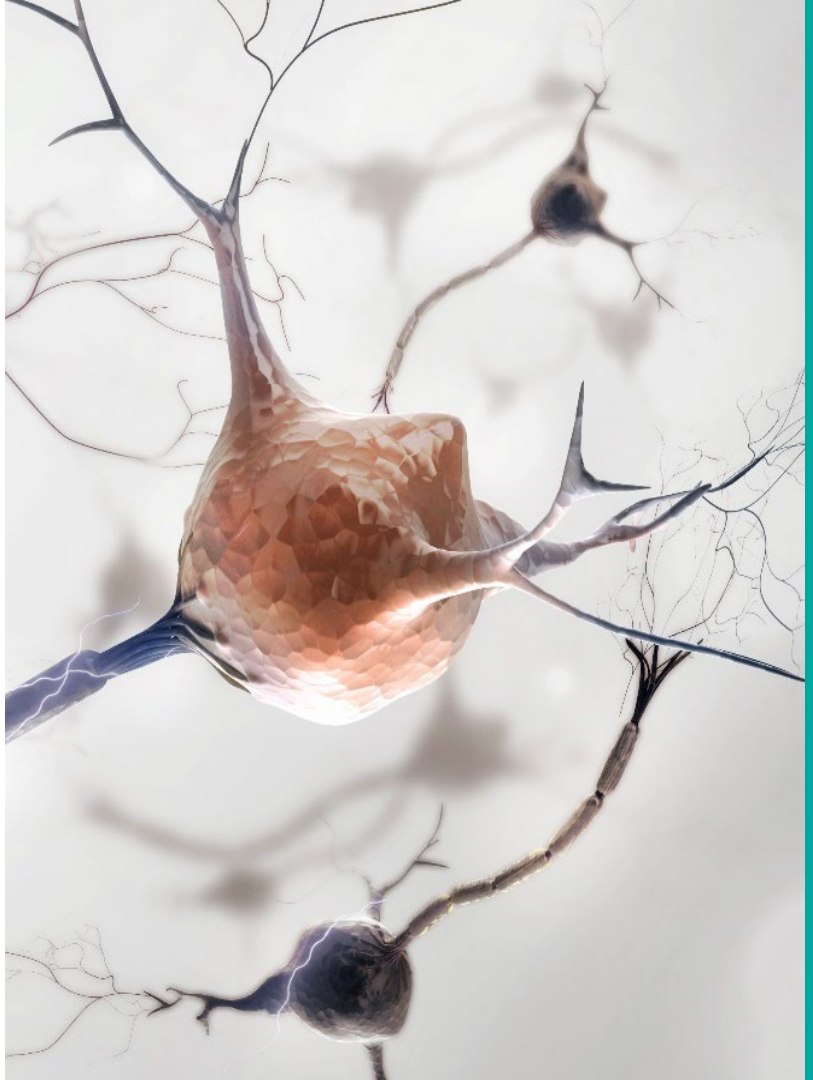


Publish or perish:

How the rush to publish risks misleading research and delays in cure discovery ?

Parkinson's disease by numbers

Prevalence: 10 millions patients *2024*

Cost: $60 billions annual

Prevalence worldwide

12-17 millions 2040

60% increase in the number of cases over 20 years

Prevalence: 15'000 patients *2007**

CHFs 1-2 billions annual

In Switzerland

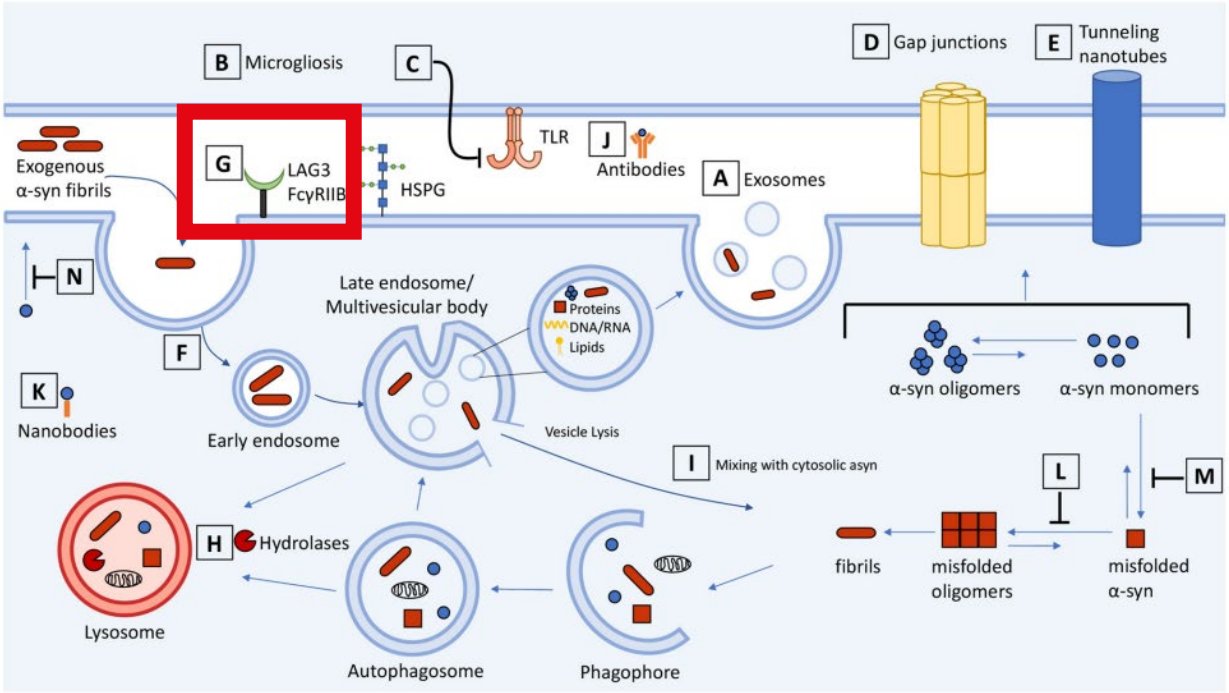
3'000 new cases/year

https://neurochirurgie.insel.ch/fr/maladies-traitees-specialites/neurochirurgie-fonctionnelle-et-douleur/maladie-de-parkinson

***No recent data for Switzerland**

- Prevalence : 0,2 à 0,3 % of the global population – estimation 15'000 < Swiss patients < *28'000 ?*

Cell-to-cell transmission, internalization, and trafficking of aSyn and therapeutic targets along the pathways



Menon et al., 2022

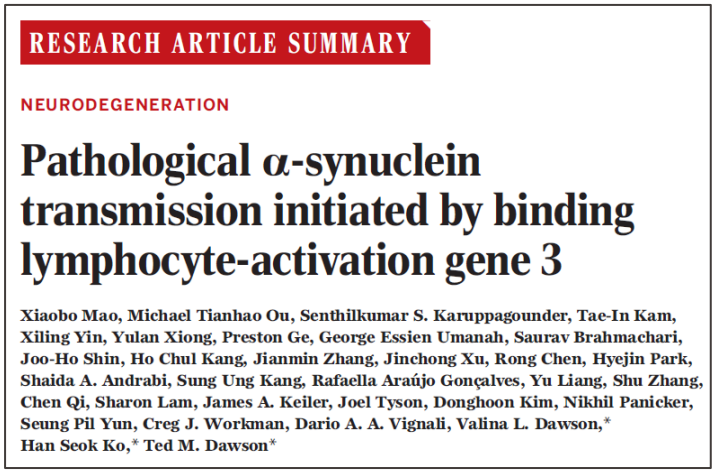
TABLE 1 | Therapeutic targets and drugs from **Figure 1**.

Target	Drugs
1) Inhibitors of microglial activation **Figure 1B**	Hypoestoxide Lenalidomide Candesartan cilexetil
2) Microglial toll-like receptor inhibitors **Figure 1C**	NPT520-34 CU-CPT22
3) Gap junction blockers **Figure 1D**	CBX Gap3211 Gap2409 Gap2605
4) Endocytosis inhibitors **Figure 1F**	Dynasore Sertraline
5) Autophagy and lysosome inducers **Figure 1H**	Rapamycin Metformin Trehalose Nilotinib KYP-2407 Ambroxol AR7
6) Misfolding inhibitors **Figures 1L,M**	NPT200-11 Clr01 EGCG Anle1386 Plant extracts and phytochemicals SynuClean-D Apigenin
7) Lipid-induced aggregation inhibitors **Figure 1N**	ENT-01 Trodusquenine NPT200-11

Learn how to engage in critical thinking:

Comparing two scientific papers that present contradictory conclusions on the same topic

1



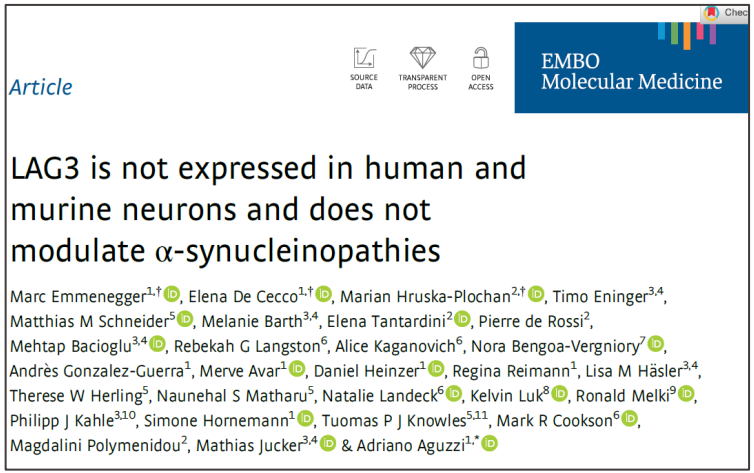
RESEARCH ARTICLE SUMMARY

NEURODEGENERATION

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*

2



Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

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,*]

PDFs are in the **Moodle Bio480/Folder « Impact of publication in therapeutic strategy »**

Carefully read both papers in the indicated order (1 then 2) and find the controversy and how this can impact therapeutic stretegies!

Learn how to engage in critical thinking: Tips and Hints

Comparing two scientific papers that present contradictory conclusions on the same topic

For each paper, identify and summarize the following components:

A. Identify key components:

- **Research question:** What question or problem is the paper trying to address?
- **Hypothesis:** What is the hypothesis or hypotheses stated in the paper?
- ***Methodology:*** *What methods were used to conduct the research? Consider sample size, experimental design, data collection methods, and any controls.*
- **Results:** What were the key findings of the study? Summarize the results briefly.
- **Conclusions:** What conclusions did the authors draw from their results?
- ***Strengths and weaknesses:*** *What are the strengths and weaknesses of each paper? Consider aspects such as sample size, methodological rigor, potential biases, and the validity of the conclusions.*

B. Compare and contrast:

- **Differences in methodology:** How do the methodologies differ between the two studies? How might these differences affect the results and conclusions?
- **Contradictory results:** What are the key points of contradiction between the results and conclusions of the two papers?
- **Evaluation of evidence:** Evaluate the evidence presented in each paper. Which paper do you find more convincing and why? Consider the reliability and validity of the data and the soundness of the arguments presented.
- **Bias and limitations:** Are there any apparent biases or limitations in either paper that could affect the results? Discuss any potential conflicts of interest, funding sources, or other factors that could introduce bias.

Learn how to engage in critical thinking: Tips and Hints

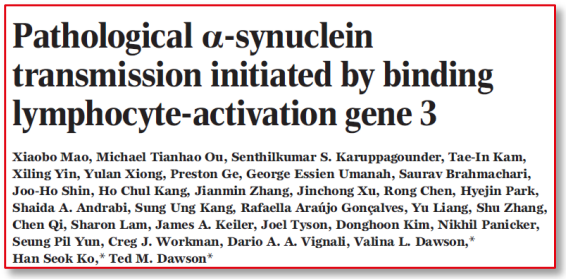
Comparing two scientific papers that present contradictory conclusions on the same topic

Title	Authors (1st and last)	Keywords	Methods	Main results	Conclusions	Key figures	Others comments

How to read a scientific paper efficiently?
Practical exercices

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

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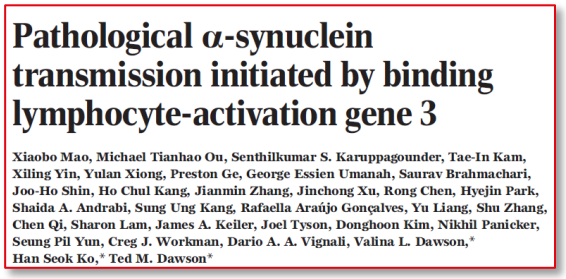

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Title	Authors (1st and Last)	Keywords	Rationale	Methods	Main results	Key Figures	Conclusions	What's next ?	Key Figures	Others comments

- **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?

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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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  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 ?

Implications for therapeutic strategies ? Hope for patients ?

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 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) ?

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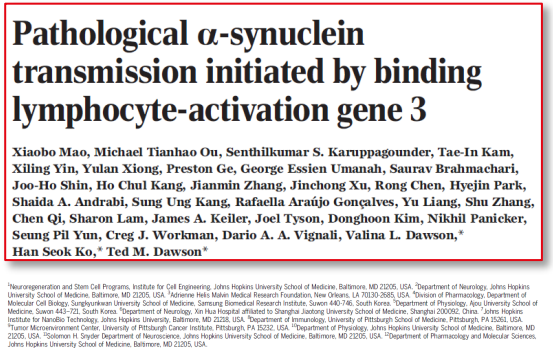
How to read a scientific paper (efficiently) ?

Engage in critical thinking – reproducibility across independent studies



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[1]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. [2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. [3]Adrienne Helis Malvin Medical Research Foundation, New Orleans, LA 70130-2685, USA. [4]Division of Pharmacology, Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Samsung Biomedical Research Institute, Suwon 440-746, South Korea. [5]Department of Physiology, Ajou University School of Medicine, Suwon 443-721, South Korea. [6]Department of Neurology, Xin Hua Hospital affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200092, China. [7]Johns Hopkins Institute for NanoBio Technology, Johns Hopkins University, Baltimore, MD 21218, USA. [8]Department of Immunology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15261, USA. [9]Tumor Microenvironment Center, University of Pittsburgh Cancer Institute, Pittsburgh, PA 15232, USA. [10]Department of Physiology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. [11]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. [12]Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA.

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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
7 Department of Physiology, Anatomy and Genetics, Oxford Parkinson's Disease Center (OPDC), Oxford University, Oxford, UK
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) ?

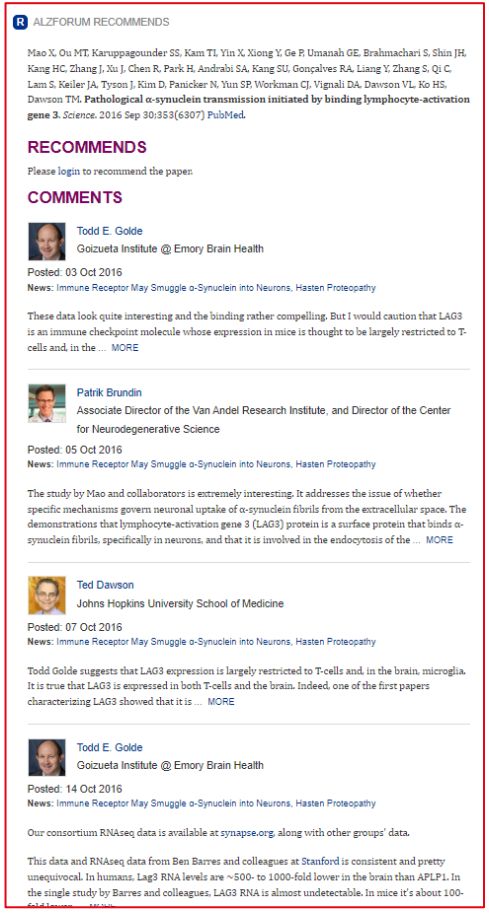
Engage in critical thinking – Community consensus

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

In general
Pubpeer
https://pubpeer.com/static/about

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

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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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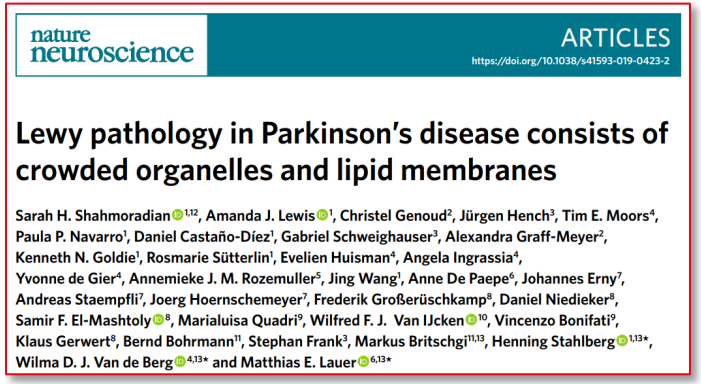

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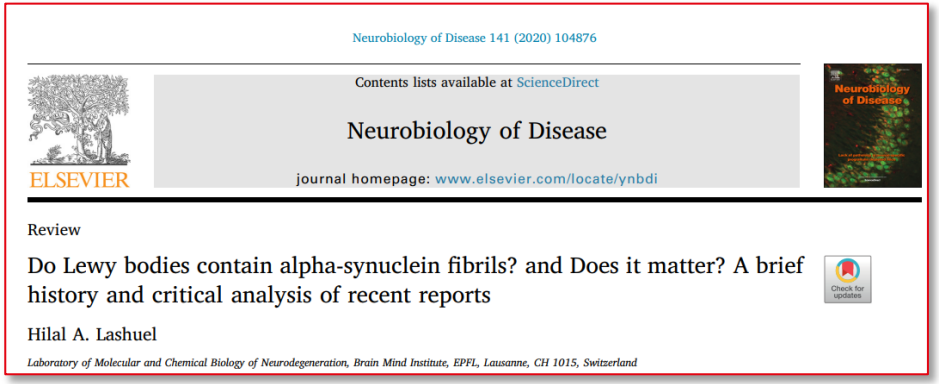

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Alma mater	RWTH Aachen University University of Göttingen (PhD)
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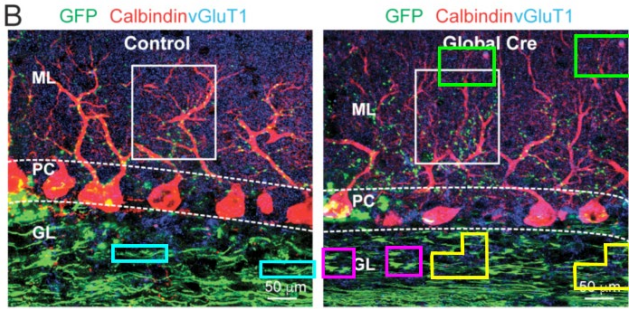

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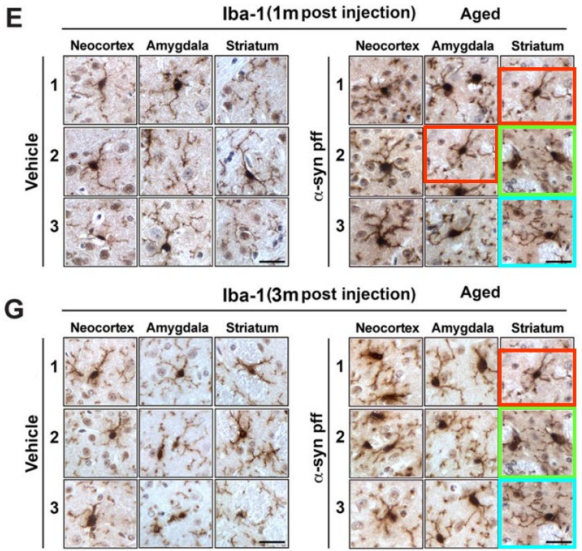

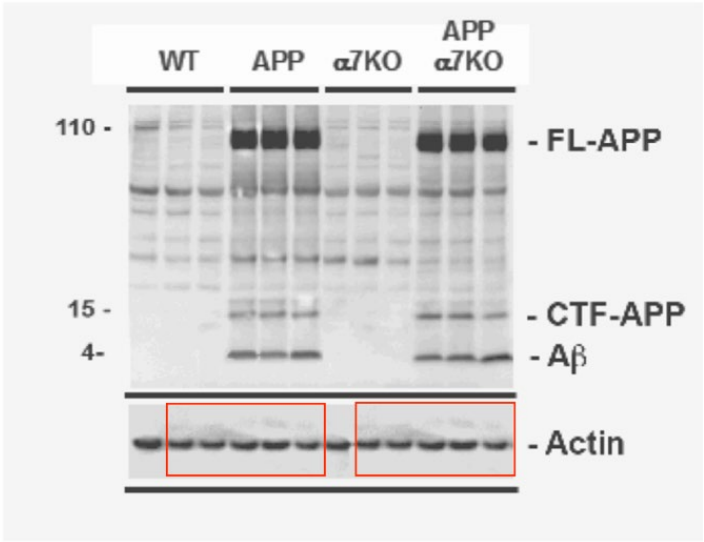

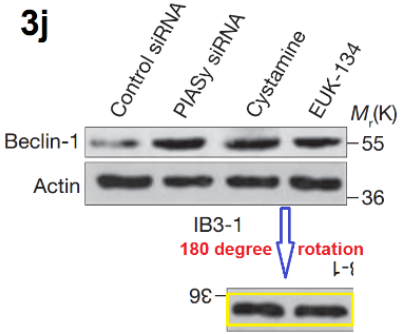

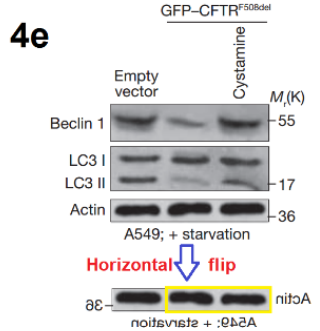

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