

F1000

Bringing Transparency to Peer Review

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18 March 2016



F1000

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F1000**Workspace**

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An open science publishing platform for life scientists that offers immediate publication and transparent peer review.

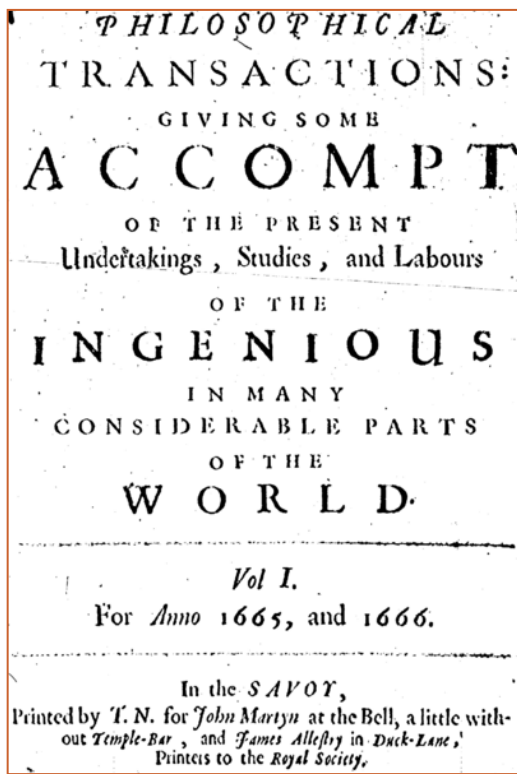
F1000**Research**

AGENDA

- Problems with traditional peer review
- New peer review models
- F1000Research's peer review model
- Challenges and benefits
- Future challenges and opportunities
- Summary Open peer review
- F1000Prime
- F1000Workspace

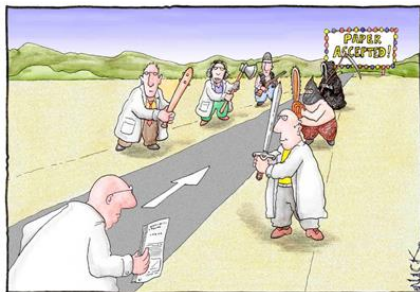
HISTORY OF PEER REVIEW

- First scientific journals were not peer reviewed.
- Peer review was introduced later, and developed as a method to select what is fit to print in limited available space.
- Journals as gatekeepers.
- Current popular system of peer review dates from mid-twentieth century.



PROBLEMS WITH TRADITIONAL PUBLISHING

- Extensive delays in publication
- Repeat refereeing of work for different journals
- Time and money wasted by authors restructuring manuscripts for different journals
- Anonymous pre-publication peer review conceals referee and editorial bias
- Lack of reproducibility of much published science
- Publication bias: much good science is never shared or published, e.g. negative/null results, small studies, replication studies



Most scientists regarded the new streamlined peer-review process as "quite an improvement."

TYPES OF PEER REVIEW

Time of review:

- Before publication:
 - Cascading review
 - Third-party review
- Post-publication peer review:



Transparency of review:

- Single-blind
- Double-blind
- Triple Blind
- Open peer review
 - Partial
 - Full

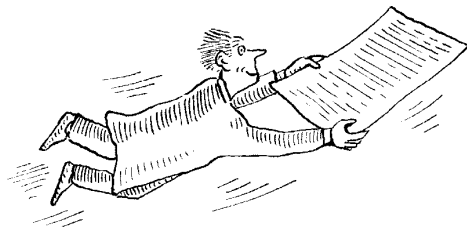


WHAT IS F1000RESEARCH?

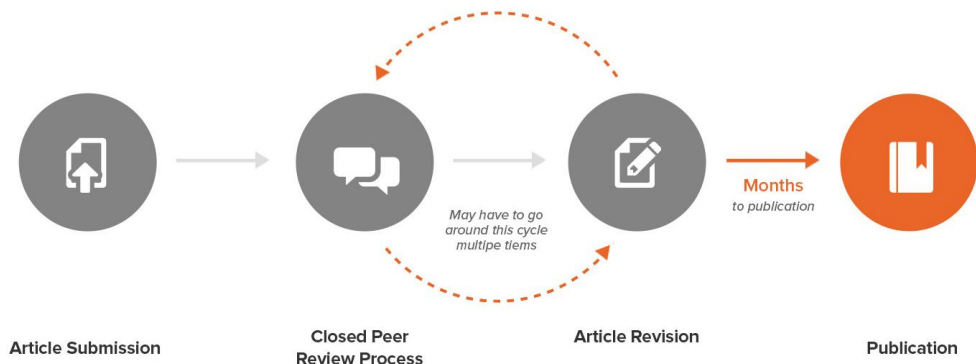
Open Science Publishing Platform

Scope: all research – big and small – across the life sciences and medicine

- Immediate publication
- Transparent refereeing
- No editorial bias
- All source data included
- Indexed in PubMed

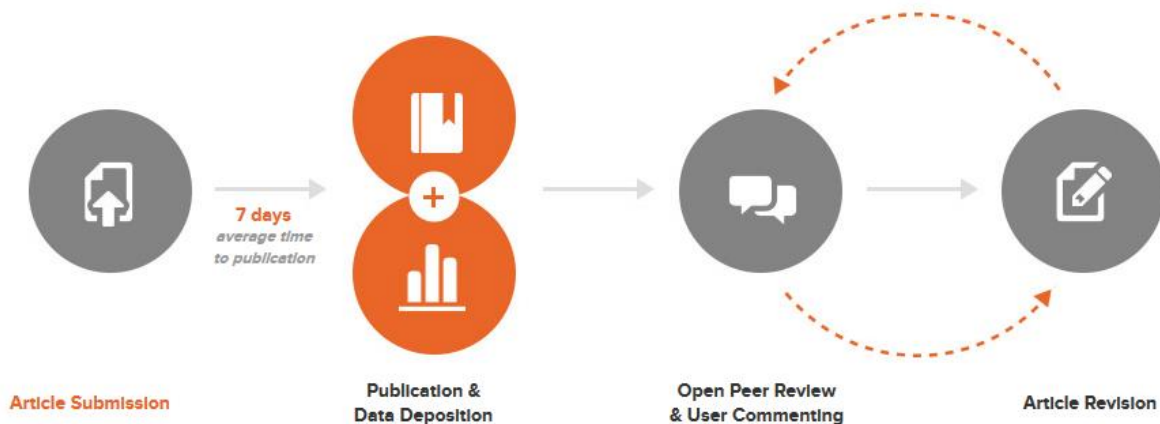


Traditional Publishing Process



- Most journals publish articles after they pass peer review.
- The peer review process can take months – sometimes years.
- After rejection, start over again with another journal.
- This delays publication.

Our Publishing Process



- *F1000Research* articles are published online after an in-house pre-refereeing check, on average, within 7 days.
- Peer review and revisions are carried out publicly.
- Invited referees judge whether the work is scientifically sound.
- Articles with sufficient positive referee reports are indexed in PubMed.

F1000RESEARCH REFEREE REPORT

Referee names are visible.

Referee Report 09 May 2014

Christine Mummery Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, Netherlands

✓ Approved

The authors describe their attempt to reproduce a study in which it was claimed that mild acid treatment was sufficient to reprogramme postnatal splenocytes from a mouse expressing GFP in the oct4 lineage into pluripotent stem cells. The authors followed ... [Continue reading](#)

Author Response 12 May 2014

Kenneth Lee, School of Biomedical Sciences, Chinese University of Hong Kong, Hong Kong
Professor Mummery has provided some excellent suggestions for changes to improve the paper. We will do our best and accommodate her requests 1-3 by doing some new additional experiments.

Request 4 ... [Continue reading](#)

[+ Respond or Comment](#)

View count shows how many people read the referee report

Views

614

[Cite](#)

How to cite this report:

Mummery C. Referee Report For: Transient acid treatment cannot induce neonatal somatic cells to become pluripotent stem cells [v1; ref status: indexed, <http://f1000r.es/3dqj>] *F1000Research* 2014, 3:102 (doi: [10.5256/f1000research.4382.r4727](https://doi.org/10.5256/f1000research.4382.r4727))

NOTE: It is important to ensure the information in square brackets after the title is included in all citations of this report.

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Referee reports and author comments are visible to anyone.

Referee reports are citable with a DOI.

REFeree SCORES



- Approved



- Approved with reservations



- Not approved

Articles with sufficient positive evaluations are indexed in PubMed, Scopus, and Embase



or



Minimal requirements for indexing

Articles that haven't yet reached this threshold can be revised and re-reviewed (no time limit)

Open Peer Review

Referee Status:

	Invited Referees		
	1	2	3
REVISED version 3 published 14 Nov 2013			report
		↑	↑
REVISED version 2 published 01 Nov 2013	report	report	report
	↑		
version 1 published 25 Sep 2013		report	

1 Maximiliano Gutierrez, MRC National Institute for Medical Research, UK
2 Yoshiko Takahashi, Kyoto University, Japan
3 Tom Gillis, Louisiana State University School of Medicine, USA

Read the reports (6), Responses (1)

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Comments (0)

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VERSIONS

Different versions of the article are tracked

Referees can update the approval status

F1000Research » Articles

SHORT RESEARCH ARTICLE

REVISED Reprogramming diminishes retention of *Mycobacterium leprae* in Schwann cells and elevates bacterial transfer property to fibroblasts [v3; ref status: indexed, <http://f1000r.es/2ae>]

Toshihiro Masaki^{1,2,4}, Aidan McGlinchey¹, Simon R. Tomlinson¹, Jinrong Qu⁴, Anura Rambukkana¹⁻⁴

Author affiliations

Grant information

Abstract

Background: Bacterial pathogens can manipulate or subvert host tissue cells to their advantage at different stages during infection, from initial colonization in primary host niches to dissemination. Recently, we have shown that *Mycobacterium leprae* (ML), the causative agent of human leprosy, reprogrammed its preferred host niche de-differentiated adult Schwann cells to progenitor/stem cell-like cells (pSLC).

Results: Using pSLCs, we studied how this cell fate change influences bacterial retention and transfer after reprogramming. We found that non-reprogrammed Schwann cells, which have high bacterial retention capacity when co-cultured with skin fibroblasts at higher numbers even after co-culture for 5 days. In contrast, pSLCs, which are derived from the same Schwann cells but have lost Schwann cell lineage markers due to reprogramming, efficiently transferred bacteria to fibroblasts within 24 hours.

Conclusions: ML-induced reprogramming converts lineage-committed Schwann cells with high bacterial retention capacity to cell fate with pSLCs with effective bacterial transfer properties. We propose that such changes in



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Referee Status: ☒ ☒ ☒

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1 2 3

REVISED
version 3
published
14 Nov 2013

☒ report

REVISED
version 2
published
01 Nov 2013

☒ report

☒ report

☐ ? report

version 1
published
25 Sep 2013

☐ ? report

- 1 Maximiliano Gutierrez, MRC National Institute for Medical Research, UK
- 2 Yoshiko Takahashi, Kyoto University, Japan
- 3 Tom Gillis, Louisiana State University School of Medicine, USA

Read the reports (6), Responses (1)

Unique DOI for each version

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CITATIONS

Scopus

1



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- Mentioned by 1 peer review site
- 9 readers on Mendeley

Values are totals across all versions of this article

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Referee Status: ☒ ☒ ☒

Invited Referees

1 2 3

version 1
published
04 Oct 2013



report



report



report

- 1 Mario Costa, National Research Council, Italy, Italy
- 2 Jean-François Brunet, Institut de Biologie de l'Ecole normale supérieure, France
- 3 Mike Johnston, Kennedy Krieger Institute, USA

Read the reports (3)

Discuss this article

Comments (0)

Add a Comment

BENEFITS OF TRANSPARENT REVIEW

- Authors can talk directly to referees and demonstrate that their paper was reviewed by top people in their field.
- Visible discussion between referees and authors (and editors) puts paper in context.
- Referees are more thoughtful about what they write. And rarely ask for unreasonable additional experiments.
- Referees can take credit for their hard work.
- Educational aspect of open peer review

OTHER BENEFITS OF PUBLISHING IN F1000RESEARCH

- Publishes unusual article types such as:
 - Data notes
 - Antibody Validations
 - Negative/null results
 - Observation studies
- All source data included
- Unlimited ability to update and improve your articles
- Altmetrics for your paper provided

OTHER POST-PUBLICATION REVIEW JOURNALS

Copernicus journals – launched 2001



- Invited reviewers
- Articles discussed by reviewers and others in discussion forum (formally published)
- Articles that pass review are published in journal

ScienceOpen Research – launched 2014



- Can invite own reviewers
- Reviewers must have 5 publications in ORCID
- In talks with indexing services

The Winnower – launched 2014



- Can invite own reviewers
- Anyone can review (with account)
- Not indexed

POTENTIAL CHALLENGES OF TRANSPARENT PEER REVIEW

- Post-publication peer review often gets confused with post-publication **commenting**
(e.g. PubMed Commons, Publons, Libre, PubPeer)

- Referees need checking more stringently

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

- The Editor can't just do it themselves
- Exposes when referee does poor job or just provides one line
- Exposes if no-one wants to referee the article or takes a long time
 - When do you stop?
 - Should the number of referees invited be listed?
 - Should a note be added after a time to say all agree not to continue?
 - What if manage to get one referee but can't get anyone else to do it?

CONCERNS PEOPLE SOMETIMES HAVE

- Will referees be publicly critical?
 - Yes, looks bad on referee if overly positive, but makes them more constructive
 - Openness may make them more careful not to miss issues
- Will authors be willing to publish where their work might be openly criticised?
 - Seems so! Authors often publish with us when especially worried will be treated fairly
 - Improves quality of what is submitted
- Will junior researchers criticise more senior ones openly?

The screenshot displays a F1000Research article interface. At the top, a red banner indicates 'Version 2'. Below this, the article title 'Referee Report 29 Oct 2012' is shown. The authors listed are Mihaela Pertea and Steven Salzberg, both affiliated with the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins University School of Medicine, USA. A red 'X' icon and the text 'Not Approved' are prominently displayed. A detailed explanation follows: 'Our 'Not Approved' status still maintains. It seems like he has made some nice improvements but the paper doesn't address our fundamental concern that, despite its claims, it doesn't evaluate aligners, but their capacity to work with the GATK pipeline. ... Continue reading'. On the right side, there is a 'Views' counter showing 41 and a 'Cite' button. At the bottom, a 'Reader Comment' from Attila Berces, dated 07 Jan 2013, is visible. The comment discusses computational evidence supporting Oliver's experimental design and mentions a conflict of interest.

Version 2

Referee Report 29 Oct 2012

Mihaela Pertea, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, USA
Steven Salzberg, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, USA

Not Approved

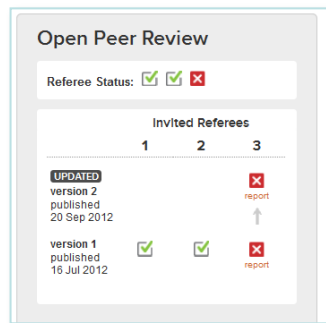
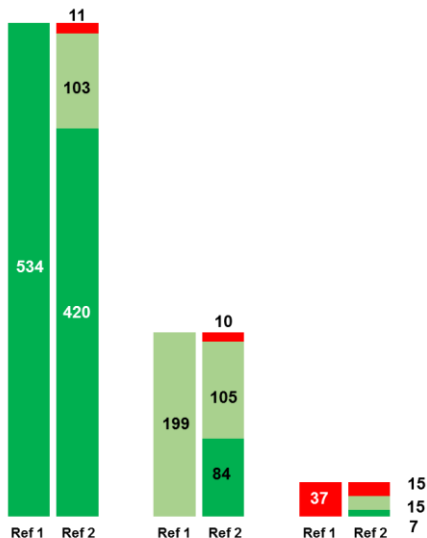
Our 'Not Approved' status still maintains. It seems like he has made some nice improvements but the paper doesn't address our fundamental concern that, despite its claims, it doesn't evaluate aligners, but their capacity to work with the GATK pipeline. ... [Continue reading](#)

Reader Comment 07 Jan 2013
Attila Berces, Omixon, Hungary
In this review I make arguments based on some computational evidence in support of Oliver's experimental design and make some observations on the reviews made by Pertea and Salzberg. I declare conflict of interest since I am involved with one of the alignment software reviewed in Oliver's paper. I note that Pertea and Salzberg chose not to declare conflict of interest in a similar position.

Views 41
Cite

CONCERNS PEOPLE SOMETIMES HAVE - II

- Will referees only confirm what previous referees for that article have said?



Days between submissions	Kappa	% agreement
0	0.359	70.57%
>1	0.372	70.74%
>5	0.389	70.93%

FUTURE PEER REVIEW CHALLENGES AND OPPORTUNITIES

- Increasing range of scientific outputs for peer review:
 - Datasets and data papers
 - Software papers
 - Small findings / posters
- Decoupling of publishing and peer review/curation



- Journal-level metrics not appropriate for individual assessment



DO WE NEED JOURNALS AND PUBLISHERS?

SUMMARY

- Peer review is an important part of scientific dissemination
- The problems with the traditional process are well known
- Many new models being developed to tackle the issues
- Several publishers now working towards a post-publication open peer review system
- Still challenges, but most scientists agree this is ultimately the right way to share science
- What role should publishers play in this?
 - Move away from trying to own the content and process
 - Become service providers that enable the sharing, debate and discussion of science.

F1000Prime

INTRODUCTION

Directory of recommendations of the best research in
biology and medicine from a faculty of global experts.
(Launched 2002)

F1000Prime has a Faculty of over 5,000 leading experts who:

>>**Hand-pick** the best research articles in biology and medicine

>>Write a **concise recommendation of each article** plus provide a rating

F1000Prime's unique collection of innovative tools, including intelligent SmartSearches, brings you the most relevant article recommendations in your field.

The image displays three overlapping screenshots of the F1000Prime website interface, illustrating its features and content.

Left Screenshot: Shows the "FACULTY of 1000" section. It states: "FACULTY of 1000 is composed of 5,000 Faculty Members — senior scientists and leading experts in all areas of biology and medicine — plus their associates. The Faculty recommends the most important articles, rating them and providing short explanations for their selections."

Middle Screenshot: Shows the "My F1000Prime Homepage" section. It lists recommended articles with titles, authors, and brief descriptions. Examples include:

- "Two distinct functions for PKA-kinases in macrophages." by Hessler G, Bousquet P, Clark J, Stephens LR, Hawkins PT, Warner GD, Waters G, Kay RM. J Cell Sci. 2013 May 15; 125(Pt 10):4299-307. [Recommendation]
- "Removal of centrosomal PP1 by HSPA4 kinase unlocks the MPP feedback loop to promote mitotic commitment in S. pombe." by Grollman A, Chen XT, Alonso-Huertas M, Soudré B, Robertson A, Ohtani SM, Smith DL, Hagan M. Cell Rep. 2013 Apr 4; 2(5):573-23. [Recommendation]

Right Screenshot: Shows a detailed article recommendation for "The decline in rat hippocampal theta activity during response inhibition for the compound stimulus of negative patterning and simultaneous feature-negative tasks." by Suleyman Y. Suleymanov and Behar Bran Rex. It includes a "RECOMMENDED" badge, a "GET MORE LIKE THIS" button, and a "SMARTSEARCH" button.

WHO ARE THE FACULTY?

The Faculty include:

- 9 Nobel Prize winners
- 12 Lasker Award winners
- Over 100 Fellows of The Royal Society
- Over 140 members of the National Academy of Sciences

WHAT DOES F1000PRIME DO?

- Identify the most important papers
- Include expert comments explaining why an article is important
- Assign a rating of Exceptional, Very Good or Good
- Add relevant classifications (e.g. Novel drug target, Review etc.)



An astrocyte-dependent mechanism for neuronal rhythmicogenesis.

Marquette P¹, Verdier D¹, Kadala A¹, F  thi  re J², Philippe AG³, Robitaille R¹, Kolta A⁴
show author affiliations

Nat Neurosci. 2015 Jun; 18(6):844-54



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INTERESTING ARTICLE? GET MORE LIKE IT SMART SEARCH

RECOMMENDATIONS 1 | ABSTRACT | COMMENTS

expand all

*** Exceptional

Staff use: edit 04 Jun 2015



FM Giovanni Marsicano
F1000 Neuroscience
INSERM, Bordeaux, France.

F FOLLOW

CONTRVERSIAL | INTERESTING HYPOTHESIS | NEW FINDING

DOI: 10.3410/f.725465134.793507109

Rhythmic activity is a key functional determinant of neuronal networks. Several mechanisms regulate oscillation patterns in the nervous system. Astrocytes, by regulating several central functions, likely contribute to the coding of information. In this article, Marquette and colleagues nicely show that rhythmic activity in the trigeminal sensorimotor circuit for mastication requires astroglial signaling. This is an extremely interesting study, definitely showing the importance of astroglial cells in nervous system functions.

Disclosures

None declared

Add a comment

Cite this Recommendation

ABSTRACT

Communication between neurons rests on their capacity to change their firing pattern to encode different messages. For several vital functions, such as respiration and mastication, neurons need to generate a rhythmic firing pattern. Here we show in the rat trigeminal sensorimotor circuit for mastication that this ability depends on regulation of the extracellular Ca^{2+} concentration ($[Ca^{2+}]_e$) by astrocytes. In this circuit, astrocytes respond to sensory stimuli that induce neuronal rhythmic activity, and their blockade with a Ca^{2+} ...

more »

DOI: 10.1038/nn.4013
PMID: 25938883



Abstract courtesy of PubMed: A service of the National Library of Medicine and the National Institutes of Health.

RELATED ARTICLES

Recommended PubMed

- 1 Neuron-to-astrocyte signaling is central to the dynamic control...
- 2 Astrocytes control breathing through pH-dependent release of ATP.
- 3 Neuronal activity and glutamate uptake decrease mitochondrial...
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INTRODUCTION

F1000 has introduced a new set of tools to help scientists

- Write articles
- Collaborate with co-authors
- Organise, annotate and manage references



DISCOVER

Discover the top papers in your field



WRITE

Access powerful tools while you write



COLLABORATE

Manage, annotate and share your references



PUBLISH

Publish with confidence

IMPORT REFERENCES

ALL REFERENCES

UNSORTED REFERENCES

PROJECTS

🔒 *private*

▶ Cell Biology project

▶ Ecology course

liver disease

May 7

▶ Neuroscience

PROJECTS

🔗 *shared*

▶ Manuscript

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liver disease

review

X-linked diseases

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Introduction

The creatine (Cr) transporter (CrT, alias CRTR, MGC87396, CT1, SLC6A8, OMIM 300036) deficiency (CCDS1, OMIM #300352) is an X-linked inherited metabolic disorder characterized by cerebral Cr deficiency which results in intellectual disability, language and speech impairment, seizures and movement and behavioral disturbances, and affects about 1% of males with non-syndromic mental disability (van de Kamp *et al.*, 2014). CrT loss of function is mostly caused by missense mutations and small deletions which are concentrated in the transmembrane domains 7 and 8 of the protein (van de Kamp *et al.*, 2014). In physiological conditions, about half of our non-muscle Cr is synthesized *de novo* endogenous synthesis of Cr takes place mainly in the kidney, liver and brain. In the liver, Cr is synthesized from L-arginine: glycine amidinotransferase (AGAT) and S-adenosyl-L-methionine (SAM) (Wyss & Kaddurah-Daouk, 2000). Cr is a polar hydrophilic molecule which uses a Na⁺- and Cl⁻- dependent plasma membrane CrT to enter the cells (Nash *et al.*, 1994). CrT is widely expressed in the brain tissue with a prominent presence in the cortical and subcortical regions involved in motor and sensory processing, learning and memory, and regulation of emotion-related behavior (Lowe *et al.*, 2014; Mak *et al.*, 2009).



Very interesting finding!

Neuroscience

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Cell Biology project

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May 7

Neuroscience

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review X-linked diseases

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All references

0 out of 114 selected

View Columns Rows 25

Go to page 1 1 out of 5

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Authors	Year	Title	Full Text	Journal	Date added	Notes	Tags
<input type="checkbox"/> Catalanotti F, R...	2009	F A Mek1-Mek2 heterodimer deter...	Full Text	Nat Struct Mol ...	07 May 2015		
<input type="checkbox"/> Yamashita H, K...	2014	F Role of the protein tyrosine phos...	Full Text	PLoS ONE	07 May 2015		
<input type="checkbox"/> Lee SA, Gallag...	2015	F General and condition-specific es...	Full Text	Proc Natl Acad ...	07 May 2015		
<input type="checkbox"/> Creta E, Fabbri ...	2015	Genetics of second-generation antip...	Full Text	Pharmacogenet...	07 May 2015		
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<input type="checkbox"/> Kalai Chelvam ...	2015	Variable Responses to Carbon Utiliz...	Full Text	PLoS ONE	07 May 2015	(1) interesting	
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<input type="checkbox"/> Alfonso-Morale...	2015	Evaluation of a Phylogenetic Marker ...	Full Text	PLoS ONE	07 May 2015		+
<input type="checkbox"/> Jacchia S, Nard...	2015	International ring trial for the validati...	Full Text	J Agric Food C...	07 May 2015		
<input type="checkbox"/> Wang Y, Lee Y...	2014	MELK is an oncogenic kinase essenti...	Full Text	elife	05 May 2015		
<input type="checkbox"/> Arum O, Saleh ...	2015	Interaction of <i>growth</i> <i>horm...	Full Text	F1000Res	05 May 2015		
<input type="checkbox"/> Holland B, Won...	2013	Identification of human microRNA-lik...	Full Text	PLoS ONE	05 May 2015		
<input type="checkbox"/> Persaud A, Alb...	2009	Comparison of substrate specificity ...	Full Text	Mol Syst Biol	05 May 2015		
<input type="checkbox"/> Kutschera VE, ...	2014	Bears in a forest of gene trees: Phylo...	Full Text	Mol Biol Evol	05 May 2015		
<input type="checkbox"/> Ammar R, Pato...	2015	Long read nanopore sequencing for ...	Full Text	F1000Res	05 May 2015		

FACULTY RECOMMENDATIONS

[< BACK](#) Faculty recommended

Added on 27 Jan 2015 by You via www.ncbi.nlm.nih.gov

Dopamine-induced α -synuclein oligomers show self- and cross-propagation properties.

Planchard MS, Exley SE, Morgan SE, Rangachari V

SHOW AFFILIATIONS 

Protein Sci. 2014 Jul 16

Abstract

Notes (0)

Related articles

Faculty recommendations

1



FM | Vladimir Uversky
Structural Biology

University of South Florida, Tampa, FL, USA

★☆☆ Good

20 Aug 2014

 Good for teaching  Confirmation  New finding  Interesting hypothesis

DOI: 10.3410/f.718500794.793498874

The authors purified and characterized various low-molecular-weight oligomers produced by incubation of purified recombinant human α -synuclein (a protein implicated in the pathogenesis of Parkinson's disease [PD]) with dopamine. These dopamine-derived α -synuclein oligomers (DSOs) are characterized by a wide range of oligomerization degree (ranging from dimers to 13-mers), possess coil-like secondary structure, are able to self-propagate, and are capable of cross-propagation efficiently initiating the formation of the amyloid- β ($A\beta$) aggregates involved in Alzheimer's disease (AD). The mechanisms of self- and cross-propagation are very different, since in the self-propagation process, DSOs stay mostly disordered, but noticeable β -sheet structure is formed in the cross-propagation reaction with $A\beta$. Based on these observations, the authors hypothesized that DSOs not only are involved in the PD pathogenesis but also may play a role in the appearance of AD-like pathology in PD patients.




FULL TEXT ARTICLE



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SUPPLEMENTARY DATA


UPLOAD FILES 

TAGS

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PROJECTS

 Neuroscience project
neurodegenerative diseases

 Manuscript

For introduction

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MEMBERS

The following people can see shared notes on this reference.

EA

Eva Amsen

Manuscript, For introduction...

MP

Maeike Pols

Manuscript, For introduction...

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ARTICLE RECOMMENDATIONS



Cell Biology project

REFERENCES **RECOMMENDATIONS** NOTES ACTIVITY

Invite members



1 out of 3 < >

Research we think might be relevant to your project

How it works

Malaria-associated atypical memory B cells exhibit markedly reduced B cell receptor signaling and effector function.

Portugal S, Tipton CM, Sohn H, Kone Y, Wang J, Li S, Skinner J, Virtaneva K, Sturdevant DE, Porcella ...
eLife. 2015 May 08; 4

SHOW ABSTRACT ▾

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DISMISS

[Full text](#)

Single fibril growth kinetics of α -synuclein.

Wördehoff MM, Bannach O, Shaykhalishahi H, Kulawik A, Schiefer S, Willbold D, Hoyer W, Birkmann E
J Mol Biol. 2015 Feb 04

SHOW ABSTRACT ▾

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DISMISS

[Full text](#)

NOTES

Neuroscience

REFERENCES RECOMMENDATIONS **NOTES** ACTIVITY

Invite members



Place cells, grid cells, and the brain's spatial representation system.

Moser et al, 2008

JW

You noted on 8 May 2015 2:12 PM
note

are part of a broader circuit for dynamic representation of self-location. A key component of this network is the entorhinal grid cells, which, by virtue of their tessellating firing fields, may provide the elements of a path integration-based neural map. Here we review how place cells and grid cells may form the basis for quantitative spatiotemporal representation of places, routes, and associated experiences during behavior and in memory. Because these cell types have some of the most conspicuous behavioral corre

[> COMMENT](#)

Microstructure of a spatial map in the entorhinal cortex.

Hafting et al, 2005

JW

You noted on 27 Jan 2015 10:42 AM
Nobel Prize 2014

Its key unit is the 'grid cell'

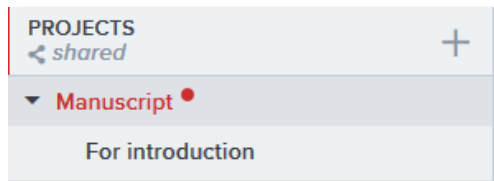
JW

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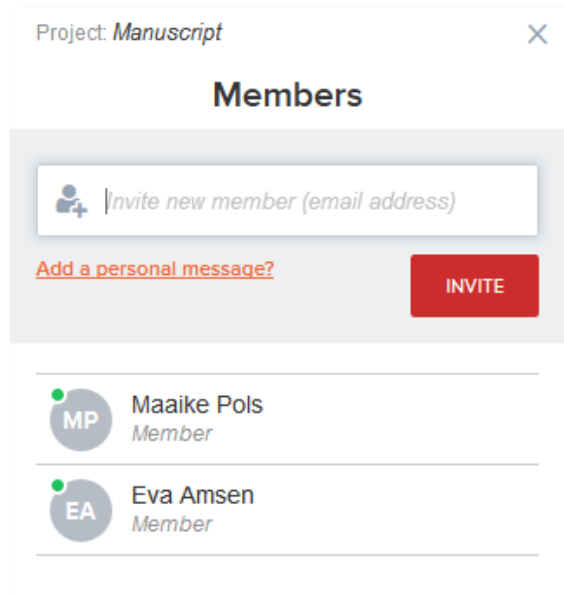
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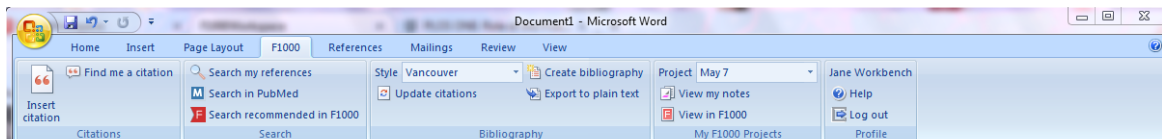


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Introduction

Lysosomes are the primary catabolic compartments of eukaryotic cells^{1,2}. A functional lysosome requires two classes of proteins: soluble lysosomal acid hydrolases and integral lysosomal membrane proteins. The about 25 known lysosomal membrane proteins³⁻⁴ have diverse functions, including acidification of the lysosomal lumen, protein import and export from and to the cytosol⁵, homo- and heterotypic lysosomal fusion and maintaining integrity of the lysosomal membrane⁶⁻⁸.

Newly synthesized lysosomal proteins can take a *direct trans*-Golgi network (TGN)-to-endosome pathway or an *indirect* pathway, involving transport to the plasma membrane and subsequent endocytosis. The best understood direct TGN-to-endosome pathway is mannose 6-phosphate receptor (MPR)-dependent transport of lysosomal hydrolases⁹. MPRs bind to the heterotetrameric adaptor-protein complex (AP)-1 and the Golgi-localized, γ -ear-containing, Arf-binding family of proteins (GGA) that both act as clathrin adaptors¹⁰⁻¹³. Subsequent transport to endosomes occurs via 60-100nm clathrin-coated vesicles^{12,14-16} or pleiomorphic membranes¹⁷ that fuse with early endosomes^{16,18}.

Considerably less is known about the targeting of lysosomal membrane proteins¹². The lysosome-associated membrane proteins (LAMP)-1 and -2 are the most abundant lysosomal membrane proteins²⁰. They bear a GYXXQ sorting motif in their cytosolic tail that interacts with the μ subunits of AP-1, AP-2 and AP-3, which are adaptor protein complexes implicated in vesicle formation at the TGN/endosome, plasma membrane and recycling endosomes, respectively²¹. In accordance, LAMP-1 has been found in AP-1/clathrin positive TGN-derived vesicles^{22,23}. Several observations, however, indicate that in the absence of AP-1 and/or clathrin or when the AP-1 binding motif GYXXQ is mutated, LAMPs still reach lysosomes by a direct pathway²⁴⁻²⁷. The characteristics of this alternative pathway have thus far remained unresolved.

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One common neurodegenerative disease, Parkinson's disease, has been linked to exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and to inhaled manganese. Similarly, inhaled aluminum dust has been associated with neurotoxic effects and pre-clinical cognitive impairment. Certain inhalation anesthetics have also been implicated in elevating AD risk, possibly by exacerbating the neurotoxic oligomerization of the amyloid- β (A β) peptide. The early involvement of the olfactory cortex in AD has caused longtime speculation that some inhaled agent might play a role in AD risk.

Recently, AD pathology was identified in young people living in areas with high levels of air pollution. Furthermore, impaired cognition has been recently attributed to air pollution exposure in some populations. These converging lines of evidence led us to analyze brain levels of A β 40 and A β 42 in mice exposed to an inhaled particulate matter (nickel nanoparticle; Ni NP) model of air pollution.(1,2)

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Endoscopic screening for detecting cancer and cancer precursors in Barrett's esophagus (BE) is currently informed by repeated systematic biopsying of the metaplastic BE tissue. Here we present a comprehensive multiscale model of the natural history of esophageal adenocarcinoma (EAC), which describes the entire multistage process beginning with the conversion event of normal squamous esophageal tissue to BE metaplasia, the spatio-temporal formation of independent dysplastic and malignant clones at the cell level, and finally the appearance of symptomatic EAC in BE. This model lends itself to a systematic exploration of the efficacy and sensitivity of current biopsy-based screening methods to detect neoplasia in BE patients, as well as alternative screening techniques based on high-resolution imaging of the BE tissue. Moreover, the model can also be used to predict the impact of ablative treatments on the risk of occurrence or recurrence of dysplasia or cancer. Due to the lack of studies that attempt to explicitly model the physical and biological dimensions of the screening process itself, our computational model provides a unique, publicly-available tool to improve understanding of factors that limit the efficacy of current screening protocols for BE patients.

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