How to read a scientific paper efficiently?

Dr. Anne-Laure Mahul-Mellier

Course objectives:

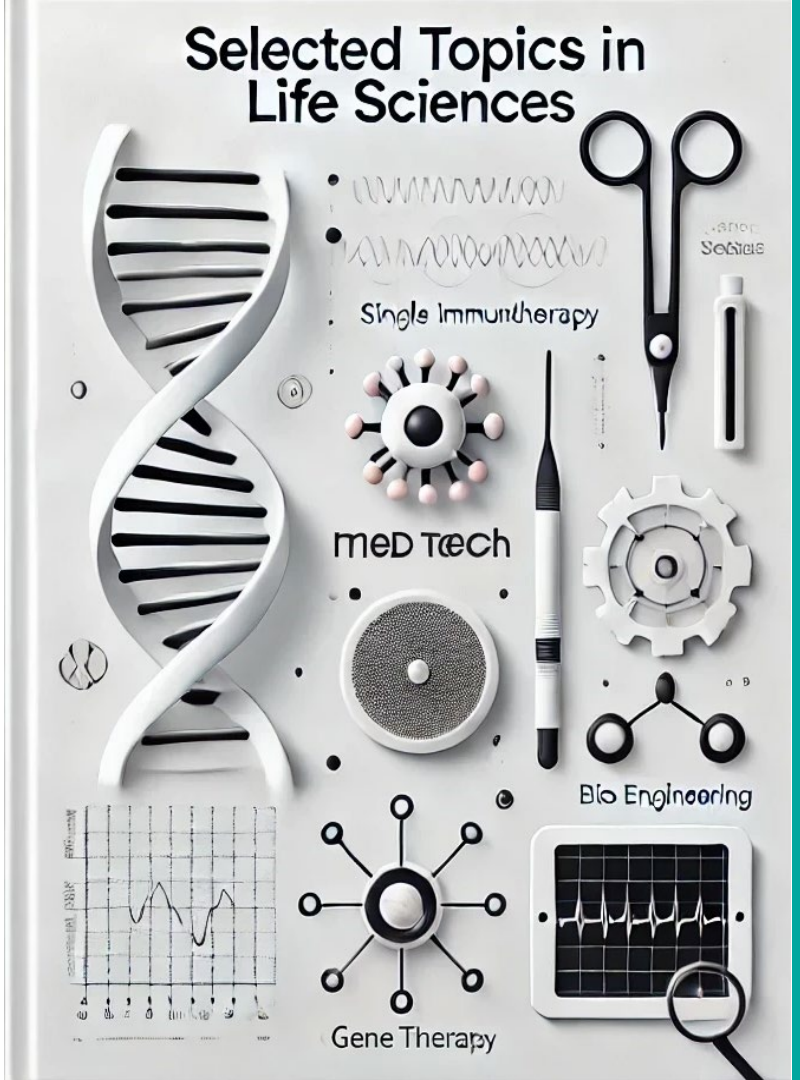
- The importance of reading scientific papers in Life Sciences
  Understanding the significance of reading scientific papers is crucial for anyone in the life sciences field (true for all the fields!).
  It helps in staying informed about the latest research developments, methodologies, and innovations.

- Tips and tricks: where to find papers and stay updated efficiently?
  Discover effective methods to locate scientific papers and maintain up-to-date knowledge in your field.
  Learn how to use academic databases, journals, and alert systems for efficient updates.

- Strategies and techniques for reading scientific papers effectively
  Explore various approaches to reading scientific papers, including skimming abstracts, focusing on key sections, and understanding research context for efficient comprehension.

- Techniques for efficient information retrieval and better retention
  Learn how to quickly extract relevant information from papers and employ methods to improve retention and recall of key concepts and findings.

- Developing critical analysis skills
  Enhance your ability to critically evaluate scientific literature, assess the validity of research findings, and develop a deeper understanding of study methodologies and their implications.



How to read a scientific paper efficiently?

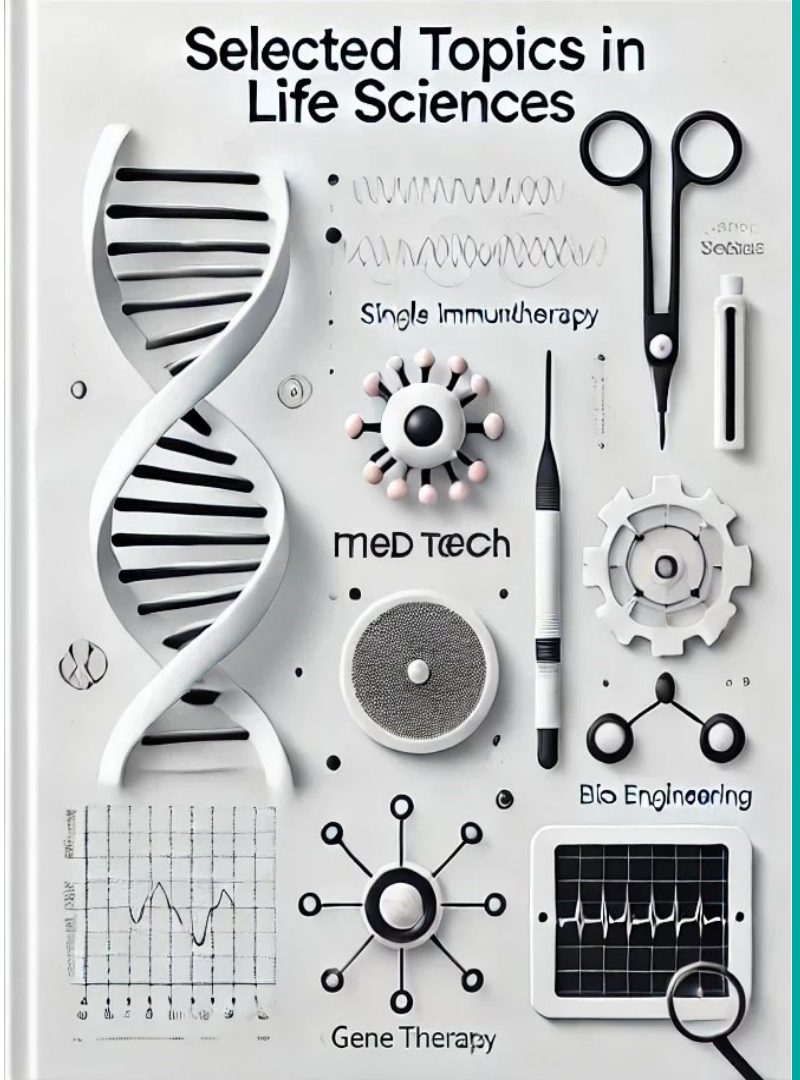
1. Why reading scientific papers ?

2. Tips and tricks: where to find papers and stay updated efficiently?

3. Strategies and techniques for reading scientific papers effectively

4. Techniques for efficient information retrieval and better retention

5. Developing critical analysis skills



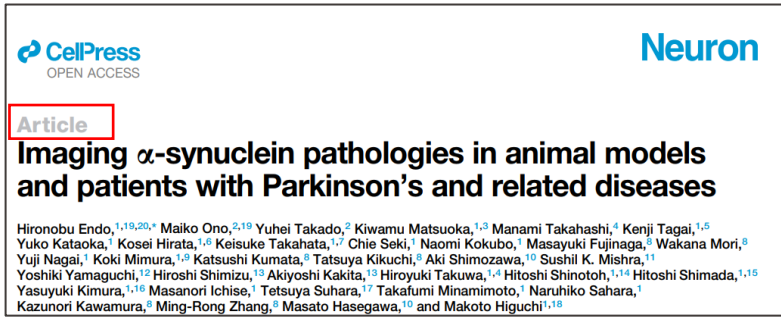
How to read a scientific paper efficiently?

1. Why reading scientific papers ?

What do we mean by scientific paper?

Primary research articles:

- Original research data, methodologies and conclusions
- Details on how experiments were done including samples size, statistical tests, replicates……



CellPress
OPEN ACCESS

Neuron

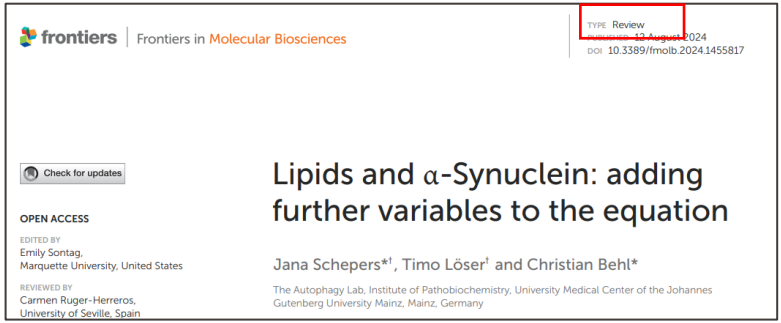
Article

Imaging α-synuclein pathologies in animal models and patients with Parkinson's and related diseases

Hironobu Endo,[1,19,20,*] Maiko Ono,[2,19] Yuhei Takado,[2] Kiwamu Matsuoka,[1,3] Manami Takahashi,[4] Kenji Tagai,[1,5] Yuko Kataoka,[1] Kosei Hirata,[1,6] Keisuke Takahata,[1,7] Chie Seki,[1] Naomi Kokubo,[1] Masayuki Fujinaga,[3] Wakana Mori,[8] Yuji Nagai,[1] Koki Mimura,[1,9] Katsushi Kumata,[8] Tatsuya Kikuchi,[8] Aki Shimozawa,[10] Sushil K. Mishra,[11] Yoshiki Yamaguchi,[12] Hiroshi Shimizu,[13] Akiyoshi Kakita,[13] Hiroyuki Takuwa,[1,4] Hitoshi Shinotoh,[1,14] Hitoshi Shimada,[1,15] Yasuyuki Kimura,[1,16] Masanori Ichise,[1] Tetsuya Suhara,[17] Takafumi Minamimoto,[1] Naruhiko Sahara,[1] Kazunori Kawamura,[8] Ming-Rong Zhang,[8] Masato Hasegawa,[10] and Makoto Higuchi[1,18]

Review articles:

- Summarizes data and conclusions from multiple studies
- Provides an overview of a scientific field or topic
- Tips: great resource, but always cross-check the cited primary sources to ensure accuracy and reliability
- Tips: Read multiple review articles on the same topic by different authors to avoid bias



frontiers | Frontiers in Molecular Biosciences

TYPE Review
DOI 10.3389/fmolb.2024.1455817

Check for updates

OPEN ACCESS

EDITED BY
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Marquette University, United States

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University of Seville, Spain

Lipids and α-Synuclein: adding further variables to the equation

Jana Schepers*†, Timo Löser† and Christian Behl*

The Autophagy Lab, Institute of Pathobiochemistry, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

Why is reading scientific papers important ?

Why is reading scientific papers important ?

To prepare an assignment

Personal intellectual curiosity

Stay informed about latest research in your field

Generate new ideas and hypotheses

Develop critical thinking and analytical skills

Cite relevant literature (master project, PhD thesis, grant application….)

Deepen understanding of a subject/Field of research

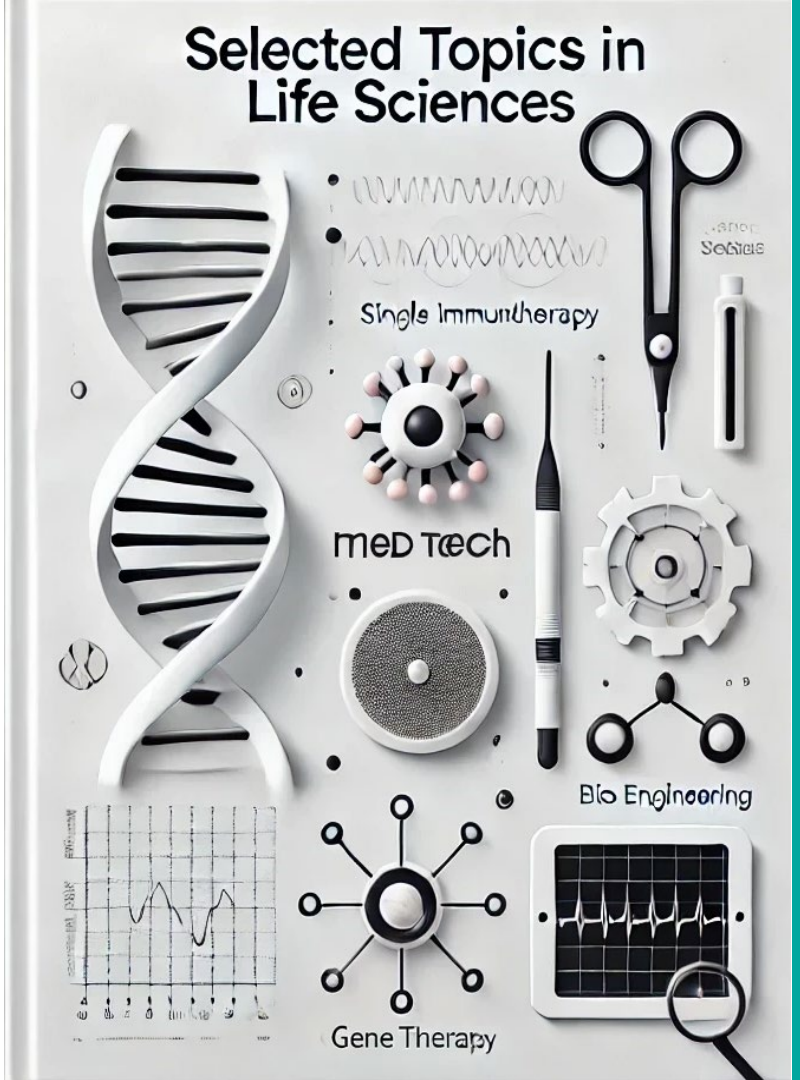
Understand research methodologies

Collaborative work

Gain insights from other fields

Staying ahead in your research field

Enhancing academic and professional writing skills



How to read a scientific paper efficiently?

2. Tips and tricks: where to find papers and stay updated efficiently?

Where to find papers and stay updated efficiently ?

Where to find papers?

PubMed® https://pubmed.ncbi.nlm.nih.gov/

PubChem

Google

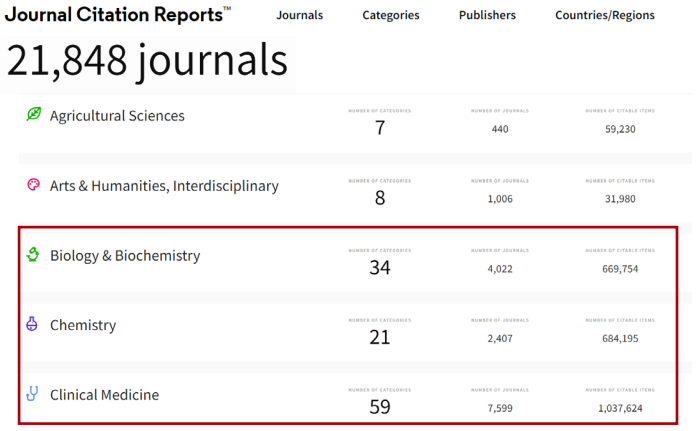
Google Scholar https://scholar.google.com/

Web of Science™ https://www.webofscience.com/wos/woscc/basic-search

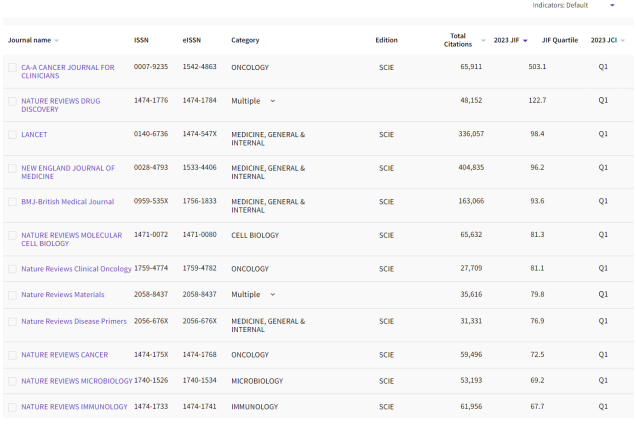
ScienceDirect® https://www.sciencedirect.com/

Impact factors and more

https://jcr.clarivate.com/jcr/home

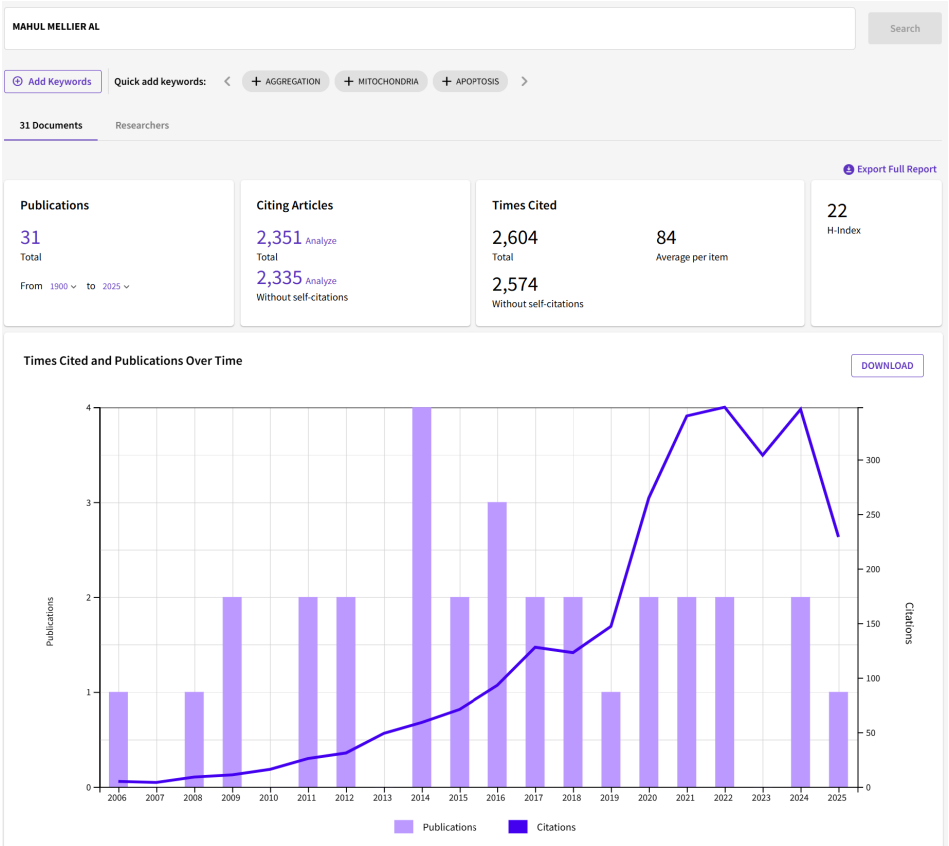


https://jcr.clarivate.com/jcr/browse-journals



Impact factors and more

https://www.webofscience.com/wos/author/search



Mahul-Mellier, Anne-Laure

This is an algorithmically generated author record.

Ecole Polytechnique Federale de Lausanne - EPFL School of Life Sciences - LAUSANNE, SWITZERLAND

Identifiers	Web of Science ResearcherID: FJF-8554-2022
Published names	Mahul-Mellier, Anne-Laure Mahul-Mellier, A-L Mahul-Mellier, A. -L. Mahul-Mellier, AL
Organizations	Ecole Polytechnique Federale de Lausanne Ecole Polytech Lausanne Fed EPFL Imperial College London Institut National de la Sante et de la Recherche Medicale (Inserm) Universite Grenoble Alpes (UGA)
Subject Categories	Biochemistry & Molecular Biology; Cell Biology; Science & Technology - Other Topics; Optics; Neurosciences & Neurology

How to stay up-to-date (efficiently) ?

How to stay up-to-date (efficiently) ?

•**Subscribe to alerts and newsletters**:

Many academic journals and databases offer email alerts or newsletters that notify you of the latest publications in your field.

Tuto with the link below:
https://youtu.be/WbFjV91YNNY

Creating Alerts: PubMed

Setting up alerts with PubMed is an easy process of just a few steps:

1.Navigate to the "Sign in to MyNCBI" link at the top right of the PubMed homepage to sign in, or to register for a new account.

2.Perform a search of interest (**Keywords or name of authors**) for which you would like to set up an alert.

3.Click the "Create Alert" link located below the search box. You can create as many alerts that you want.

4.Save the search and set the frequency and day for email results.

How to stay up-to-date (efficiently) ?

From	Subject	Received	Size	Categories
My NCBI	What's new for 'alpha-synuclein degradation' in PubMed	sam. 24.08.2024 ...	38 KB	
This message contains My NCBI what's new results from the National Center for Biotechnology Information (NCBI <http://www.ncbi.nlm.nih.gov>) at the U.S. National Library of				
My NCBI	What's new for 'alpha-synuclein structure' in PubMed	sam. 24.08.2024 ...	37 KB	
This message contains My NCBI what's new results from the National Center for Biotechnology Information (NCBI <http://www.ncbi.nlm.nih.gov>) at the U.S. National Library of				
My NCBI	What's new for 'alpha synuclein fibrils' in PubMed	sam. 24.08.2024 ...	36 KB	
This message contains My NCBI what's new results from the National Center for Biotechnology Information (NCBI <http://www.ncbi.nlm.nih.gov>) at the U.S. National Library of				
My NCBI	What's new for 'alpha-synuclein degradation' in PubMed	sam. 24.08.2024 ...	38 KB	
This message contains My NCBI what's new results from the National Center for Biotechnology Information (NCBI <http://www.ncbi.nlm.nih.gov>) at the U.S. National Library of				
ResearchGate	**Anne-Laure, an article cited your research**	**sam. 24.08.2024...**	**66 KB**	
Anne-Laure, an article cited your research				
Nature Careers	**Cash for catching scientific errors**	**sam. 24.08.2024...**	**141 KB**	
The ERROR project offers researchers a bounty for spotting mistakes in published papers — a strategy borrowed from the software industry.				

What's new for 'alpha-synuclein degradation' in PubMed

MN My NCBI <efback@ncbi.nlm.nih.gov>
To Anne-Laure Mahul Mellier

Reply | Reply All | Forward

sam. 24.08.2024 13:3

If there are problems with how this message is displayed, click here to view it in a web browser.

PubMed Results

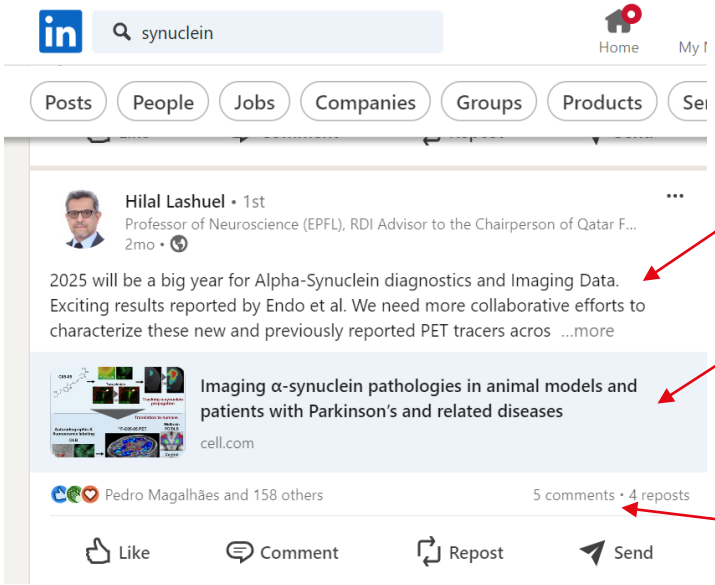
Items 1-2 of 2 (Display the 2 citations in PubMed)

1. Quantitative systems pharmacology model of α-synuclein pathology in Parkinson's disease-like mouse for investigation of passive immunotherapy mechanisms.
   Ivanova O, Karelina T.
   CPT Pharmacometrics Syst Pharmacol. 2024 Aug 23. doi: 10.1002/psp4.13223. Online ahead of print.
   PMID: 39177164
2. Contribution of alpha-synuclein pathology to cerebral glucose metabolism in patients with amnestic MCI.
   Abu-Rumeileh S, Arajyan G, Reiman EM, Otto M, Weise CM; Alzheimer's Disease Neuroimaging Initiative.
   Alzheimers Dement. 2024 Aug 23. doi: 10.1002/alz.14151. Online ahead of print.
   PMID: 39177111

How to stay up-to-date (efficiently) ?

•**Use social media and academic networks**:

Platforms like ResearchGate, LinkedIn, or Twitter often have active communities of researchers who share new publications and discuss recent advances.



https://www.linkedin.com/feed/

Providing context:
Understanding why this paper is important for your research community

Identifying breakthroughs or innovations
Staying up-to-date with recent publications

Comments from the field Community:
-Gauge the paper's impact and controversy
-Understand different perspectives and interpretations
-Identify strengths and weaknesses
-Stay informed about ongoing debates

X
https://twitter.com

How to stay up-to-date (efficiently) ?

•**Engage with preprint servers**: Platforms like arXiv, bioRxiv, or medRxiv provide access to preprints, which are early versions of research papers shared before peer review. This can be a way to get the very latest information on cutting-edge research.

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

ChemRxiv®

arXiv

Info about weekly release on X (Twitter)

X
https://twitter.com

How to stay up-to-date (efficiently) ? Pre-prints articles

Advantages of preprint papers:

How to stay up-to-date (efficiently) ? Pre-prints articles

Advantages of preprint papers:

1.Rapid dissemination of research findings: Preprints allow researchers to share their findings with the scientific community quickly, bypassing the often lengthy peer-review process required by traditional journals.

2. Increased visibility and feedback:
Community feedback: Preprints are accessible to the entire scientific community and the public, allowing researchers to receive feedback and comments from a broader audience before formal peer review. This can help improve the paper by addressing potential flaws or incorporating additional perspectives. For example, a researcher might receive valuable methodological suggestions from peers that could strengthen the study.
Enhanced visibility: Publishing a preprint increases the visibility of the research, potentially leading to greater citations and recognition. It can help establish a researcher's priority on a discovery, especially in competitive fields.

3. Open access and accessibility/Free Access:
Preprint servers typically provide free access to research, which supports the open science movement and ensures that researchers worldwide, regardless of institutional access to journals, can read and build upon the findings. This is particularly important for researchers in low-resource settings who may not have access to subscription-based journals.

4. Proof of work for grant and career advancement:
Proof of productivity: Posting preprints can demonstrate ongoing productivity to funding agencies, potential collaborators, and hiring committees. This is especially useful for early-career researchers who need to showcase their work to secure funding or academic positions.
Grant application support: Preprints can serve as preliminary evidence of research progress in grant applications, showing that the work is actively being developed and disseminated.

How to stay up-to-date (efficiently) ? Pre-prints articles

Disadvantages of preprint papers:

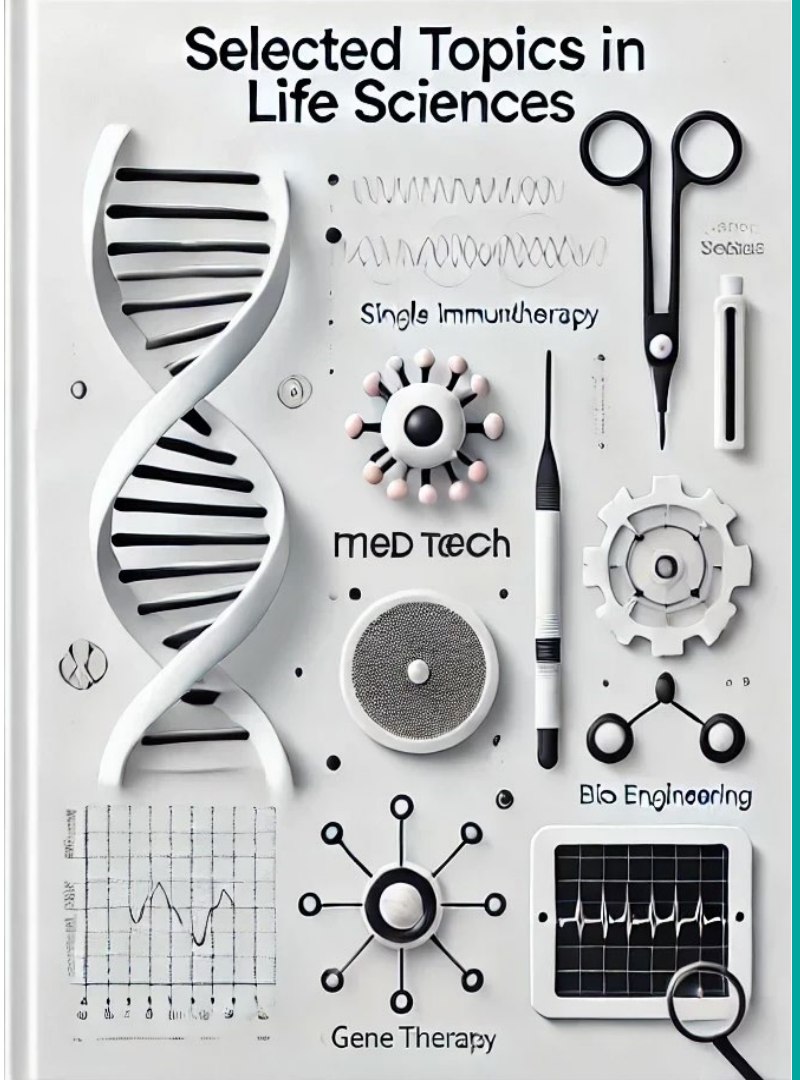
How to stay up-to-date (efficiently) ? Pre-prints articles

Disadvantages of preprint papers:

1.Lack of peer review and quality assurance:
No formal peer review: Unlike traditional journal articles, preprints have not undergone peer review, which means they have not been evaluated for methodological rigor, accuracy, or validity. This lack of scrutiny can lead to the dissemination of low-quality or even flawed research. For example, preprints may contain statistical errors, incorrect interpretations, or unsupported claims.
Potential for misinformation: Because preprints are publicly accessible, there is a risk of the public, media, or policymakers misinterpreting preliminary findings as conclusive evidence, which can lead to misinformation or panic, especially in health-related fields.

2. Intellectual property concerns:
Risk of idea theft: Posting a preprint makes the research publicly available, which can increase the risk of idea theft or "scooping" by other researchers who might use the information without proper attribution. This is a significant concern in highly competitive fields.
Patent and commercialization issues: If the research has potential commercial applications, publishing a preprint might compromise the ability to secure patents or intellectual property rights, as public disclosure can affect patentability in some jurisdictions.

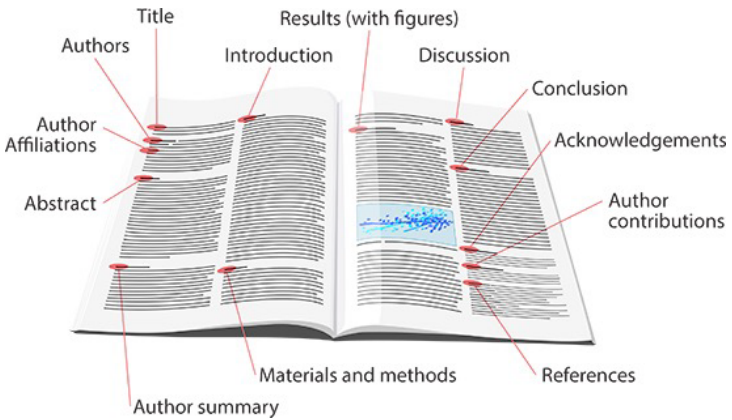
3. Premature publicity:
High-profile preprints can attract media attention and public scrutiny before the findings have been validated through peer review, leading to premature conclusions or public controversy.



How to read a scientific paper efficiently?

3. Strategies and techniques for reading scientific papers effectively

The anatomy of a paper



Title: short, succint and catchy
Provides a concise and informative summary of the paper's main topic and key findings

Abstract: Why and Why ?
Summarizes the entire paper in a brief paragraph (typically 150-250 words). The abstract provides a quick overview of the research, including the background, objectives, methods, key results, and conclusions.

Introduction:
When, whom, why, what and how ?
Presents background and research questions

Material and Method:
How ?
Describes the experimental approach and techniques

Results:
What ?
Summarizes the data and findings

Discussion:
Why and where ?
Interprets results and discusses their implications

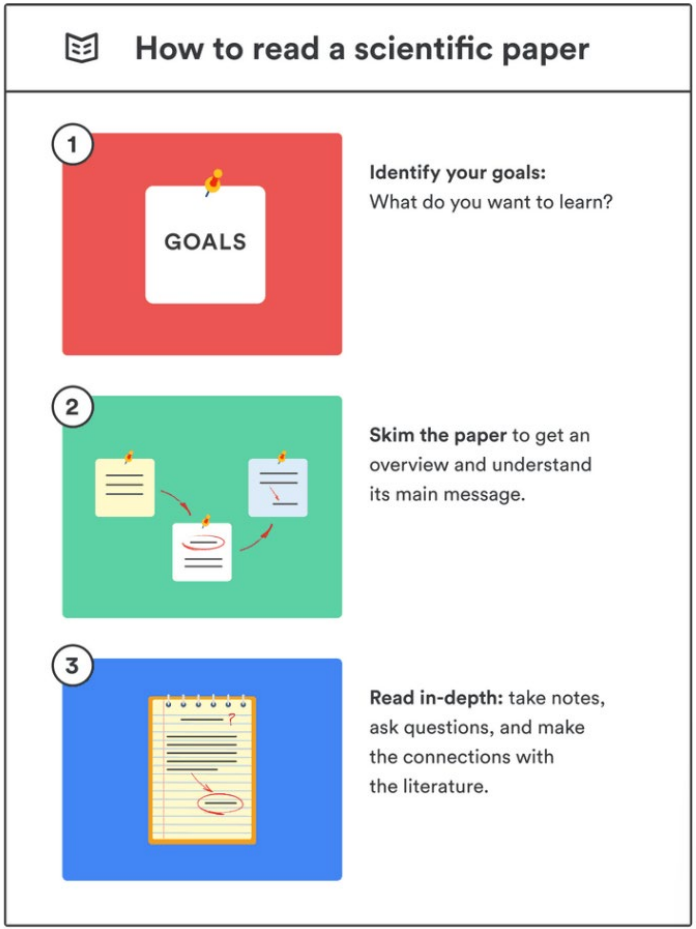
* Some journals allow the results and discussions to be combined

How to read a scientific paper (efficiently)?

ChatGPT or not ChatGPT ?

Tip #1: NO ChatGPT for reading a paper - EVER

How to read a scientific paper (efficiently) – 3 steps ?



How to read a scientific paper (efficiently) ?

Step #1: Identify your motivations for reading a scientific paper

Before you sit down to read a scientific paper, ask yourself these questions:

- Why do I need to read this paper?
- What information am I looking for?
- Which sections of the paper are most likely to contain the information I need?
- Is this paper serving as background reading or part of a literature review for a current research project?
- Are you exploring a new area of research?
- Are you looking to compare your findings with those reported in the paper?
- Are you tracking the work of a particular researcher to stay updated on their latest studies?
- Are you monitoring new and emerging methods within your field?

All of these intentions require a different reading approach.

How to read a scientific paper (efficiently) ?

Step #1: Identify your motivations for reading a scientific paper

- **Exploring a new research area?**
  Focus on reading the introduction thoroughly to gather foundational information and key references. Additionally, the discussion section is valuable for understanding the broader implications of the findings. Consult both primary research articles and review papers to gain a comprehensive overview.

- **Interested in study design, techniques, or methodology?**
  Allocate most of your reading time to the methods section to fully understand the experimental approaches and techniques used.

- **Planning to build upon existing research?**
  If this study will form the foundation for your own work, it is essential to read the entire paper carefully.

- **Looking for arguments to support or challenge your own research?**
  A detailed reading of the full paper with a special attention to the discussion is necessary to engage in-depth with the content. This allows you to compare and contrast your findings with the study's results and potentially discuss future applications or directions for your research.

Tip: Understanding your purpose for reading a paper helps determine your reading strategy. Depending on what you aim to achieve, you might choose either a quick overview **or** a more thorough, detailed reading. Knowing your objective allows you to focus on the most relevant sections, making your reading more efficient and less overwhelming.

How to read a scientific paper (efficiently) ?

Step #2: Skim the paper

Start by getting an overall sense of the paper by following these straightforward steps:

1. Examine the title: Determine the type of document you are reading—is it a journal article, a review, a methods paper, or a commentary?

2. Read the abstract: This section provides a concise overview of the study. Consider what the research is about, the main question it addresses, the methods used, the findings, and the implications suggested by the authors.
This will help you decide whether the paper is worth a more thorough read (Go/No Go).

3. Quickly browse the introduction: The introduction is generally structured in a predictable way. The opening paragraphs provide background information on the topic, which might be essential for those new to the field but less so for experts. The introduction then narrows to highlight the gap in knowledge that the study aims to fill, identifying what remains unknown and what problems need solving. By the end of the introduction, the study's objectives, research questions, or hypotheses should be clear. Does it address what you are looking for (Go/No Go)?

4. Review figures and tables: This is where the core data of the study is presented. Try to interpret the figures and tables independently of the results section. Keep the detailed reading for later.
Does it address what you are looking for (Go/No Go)?

5. Go through the methods section: Obtain a quick overview of the techniques and methodologies used.
Does the methodology/cellular models/assays address what you are looking for (Go/No Go)?
Depending on your needs, you may decide to spend more time here during a second reading.

How to read a scientific paper (efficiently) ?

Step #2: Skim the paper

6. Skim the discussion section: This part typically starts by summarizing the findings and their significance, followed by a discussion of the study's limitations.
The discussion often ends with conclusions or suggestions for future research.

8. Summarize the paper's key message: Try to condense the main point of the paper into a sentence or two.
Evaluate whether you have obtained the information you were seeking.

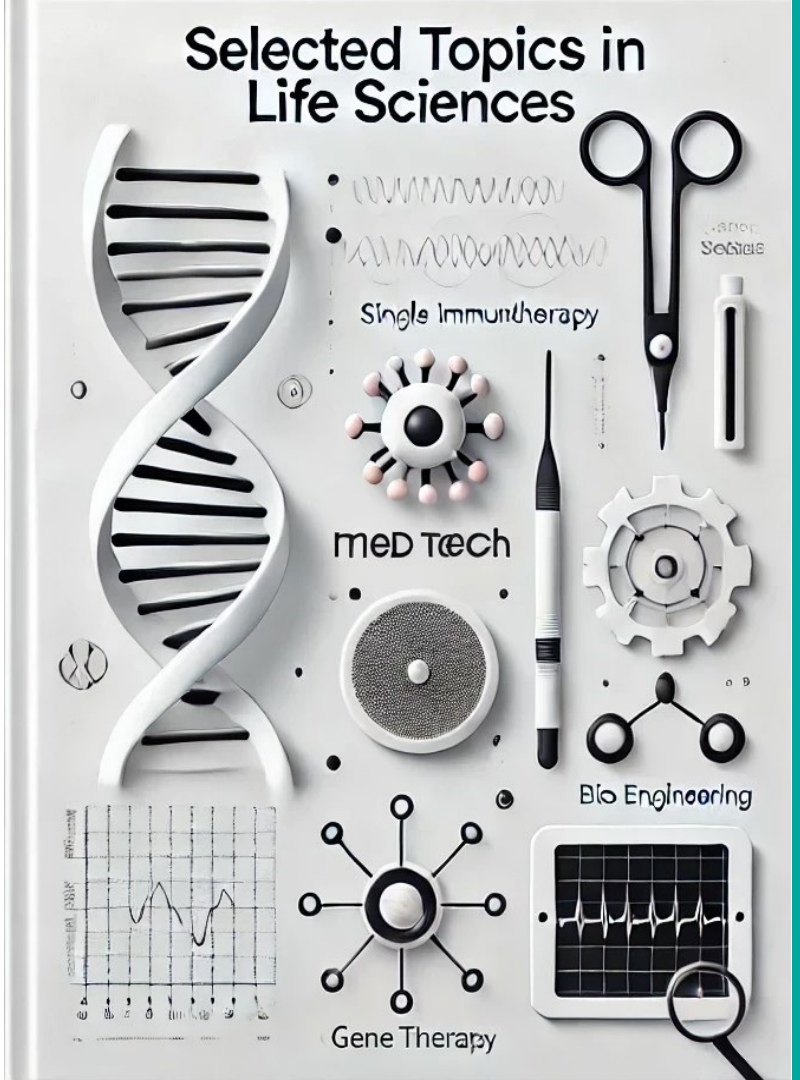
9. Note any unfamiliar terms: List any concepts or terminology you need to research further before you revisit the paper.

10. Scan the references: Identify any additional studies or reviews that could provide valuable background or supplementary information for a deeper understanding of the paper.

How to read a scientific paper (efficiently) ?

Step #3: Read in depth

Everything is in the title, but always remember steps #1 and #2 to ensure efficient reading



How to read a scientific paper efficiently?

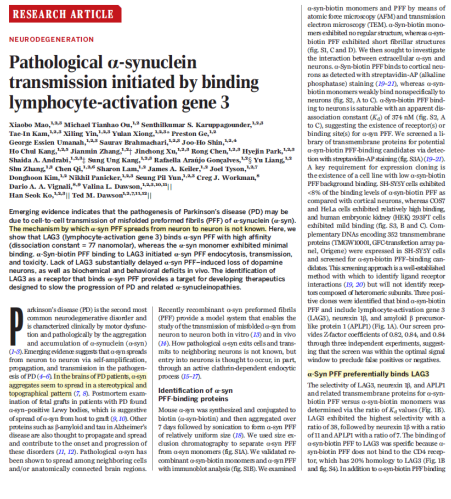
4. Techniques for efficient information retrieval and better retention

How to read a scientific paper (efficiently) ?

Be an active reader

- Highlight key points, underline text, write comments or questions in the margins
- Re-read sections to focus on central points
- BUT avoid highlighting large blocks of text

DO



RESEARCH ARTICLE

NEURODEGENERATION

Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3

Xiaobo Mao,[1,5,†] Michael Tianhao Ou,[1,†] Senthilkumar S. Karuppagounder,[1,2,3] Tae-In Kam,[1,2,3] Xiling Yin,[1,4,5] Yulan Xiong,[1,5,6,‡] Preston Ge,[1,2] George Eoslen Umanah,[1,2,3] Saurav Brahmachari,[1,2,3] Joo-Ho Shin,[1,2,4] Ho Chul Kang,[1,2,3] Jiannin Zhang,[1,7‡] Jinshong Xu,[1,2,3] Rong Chen,[1,2,3] Hyejin Park,[1,2,3] Shaida A. Andrabi,[1,2,3,‡] Seng Ung Kang,[1,2,3] Rafaella Araújo Gonçalves,[1,8‡] Yu Liang,[1,2] Shu Zhang,[1,9] Chen Qi,[1,2,3] Sharon Lam,[1,2] James A. Keller,[1,2] Joel Tyson,[1,3,7] Donghoon Kim,[1,2] Nikhil Panicker,[1,3,7] Seung Pil Yun,[1,2,3] Creg J. Workman,[8] Dario A. A. Vignali,[8,9] Valina L. Dawson,[1,2,3,10,11,‡] Han Seok Ko,[1,2,3,‡] Ted M. Dawson[1,2,3,11,12,‡]

Emerging evidence indicates that the pathogenesis of Parkinson's disease (PD) may be due to cell-to-cell transmission of misfolded preformed fibrils (PFF) of α-synuclein (α-syn). The mechanism by which α-syn PFF spreads from neuron to neuron is not known. Here, we show that LAG3 (lymphocyte-activation gene 3) binds α-syn PFF with high affinity (dissociation constant = 77 nanomolar), whereas the α-syn monomer exhibited minimal binding. α-Syn-biotin PFF binding to LAG3 initiated α-syn PFF endocytosis, transmission, and toxicity. Lack of LAG3 substantially delayed α-syn PFF–induced loss of dopamine neurons, as well as biochemical and behavioral deficits in vivo. The identification of LAG3 as a receptor that binds α-syn PFF provides a target for developing therapeutics designed to slow the progression of PD and related α-synucleinopathies.

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized clinically by motor dysfunction and pathologically by the aggregation and accumulation of α-synuclein (α-syn) (*1–3*). Emerging evidence suggests that α-syn spreads from neuron to neuron via self-amplification, propagation, and transmission in the pathogenesis of PD (*4–6*). In the brains of PD patients, α-syn aggregates seem to spread in a stereotypical and topographical pattern (*7, 8*). Postmortem examination of fetal grafts in patients with PD found α-syn–positive Lewy bodies, which is suggestive of spread of α-syn from host to graft (*9, 10*). Other proteins such as β-amyloid and tau in Alzheimer's disease are also thought to propagate and spread and contribute to the onset and progression of these disorders (*11, 12*). Pathological α-syn has been shown to spread among neighboring cells and/or anatomically connected brain regions. Recently reconstituent α-syn preformed fibrils (PFF) provide a model system that enables the study of the transmission of misfolded α-syn from neuron to neuron both in vitro (*13*) and in vivo (*14*). How pathological α-syn exits cells and transmits to neighboring neurons is not known, but entry into neurons is thought to occur, in part, through an active clathrin-dependent endocytic process (*15–17*).

α-Syn PFF preferentially binds LAG3

The selectivity of LAG3, neurexin 1β, and APLP1 and related transmembrane proteins for α-synbiotin PFF versus α-syn-biotin monomers was determined via the ratio of K_d values (Fig. 1E). LAG3 exhibited the highest selectivity with a ratio of 38, followed by neurexin 1β with a ratio of 11 and APLP1 with a ratio of 7. The binding of α-syn-biotin PFF to LAG3 was specific because α-syn-biotin PFF does not bind to the CD4 receptor, which has 20% homology to LAG3 (Fig. 1B and fig. S4). In addition to α-syn-biotin PFF binding to α-syn-biotin monomers and PFF by means of atomic force microscopy (AFM) and transmission electron microscopy (TEM). α-Syn-biotin monomers exhibited no regular structure, whereas α-syn-biotin PFF exhibited short fibrillar structures (fig. S1, C and D). We then sought to investigate the interaction between extracellular α-syn and neurons. α-Syn-biotin PFF binds to cortical neurons as detected with streptavidin-AP (alkaline phosphatase) staining (*19–21*), whereas α-syn-biotin monomers weakly bind nonspecifically to neurons (fig. S2, A to C). α-Syn-biotin PFF binding to neurons is saturable with an apparent dissociation constant (K_d) of 374 nM (fig. S2, A to C), suggesting the existence of receptor(s) or binding site(s) for α-syn PFF. We screened a library of transmembrane proteins for potential α-syn-biotin PFF-binding candidates via detection with streptavidin-AP staining (fig. S3A) (*19–21*). A key requirement for expression cloning is the existence of a cell line with low α-syn-biotin PFF background binding. SH-SY5Y cells exhibited <8% of the binding levels of α-syn-biotin PFF as compared with cortical neurons, whereas COS7 and HeLa cells exhibited relatively high binding, and human embryonic kidney (HEK) 293FT cells exhibited mild binding (fig. S3, B and C). Complementary DNAs encoding 323 transmembrane proteins (TMEM3001, GFC-transfection array panel, Origene) were expressed in SH-SY5Y cells and screened for α-syn-biotin PFF–binding candidates. This screening approach is a well-established method with which to identify ligand receptor interactions (*18, 20*) but will not identify receptors composed of heteromeric subunits. Three positive clones were identified that bind α-syn-biotin PFF and include lymphocyte-activation gene 3 (LAG3), neurexin 1β, and amyloid β precursor-like protein 1 (APLP1) (Fig. 1A). Our screen provides Z-factor coefficients of 0.82, 0.84, and 0.84 through three independent experiments, suggesting that the screen was within the optimal signal window to preclude false positives or negatives.

Identification of α-syn PFF-binding proteins

Mouse α-syn was synthesized and conjugated to biotin (α-syn-biotin) and then aggregated over 7 days followed by sonication to form α-syn PFF of relatively uniform size (*19*). We used size exclusion chromatography to separate α-syn PFF from α-syn monomers (fig. S1A). We validated recombinant α-syn-biotin monomers and α-syn PFF with immunoblot analysis (fig. S1B). We examined

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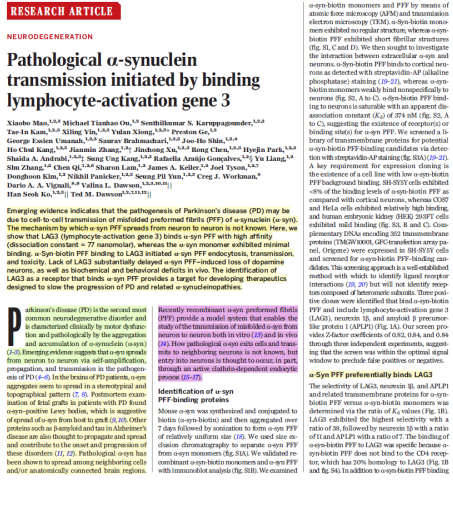

RESEARCH ARTICLE

NEURODEGENERATION

Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3

Xiaobo Mao,[1,5,†] Michael Tianhao Ou,[1,†] Senthilkumar S. Karuppagounder,[1,2,3] Tae-In Kam,[1,2,3] Xiling Yin,[1,4,5] Yulan Xiong,[1,5,6,‡] Preston Ge,[1,2] George Eoslen Umanah,[1,2,3] Saurav Brahmachari,[1,2,3] Joo-Ho Shin,[1,2,4] Ho Chul Kang,[1,2,3] Jiannin Zhang,[1,7‡] Jinshong Xu,[1,2,3] Rong Chen,[1,2,3] Hyejin Park,[1,2,3] Shaida A. Andrabi,[1,2,3,‡] Seng Ung Kang,[1,2,3] Rafaella Araújo Gonçalves,[1,8‡] Yu Liang,[1,2] Shu Zhang,[1,9] Chen Qi,[1,2,3] Sharon Lam,[1,2] James A. Keller,[1,2] Joel Tyson,[1,3,7] Donghoon Kim,[1,2] Nikhil Panicker,[1,3,7] Seung Pil Yun,[1,2,3] Creg J. Workman,[8] Dario A. A. Vignali,[8,9] Valina L. Dawson,[1,2,3,10,11,‡] Han Seok Ko,[1,2,3,‡] Ted M. Dawson[1,2,3,11,12,‡]

Emerging evidence indicates that the pathogenesis of Parkinson's disease (PD) may be due to cell-to-cell transmission of misfolded preformed fibrils (PFF) of α-synuclein (α-syn). The mechanism by which α-syn PFF spreads from neuron to neuron is not known. Here, we show that LAG3 (lymphocyte-activation gene 3) binds α-syn PFF with high affinity (dissociation constant = 77 nanomolar), whereas the α-syn monomer exhibited minimal binding. α-Syn-biotin PFF binding to LAG3 initiated α-syn PFF endocytosis, transmission, and toxicity. Lack of LAG3 substantially delayed α-syn PFF–induced loss of dopamine neurons, as well as biochemical and behavioral deficits in vivo. The identification of LAG3 as a receptor that binds α-syn PFF provides a target for developing therapeutics designed to slow the progression of PD and related α-synucleinopathies.

Parkinson's disease (PD) is the second most common neurodegenerative disorder and is characterized clinically by motor dysfunction and pathologically by the aggregation and accumulation of α-synuclein (α-syn) (*1–3*). Emerging evidence suggests that α-syn spreads from neuron to neuron via self-amplification, propagation, and transmission in the pathogenesis of PD (*4–6*). In the brains of PD patients, α-syn aggregates seem to spread in a stereotypical and topographical pattern (*7, 8*). Postmortem examination of fetal grafts in patients with PD found α-syn–positive Lewy bodies, which is suggestive of spread of α-syn from host to graft (*9, 10*). Other proteins such as β-amyloid and tau in Alzheimer's disease are also thought to propagate and spread and contribute to the onset and progression of these disorders (*11, 12*). Pathological α-syn has been shown to spread among neighboring cells and/or anatomically connected brain regions. Recently reconstituent α-syn preformed fibrils (PFF) provide a model system that enables the study of the transmission of misfolded α-syn from neuron to neuron both in vitro (*13*) and in vivo (*14*). How pathological α-syn exits cells and transmits to neighboring neurons is not known, but entry into neurons is thought to occur, in part, through an active clathrin-dependent endocytic process (*15–17*).

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α-syn-biotin monomers and PFF by means of atomic force microscopy (AFM) and transmission electron microscopy (TEM). α-Syn-biotin monomers exhibited no regular structure, whereas α-syn-biotin PFF exhibited short fibrillar structures (fig. S1, C and D). We then sought to investigate the interaction between extracellular α-syn and neurons. α-Syn-biotin PFF binds to cortical neurons as detected with streptavidin-AP (alkaline phosphatase) staining (*19–21*), whereas α-syn-biotin monomers weakly bind nonspecifically to neurons (fig. S2, A to C). α-Syn-biotin PFF binding to neurons is saturable with an apparent dissociation constant (K_d) of 374 nM (fig. S2, A to C), suggesting the existence of receptor(s) or binding site(s) for α-syn PFF. We screened a library of transmembrane proteins for potential α-syn-biotin PFF-binding candidates via detection with streptavidin-AP staining (fig. S3A) (*19–21*). A key requirement for expression cloning is the existence of a cell line with low α-syn-biotin PFF background binding. SH-SY5Y cells exhibited <8% of the binding levels of α-syn-biotin PFF as compared with cortical neurons, whereas COS7 and HeLa cells exhibited relatively high binding, and human embryonic kidney (HEK) 293FT cells exhibited mild binding (fig. S3, B and C). Complementary DNAs encoding 323 transmembrane proteins (TMEM3001, GFC-transfection array panel, Origene) were expressed in SH-SY5Y cells and screened for α-syn-biotin PFF–binding candidates. This screening approach is a well-established method with which to identify ligand receptor interactions (*18, 20*) but will not identify receptors composed of heteromeric subunits. Three positive clones were identified that bind α-syn-biotin PFF and include lymphocyte-activation gene 3 (LAG3), neurexin 1β, and amyloid β precursor-like protein 1 (APLP1) (Fig. 1A). Our screen provides Z-factor coefficients of 0.82, 0.84, and 0.84 through three independent experiments, suggesting that the screen was within the optimal signal window to preclude false positives or negatives.

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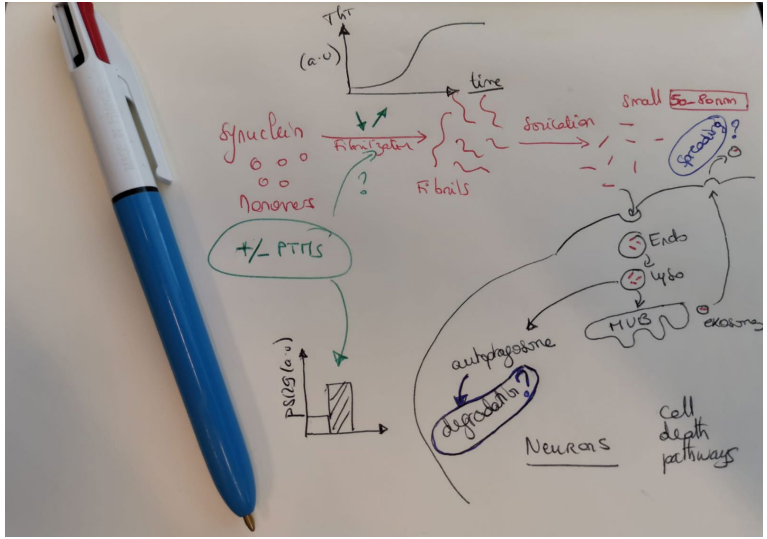
How to read a scientific paper (efficiently) ?

Be an active reader

- Draw scheme and diagrams
- **Create a Mind-Map along your reading (hand-written for better retention)**

  (draw signalling/cellular pathways, note the keywords, main conclusions)



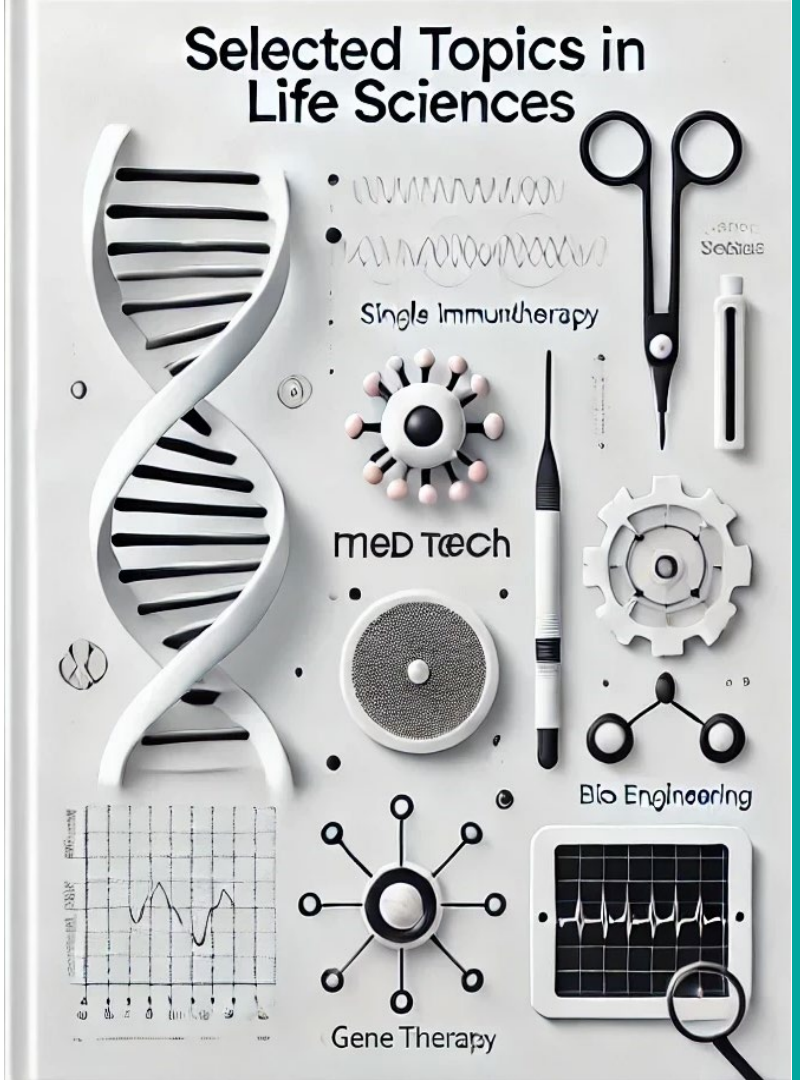
How to read a scientific paper (efficiently) ?

Be an active reader

Discuss with others

- Try to explain the content to yourself or someone else to solidify understanding.
- Engage in discussions with peers, teachers, or a study group.
- Explaining your understanding helps clarify ideas and uncover new insights.

➔ In many labs (academia or even industry), some time (weekly, monthly…) is dedicated to discuss papers during “Journal club” session



How to read a scientific paper efficiently?

5. Developing critical analysis skills

When reading a scientific paper efficiently, which questions should you ask yourself?

Engage in critical thinking

How to read a scientific paper (efficiently) ?

Engage in critical thinking

- Do you agree with how the authors set up their experiments /the reasoning behind the experimental design?
- Do you think the experiments were performed properly, with a sufficient number of repeats or adequate sample size to support the main findings and conclusions?
- Do you agree with the authors' conclusions based on the presented data?
- Are there alternative explanations for the results?
- What are your thoughts on the proposed future directions and next steps?
- What additional questions would you ask, or what future research directions would you suggest?

How to read a scientific paper (efficiently) ?

Engage in critical thinking

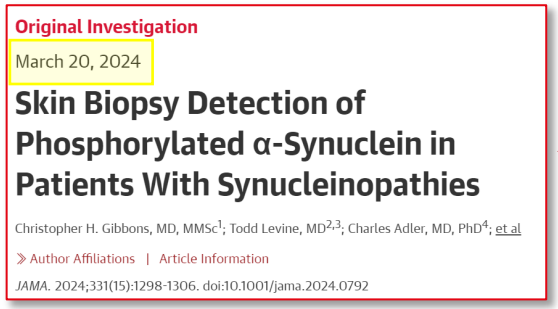
Tips:

1. **Just because it is published, it does not mean it is right**
2. **Just because it is a High-impact factor paper, it does not mean it is right**

- What have other researchers said about this paper on platforms such as X, LinkedIn, Google, or in journal responses, PubPeer?
- Engage in discussions about the findings with your colleagues, such as during lab meetings or journal clubs.

How to read a scientific paper (efficiently) ?

Engage in critical thinking – always try to be constructive



Original Investigation

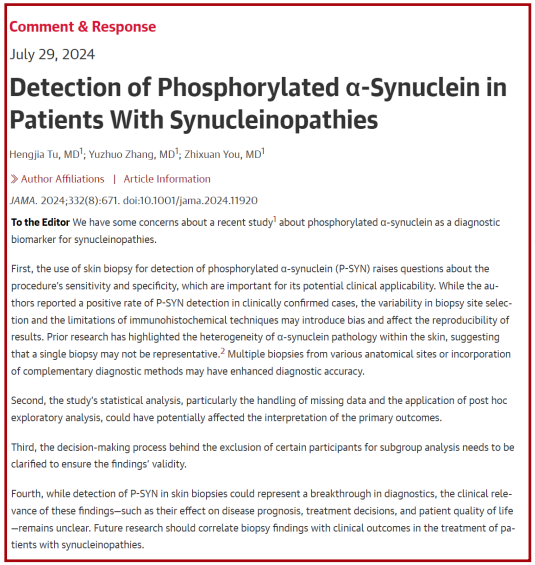
March 20, 2024

Skin Biopsy Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies

Christopher H. Gibbons, MD, MMSc[1]; Todd Levine, MD[2,3]; Charles Adler, MD, PhD[4]; et al

» Author Affiliations | Article Information

JAMA. 2024;331(15):1298-1306. doi:10.1001/jama.2024.0792



Comment & Response

July 29, 2024

Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies

Hengjia Tu, MD[1]; Yuzhuo Zhang, MD[1]; Zhixuan You, MD[1]

» Author Affiliations | Article Information

JAMA. 2024;332(8):671. doi:10.1001/jama.2024.11920

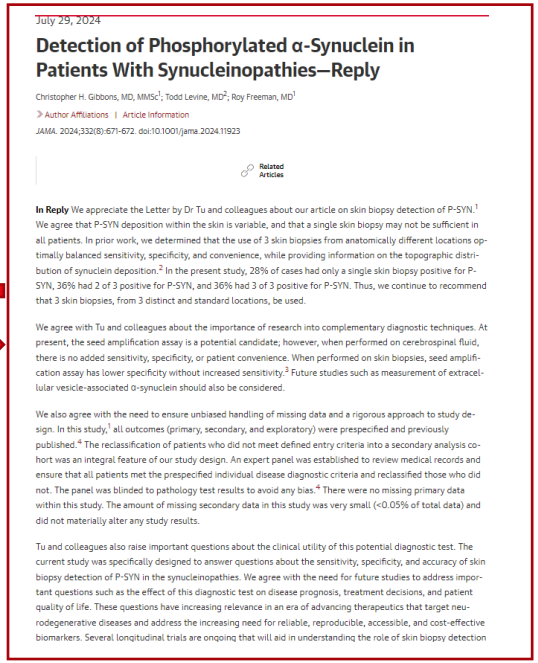
To the Editor We have some concerns about a recent study[1] about phosphorylated α-synuclein as a diagnostic biomarker for synucleinopathies.

First, the use of skin biopsy for detection of phosphorylated α-synuclein (P-SYN) raises questions about the procedure's sensitivity and specificity, which are important for its potential clinical applicability. While the authors reported a positive rate of P-SYN detection in clinically confirmed cases, the variability in biopsy site selection and the limitations of immunohistochemical techniques may introduce bias and affect the reproducibility of results. Prior research has highlighted the heterogeneity of α-synuclein pathology within the skin, suggesting that a single biopsy may not be representative.[2] Multiple biopsies from various anatomical sites or incorporation of complementary diagnostic methods may have enhanced diagnostic accuracy.

Second, the study's statistical analysis, particularly the handling of missing data and the application of post hoc exploratory analysis, could have potentially affected the interpretation of the primary outcomes.

Third, the decision-making process behind the exclusion of certain participants for subgroup analysis needs to be clarified to ensure the findings' validity.

Fourth, while detection of P-SYN in skin biopsies could represent a breakthrough in diagnostics, the clinical relevance of these findings—such as their effect on disease prognosis, treatment decisions, and patient quality of life—remains unclear. Future research should correlate biopsy findings with clinical outcomes in the treatment of patients with synucleinopathies.



July 29, 2024

Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies—Reply

Christopher H. Gibbons, MD, MMSc[1]; Todd Levine, MD[2]; Roy Freeman, MD[1]

» Author Affiliations | Article Information

JAMA. 2024;332(8):671-672. doi:10.1001/jama.2024.11923

Related Articles

In Reply We appreciate the Letter by Dr Tu and colleagues about our article on skin biopsy detection of P-SYN.[1] We agree that P-SYN deposition within the skin is variable, and that a single skin biopsy may not be sufficient in all patients. In prior work, we determined that the use of 3 skin biopsies from anatomically different locations optimally balanced sensitivity, specificity, and convenience, while providing information on the topographic distribution of synuclein deposition.[2] In the present study, 28% of cases had only a single skin biopsy positive for P-SYN, 36% had 2 of 3 positive for P-SYN, and 36% had 3 of 3 positive for P-SYN. Thus, we continue to recommend that 3 skin biopsies, from 3 distinct and standard locations, be used.

We agree with Tu and colleagues about the importance of research into complementary diagnostic techniques. At present, the seed amplification assay is a potential candidate; however, when performed on cerebrospinal fluid, there is no added sensitivity, specificity, or patient convenience. When performed on skin biopsies, seed amplification assay has lower specificity without increased sensitivity.[3] Future studies such as measurement of extracellular vesicle-associated α-synuclein should also be considered.

We also agree with the need to ensure unbiased handling of missing data and a rigorous approach to study design. In this study,[1] all outcomes (primary, secondary, and exploratory) were prespecified and previously published.[4] The reclassification of patients who did not meet defined entry criteria into a secondary analysis cohort was an integral feature of our study design. An expert panel was established to review medical records and ensure that all patients met the prespecified individual disease diagnostic criteria and reclassified those who did not. The panel was blinded to pathology test results to avoid any bias.[4] There were no missing primary data within this study. The amount of missing secondary data in this study was very small (<0.05% of total data) and did not materially alter any study results.

Tu and colleagues also raise important questions about the clinical utility of this potential diagnostic test. The current study was specifically designed to answer questions about the sensitivity, specificity, and accuracy of skin biopsy detection of P-SYN in the synucleinopathies. We agree with the need for future studies to address important questions such as the effect of this diagnostic test on disease prognosis, treatment decisions, and patient quality of life. These questions have increasing relevance in an era of advancing therapeutics that target neurodegenerative diseases and address the increasing need for reliable, reproducible, accessible, and cost-effective biomarkers. Several longitudinal trials are ongoing that will aid in understanding the role of skin biopsy detection

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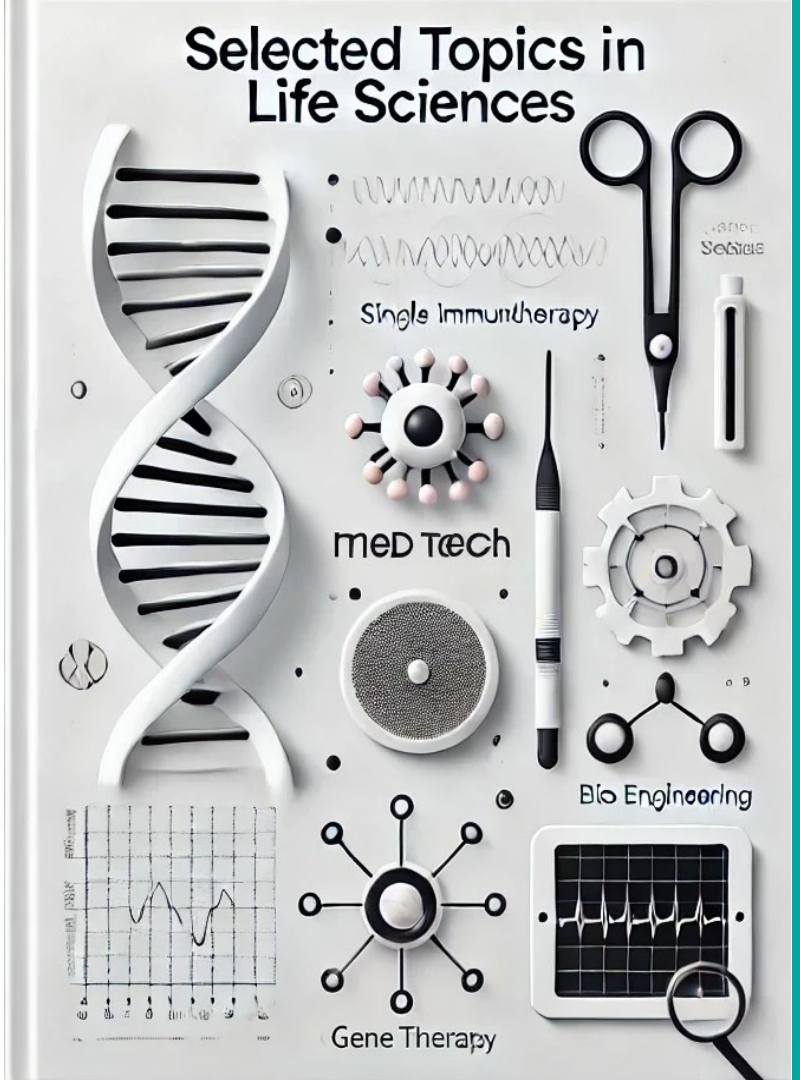

How to read a scientific paper efficiently?

Last but not least

The tricks and tips section

How to read a scientific paper (efficiently) ?

Last tricks and tips ….. How long should it take to read a paper (without ChatGPT)?

How to read a scientific paper (efficiently) ?

Last tricks and tips ….. How long should it take to read a paper ?

- You do not have to read the entire paper all at once.

  You can break it per 10-20 minutes slot over few days
- You can divide your reading into shorter sessions of 10-20 minutes over a few days.
- After you become more familiar with the process (after going through several papers), aim to limit your reading to 20-30 minutes per paper. Remember, you can always return to the paper later if you need more information on a particular topic.

How to read a scientific paper (efficiently) ?

Last tricks and tips ….. Keep the information for later use

Title	Authors (1st and Last)	Keywords	Rationale	Methods	Main results	Key Figures	Conclusions	What's next ?	Key Figures	Others comments

How to read a scientific paper (efficiently) ?

Last tricks and tips ….. Organize your library

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How to read a scientific paper (efficiently) ?

To read more about this topic

Published articles

"How to read a scientific paper" by John W. Little and Roy Parker
This guide, often cited in academic settings, provides a step-by-step approach to reading scientific papers. It discusses understanding the structure of a paper, what to look for in each section, and tips for evaluating the study's quality.

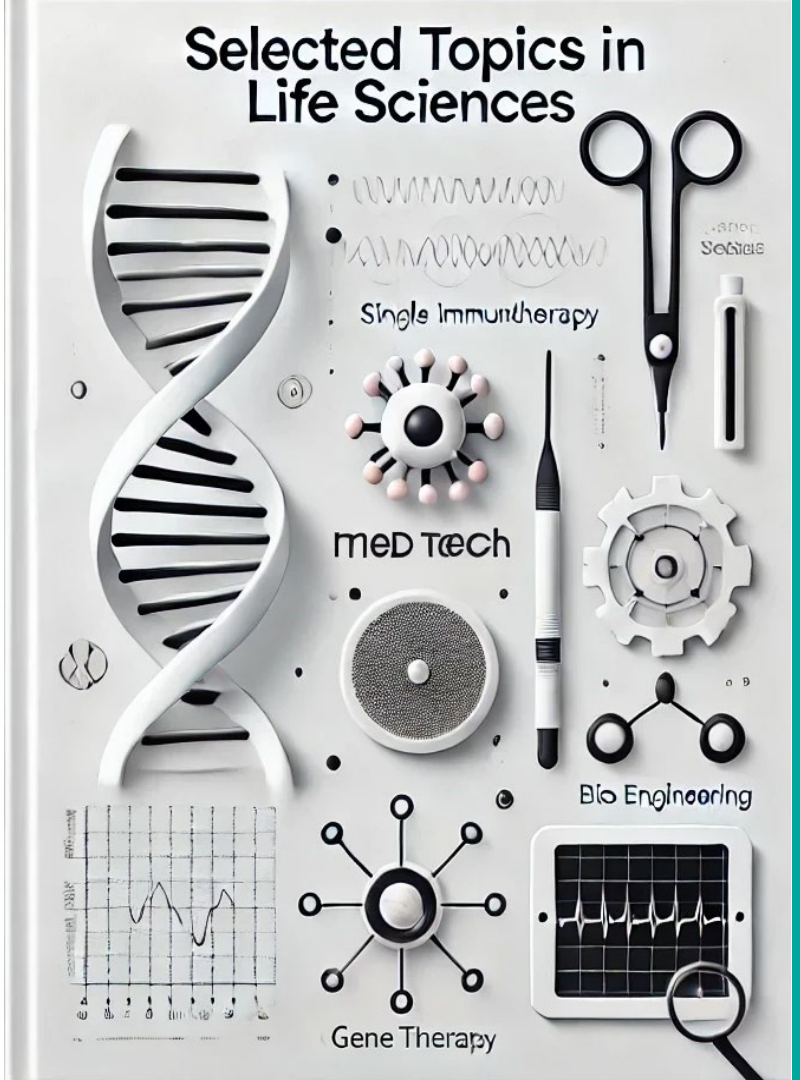
"Ten Simple Rules for Reading a Scientific Paper" by N. P. Steneck
Published in the journal "PLoS Computational Biology", this paper provides ten straightforward guidelines for understanding scientific literature. It is especially helpful for beginners who need a structured approach.

YouTube Tutorials

Many universities and educators provide free lectures on platforms like YouTube that offer insights into how to approach scientific literature.
Searching for "how to read a scientific paper" on YouTube can yield many valuable video tutorials.

Online Lectures

Searching for "how to read a scientific paper" – other point of view
https://bitesizebio.com/11060/how-to-read-a-scientific-paper/



How to read a scientific paper efficiently?

Practical Exercices

How to read a scientific paper efficiently?
Practical exercices

How to read a scientific paper efficiently?
Practical exercices

1. Time management and reading Strategies:

- How long did it take for you to read the two papers?
- Were there any particular sections that took more time than others? If so, why?
- Did you find any strategies that helped you read more efficiently or understand the content better?

2. Difficulties encountered:

- How did you find the readings? Were they easy, difficult, or somewhere in between?
- What aspects of the reading were challenging?

3. Reflection on learning experience:

- Was there a particular technique or strategy that you found especially useful in managing your time or understanding the material better (and that we did not mention during the class?)

How to read a scientific paper efficiently?

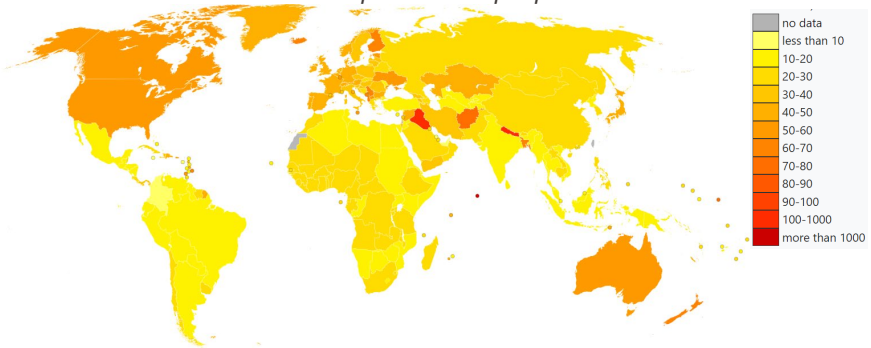
Understand the context

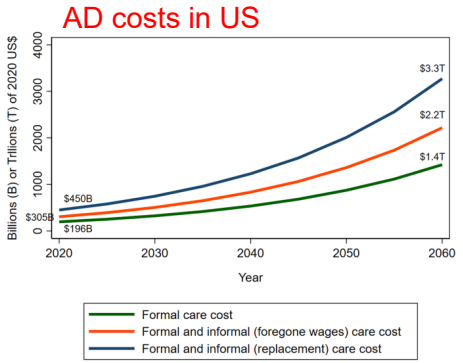
Global health and economic burden of NDDs

- **Global Prevalence**: ~65-70 million people globally suffer from neurodegenerative diseases, and this number is expected to more than double by 2050 due to ageing populations.
  E.g.,: 50-60 million of people with AD (1st NDD)
- **Economic Costs**:

The combined annual cost of neurodegenerative diseases globally is projected to surpass **$1 trillion by 2030**.

AD Prevalence: cases number per 100'000 people





https://ourworldindata.org/grapher/alzheimers-parkinsons-prevalence?tab=table
https://www.nature.com/articles/s41514-024-00136-6

Parkinson's Disease in numbers

Prevalence:
10 millions
patients
2024

worldwide

~25 millions
2050
+112%

60% increase in the number of cases over 20 years
20'000 euros/patient/year

Cost:
€250
billions
annual

Prevalence:
15'000
patients
*2007**

Fondation pour la recherche en biologie et médecine

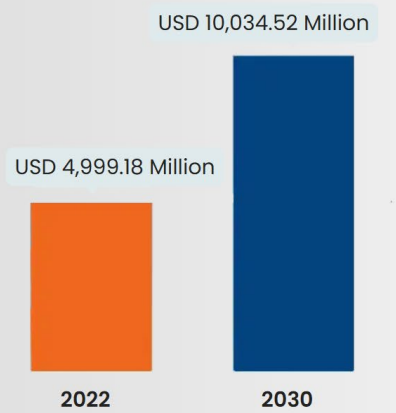
EPFL HUG CHUV

Parkinson’s Disease in numbers
Pharma point of view

Global Parkinsons Disease Treatment Market

Market Size in USD Billion

CAGR : 9.10%



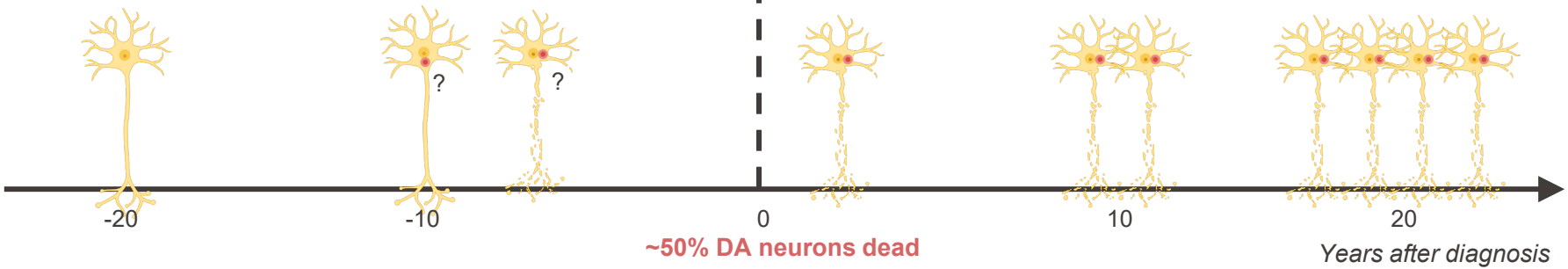
Forecast Period	2023 –2030
Market Size (Base Year)	USD 4,999.18 Million
Market Size (Forecast Year)	USD 10,034.52 Million
CAGR	9.10 %
Major Markets Players	• GlaxoSmithKline plc. • Teva Pharmaceutical Industries Ltd. • Boehringer Ingelheim International GmbH. • Impax Laboratories LLC • AbbVie Inc.

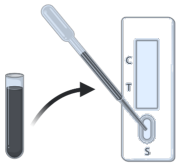
Parkinson's Disease:
begins years before motor symptoms appear

Non-motor symptoms
Constipation
Depression
Sleep disorders
Loss of smell

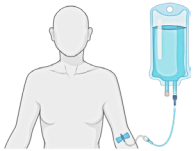
Diagnosis
~58 years

Motor Symptoms
Tremor (involuntary, rhythmic shaking)
Freezing
Bradikinesia (slowness of movement)





No biomarker
No test for early diagnosis



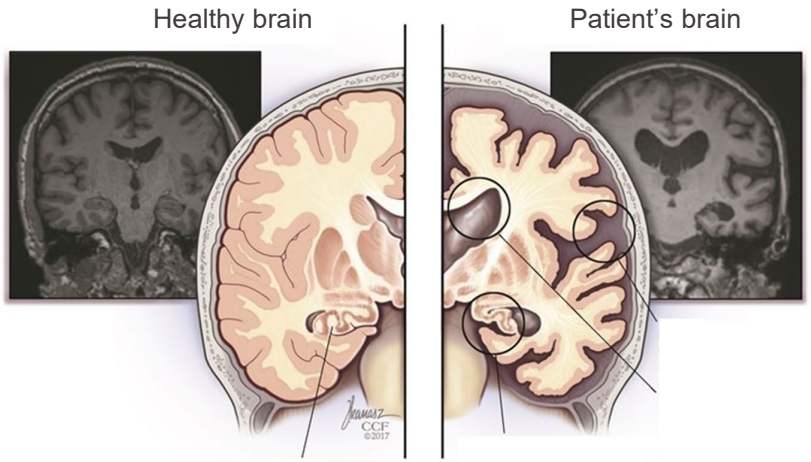
No disease modifying therapies to prevent, slow down or halt PD

How to read a scientific paper efficiently?

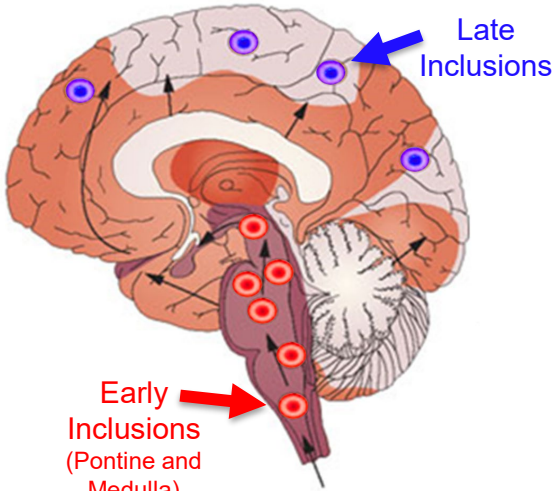
Understand the context

Main features of the neurodegenerative diseases (NDD) or the prion-like hypothesis

2. Neuronal loss in the brain

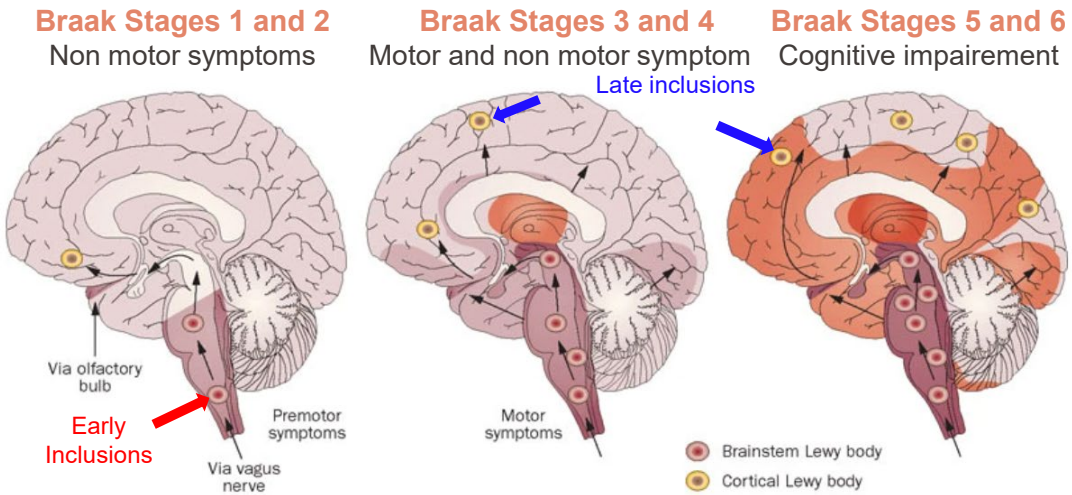


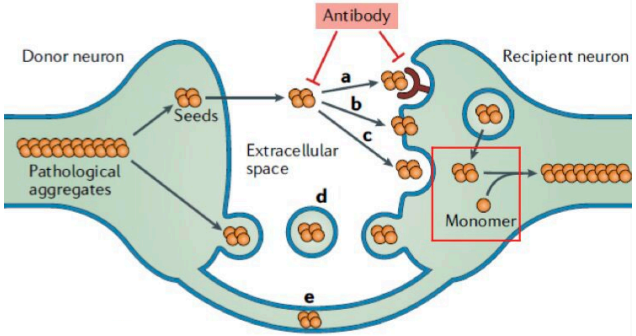
1. Inclusions Spread Throughout the Brain



Modified from: Halliday, G. *et al*, 2011

How to read a scientific paper efficiently?
Understand the context





Peng et al, 2020

How to read a scientific paper efficiently?
Understand the context

The Importance of identifying receptors in the development of drug therapies for α-Synuclein pathology

1.Key to understanding disease mechanisms:
Finding the receptor responsible for α-synuclein (aSyn) transmission between cells is critical for unraveling the mechanisms driving neurodegenerative diseases, such as Parkinson's.

2.Targeted drug development:
Identifying this receptor allows the design of therapies that can block or modify the cell-to-cell spread of aSyn pathology, a process that exacerbates disease progression.

3.Innovative therapeutic approaches:
With a clear receptor target, researchers can focus on developing precision drugs that can inhibit aSyn aggregation and propagation, potentially slowing or halting disease progression.

4.Potential for disease modulation:
Therapeutics targeting this receptor could transform how we treat aSyn-related disorders by addressing one of the root causes rather than just managing symptoms.

Pinpointing the receptor mediating aSyn transmission represents a pivotal breakthrough in developing disease-modifying therapies that could revolutionize treatment for neurodegenerative diseases.

How to read a scientific paper efficiently?

Paper 1: Pathological aSyn transmission initiated by binding LAG3

Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3

Xiaobo Mao, Michael Tianhao Ou, Senthilkumar S. Karuppagounder, Tae-In Kam, Xiling Yin, Yulan Xiong, Preston Ge, George Essien Umanah, Saurav Brahmachari, Joo-Ho Shin, Ho Chul Kang, Jianmin Zhang, Jinchong Xu, Rong Chen, Hyejin Park, Shaida A. Andrabi, Sung Ung Kang, Rafaella Araújo Gonçalves, Yu Liang, Shu Zhang, Chen Qi, Sharon Lam, James A. Keiler, Joel Tyson, Donghoon Kim, Nikhil Panicker, Seung Pil Yun, Creg J. Workman, Dario A. A. Vignali, Valina L. Dawson,* Han Seok Ko,* Ted M. Dawson*

Title	Authors (1st and Last)	Keywords	Rationale	Methods	Main results	Key Figures	Conclusions	What's next ?	Key Figures	Others comments

- Keywords:
  Parkinson's disease; alpha-synuclein; LAG3; receptor; internalization; transmission; spreading; brain

- Methods:
  Cellular and in vivo models:
  mammalian cells (SH-SY5Y), primary neurons (cortical), in vivo mice model
  Read-out:
  immunocytochemistry/immunohistochemistry, confocal microscopy (imaging), Western Blot (biochemistry), ELISA, IP

How to read a scientific paper efficiently?

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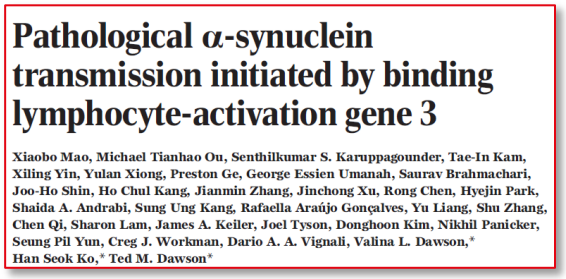

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Title	Authors (1st and Last)	Keywords	Rationale	Methods	Main results	Key Figures	Conclusions	What's next ?	Key Figures	Others comments

- **Rationale:**

  The rationale of this paper is to explore the mechanisms by which pathologic alpha-synuclein spreads between cells in the brain of Parkinson's disease patients, potentially driving the disease's progression. Understanding the mechanisms of pathologic alpha-synuclein transmission is crucial because it could reveal key processes driving the progression of Parkinson's disease, potentially leading to the development of targeted therapies that could slow or stop the disease's advancement by interrupting these transmission pathways.

- **Main results and key Figures:**

  - Pathological alpha-synuclein binds to the lymphocyte-activation gene 3 (LAG3) receptor on neurons (Fig 1).
  - This binding promotes the internalization (Fig 2) and cell-to-cell transmission of alpha-synuclein aggregates (Fig 4).
  - The spread of alpha-synuclein aggregates is implicated in the progression of Parkinson's disease (Fig 5 and 6).

How to read a scientific paper efficiently?

Paper 1: Pathological aSyn transmission initiated by binding LAG3

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Title	Authors (1st and Last)	Keywords	Rationale	Methods	Main results	Key Figures	Conclusions	What's next ?	Key Figures	Others comments

- **Conclusions:**

  - Targeting LAG3 may offer a potential therapeutic strategy to slow or prevent the spread of alpha-synuclein and, consequently, Parkinson's disease progression.

- **What's next ?:**

  - Test or develop pharmaceutical compounds that block LAG3

How to read a scientific paper efficiently?

Paper 2: LAG3 is not expressed in human and murin neurons and does not modulate synucleinopathies

LAG3 is not expressed in human and murine neurons and does not modulate α-synucleinopathies

Marc Emmenegger[1,†], Elena De Cecco[1,†], Marian Hruska-Plochan[2,†], Timo Eninger[3,4], Matthias M Schneider[5], Melanie Barth[3,4], Elena Tantardini[2], Pierre de Rossi[2], Mehtap Bacioglu[3,4], Rebekah G Langston[6], Alice Kaganovich[6], Nora Bengoa-Vergniory[7], Andrès Gonzalez-Guerra[1], Merve Avar[1], Daniel Heinzer[1], Regina Reimann[1], Lisa M Häsler[3,4], Therese W Herling[5], Naunehal S Matharu[5], Natalie Landeck[6], Kelvin Luk[8], Ronald Melki[9], Philipp J Kahle[3,10], Simone Hornemann[1], Tuomas P J Knowles[5,11], Mark R Cookson[6], Magdalini Polymenidou[2], Mathias Jucker[3,4] & Adriano Aguzzi[1,*]

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- **Keywords:**
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- **Methods:**
  Cellular and in vivo models:
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  Read-out:
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How to read a scientific paper efficiently?

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Title	Authors (1st and Last)	Keywords	Rationale	Methods	Main results	Key Figures	Conclusions	What's next ?	Key Figures	Others comments

- **Rationale:**

The rationale of this paper is to investigate the expression of LAG3 in human and murine neurons and to assess its potential role in modulating alpha-synucleinopathies. The study aims to clarify whether LAG3 is involved in the transmission and progression of alpha-synuclein-related neurodegenerative processes, such as those seen in Parkinson's disease, challenging previous findings that suggested LAG3 plays a significant role in these diseases.

- **Main results and key Figures:**

- LAG3 is not detected in human or mouse neurons (Fig.1 and 2)
- Deleting or blocking LAG3 in mouse models does not affect the spread or pathology of aSyn aggregates (Fig 4 and 5).
- LAG3 does not contribute to the development or progression of alpha-synucleinopathies, including Parkinson's disease, in experimental models (Fig 4 and 5).

How to read a scientific paper efficiently?

Paper 2: LAG3 is not expressed in human and murin neurons and does not modulate synucleinopathies

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Title	Authors (1st and Last)	Keywords	Rationale	Methods	Main results	Key Figures	Conclusions	What's next ?	Key Figures	Others comments

- **Conclusions:**

- The study concludes that LAG3 is not expressed in human or mouse neurons and does not play a role in the transmission or pathology of alpha-synuclein in neurodegenerative diseases.
- Previous findings suggesting that LAG3 facilitates the spread of alpha-synuclein are not supported by the current data.
- The role of LAG3 in alpha-synucleinopathies is likely minimal or nonexistent, indicating that LAG3 is not a viable therapeutic target for treating aSyn-related neurodegenerative diseases.

- **What's next ?:**

- Further research is needed to identify the actual mechanisms and receptors involved in the spread of alpha-synuclein pathology.

How to read a scientific paper (efficiently) ?

Engage in critical thinking – always try to be constructive

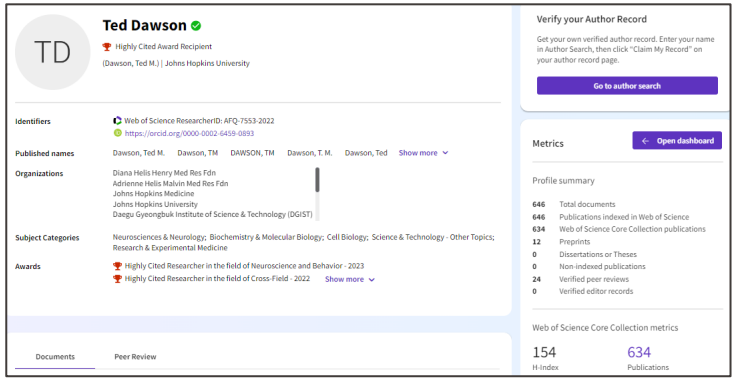
Who is right ? Who is wrong ?

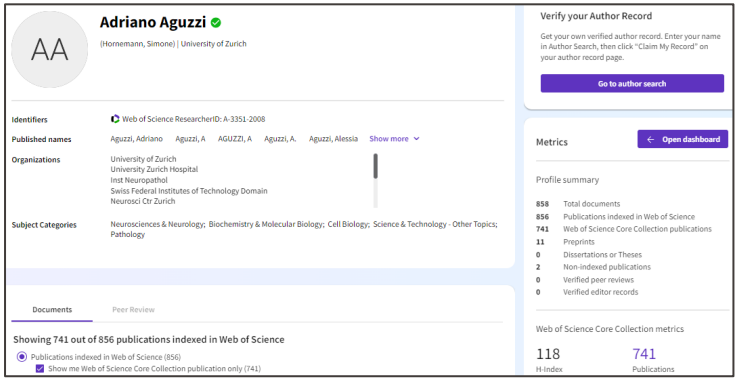
How to read a scientific paper (efficiently) ?

Engage in critical thinking – always try to be constructive

- **Study design and methodology, statistical significance and effect size :** Evaluate the robustness of each study's design, sample size, controls, and statistical analysis.
- **Quality of evidence:** Evaluate the overall quality and consistency of the evidence presented.
- **Biological plausibility:** Assess whether the findings align with current scientific understanding and known mechanisms.
- **Journal and author credibility:** Consider the reputation of the journals and expertise of the (last) authors.

https://www.webofscience.com/wos/woscc/basic-search





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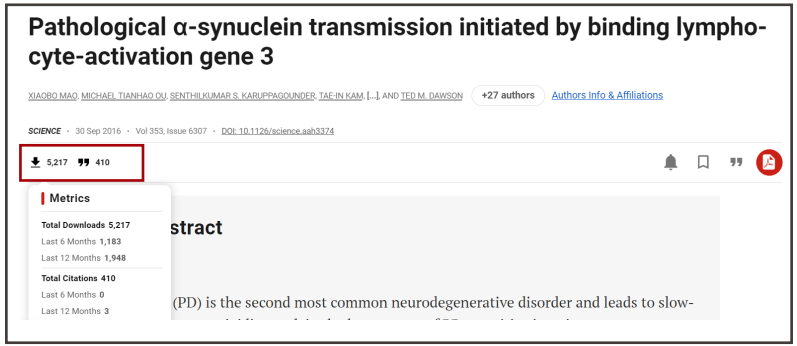

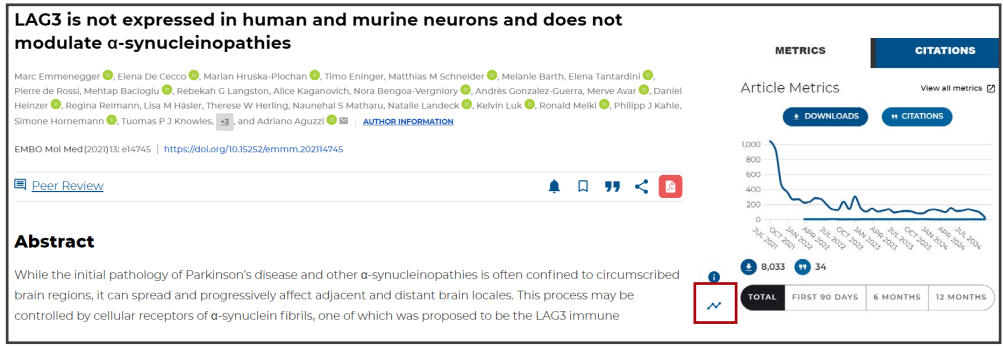

How to read a scientific paper (efficiently) ?

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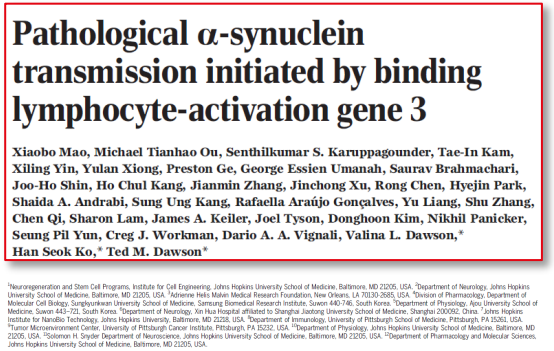
- **Biological plausibility:** Assess whether the findings align with current scientific understanding and known mechanisms.
- **Journal and author credibility:** Consider the reputation of the journals and expertise of the authors.
- **Conflicts of interest:** Identify any potential biases from funding sources or affiliations (check this section in the paper).
- **Reproducibility:** Check if findings have been independently replicated by other studies.
- **Community consensus:** Consider expert opinions and the overall consensus in the scientific community.
- **Follow-up research:** Look for further studies that clarify or resolve conflicting findings.

How to read a scientific paper (efficiently) ?

Engage in critical thinking – reproducibility across independent studies



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LAG3 is not expressed in human and murine neurons and does not modulate α-synucleinopathies

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1 Institute of Neuropathology, University of Zurich, Zurich, Switzerland
2 Department of Quantitative Biomedicine, University of Zurich, Zurich, Switzerland
3 German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany
4 Department of Cellular Neurology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
5 Yusuf Hamied Department of Chemistry, Centre for Misfolding Diseases, University of Cambridge, Cambridge, UK
6 Cell Biology and Gene Expression Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, MD, USA
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8 Department of Pathology and Laboratory Medicine and Center for Neurodegenerative Disease Research, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
9 Laboratory of Neurodegenerative Diseases, CNRS, Institut François Jacob (MIRCen), CEA, Fontenay-aux-Roses, France
10 Department of Neurodegeneration, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany
11 Cavendish Laboratory, Department of Physics, University of Cambridge, Cambridge, UK
*Corresponding author. Tel: +41 44 255 21 07; E-mail: adriano.aguzzi@usz.ch
†These authors contributed equally to this work

Studies gain more power and credibility when a **consortium of independent laboratories** from **different locations** around the world replicate the same findings. This approach, known as **translational validation**, ensures that results are not specific to one lab's conditions, techniques, or biases, but rather reflect a more universal scientific truth.

By confirming findings across various settings and labs, the scientific community can be more confident in the **robustness** and applicability of the results. Additionally, global collaboration can pool resources, expertise, and unique perspectives, further enhancing the **quality and impact of research**.

How to read a scientific paper (efficiently) ?

Engage in critical thinking – Community consensus

Search online to see if there is any debate, or published response/review regarding studies with opposing findings.

In general
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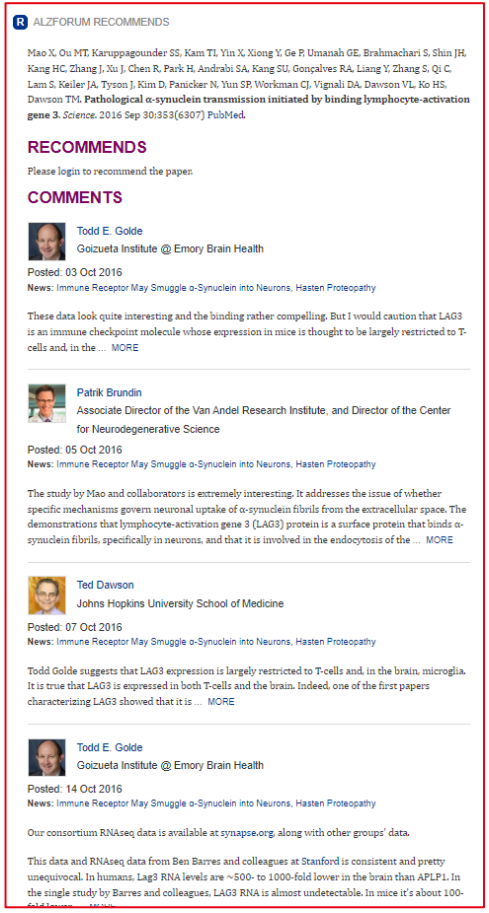
For the neurodegenerative diseases field of research:

https://www.alzforum.org/



ALZFORUM RECOMMENDS

Mao X, Ou MT, Karuppagounder SS, Kam TI, Yin X, Xiong Y, Ge P, Umanah GE, Brahmachari S, Shin JH, Kang HC, Zhang J, Xu J, Chen R, Park H, Andrabi SA, Kang SU, Gonçalves RA, Liang Y, Zhang S, Qi C, Lam S, Keiler JA, Tyson J, Kim D, Panicker N, Yun SP, Workman CJ, Vignali DA, Dawson VL, Ko HS, Dawson TM. **Pathological α-synuclein transmission initiated by binding lymphocyte-activation gene 3.** *Science.* 2016 Sep 30;353(6307) PubMed.

RECOMMENDS

Please login to recommend the paper.

COMMENTS

Todd E. Golde
Goizueta Institute @ Emory Brain Health
Posted: 03 Oct 2016
News: Immune Receptor May Smuggle α-Synuclein into Neurons, Hasten Proteopathy

These data look quite interesting and the binding rather compelling. But I would caution that LAG3 is an immune checkpoint molecule whose expression in mice is thought to be largely restricted to T-cells and, in the ... MORE

Patrik Brundin
Associate Director of the Van Andel Research Institute, and Director of the Center for Neurodegenerative Science
Posted: 05 Oct 2016
News: Immune Receptor May Smuggle α-Synuclein into Neurons, Hasten Proteopathy

The study by Mao and collaborators is extremely interesting. It addresses the issue of whether specific mechanisms govern neuronal uptake of α-synuclein fibrils from the extracellular space. The demonstrations that lymphocyte-activation gene 3 (LAG3) protein is a surface protein that binds α-synuclein fibrils, specifically in neurons, and that it is involved in the endocytosis of the ... MORE

Ted Dawson
Johns Hopkins University School of Medicine
Posted: 07 Oct 2016
News: Immune Receptor May Smuggle α-Synuclein into Neurons, Hasten Proteopathy

Todd Golde suggests that LAG3 expression is largely restricted to T-cells and, in the brain, microglia. It is true that LAG3 is expressed in both T-cells and the brain. Indeed, one of the first papers characterizing LAG3 showed that it is ... MORE

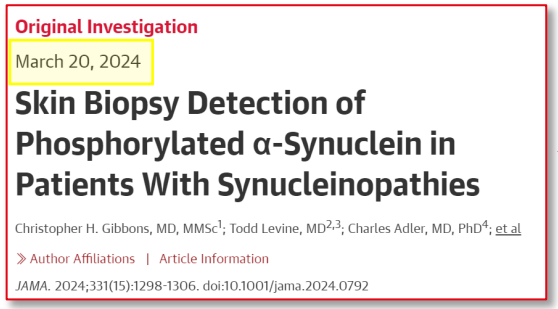
Todd E. Golde
Goizueta Institute @ Emory Brain Health
Posted: 14 Oct 2016
News: Immune Receptor May Smuggle α-Synuclein into Neurons, Hasten Proteopathy

Our consortium RNAseq data is available at synapse.org, along with other groups' data.

This data and RNAseq data from Ben Barres and colleagues at Stanford is consistent and pretty unequivocal. In humans, Lag3 RNA levels are ~500- to 1000-fold lower in the brain than APLP1. In the single study by Barres and colleagues, LAG3 RNA is almost undetectable. In mice it's about 100-

How to read a scientific paper (efficiently) ?

Engage in critical thinking – Community consensus



Original Investigation

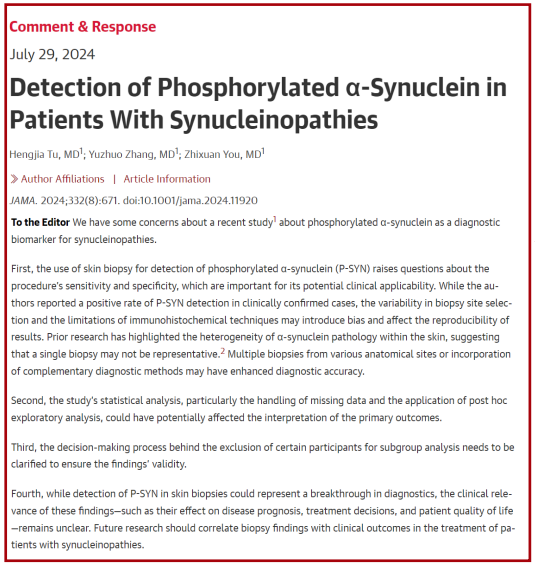
March 20, 2024

Skin Biopsy Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies

Christopher H. Gibbons, MD, MMSc[1]; Todd Levine, MD[2,3]; Charles Adler, MD, PhD[4]; et al

Author Affiliations | Article Information

JAMA. 2024;331(15):1298-1306. doi:10.1001/jama.2024.0792



Comment & Response

July 29, 2024

Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies

Hengjia Tu, MD[1]; Yuzhuo Zhang, MD[1]; Zhixuan You, MD[1]

Author Affiliations | Article Information

JAMA. 2024;332(8):671. doi:10.1001/jama.2024.11920

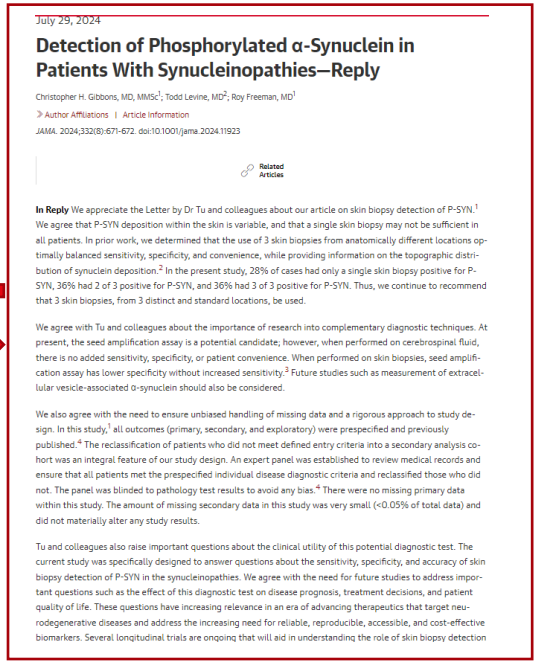
To the Editor We have some concerns about a recent study[1] about phosphorylated α-synuclein as a diagnostic biomarker for synucleinopathies.

First, the use of skin biopsy for detection of phosphorylated α-synuclein (P-SYN) raises questions about the procedure's sensitivity and specificity, which are important for its potential clinical applicability. While the authors reported a positive rate of P-SYN detection in clinically confirmed cases, the variability in biopsy site selection and the limitations of immunohistochemical techniques may introduce bias and affect the reproducibility of results. Prior research has highlighted the heterogeneity of α-synuclein pathology within the skin, suggesting that a single biopsy may not be representative.[2] Multiple biopsies from various anatomical sites or incorporation of complementary diagnostic methods may have enhanced diagnostic accuracy.

Second, the study's statistical analysis, particularly the handling of missing data and the application of post hoc exploratory analysis, could have potentially affected the interpretation of the primary outcomes.

Third, the decision-making process behind the exclusion of certain participants for subgroup analysis needs to be clarified to ensure the findings' validity.

Fourth, while detection of P-SYN in skin biopsies could represent a breakthrough in diagnostics, the clinical relevance of these findings—such as their effect on disease prognosis, treatment decisions, and patient quality of life—remains unclear. Future research should correlate biopsy findings with clinical outcomes in the treatment of patients with synucleinopathies.



July 29, 2024

Detection of Phosphorylated α-Synuclein in Patients With Synucleinopathies—Reply

Christopher H. Gibbons, MD, MMSc[1]; Todd Levine, MD[2]; Roy Freeman, MD[1]

Author Affiliations | Article Information

JAMA. 2024;332(8):671-672. doi:10.1001/jama.2024.11923

Related Articles

In Reply We appreciate the Letter by Dr Tu and colleagues about our article on skin biopsy detection of P-SYN.[1] We agree that P-SYN deposition within the skin is variable, and that a single skin biopsy may not be sufficient in all patients. In prior work, we determined that the use of 3 skin biopsies from anatomically different locations optimally balanced sensitivity, specificity, and convenience, while providing information on the topographic distribution of synuclein deposition.[2] In the present study, 28% of cases had only a single skin biopsy positive for P-SYN, 36% had 2 of 3 positive for P-SYN, and 36% had 3 of 3 positive for P-SYN. Thus, we continue to recommend that 3 skin biopsies, from 3 distinct and standard locations, be used.

We agree with Tu and colleagues about the importance of research into complementary diagnostic techniques. At present, the seed amplification assay is a potential candidate; however, when performed on cerebrospinal fluid, there is no added sensitivity, specificity, or patient convenience. When performed on skin biopsies, seed amplification assay has lower specificity without increased sensitivity.[3] Future studies such as measurement of extracellular vesicle-associated α-synuclein should also be considered.

We also agree with the need to ensure unbiased handling of missing data and a rigorous approach to study design. In this study,[1] all outcomes (primary, secondary, and exploratory) were prespecified and previously published.[4] The reclassification of patients who did not meet defined entry criteria into a secondary analysis cohort was an integral feature of our study design. An expert panel was established to review medical records and ensure that all patients met the prespecified individual disease diagnostic criteria and reclassified those who did not. The panel was blinded to pathology test results to avoid any bias.[4] There were no missing primary data within this study. The amount of missing secondary data in this study was very small (<0.05% of total data) and did not materially alter any study results.

Tu and colleagues also raise important questions about the clinical utility of this potential diagnostic test. The current study was specifically designed to answer questions about the sensitivity, specificity, and accuracy of skin biopsy detection of P-SYN in the synucleinopathies. We agree with the need for future studies to address important questions such as the effect of this diagnostic test on disease prognosis, treatment decisions, and patient quality of life. These questions have increasing relevance in an era of advancing therapeutics that target neurodegenerative diseases and address the increasing need for reliable, reproducible, accessible, and cost-effective biomarkers. Several longitudinal trials are ongoing that will aid in understanding the role of skin biopsy detection

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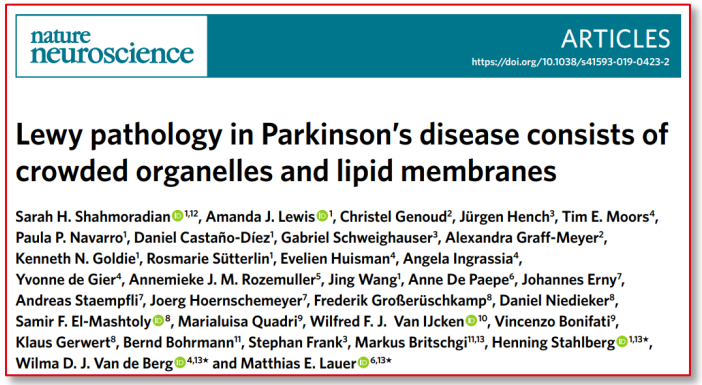


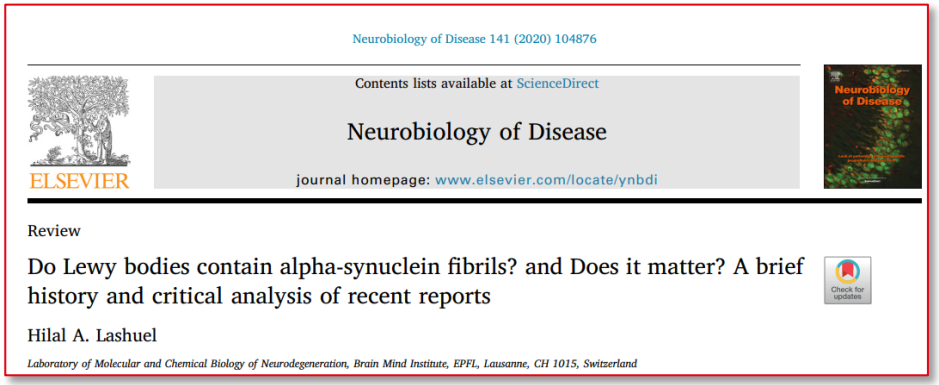
nature neuroscience

ARTICLES

https://doi.org/10.1038/s41593-019-0423-2

Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes

Sarah H. Shahmoradian[1,12], Amanda J. Lewis[1], Christel Genoud[2], Jürgen Hench[3], Tim E. Moors[4], Paula P. Navarro[1], Daniel Castaño-Díez[1], Gabriel Schweighauser[3], Alexandra Graff-Meyer[2], Kenneth N. Goldie[1], Rosmarie Sütterlin[1], Evelien Huisman[4], Angela Ingrassia[4], Yvonne de Gier[4], Annemieke J. M. Rozemuller[5], Jing Wang[1], Anne De Paepe[6], Johannes Erny[7], Andreas Staempfli[7], Joerg Hoernschemeyer[7], Frederik Großerüschkamp[8], Daniel Niedieker[8], Samir F. El-Mashtoly[8], Marialuisa Quadri[9], Wilfred F. J. Van IJcken[10], Vincenzo Bonifati[9], Klaus Gerwert[8], Bernd Bohrmann[11], Stephan Frank[3], Markus Britschgi[11,13], Henning Stahlberg[1,13]*, Wilma D. J. Van de Berg[4,13]* and Matthias E. Lauer[6,13]*



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Review

Do Lewy bodies contain alpha-synuclein fibrils? and Does it matter? A brief history and critical analysis of recent reports

Hilal A. Lashuel

Laboratory of Molecular and Chemical Biology of Neurodegeneration, Brain Mind Institute, EPFL, Lausanne, CH 1015, Switzerland

- **Study design and methodology**
- **Quality of evidence**
- **Journal and author credibility:** Consider the reputation of the journals and expertise of the authors.
- **Conflicts of interest:** Identify any potential biases from funding sources or affiliations (check this section in the paper)
- **Biological plausibility:** Assess whether the findings align with current scientific understanding and known mechanisms.
- **Reproducibility:** Check if findings have been independently replicated by other studies.
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Engage in critical thinking – author credibility

Thomas Südhof

Südhof in 2024

Born	Thomas Christian Südhof December 22, 1955 (age 68) Göttingen, Germany
Nationality	German American[3][4]
Alma mater	RWTH Aachen University University of Göttingen (PhD)
Known for	Presynaptic Neuron Synaptic Transmission
Spouse	Lu Chen
Awards	Lasker Award (2013) Nobel Prize (2013)

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Neurexin-2: An inhibitory neurexin that restricts excitatory synapse formation in the hippocampus

Pei-Yi Lin, Lulu Y. Chen, Man Jiang, Justin H. Trotter, Erica Seigneur, Thomas C. Südhof

Author response

Science Advances (2023) — 12 comments

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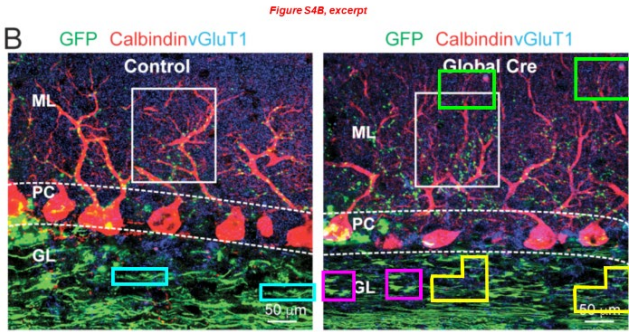
Conditional Deletion of All Neurexins Defines Diversity of Essential Synaptic Organizer Functions for Neurexins

Lulu Y. Chen, Man Jiang, Bo Zhang, Ozgun Gokce, Thomas C. Südhof

Author response

Neuron (2017) — 67 comments



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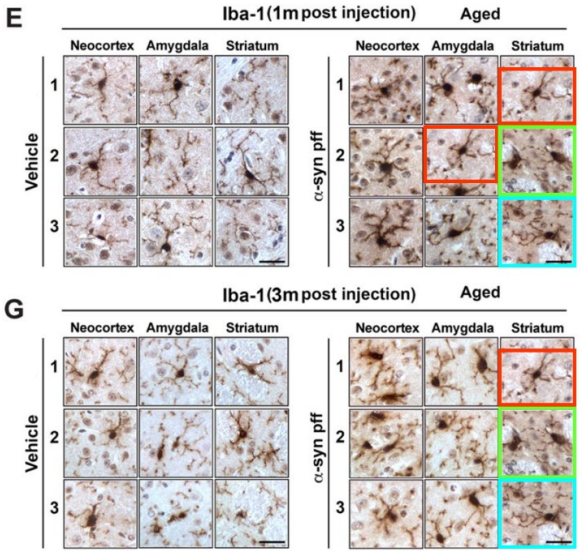

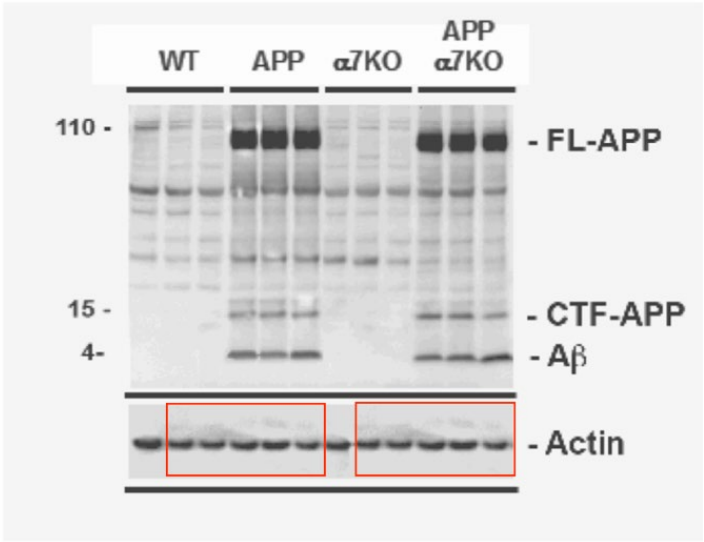

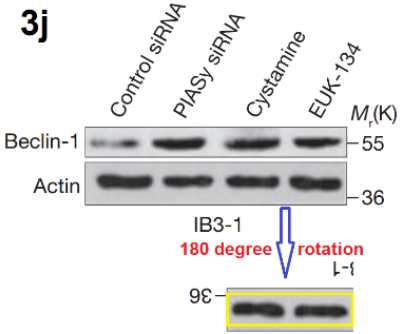

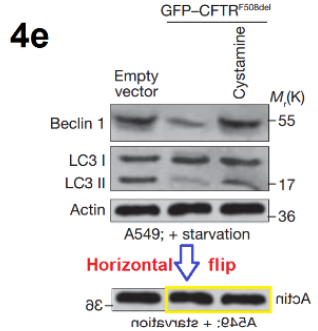

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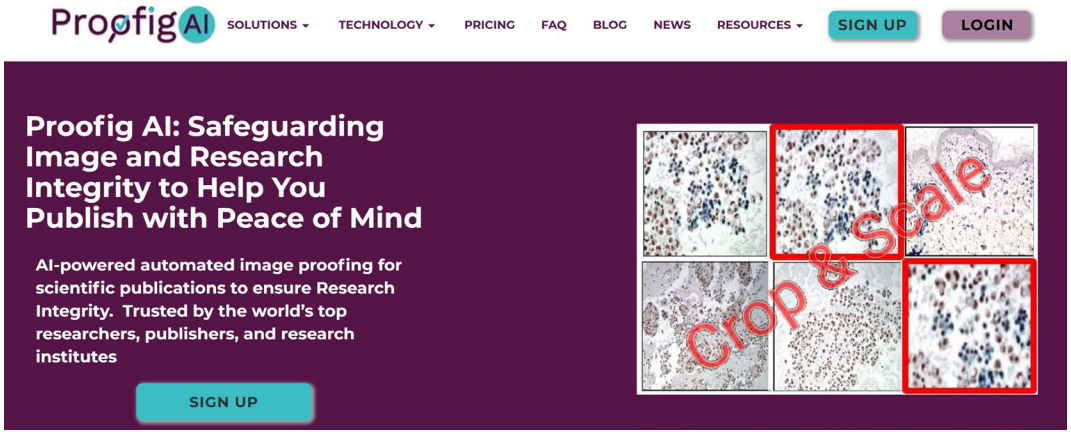

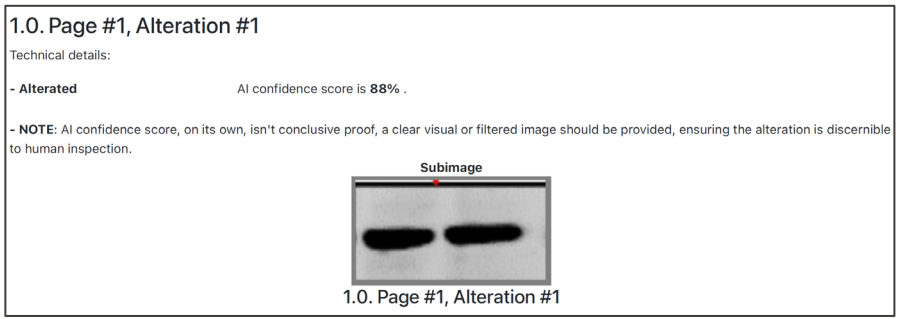

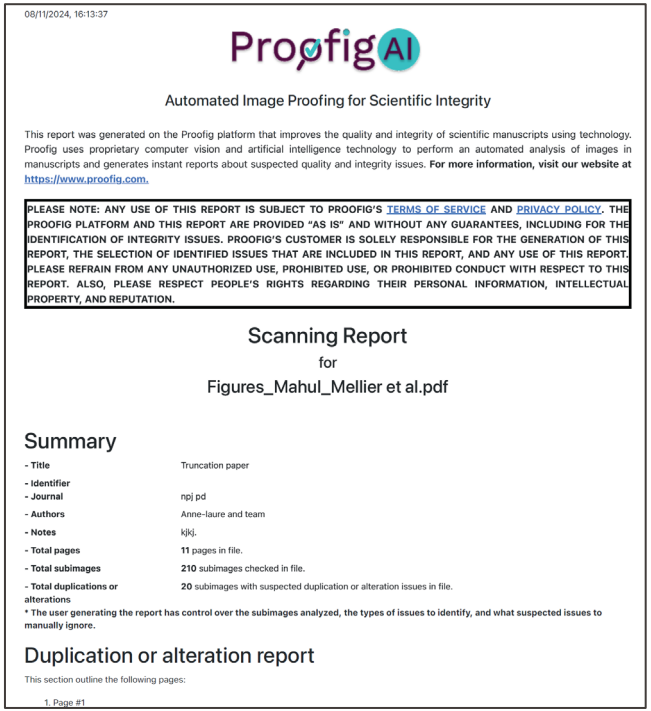

How to read a scientific paper efficiently?

Any questions ?

Organisation of the groups for the Q/A session

22/22	Name First Name	Section	e-Mail	Semester of registration	Group
1	Aktas **Mesra**	CGC_ING	feriha.aktas@epfl.ch	Master semester 1	Group 1
2	Belgharbia **Emna**	CGC_ING	emna.belgharbia@epfl.ch	Master semester 1	Group 1
3	Bernard **Manon**	SIE	manon.bernard@epfl.ch	Master semester 3	Group 1
4	Blaga **Alexandre**	GM	alexandre.blaga@epfl.ch	Master semester 3	Group 1
5	Bonaldi **Pietro**	CGC_ING	pietro.bonaldi@epfl.ch	Master semester 1	Group 1
6	Chapi-Nitcheu **Cassandra**	SV_ECH	josee.chapi-nitcheu@epfl.ch	Autumn semester	Group 2
7	Díaz Hernández **Desireé**	CGC_ING	karina.diazhernandez@epfl.ch	Master semester 1	Group 2
8	Hamouni **Inès**	CGC_ING	ines.hamouni@epfl.ch	Master semester 1	Group 2
9	Hendrata **Jessica**	CGC_ECH	jessica.hendrata@epfl.ch	Autumn semester	Group 2
10	Idris **Mubarak**	EDBB	mubarak.idris@epfl.ch		Group 2
11	Kohany **Alanna**	CGC_ECH	alanna.kohany@epfl.ch	Autumn semester	Group 2
12	Maillard **Emilie**	SIE	emilie.maillard@epfl.ch	Master semester 1	Group 3
13	Nijm **Michael**	MT_ECH	michael.nijm@epfl.ch	Autumn semester	Group 3
14	Pachebat **Grégoire**	SV	gregoire.pachebat@epfl.ch	Master semester 3	Group 3
15	Pang **Jia**	CGC_ECH	jia.pang@epfl.ch	Autumn semester	Group 3
16	Pechorina **Dina**	ECH_MTE	dina.pechorina@epfl.ch	Autumn semester	Group 3
17	Praat **Lara**	CGC_ECH	lara.praat@epfl.ch	Autumn semester	Group 3
18	Sonnenhol **Julia**	CGC_ECH	julia.sonnenhol@epfl.ch	Autumn semester	Group 4
19	Tee **Jie**	CGC_ECH	jie.tee@epfl.ch	Autumn semester	Group 4
20	Trigon-Pacalet **Alice**	SV	alice.trigon-pacalet@epfl.ch	Master semester 1	Group 4
21	Uluç **Irem**	SV	irem.uluc@epfl.ch	Master semester 1	Group 4
22	Widén **Gustav**	MT_ECH	gustav.widen@epfl.ch	Autumn semester	Group 4

Organisation of the groups for the assignments

	23/09	30/09	7/10	14/10	21/10	28/10	4/11	11/11	18/11	25/11
	Sanna Fowler	Sébastien Nusslé	Eduardo Moraud	Juliane Da Garca	FALL BREAK	Elpida Tsika	Gregory Servotte	Madiha Derouazi	Carole Estoppey	Bernard Schneider
	Lonza	genknowme	Unil/CHUV	EPFL		AcImmune	Edwards Life siences	Acimmune	Nestlé	PTBTG
	Pharma	Start-up	Academia	Academia		BioTech	Pharma	Pharma	Industry	Academia
	https://www.lonza.com	https://genknowme.com	http://emmoraud.net/	https://www.epfl.ch/labs/dangelo-lab/		https://www.acimmune.com/	https://www.edwards.com/fr	https://www.acimmune.com	https://www.nestle.com/	https://www.epfl.ch/research/facilities/gene-therapy
Lecture assignement Groups for the Q/A session	Group 1	Group 2	Group 3	Group 4		Group 1	Group 2	Group 3	Group 4	No assignment Time will be allocated to the semester project
Groups for the Q/A session	Group 3	Group 4	Group 1	Group 2		Group 3	Group 4	Group 1	Group 2	Volunteers (bonus)

Dr. Sanna Fowler, Lonza **Next week**

Head of Strategy, Innovation & Value Chain Management

Lonza Bioconjugates

SANNA

FOWLER

Translate bioconjugates discovery to the clinic

Education & Training

DOCTOR OF PHILOSOPHY

1998-2001
Immunology, Molecular and Cellular Science
University of Oxford, UK

POSTDOCTORAL RESEARCH FELLOW

2001-2002
Immunology Research
University of Oxford, UK

SENIOR SPONSORSHIP ACCOUNT MANAGER

2002-2010
Team Alinghi SA
Americas Cup Swiss sailing

DEPUTY DIRECTOR OF COMMUNICATIONS

2011 - 2014
EPFL - Lausanne - CH

DEPUTY DIRECTOR OF DEVELOPMENT

2014 - 2017
EPFL - Lausanne - CH

EXECUTIVE DIRECTOR, HEAD OF DIVISIONAL PROJECTS

2021 - 2023
Lonza
Basel - Switzerland

HEAD OF STRATEGY, INNOVATION & VALUE CHAIN MANAGEMENT

2023 - Present
Lonza
Basel - Switzerland

Profile

Sanna Fowler is currently Head of Strategy and Innovation for Lonza's bioconjugates unit and focuses on future growth through technology and manufacturing capacity. Her goal is to support small biotech and large pharma companies translate bioconjugate discovery into the clinic and to ensure development and manufacturing keep up with the demand for innovative medicines.

Articles

CTLA-4 expression on antigen-specific cells but not IL-10 secretion is required for oral tolerance

Press

EURAXESS Researchers in motion Interview with Dr Sanna Fowler: A passionate person about Science

@ SannaFowler
linkedin.com/in/sannafowler
sanna.fowler@gmail.com

Q/A session

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5	Bonaldi **Pietro**	CGC_ING	pietro.bonaldi@epfl.ch	Master semester 1	Group 1