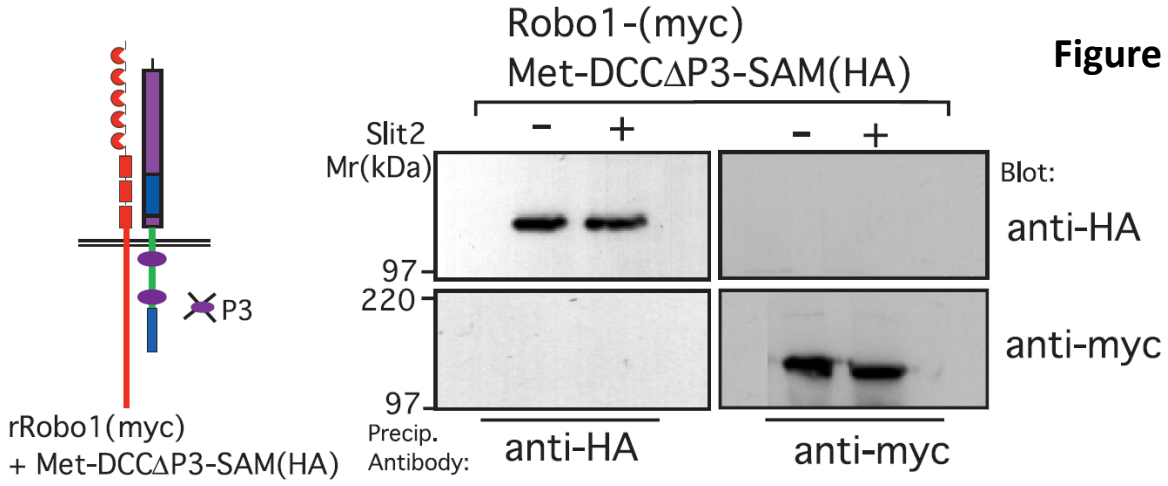
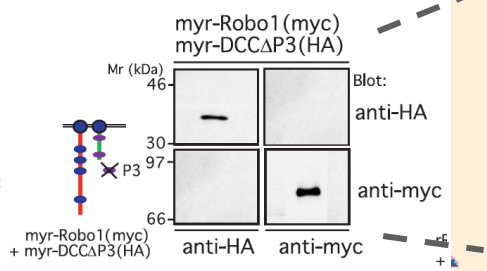
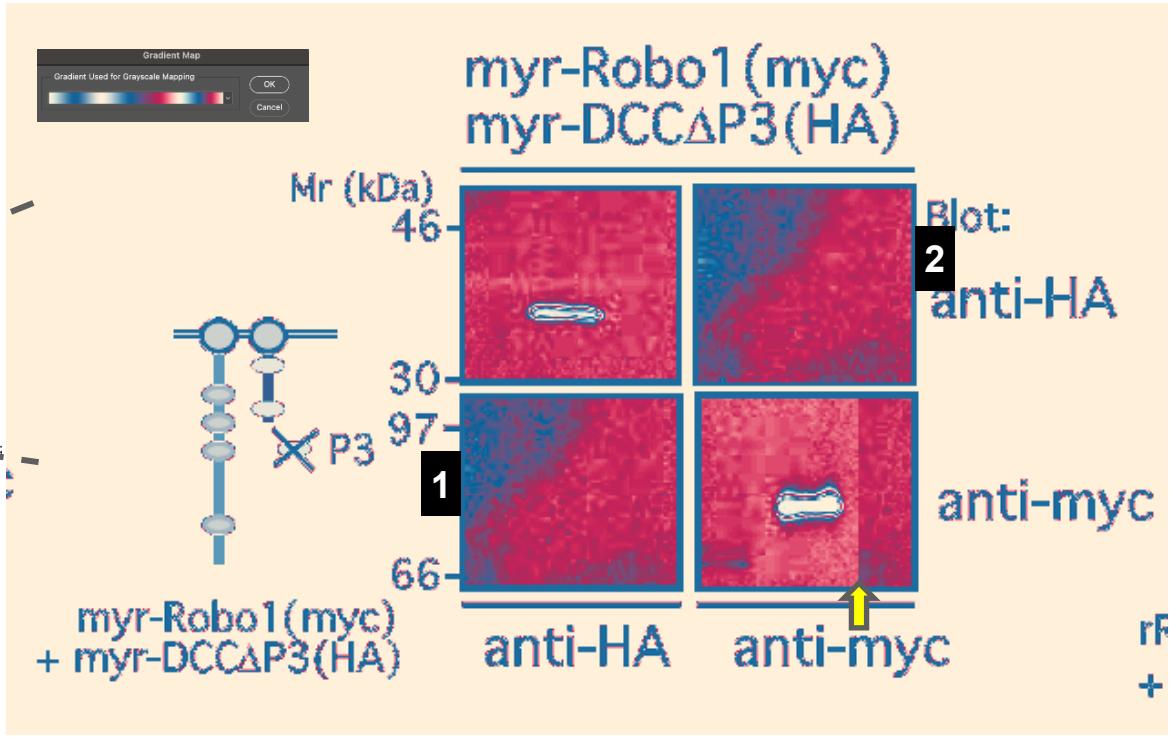


Figure 5C, Gradient Map Analysis

anti-HA/anti-myc and anti-myc/anti-HA, anti-myc/anti-myc

Image used: Snapshot of Figure 5C



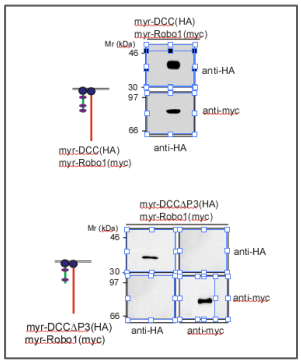


Observations:

YELLOW ARROW ↑ Published Figure 5C reviewed with Gradient Map (Red, Blue, White) demonstrates a linear interface suggesting splicing.

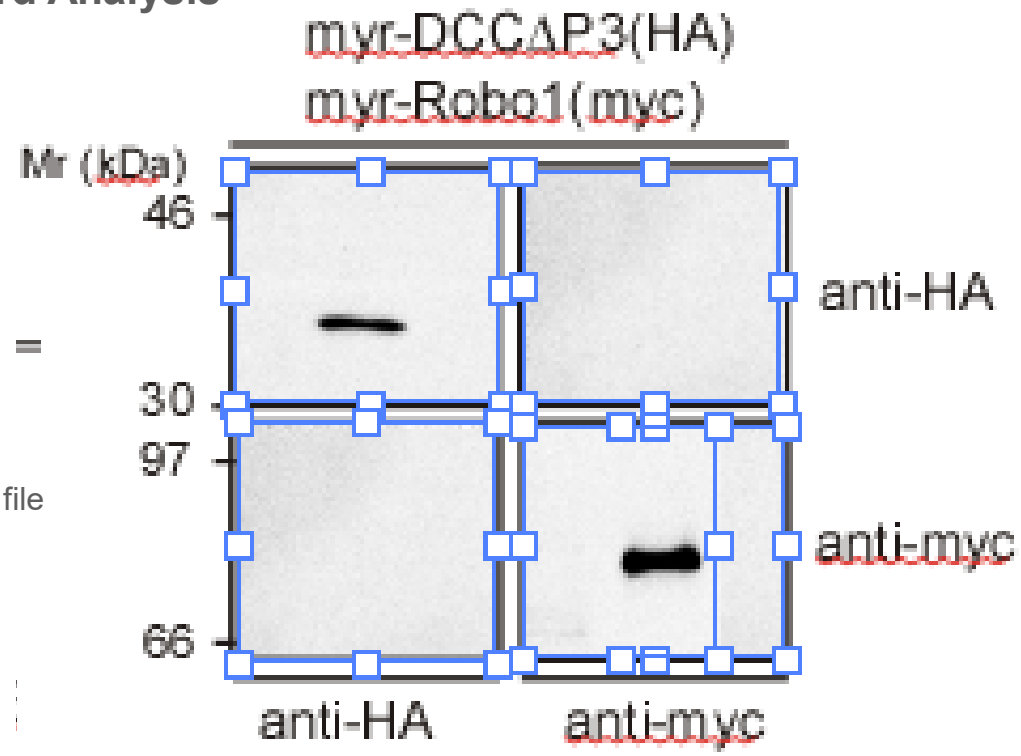
1 and 2 Retention of features in the two panels (although not identical) suggests possible duplication and re-use of images for outcomes of what are represented as two different experiments.

Figure 5C, Research Record Analysis



csh12d.cv5

Apparent Figure 5C preparation file from MTL data distribution



Observations:

Inspection of the research record shows that the bottom right quadrant was produced by splicing and duplication of the two panels, confirming the analysis above.

Figure 5D, Gradient Map Analysis

anti-HA/anti-HA
anti-HA/anti-myc (added)
anti-myc/anti-HA (added)
anti-myc/anti-myc

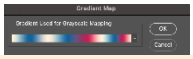
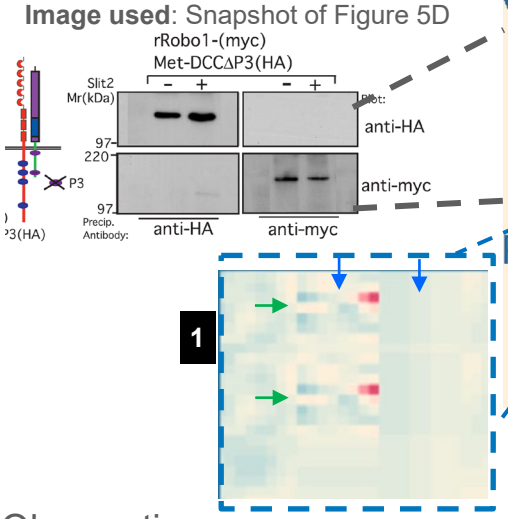
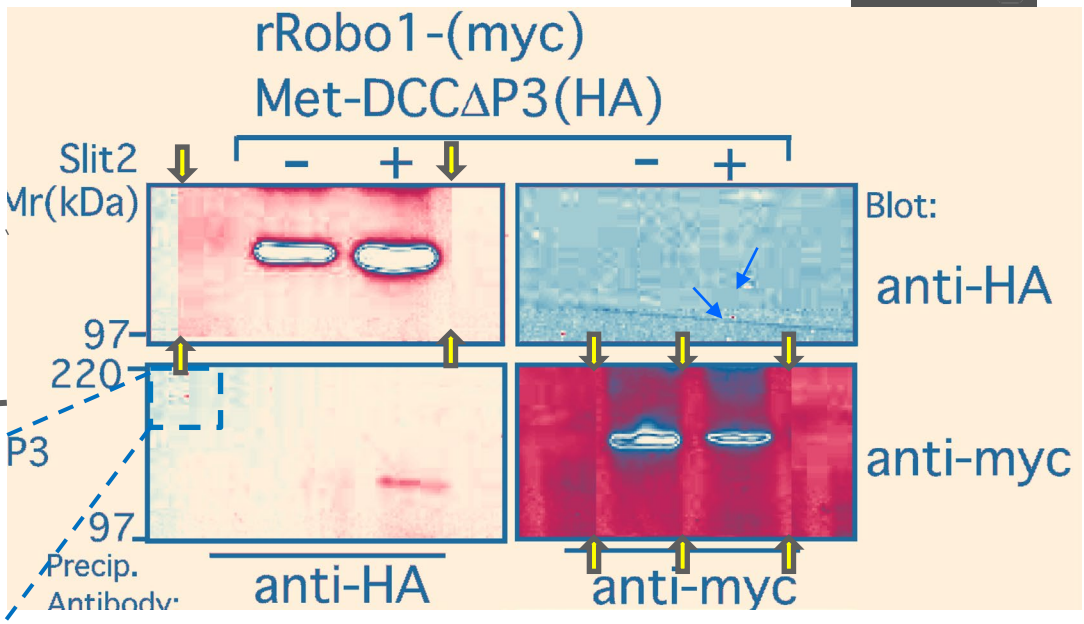


Image used: Snapshot of Figure 5D





Observations:

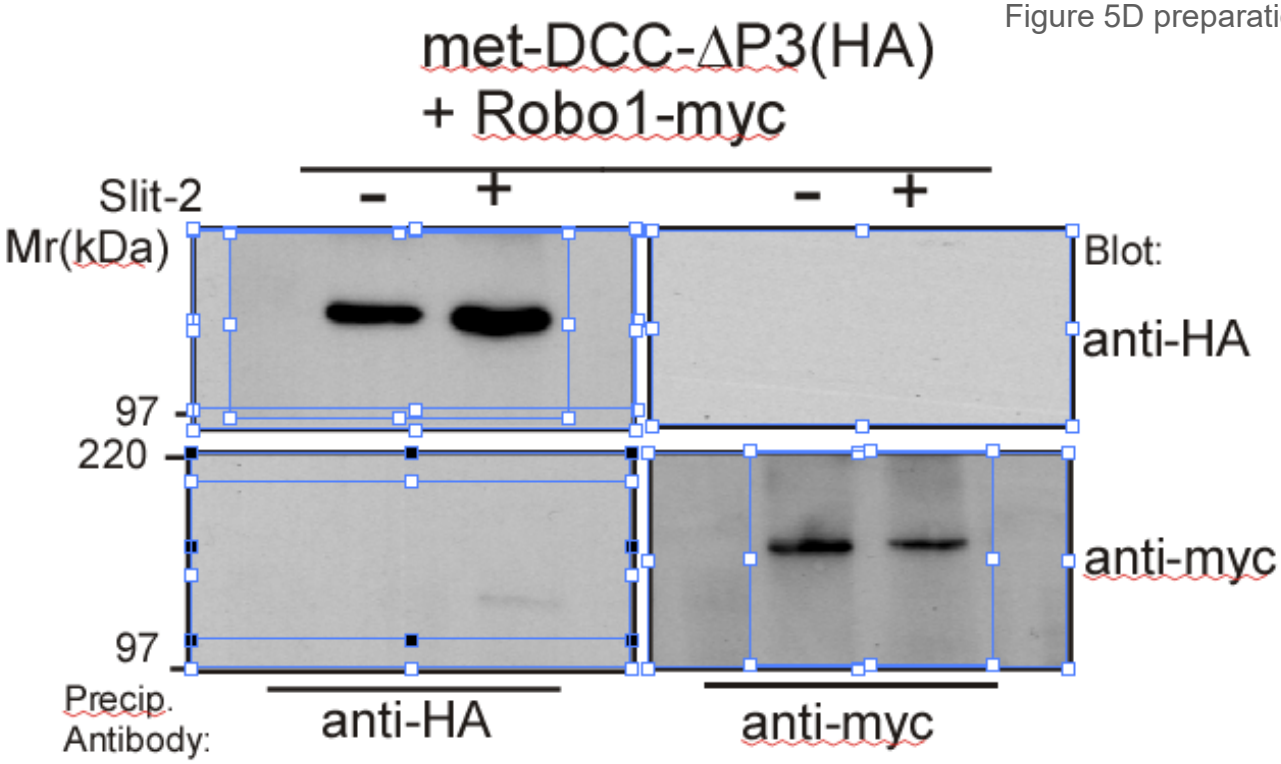
YELLOW ARROWS ↑↓ Published Figure 5D reviewed with Gradient Map (Red, Blue, White) reveals multiple instances of linear interfaces suggesting splicing.

SMALL BLUE ARROWS ↘ ↙ and ↓ ↓ [inset 1] sections of the image data demonstrate distinct resolution features, further suggesting potential image alteration.

1 SMALL GREEN ARROWS →→ duplication of features in the background.

Figure 5D, Research Record Analysis

csh12b.cv5
Figure 5D preparation file from MTL data distribution



Observations: Inspection of the research record shows that three of the four quadrants were produced by splicing, confirming the analysis above.

Figure 5E, Gradient Map Analysis

anti-myc/anti-HA

anti-myc/anti-myc

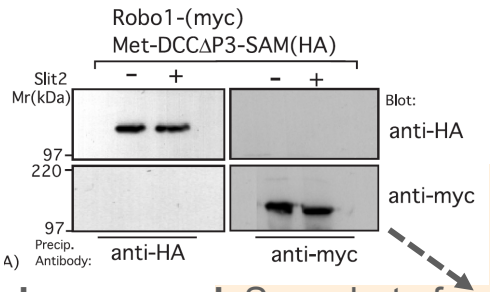
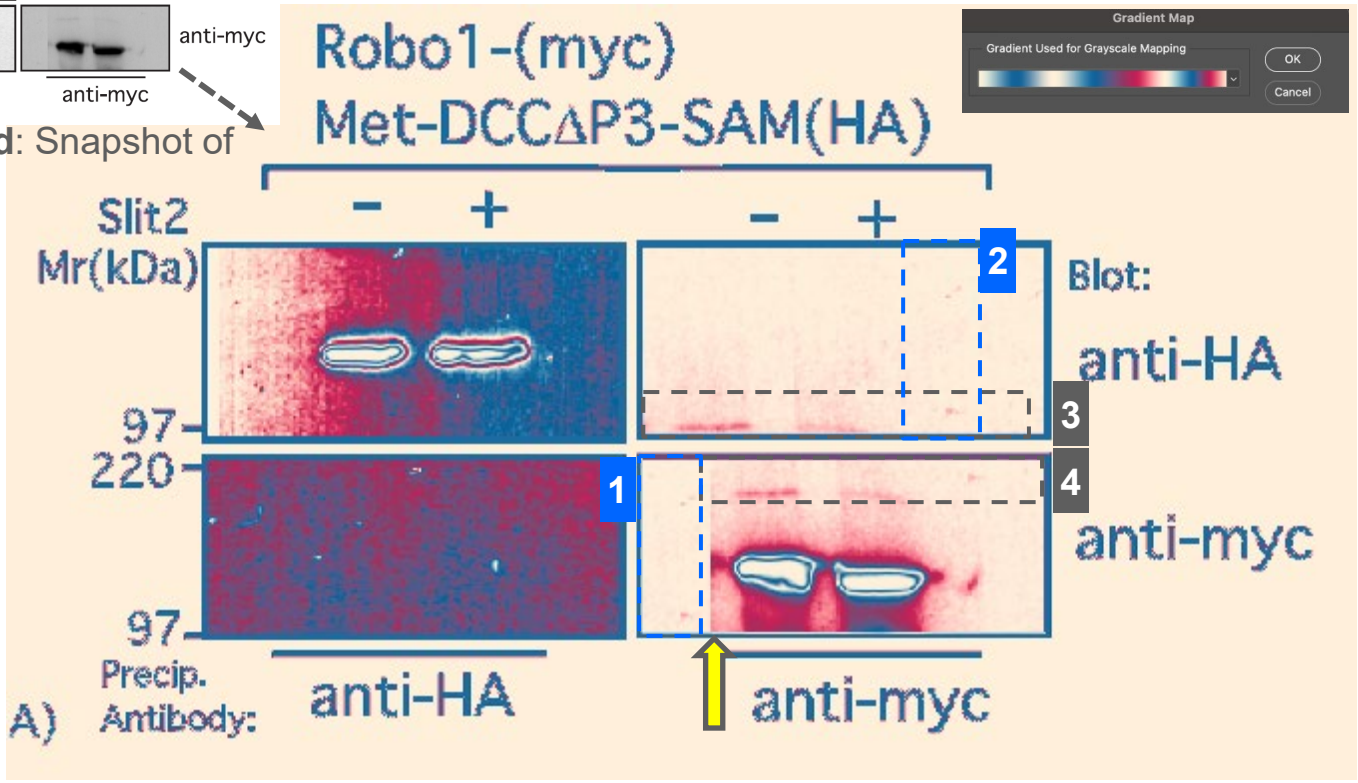
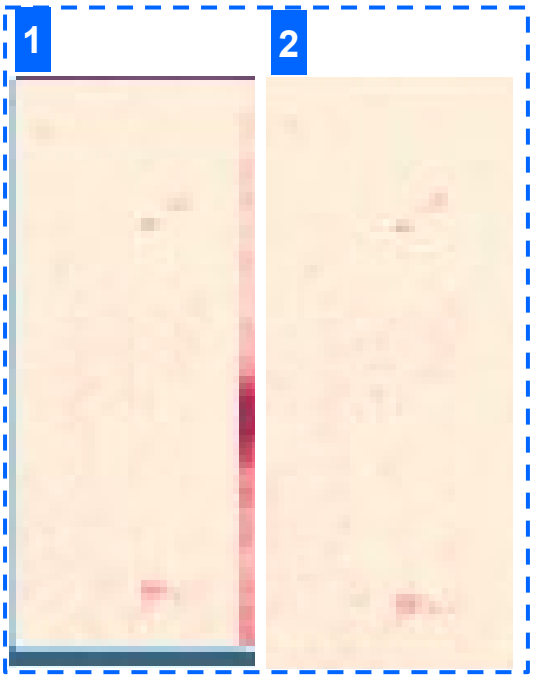


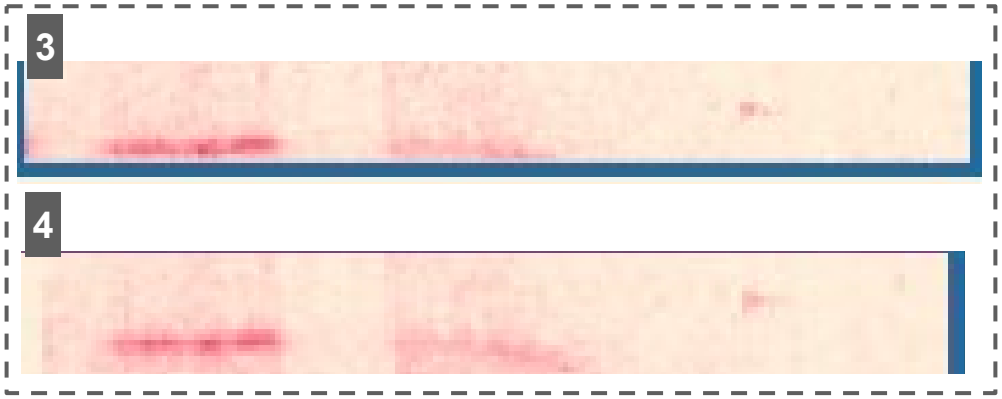
Image used: Snapshot of Figure 5E

Observations:

YELLOW ARROW ↑ Published Figure 5E reviewed with Gradient Map (Red, Blue, White) demonstrates a linear interface suggesting splicing.







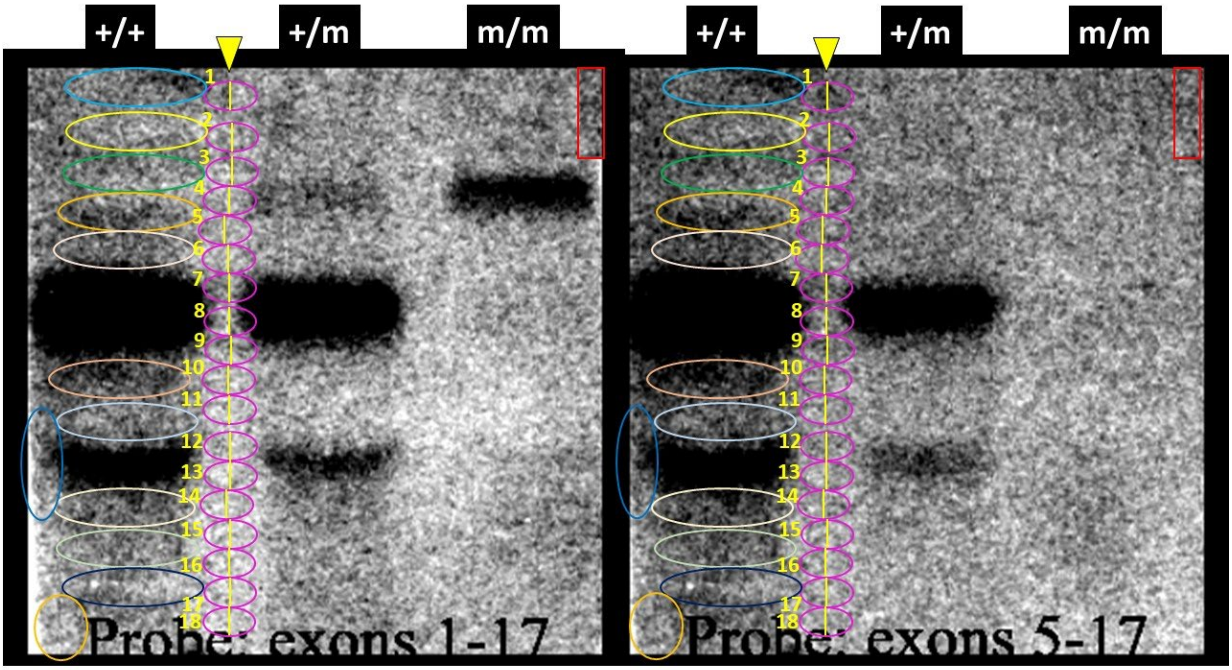
Observations:

Published Figure 5E reviewed with Gradient Map (Red, Blue, White) demonstrates retention of background features in two areas of the respective blots (1-2 and 3-4). This suggests duplication and reuse of data between the images.

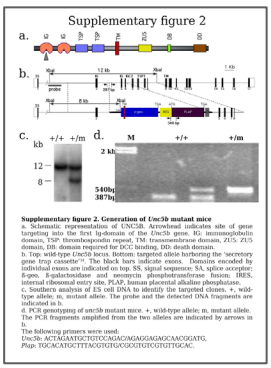
Nature ’04

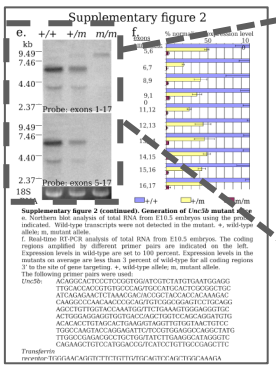
https://pubpeer.com/publications/467FA67858F959040F2EABE876A7B3

Initial Issue as represented on PubPeer December, 2022

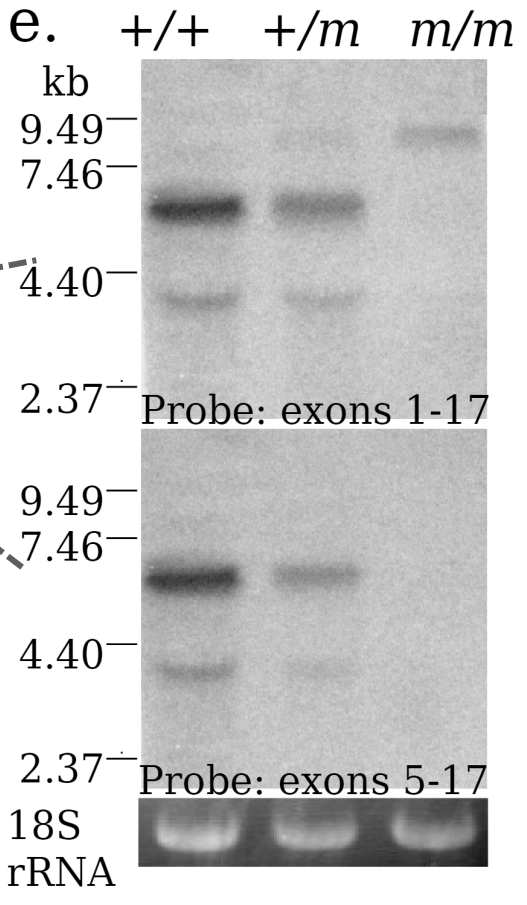


Figures used in Analysis (downloaded from website, extracted from pdf)

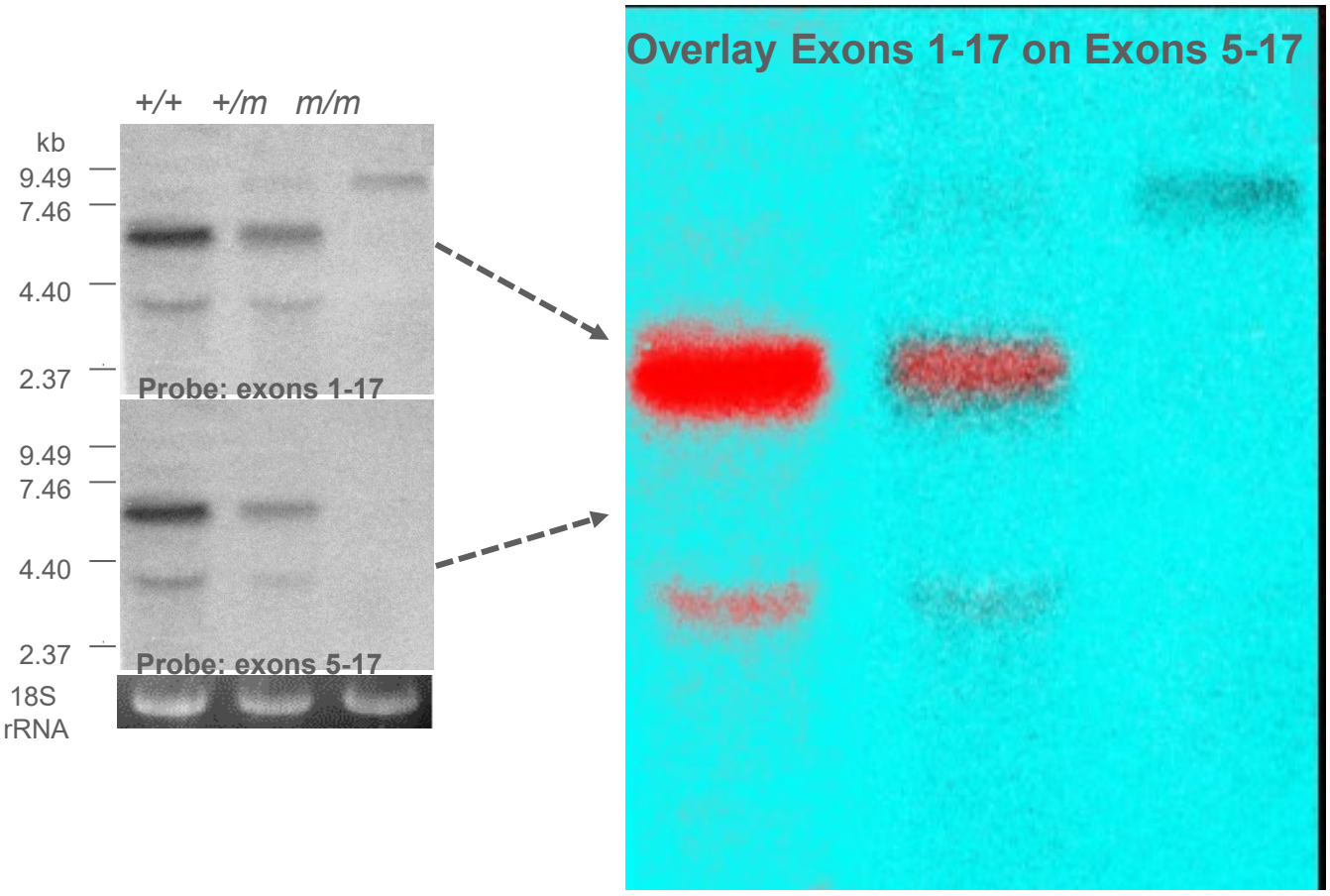


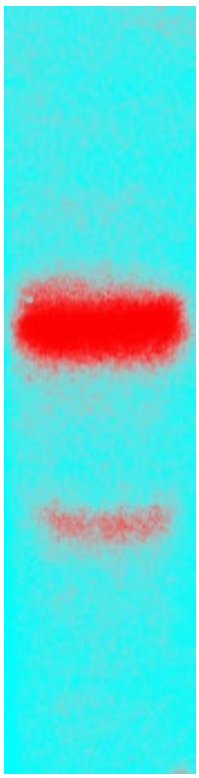


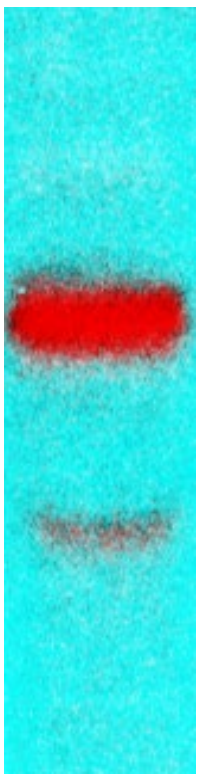
Supplementary Figure 2



Suppl. Figure 2e, Overlay Analysis







WITHIN OVERLAY
CYAN: OVERLAPPING BACKGROUND
RED: OVERLAPPING DATA
WHITE AND **BLACK**: NON-OVERLAPPING DATA

Positive Control
Exons 1-17 +/+ on self

Negative Control
Exons 1-17 +/+ on +/m

Observations: The +/+ data in the exons 1-17 and 5-17 appear highly similar. Band features described, including the band shape(s) and data distribution within the bands, and the artifact accompanying the sample lanes (including certain features demonstrated as negative space, **CYAN**) align identically without any resizing adjustment.

This is in contrast to other data within the figure (negative control) demonstrating many areas which do not align.

Suppl. Figure 2e, Overlay Analysis continued

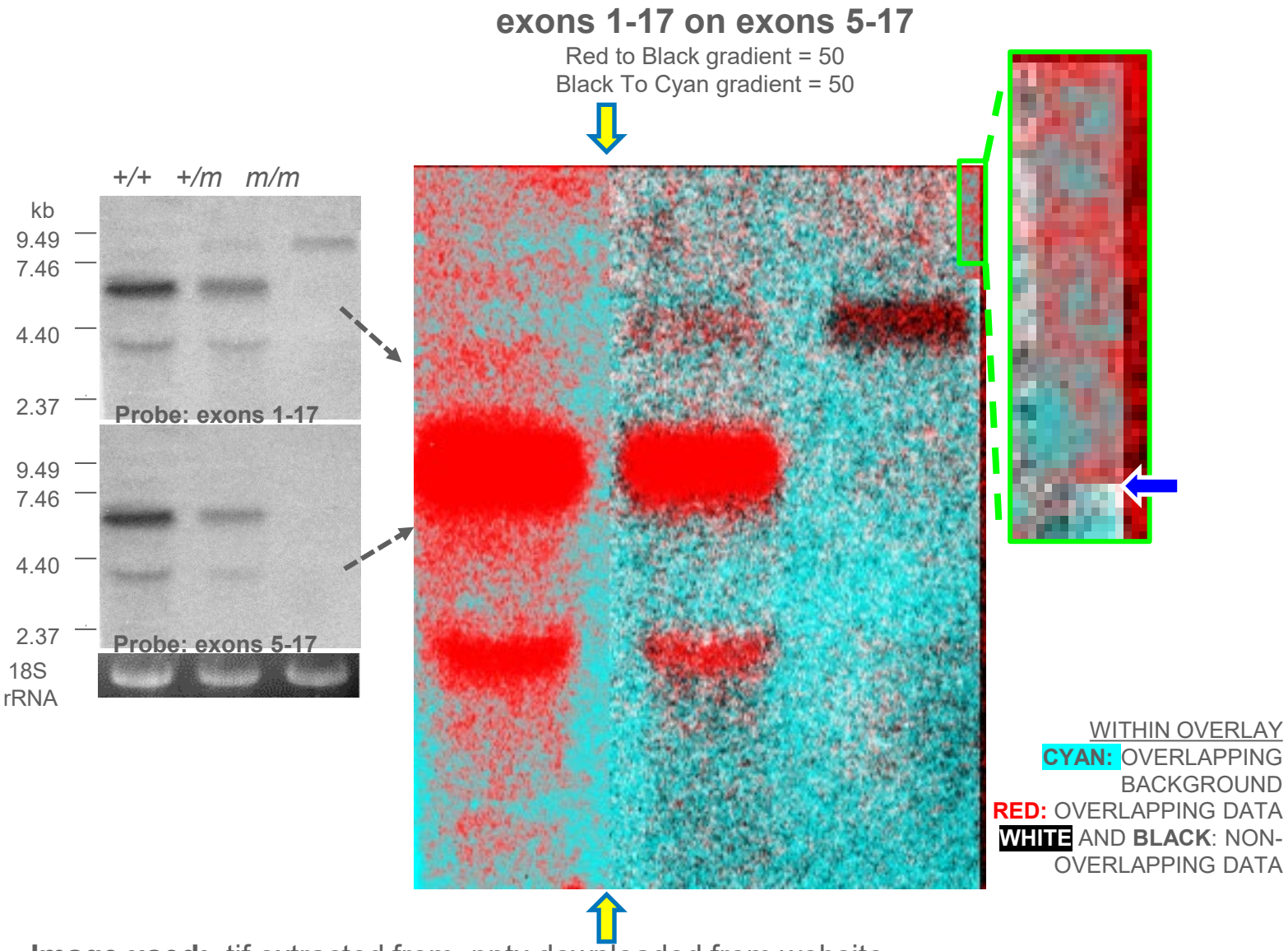


Image used: .tif extracted from .pptx downloaded from website

NOTE: The gradient is adjusted to highlight background features not otherwise visible.

Observations: The +/+ data in the exons 1-17 and 5-17 appear highly similar even upon modification of gradient to show background features.

YELLOW ARROWS ↑ ↓ A clear delineation between similar and dissimilar areas is present. A splice is not immediately apparent based on a cursory review in light of the data resolution, brightness, and contrast. However, a pixel-by-pixel analysis shows a clear separation between the areas along a linear plane.

GREEN BOX □ The top right portion of the background of the image appears to be a duplication of image data between the short exon image (5-17) and the long exon image (1-17). This duplication appears to be incorporated around a linear interface **BLUE ARROW ←** associated with the band of interest (m/m transcript reported in long exon image 1-17).

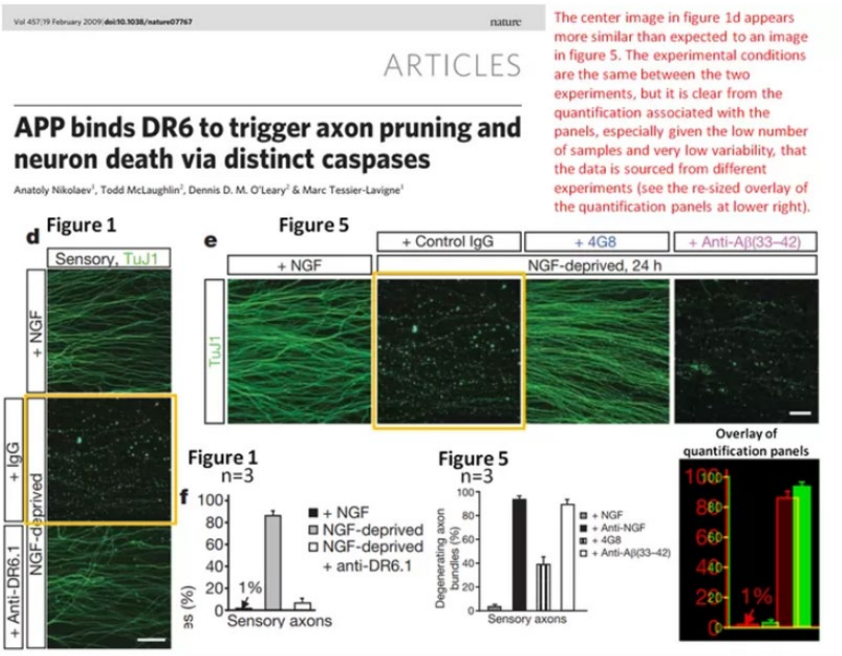
Nature ’09

https://pubpeer.com/publications/B6410F2AF1398E6F379B244E7520A1

Initial Issue as represented on PubPeer February 23, 2023

#2 **Matthew Schrag** commented February 2023

I have a concern about figures 1 and 5 in this manuscript.



Figures used in Analysis

Figure downloads from website

Figure 1

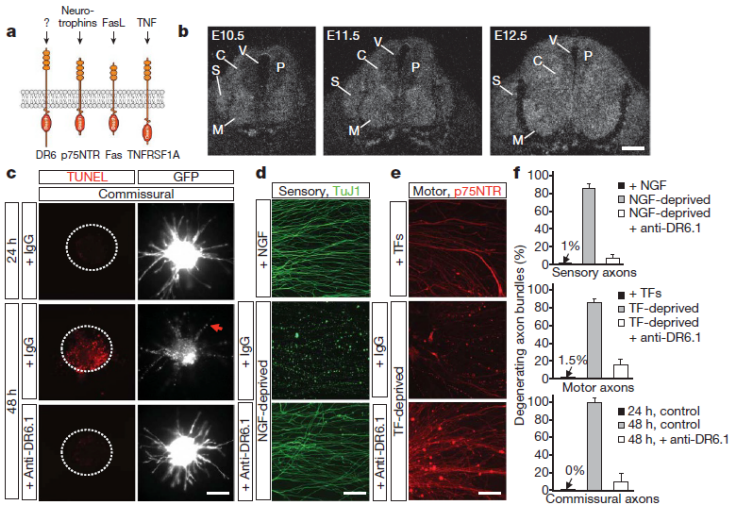


Figure 5

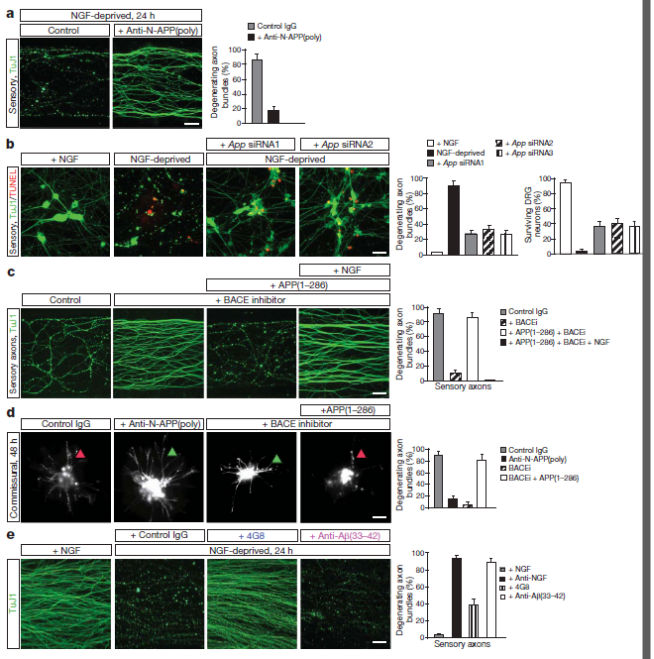
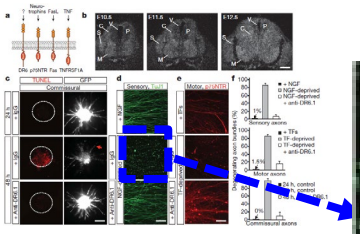


Figure 1d and 5e, Image Analysis

Figure 1d: NGF-deprived + IgG

Figure 5e: NGF-deprived, 24hr + control IgG

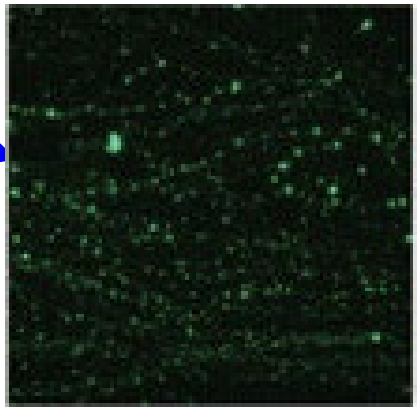
Figure 1



Images: Downloads from website

Figure 1d
panel 2 of 3
NGF-deprived + IgG
"control"

Axon visualization: TuJ1
(sensory neurons, tubulin)



≈

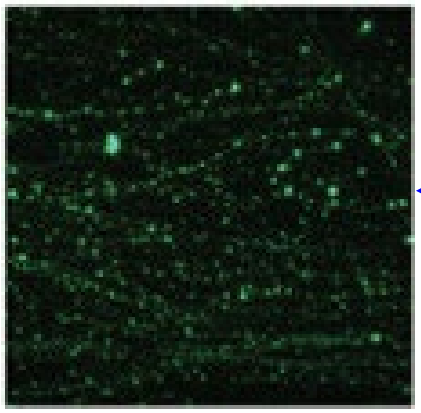


Figure 5

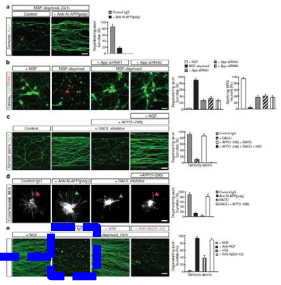
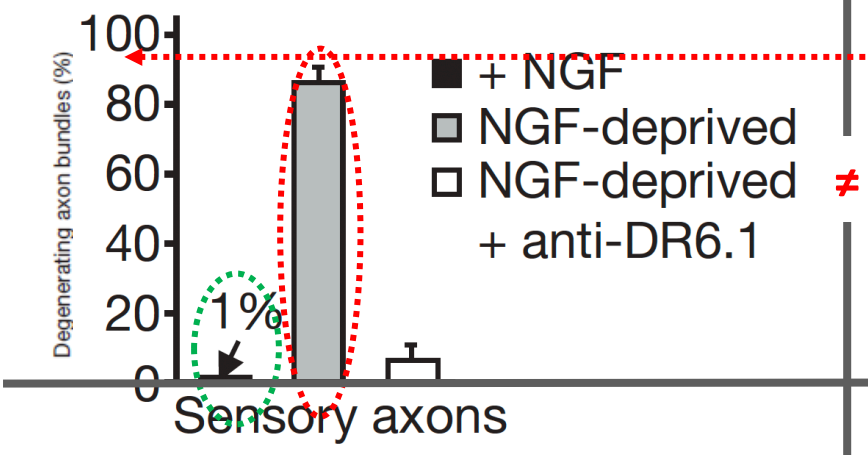


Figure 5e
panel 2 of 4
NGF-deprived, 24hr
+ control IgG
"control"

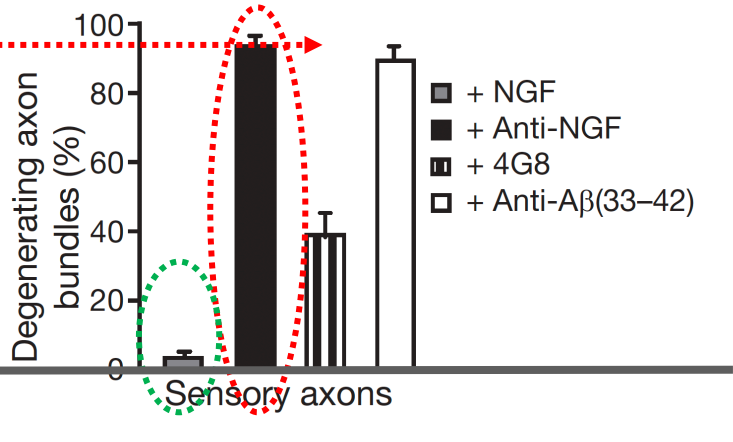
Observations 1: Images and described experimentation appear to align **[≈]**.
If this were the only concern, this control image could have been, for example, a selected 1 of n=3 for outcomes represented in **Figure 1 (+NGF, and +anti-DR6.1)** and **Figure 5 (+NGF [*different image, presumably a different "n"*] +4G8, and +anti Ab (33-42))**.

Figure 1d quantitation
(Figure 1f)



≠

Figure 5e quantitation



Observations 2:
Quantitation for the apparent "control" data **RED DASHED OVALS** ○ does not appear to align **[≠]**.

Furthermore, the +NGF (non-deprived NGF experiment) quantitation also appears to be different **GREEN DASHED OVALS** ○.

It is not clear how the +IGG control image could be a representative control image reported for both figures given the difference in quantitation, which suggests distinct experimentation.

https://pubpeer.com/publications/B6410F2AF1398E6F379B244E7520A1

Initial Issue as represented on PubPeer February 23, 2023

There is an additional concern regarding supplementary figure 9 and supplementary figure 19.

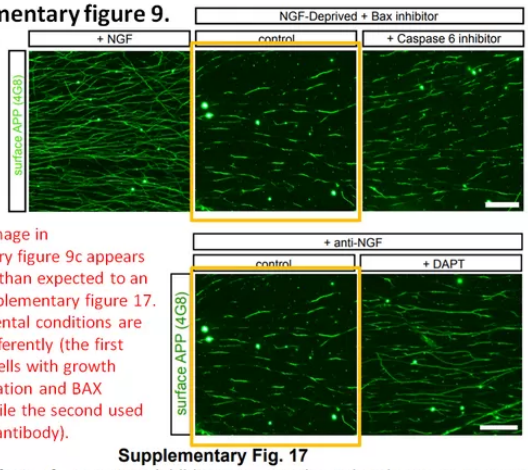
Vol 457|19 February 2009|doi:10.1038/nature07767 nature

ARTICLES

APP binds DR6 to trigger axon pruning and neuron death via distinct caspases

Anatoly Nikolaev[1], Todd McLaughlin[2], Dennis D. M. O'Leary[2] & Marc Tessier-Lavigne[1]

Supplementary figure 9.



The center image in supplementary figure 9c appears more similar than expected to an image in supplementary figure 17. The experimental conditions are described differently (the first treated the cells with growth factor deprivation and BAX inhibition while the second used an anti-NGF antibody).

Supplementary Fig. 17

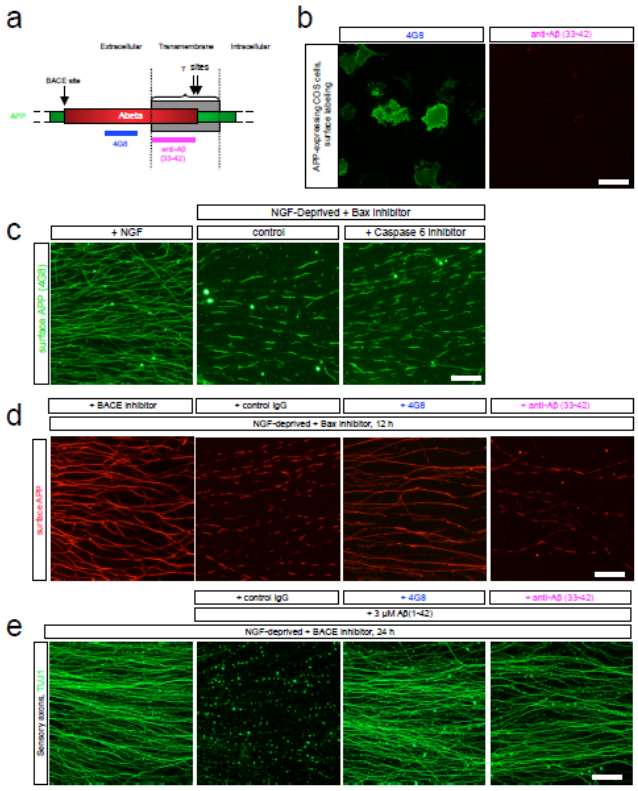
Protective effects of γ-secretase inhibitors on commissural and sensory neurons

Supplementary Figure 19 cited, but Supplementary Figure 17 shown (and subject to concern)

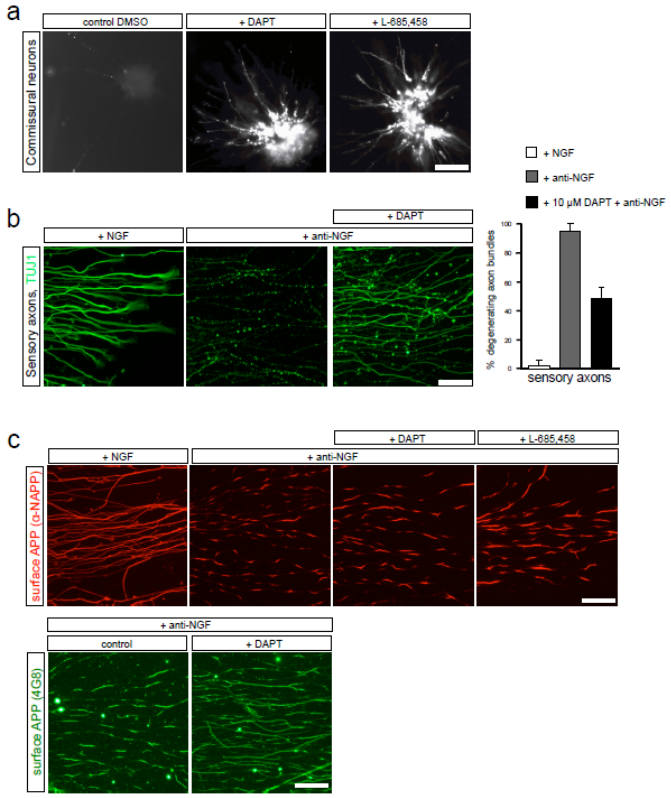
Figures used in Analysis

Figure downloads from website

Supplementary Figure 9



Supplementary Figure 17

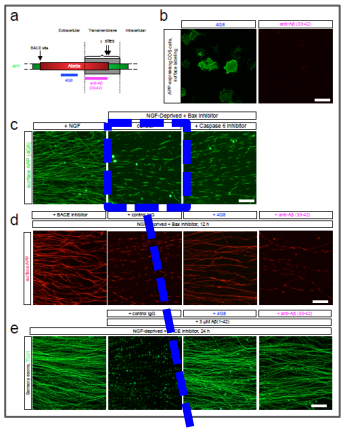


Supp. Figs 9c and 17c, Image Analysis

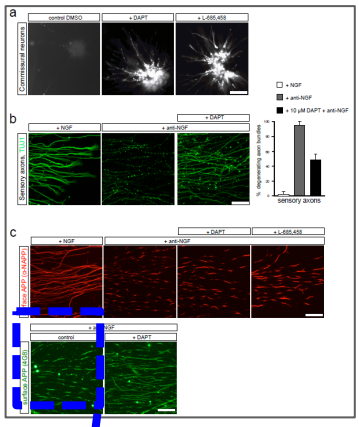
Supp Fig 9c: NGF-deprived + Bax inhibitor control

Supp Fig 17c: + Anti-NGF control

Supplementary Figure 9



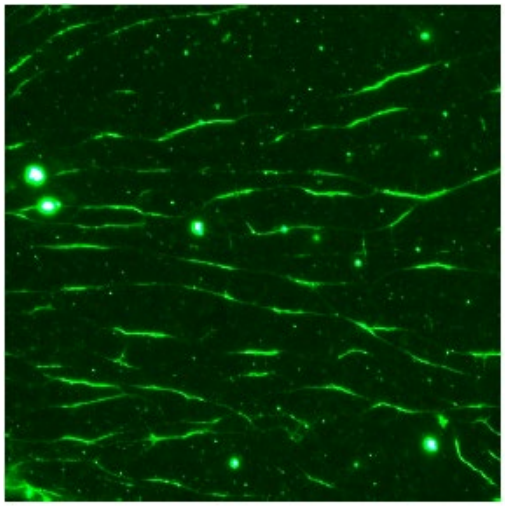
Supplementary Figure 17



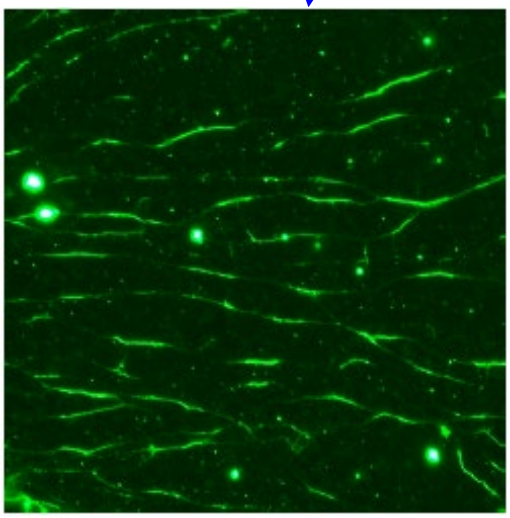
Axon visualization: surface APP (4G8)

Supp Figure 9c
panel 2 of 3

NGF-deprived
+ Bax inhibitor
"control"



≈



Supp Figure 17c
panel 1 of 2

+Anti-NGF
"control"

Images appear to align **[≈]**

Reported experimental conditions differ **[≠]**

It is not clear how the single image could be a representative control image reported for both figures given the different experimentation and samples reported

Supp. Figure 6d, Gradient Map Analysis
Caspase 6 blot

Supplementary Figure 6

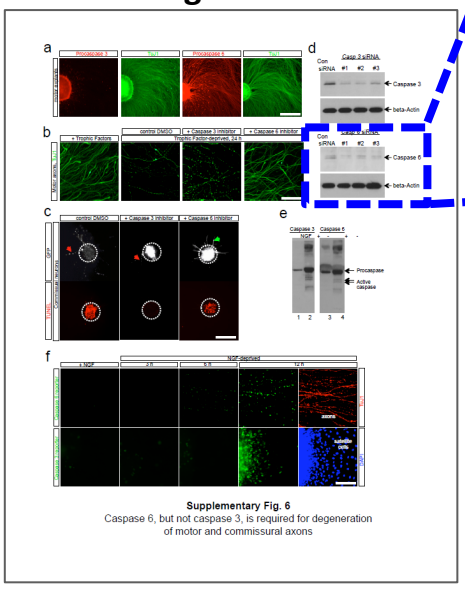
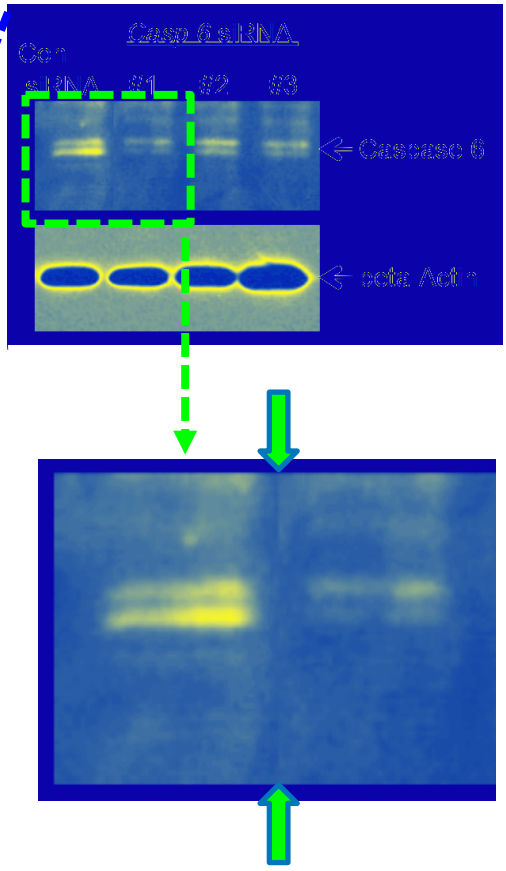
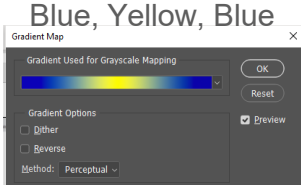


Image: Export from pdf



Supplementary Figure 6d (caspase 6 siRNA) Gradient Map applied
enlarged for review

Blue, Yellow, Blue



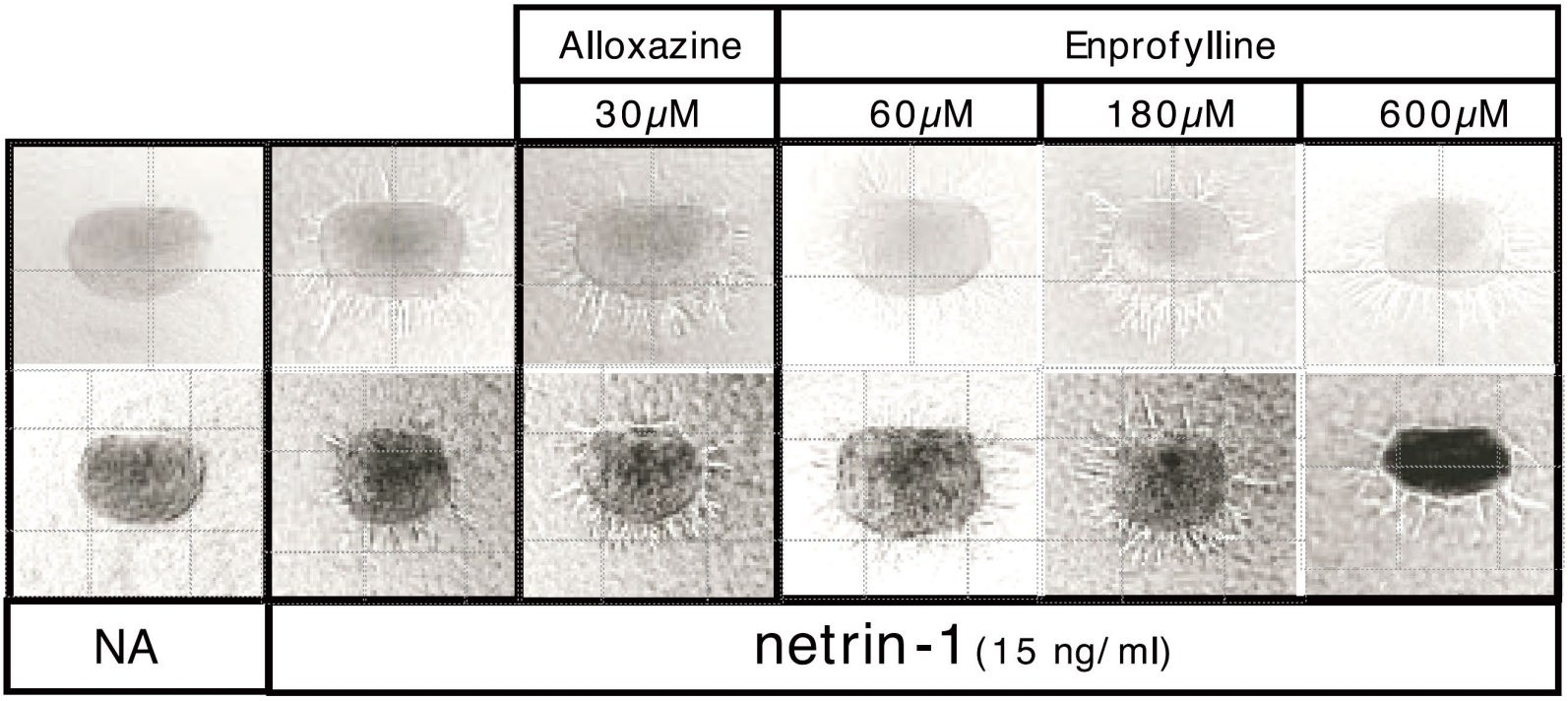
Observations:

GREEN ARROWS ↓↑ demonstrate what appears to be a splice line indicating insertion and/or removal of data within the represented blot image (within the caspase 6 blot for siRNA control data reported, not evident within accompanying β-actin blot).

Understanding Image Tiling in PDF

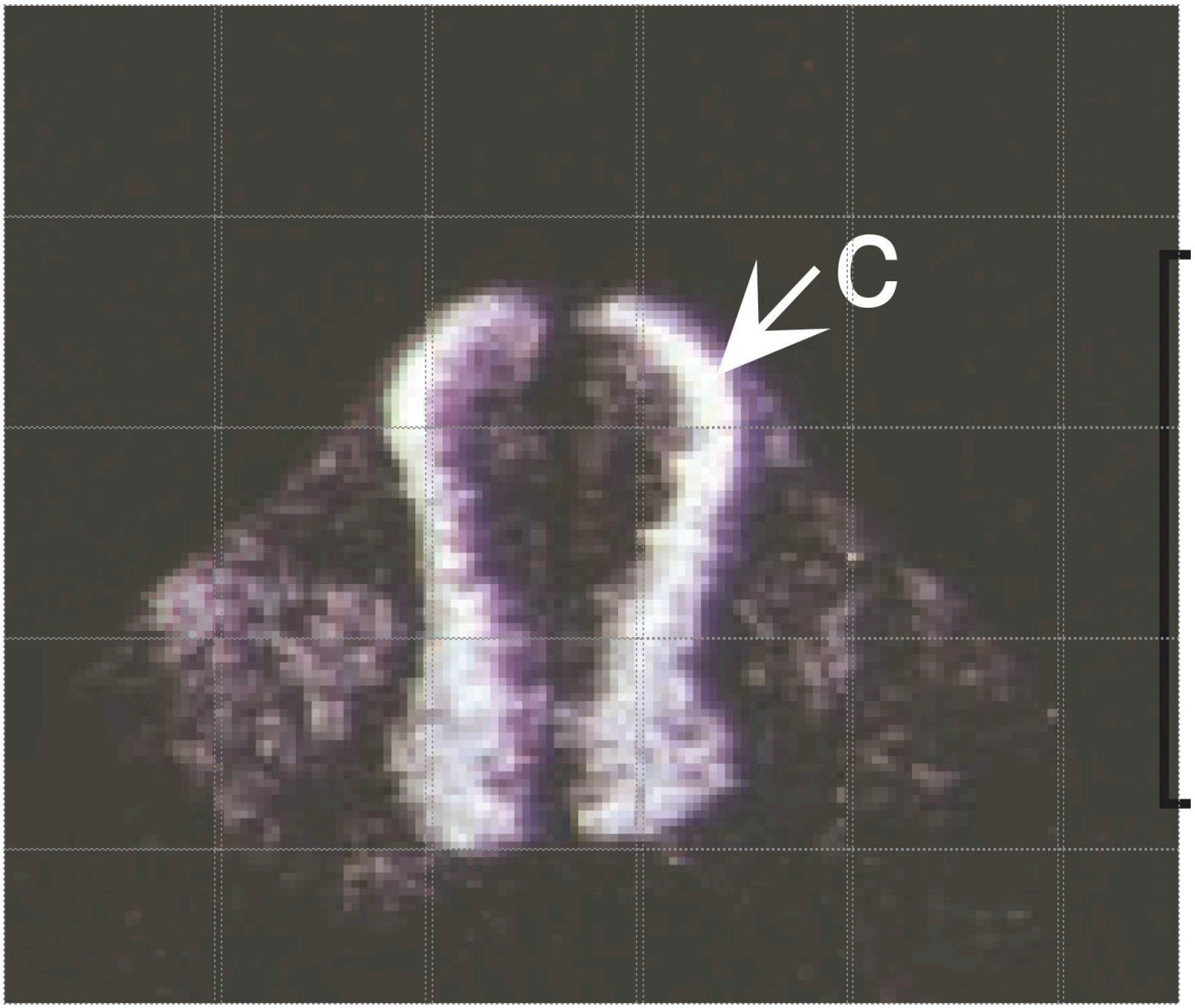
Tiling can be ordered.

Example of ordered tiling. In an unmanipulated figure, tiles can be overlapped by one pixel.



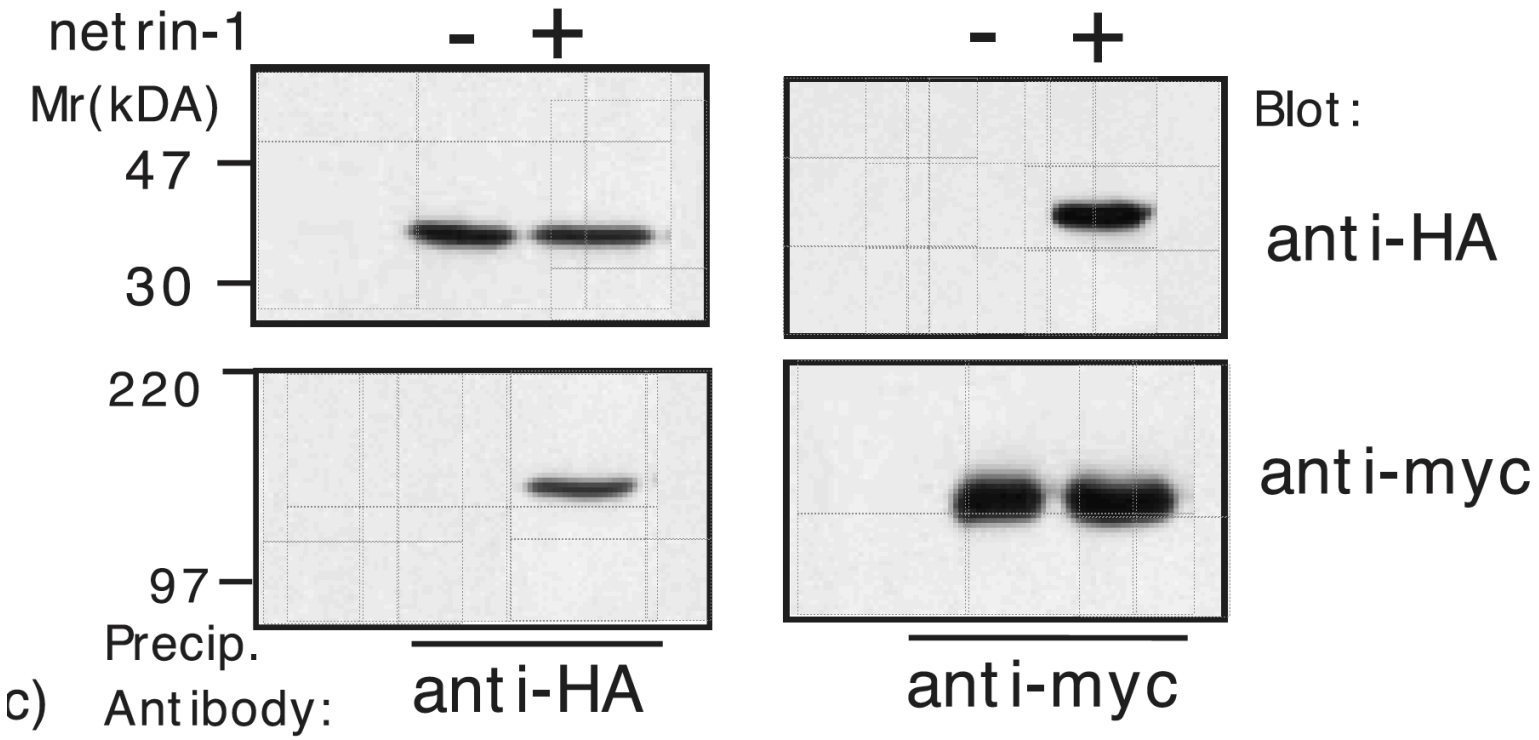
Science '01 Binding Fig. 5C

Example of ordered tiling. In an unmanipulated figure, tiles can be overlapped by one pixel.



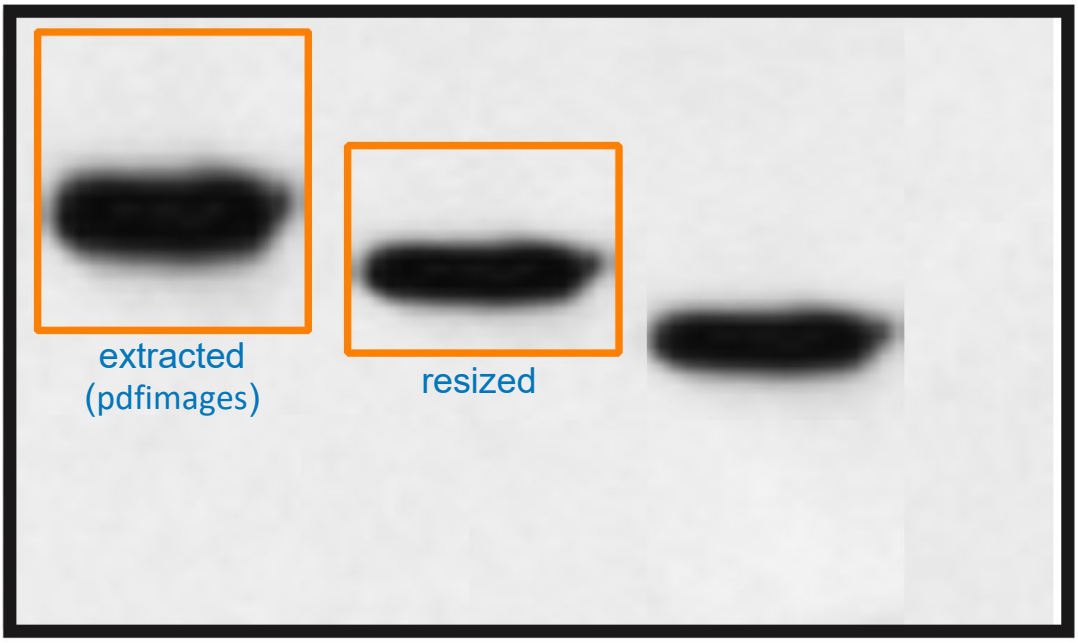
Science ’01 Binding Fig. 5A

Irregular tiling indicates digital manipulation.



Science '01 Binding Fig. 3C

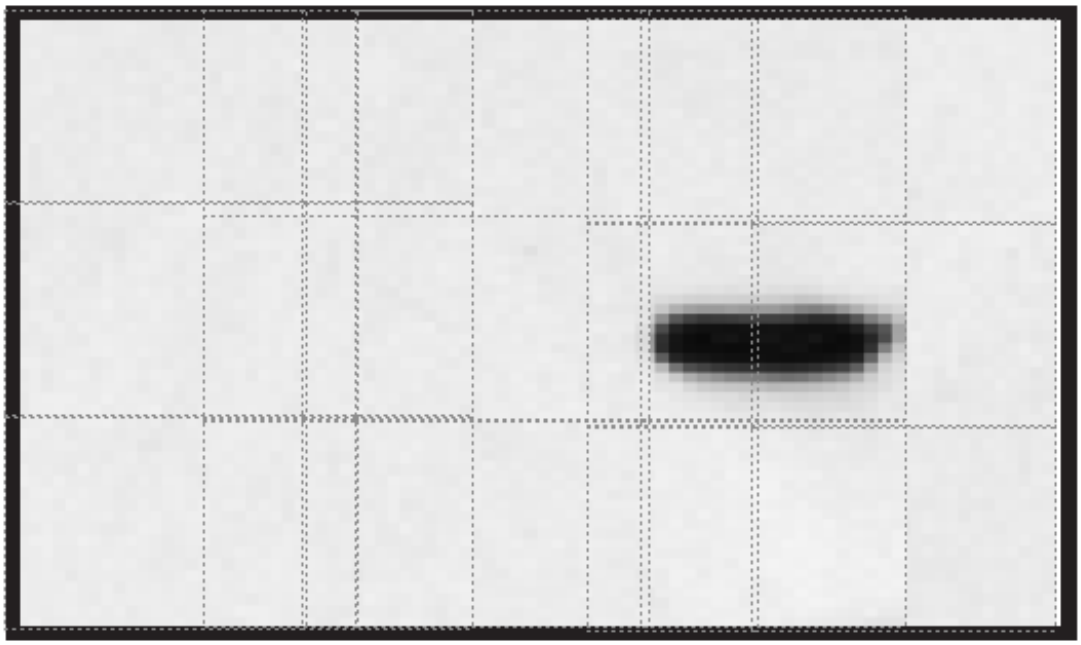
Band difference and irregular tiling indicate digital manipulation.



Science ’01 Binding Fig. 3C (upper-right panel)

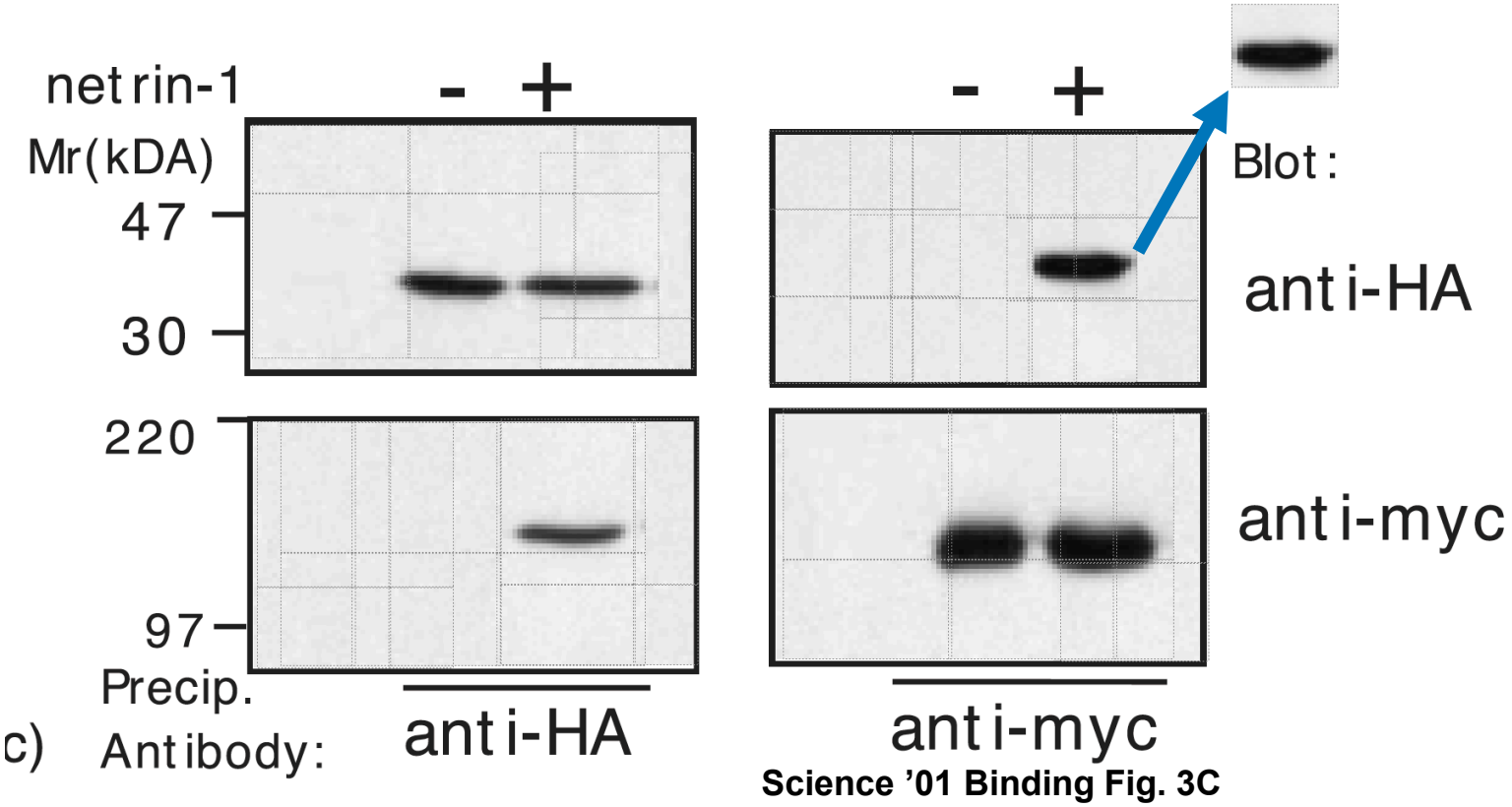
The command-line tool pdfimages is used to extract the embedded figures, revealing that the band in this panel was originally saved with a different aspect ratio (far left) and digitally manipulated from within a PDF editor (middle) to yield the band in the figure (right).

Band manipulation is consistent with irregular tiling.



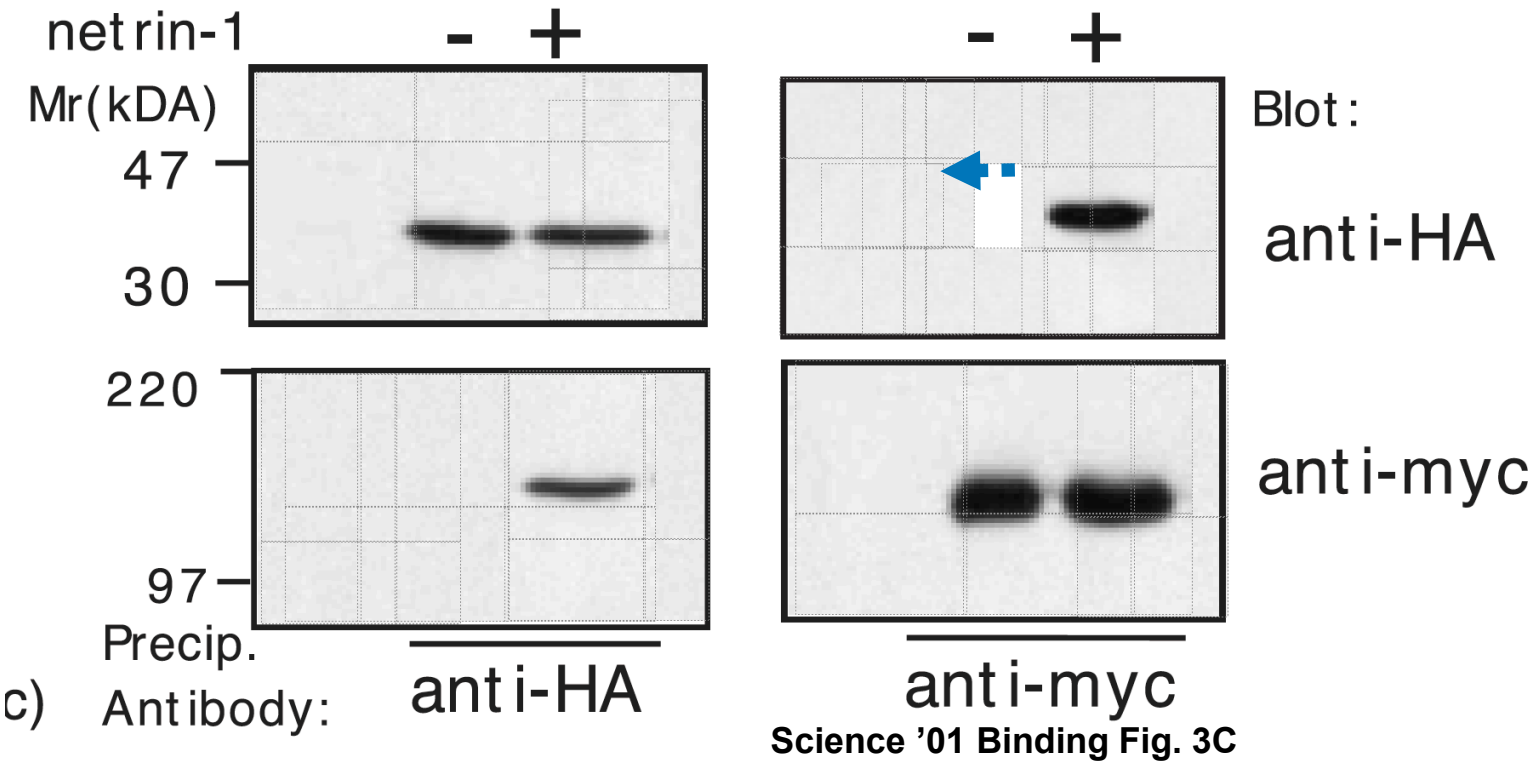
Science ’01 Binding Fig. 3C (upper-right panel)

In this case, the one-pixel overlap reveals further evidence of digital manipulation.



c)

Science '01 Binding Fig. 3C



c)

Science '01 Binding Fig. 3C