

## **Outline**

- Introduction of Wiley
- Basic Structure of a Research Article
- Choosing the Right Journal before Submission
- Surviving the Peer-review Process
- Summary

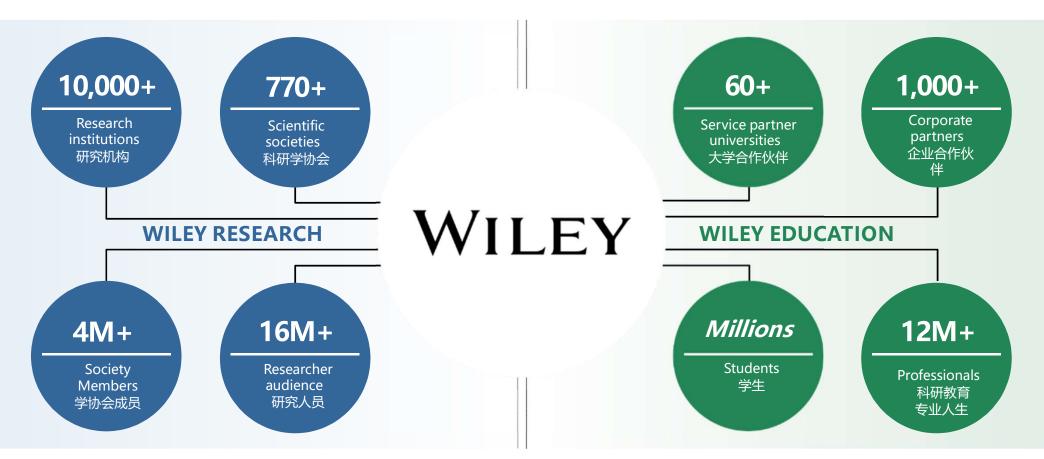


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### Article





# Mitochondrial Safeguard: a stress response that offsets extreme fusion and protects respiratory function via flickering-induced Oma1 activation

Daisuke Murata<sup>1</sup>, Tatsuya Yamada<sup>1</sup>, Takeshi Tokuyama<sup>1</sup>, Kenta Arai<sup>1</sup>, Pedro M Quirós<sup>2</sup>, Carlos López-Otín<sup>2</sup>, Miho Iijima<sup>1,\*</sup> & Hiromi Sesaki<sup>1,\*\*</sup>

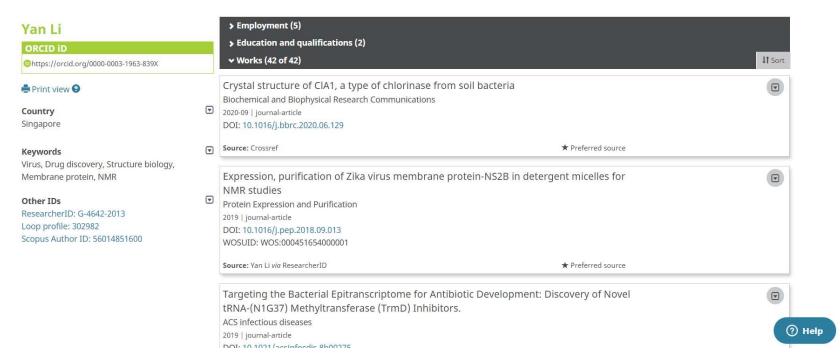
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<sup>1</sup> Department of Cell Biology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

<sup>2</sup> Departamento de Bioquímica y Biología Molecular, Facultad de Medicina, Instituto Universitario de Oncología, Universidad de Oviedo, Oviedo, Spain \*Corresponding author. Tel: +1 410 502 6836; E-mail: miijima@jhmi.edu

<sup>\*\*</sup>Corresponding author. Tel: +1 410 502 6842; E-mail: hsesaki@jhmi.edu



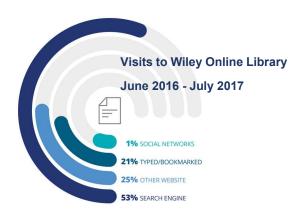




### Abstract

The connectivity of mitochondria is regulated by a balance between fusion and division. Many human diseases are associated with excessive mitochondrial connectivity due to impaired Drp1, a dynamin-related GTPase that mediates division. Here, we report a mitochondrial stress response, named mitochondrial safeguard, that adjusts the balance of fusion and division in response to increased mitochondrial connectivity. In cells lacking Drp1, mitochondria undergo hyperfusion. However, hyperfusion does not completely connect mitochondria because Opa1 and mitofusin 1, two other dynamin-related GTPases that mediate fusion, become proteolytically inactivated. Pharmacological and genetic experiments show that the activity of Oma1, a metalloprotease that cleaves Opa1, is regulated by short pulses of the membrane depolarization without affecting the overall membrane potential in Drp1-knockout cells, Re-activation of Opa1 and Mitofusin 1 in Drp1knockout cells further connects mitochondria beyond hyperfusion, termed extreme fusion, leading to bioenergetic deficits. These findings reveal an unforeseen safeguard mechanism that prevents extreme fusion of mitochondria, thereby maintaining mitochondrial function when the balance is shifted to excessive connectivity.

Keywords Drp1; mitochondrial fusion; mitofusin; Oma1; Opa1



### Introduction

The mitochondrion is an essential organelle for a variety of cellular processes, including energy production, metabolism, and signal transduction. These mitochondrial functions depend on

### Results

### An experimental system to analyze Opa1 processing

To investigate the mechanism by which the conversion of the long forms (L1 and L2) to the short forms (S3 and S5) is increased in Drp1-KO cells, we simplified our experimental platform by ectopi-

### Artificial flickering induces Opa1 cleavage

The pharmacological and genetic experiments described above suggest that flickering promotes the proteolytic cleavage of Opal in the absence of Drp1. To test whether flickering is sufficient to drive

### Discussion

Flickering—repeated, transient decreases of the membrane potential—has been observed in multiple cell types, including smooth muscle cells (Chalmers *et al*, 2015), cardiomyocytes (Duchen *et al*, 1998), and a neuroblastoma cell line (Loew *et al*, 1993). In this study, we show that flickering induces Omal-mediated Opal cleavage when mitochondrial division is decreased. Our data suggest that this Opal cleavage, along with the degradation of

### Acknowledgements

We thank past and present members of the lijima and Sesaki laboratories for helpful discussions and technical assistance. We are also grateful to Dr. Rong Li for providing the monomeric Eos plasmid. This work was supported by NIH grants to MI (GM131768) and HS (GM123266 and GM130695) and grants to HS from Diana Helis Henry Medical Research

### Materials and Methods

#### Animals

All animal work was performed according to the guideline established by the Johns Hopkins University Committee on Animal Care. Control  $(Drp1^{flox}/flox)$ , liver-specific Drp1-KO  $(Alb\text{-}Cre::Drp1^{flox}/flox)$ , Oma1-KO  $(Oma1^{-/-})$ , and Drp1Oma1-KO  $(Alb\text{-}Cre::Drp1^{flox}/flox)$ :  $Oma1^{-/-}$  mice were generated by breeding (Quiros et~al, 2012; Yamada et~al, 2018).

### Cells

HEK293T cells were cultured in Dulbecco's Modified Eagle Medium containing 10% fetal bovine serum. MEFs were cultured in Iscove's modified Dulbecco's medium containing 10% fetal bovine serum (Wakabayashi *et al.*, 2009). Stable cell lines expressing Opa1-HA were selected with 400 μg/ml G418 sulfate. To generate Drp1Opa1-KO MEFs, Drp1<sup>flox/flox</sup>Opa1<sup>flox/flox</sup> MEFs were isolated from Drp1<sup>flox/flox</sup>Opa1<sup>flox/flox</sup> embryos as described previously (Yamada *et al.*,

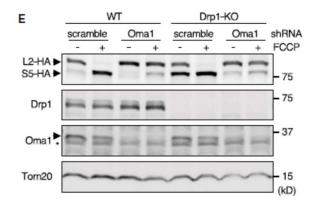
### References

Acin-Perez R, Lechuga-Vieco AV, Del Mar MM, Nieto-Arellano R, Torroja C, Sanchez-Cabo F, Jimenez C, Gonzalez-Guerra A, Carrascoso I, Beninca C et al (2018) Ablation of the stress protease OMA1 protects against heart failure in mice. Sci Transl Med 10: eaan4935

Adachi Y, Itoh K, Yamada T, Cerveny KL, Suzuki TL, Macdonald P, Frohman MA, Ramachandran R, Iijima M, Sesaki H (2016) Coincident phosphatidic acid interaction restrains Drp1 in mitochondrial division. Mol Cell 63: 1034–1043

Anand R, Wai T, Baker MJ, Kladt N, Schauss AC, Rugarli E, Langer T (2014) The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. J Cell Biol 204: 919–929





Genotype	Lentivirus	Number of mitochondria/cell	P value
	scramble	266 ± 144	•
WT	Oma1 shRNA	225 ± 72	ns
	scramble+Mfn1	167 ± 79	0.0257
	Oma1 shRNA+Mfn1	92 ± 48	< 0.0001
-	scramble	23 ± 14	
Drp1-KO	Oma1 shRNA	25 ± 10	ns
	scramble+Mfn1	24 ± 12	ns
	Oma1 shRNA+Mfn1	12±5	0.0004

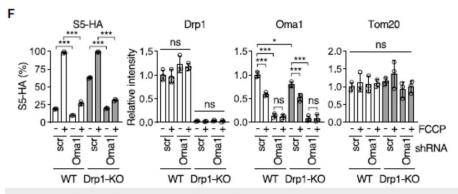
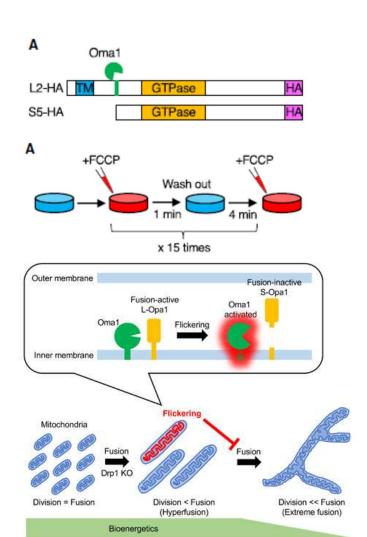


Figure 2. An experimental system to examine Opal processing.

- A L2 was tagged with HA at the C terminus and expressed from the doxycycline-inducible promoter.
- B Western blotting of WT MEFs, Drp1-KO MEFs, and Drp1-KO MEFs carrying Drp1, all of which express L2-HA, using the indicated antibodies. The expression of L2-HA was induced for 16 h (0.1 µg/ml doxycycline). The asterisk indicates non-specific bands of anti-Oma1 antibodies.
- C Quantification of band intensity. Values are average  $\pm$  SD (n=3).
- D The activation of Oma1. Oma1 is proteolytically activated and then undergoes degradation.
- E WT and Drp1-KO MEFs, both of which express L2-HA, were transduced with lentiviruses carrying either scramble or Oma1-targeted shRNAs. Whole-cell lysates were analyzed by Western blotting using the indicated antibodies. The asterisk indicates non-specific bands of anti-Oma1 antibodies.
- F Quantification of band intensity. Values are average  $\pm$  SD (n = 3).

Data information: Significance was calculated using ANOVA with post hoc Tukey in (C and F):  $^{\star}P$  < 0.05,  $^{\star\star}P$  < 0.01,  $^{\star\star\star}P$  < 0.001.





### Data availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Expanded View files.

### Data availability

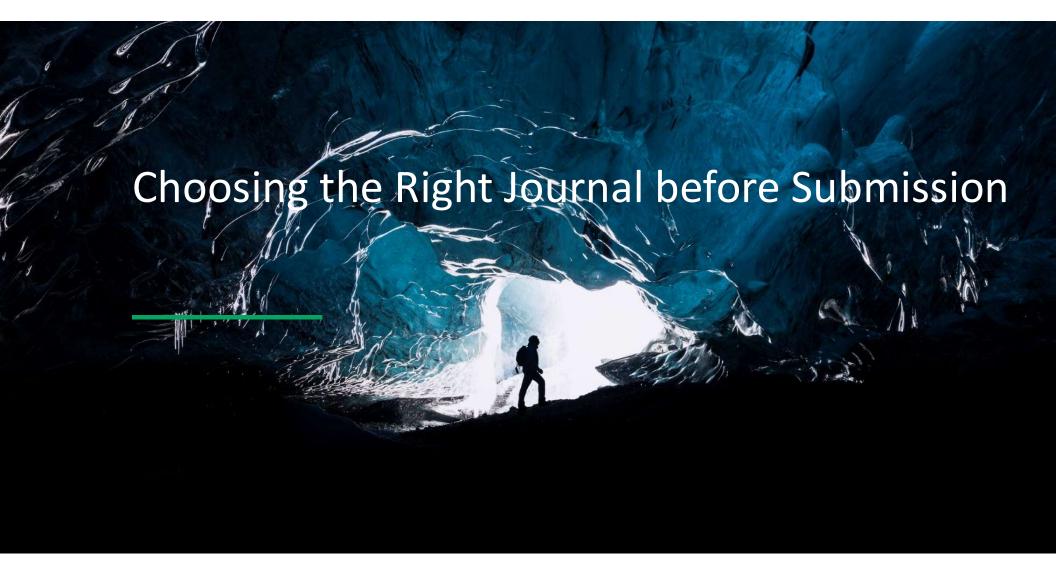
The coordinates and the maps for *horse* NHE9  $\Delta$ CTD and NHE9\* have been deposited in the Protein Data Bank (PDB) and Electron Microscopy Data Bank (EMD) with entries PDB: 6Z3Z (http://www.rcsb. org/pdb/explore/explore.do?structureId = 6Z3Z), EMD: EMD-11067 (http://www.ebi.ac.uk/pdbe/entry/EMD-11067) and PDB: 6Z3Y (http://www.rcsb.org/pdb/explore/explore.do?structureId = 6Z3Y), EMD: EMD-11066 (http://www.ebi.ac.uk/pdbe/entry/EMD-11066), respectively\*

### **Wiley's Data Sharing Policies**

Refer to the table below to understand the various standardized data sharing policy categories:

	Data availability statement is published <sup>1</sup>	Data has been shared <sup>2</sup>	Data has been peer reviewed <sup>3</sup>	Example Wiley journals
Encourages Data Sharing	Optional	Optional	Optional	
Expects Data Sharing	Required	Optional	Optional	British Journal of Social Psychology
Mandates Data Sharing	Required	Required	Optional	Ecology and Evolution
Mandates Data Sharing and Peer Reviews Data	Required	Required	Required	Geoscience Data Journal American Journal of Political Science





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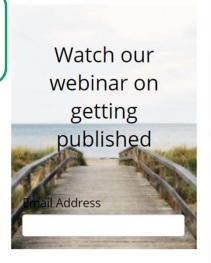
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Enter your manuscript information • Both fields are required Manuscript title Combining data from field surveys and archaeological records to predict the distribution of culturally important trees Manuscript abstract Our findings highlight similarities and differences between the predictions from these species distribution models. When validating these models against occurrences from an independent dataset, the archaeological record model performs better than the field survey model. These findings may arise because the independent dataset was collected on an unlogged island—an environment that aligns more closely with the historic forest conditions revealed by the FIND 467 of 3000 characters Matching strength: Strong Search Results Visit our Author Compliance Tool to compare against your funder or institutional polices 10 search results Open Access: **Diversity and Distributions** SUBMIT TO THIS JOURNAL Edited By: Janet Franklin 2017 ISI Ranking Impact Factor Open access Relevance 4.391 7/54 (Biodiversity Conservation) Yes 24/153 (Ecology) **Ecology and Evolution** SUBMIT TO THIS JOURNAL British Ecological Society Editors-in-Chief: Allen Moore, University of Georgia, USA and Andrew Beckerman, University of Sheffield, UK 2017 ISI Ranking Impact Factor Open access Relevance 2.34 57/153 (Ecology) Yes

1

研究相关文献 所在期刊 Where do you read papers related to your research? 2

最青睐的期刊 Which journals do you like the most? 3

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## **Writing a Good Cover Letter**

• Why is this topic/result important?

## **Key Component:**

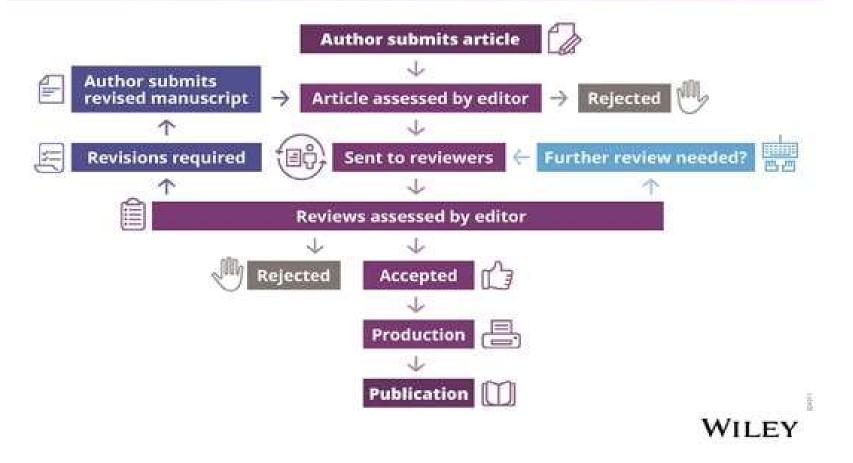
- What are the key results take home message?
- Why is it an advance on previous work?
- Why will this journal's readers read it?

## Also important:

- List related papers in press or under consideration
- Disclose conflicts of interest
- Provide reviewer suggestions
- As simple/short as possible

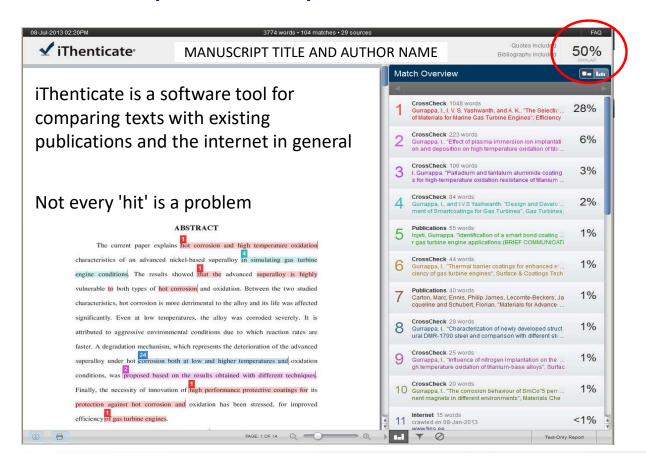


## **Peer Review Process**



## Plagiarism Detection

## Text overlap: What is acceptable and what isn't





## Case Studies: What's Plagiarism And What Isn't?

Silicon (Si) has a great potential as a photoelectrode because it is an earth-abundant element with several desirable properties, including a narrow energy band gap of -1.2 eV, high carrier mobility, stability over a wide pH range, non-toxicity, and commercial cability. [11] Si is takey material in the solid-state photoversic industry, whist modified Si has been used increasing aim scholar of the photoelectrochemical photoelectrochemical (PEC) II. production. [12-13] Metal oxides were deposited on the surface of the n-Si photoanodes as a protective layer in PEC water oxidation. [14] Although planar p-Si is promising. [15] charge carrier recombination can occur due to the low diffusion length of the minority carriers in the same absorber thickness. [16] However, a wire-array geometry possesses long optical paths for efficient photon absorption and increased collection efficiency for the minority carrier. A comparison of planar p-Si and p-Si wire arrays indicated that the latter exhibits a significantly lower reflectance [17] and 0.1–0.3 V higher anodic onset potentials in PEC water splitting processes. [13,18]

With this in mind, this study attempted, for the first time, to fabricate Sn-coupled p-Si nanowire arrays for application to solar  $CO_2$  conversion. Vertically aligned, free-standing p-Si nanowire arrays of varying lengths were grown on p-Si wafers using an electroless chemical etching technique. The wire arrays prepared using this method exhibited a > 0.5 V higher anodic onset potential compared to planar p-Si and an approximately two-fold increase in photocurrent generation and formate production. However, the Faradaic efficiencies for formate formation of the planar and wire electrodes were similar at < 10%, presumably due to the same surface characteristics. In an attempt to catalyze formate production, Sn nanoparticles were strategically photo-electrodeposited onto the p-Si electrodes because of its

### **Experimental Section**

### Fabrication of p-type Si nanowire electrodes

An Ag-catalyzed electroless chemical etching method was used to prepare vertically aligned, free anding alicon anowire array electrodes. For this, p-tyre Si (100) wafers (WaferKorea, 17.1; B-dope as 17.10) the document of the control of the contr

water. During the chemical etching process, the backsides of the Si wafers were covered with Teflon tape. The substrates were dipped in a piranha solution ( $H_2SO_4/H_2O_2 = 3$  in volume) for 5 min and then in HF (5%) for 1 min to remove the surface oxides. To deposit the Ag seed layer, the substrates were dipped into an aqueous solution of AgNO<sub>3</sub> (10 mM) and HF (5 M)

## Small matches of frequently used standard terms or expressions.

for 3 min and rinsed thoroughly with deionized water. Finally, they were immersed into an aqueous solution of  $H_2O_2$  (0.27 M) and HF (5 M) for various times (1–10 h) to grow the wire arrays. The wafers were then soaked in HNO<sub>3</sub> (60 %) to remove the residual Ag from the Si surface, rinsed with deionized water, and dried using a stream of  $N_2$ . For the photoelectrochemical tests, the Si wafers were cut into pieces (1.5 cm × 1.0 cm) onto which a silver paste (Cans, Inc.) was painted to have ohmic contact of the back side. After drying at 80 °C, the p-Si wire arrays were masked with Teflon tape and only a certain fraction of the area (0.35 cm<sup>2</sup>) was exposed to the electrolyte.



## Case Studies: What's Plagiarism And What Isn't?

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For the fully charged state (Figure 9, state 1: 3 V), the Fe and Mn nanoparticles are consumed and p 40 crystallized phases are formed. Only the first FT peak can be seen while the peak features at longer distances are attenuated, suggesting a reduction in crystallinity and/or particle size. The first FT peak located at ~1.8 Å exhibits shorter distance in comparison with the crystallized pristine Fe<sub>0.5</sub>Mn<sub>0.5</sub>S. This agrees well with

### Experimental section:

### Material synthesis 4 d characterization:

All the samples were prepared by using a solid state reaction method. For FeS, MnS and Fe<sub>x</sub>Mn<sub>1.x</sub>S (x=0.2, 0.5, 0.8), the Fe and/or Mn powder, S powder were carefully ground and tabletted. The state of the samples were ground to electrode paration. The state of the samples were ground to electrode paration. The state of the samples were ground to electrode paration. The state of the samples were ground to electrode paration. The state of the samples were ground to electrode paration. The state of the samples were produced by the samples were obtained by refining the XRD data using Fullprof.

### Eliztrochemistry test:

The working electrode was prepared by spreading the slurry of the active materials (70 wt.%), acetylene bla (20 wt.%) and sodium alginate binder (10 wt.%) on Cu foil with the distilled water as solvent. The electrode was dried at 100°C in vacuum for 10 h before use. The coin cells were assembled with pure lithium foil as the counter electrode, and a glass fiber as the separator in an argon-filled glove box. The charge/discharge measurements (31 carried out on a Land BT2000 battery test system (Wuhan, China) at a current rate of 0.1C (1C=600 mA g<sup>-1</sup>) under room temperature. The MnS and Fe<sub>x</sub>Mn<sub>1-x</sub>S (x43 2, 0.5, 0.8) electrodes were discharged and charged between the voltage range of 0.1–2.5 V. The voltage range for the FeS electrode was 1.0–2.5 V.

Looks bad, but it's about standard experimental procedures – very difficult to rephrase, and why would one intentionally describe the same method differently? That could be understood as trying to make it look new.



## Case Studies: What's Plagiarism And What Isn't?

### 1. Introduction

The increasing needs of electrical energy storage have promoted the great success of lithium-ion batheries (LIBs) in portable electronics, and they are also being developed for application in large-scale applications, such as electric vehicles and grid-scale storage. The transition from portable electronics to vehicles and grid, with exacted lifetime greater than ten years, will require substantial improvements of the LIBs in calendar and cycling life. [1.2] In addition, vehicle applications require at least a two-fold improvement of the energy and power densities. One of the promising classes of electrode materials that could meet these stringent requirements is the conversion reaction based transition metal compounds (including oxides, fluorides, sulphides and nitrides), which provide capacities several times higher than those of existing intercalation compounds, due to the multiple electron transfer per transition metal ion through the conversion reaction. [3-5] Among them, transition metal oxides [6-9] and fluorides [10-15] have been intensively investigated. It was shown that Li insertion into the MO/MF (M=Mn, Fe, Co, Ni and Cu)

The red overlap is harmless (hundreds of papers on topic published already).

The purple overlap is highly questionable. This was probably lifted intentionally from the source paper and only minimally

modified.

## 3. Questionable...

If a manuscript displays a number of such overlaps, coincidence can be ruled out – especially when the number of sources is very limited.

The editor should take action!



been effectively combined into binary atomic materials

resistant property.

Amalgam, an alloy of mercury w containing the concept of "binary served as excellent and versatile application, strength, and durability hardness, was used in the rang Ds Strockerus in about 1528[11] In this solid silver atomic lattice, resulting so it can be used to fill any desired fillings).

Besides alloys, the concept of molecular design engineering. Amy different fiel have been Owing tails, these water, hydrophilic regions (head) the hydrophobic regions (tail) in surrounding water has been replace groups at the centre with the tails of molecular structures are able to re aggregation models.

In organic electronics, terracyano [15-17], in which organic molecules a donors, suffer from the inhomogen attentions due to their controllable mo binary alternating D-A molecular de partial charge-transfer state which is weakly polarized state promotes the

properties.[18] Thus, all-organic donor

and facilitates the transport of charge transport efficiency. Recently, as no

by using binary orimenylthieno[3,2-b (DPP, acceptor)-based conjugated poly 183 Invality is an important issue inten

materials science [21, 22] Liu et. thiazolylazo)phenol (TARC18) could

LS films

allowing multi-responsive molecular fi

repeat cycles can be more than ion. achieved from well-defined molecules

fabricating novel chiral materials

Compared with binary man-made

biomacromolecules that functioning of all known living or multi-super "binary cooperative comp consisting of alternating sugars (dec extend the concept of "binary cooperative complementary" to one dimensional BCCNMs

2.1 Two dimensional wettability-switche

Thermo-driven smart surfaces. Nature p stimuli via multi-weak-interactions among hemoglobin, oxygen, and carbon conformations (bistable states) of hemoglo multi-weak-interaction between hemogle oxygen are loosely bound, which results

complementary polymer Burface-ini

has been used to fabricate thermally re nanotubes,[58] or silicon substrate,[5 superhydrophilicity (about 0°) and superhy range of about 10 °C (Figure 6c). The opp between intermolecular and intramolecu temperatures below the LCST (32-33% conformation leading to the predomin

carbonyl groups, amino groups and water

(nanochannels and fibers) and three dimens pH and others-driven smart surfaces. The change of pH value will dominate stereo configurations of binary cooperative complementary molecules, yielding hydrophilic or hydrophobic molecular segments exposed to the water contact. Smart surfaces that can switch between superhydrophilicity and superhydrophobicity using i-motif DNA have been reported. [74] This macroscopic surface phenomenon originates from the collaborative effects of surface microstructure and collective nanometer scale motion of DNA nanomachine. They modified hydrophilic DNA with a fluoride-containing hydrophobic group and immobilized it onto a gold surface through a gold-thoil bond to create an intelligent switching surface Oncer basic conditions (pH 8.5), the i-motif structure of DNA molecules on the surface converted into the stretched single-stranded structure. The original state of the DNA was able

> process [76-78] The patterned wetting-state transition can induce a localized wetting adhesion switching on liquid/solid interfaces. For example, when the applied voltage was below the threshold value of electrowetting, a drop of red ink placed on the ACNA surface was in the Cassie state, with air trapped in the troughs between the individual nanorods. Then, patterned wetting-state can transfer to the Wenzel state through the UV irradiation due to the existing electrocappillary pressure. Since the liquid/solid interface without illuminating was still governed by Cassie's state, the redundant liquid could be easily removed, yielding



patterned liquid printing.

## **Editorial Assessment**

### Conceptual advance

• What is already known in this area and related fields? What gap in knowledge motivates this research? How do the main claims of this study relate to benchmark prior publications? Is this field new, growing or mature? What new insight is offered by the current submission? If confirmation, or a negative finding, what is the value added?



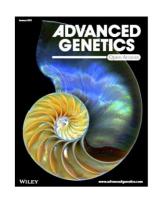
• Are many labs likely to conduct their research differently because of these findings? Is the paper likely attract readers beyond the immediate research community of the study? Is the main conclusion generalizable to other areas of genetics and genomics?

## Strength of conclusion

• What evidence and methods support the main claim of the study? Are the experimental and analytical approaches aligned with the current community standards? What are the technical issues with key datasets and workflows, what reviewer expertise might we need? Are the authors skeptical, are alternative interpretations ruled out? Is there clear separation of hypothesis generation and testing? Are conclusions replicated or supported by multiple lines of evidence?



Editor-in-chief **Myles Axton** 



Volume 1, Issue 1 December 2020

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## 同行评审类型 - 常见类型

类型	优点 Pros	缺点 Cons
单盲评审 Single Blind	Anonymity allows the reviewer to be honest	Potential for discrimination
Author Known	Knowing the author allows the reviewer to use	<ul> <li>Knowledge of the author may overshadow the</li> </ul>
Reviewer Unknown	their knowledge of previous research	quality of the work
双盲评审 <b>Double-Blind</b> • Author Unknown	<ul><li>Prevents bias</li><li>Protection against criticism for both authors</li></ul>	<ul> <li>Author still identifiable (writing style, topic, citations)</li> </ul>
Reviewer Unknown	and reviewers	<ul> <li>Knowledge of the author's identity could help the reviewer come to a more informed judgement</li> </ul>
开放同行评审 Open	Encourages accountability and civility	Some reviewers might refuse to review
Author Known	Reviewers are more motivated to do a	<ul> <li>Reviewers could be reluctant to criticize the</li> </ul>
Reviewer Known	thorough job	work of more senior researchers
Reviewer comments are sometimes published alongside paper		

## Step by Step Guide to Reviewing a Manuscript

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How to peer review

Become a reviewer

- The invitation to review contains title and abstract
- The First Read-Through:
- What is the main question addressed by the research? How original is the topic? Is the text clear and easy to read?
- Spotting potential major flaws: methodology/figures/tables
- The Second Read-Through: raise a problem, provide a solution
- Form a report and give recommendation

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## 同行评审 – 修改 Revisions requested: Before you respond

- Remember: Editors/Reviewers are just trying to help
- Don't get angry it is not personal
- Don't respond immediately
- Seek advice from your supervisor or colleagues



## 同行评审 – 修改 Revisions requested: How should I revise?

## **Carefully consider reviewer comments**

Not all changes that the reviewers want have to be made...

## **Prepare revision**

- Revise manuscript
- Highlight changes in manuscript!
- Point-by-point response to all reviewer issues
- Changes made and why which changes were not made!

## Need to convince editor and reviewers!

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## **Should I Appeal?**

## Usually, no

- Risk of long time to publication
- Good papers are noticed and cited no matter where they are published
- Criticism may be valid!

## Occasionally, yes

 Importance, impact or novelty missed by the editor / referees

(Need for a good cover letter!)

 Factual errors in referee reports that led to rejection



## 文章被接收后 Congrats, but please keep attention

- Signing copyright form your action please
- Typesetting <u>Peer reviewed version online (5 days)</u>
- Copyediting
- Proofreading your action again
  - Your last chance to check
  - Respond quickly
  - Revise minor errors only
  - Do not change house style
- Final approval by the Editor
- Published online as Early View
- Published in an issue Final version online/print with an issue

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9 promotional tools

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总结 Summary

多读,多写,多说



