

Linear assembly of TMEM161B reveals a conserved mechanism for intracellular heme management

UCSF

Cardiovascular
Research Institute

Jingxuan Yao¹, Yanchang Bian², Shiya Xu¹, Shengjian Liang¹, Zhijian Ji², Jiachen Liu¹, Yemu Chen¹, Zihao Rao^{1,*}, Dengke Ma^{2,3,4,*}, Zhiyong Lou^{1,*}

¹ School of Basic Medical Sciences, Tsinghua University, Beijing 100084, China

² Cardiovascular Research Institute, University of California San Francisco, San Francisco, California, 94158, USA

³ Department of Physiology, University of California San Francisco, San Francisco, California, 94158, USA

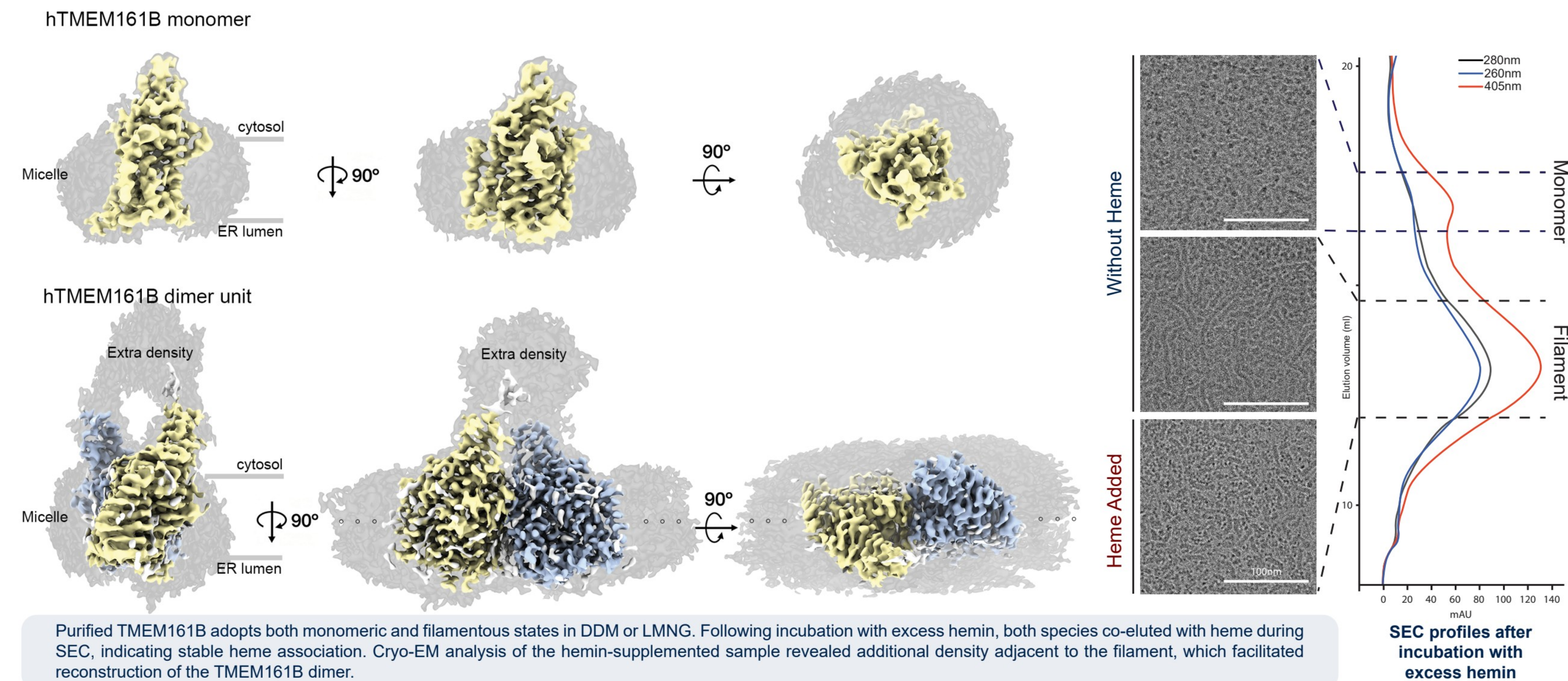
⁴ Innovative Genomics Institute, Berkeley, California, 94720, USA

* Correspondence: Z.R. (raozh@tsinghua.edu.cn), Z.L. (louzy@mail.tsinghua.edu.cn) and D.K.M. (Dengke.Ma@ucsf.edu).

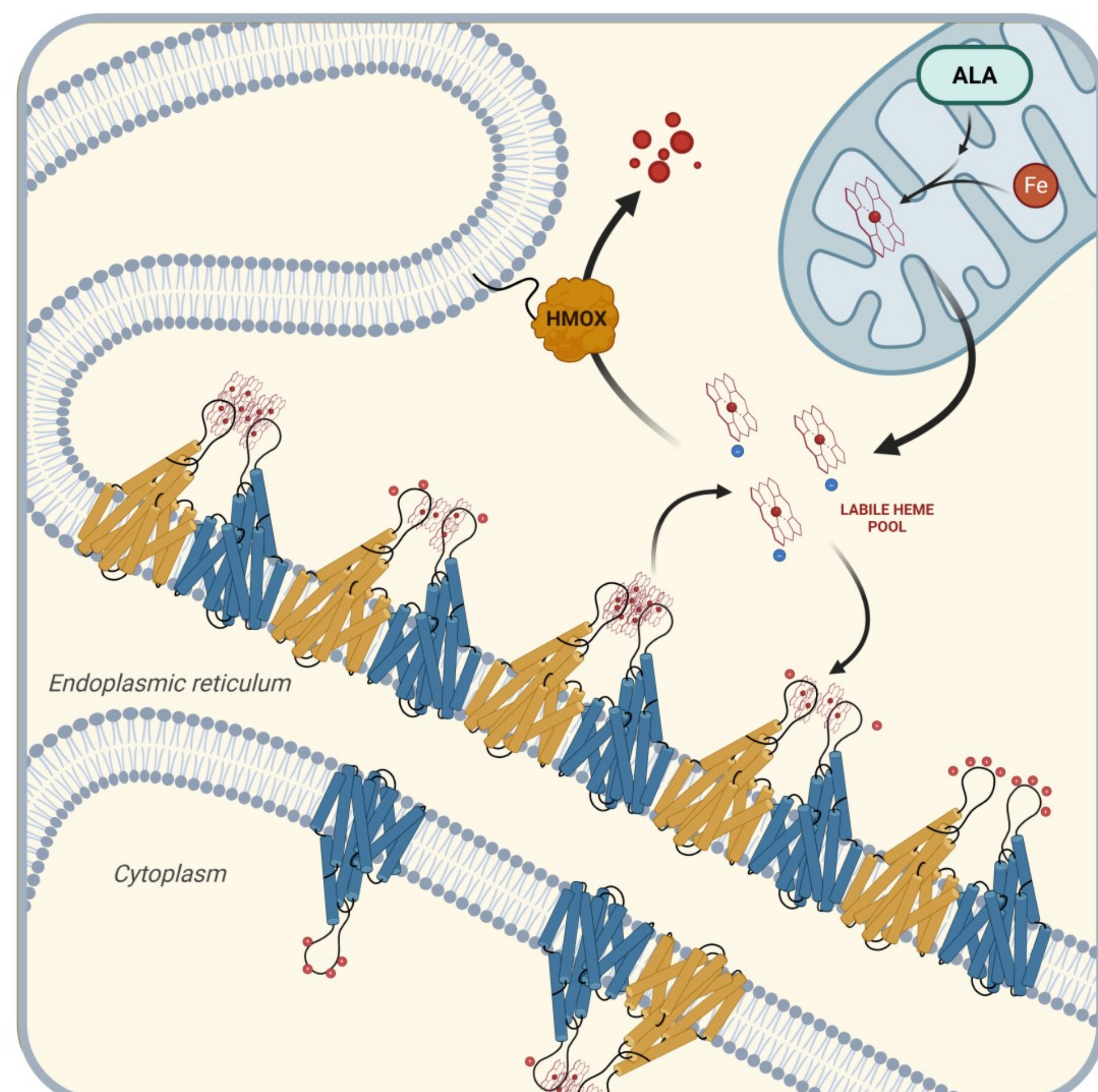
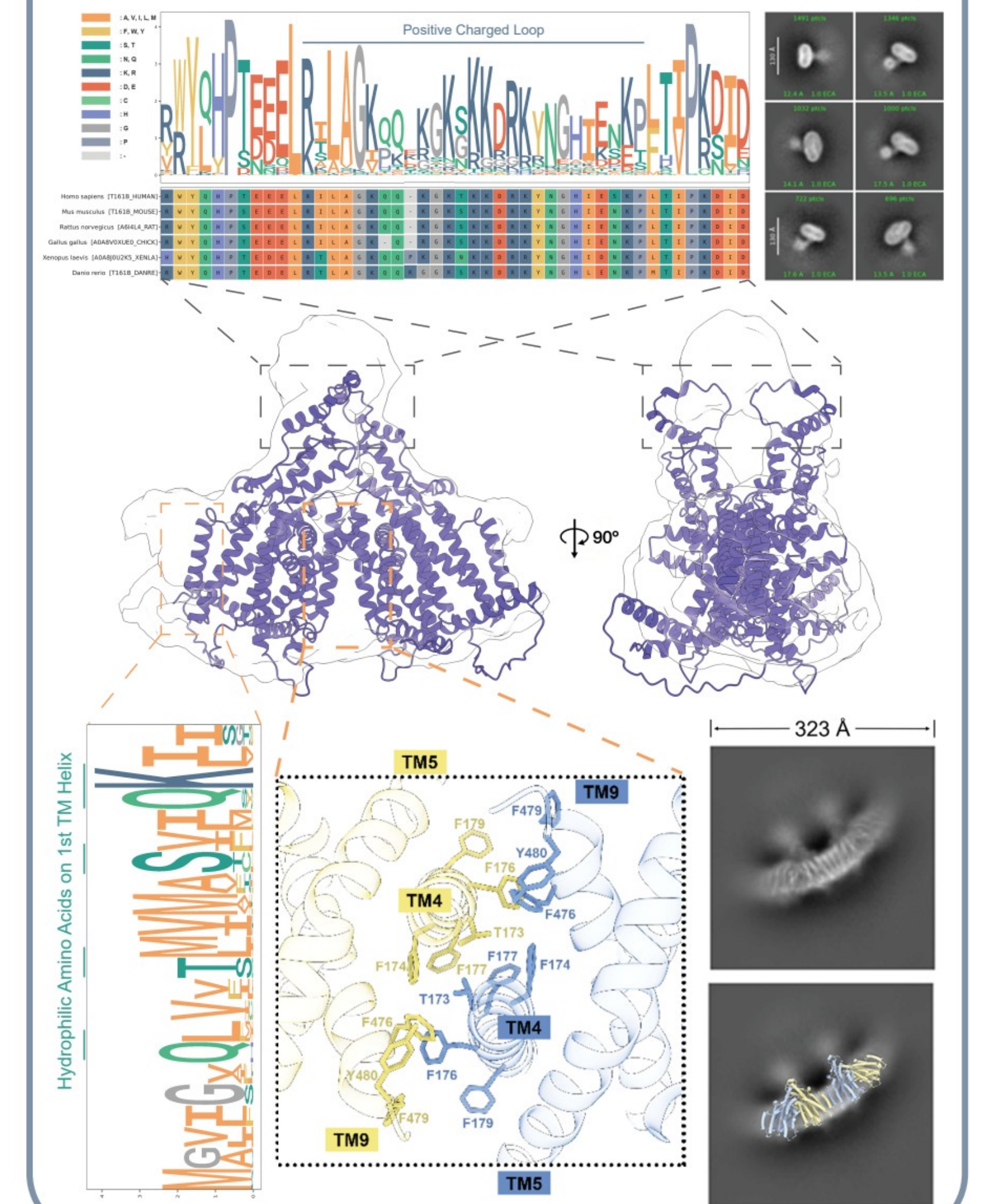
Abstract

Heme supports essential cellular processes, but its labile form is both pro-oxidant and signaling-active and must therefore be tightly controlled. Here, we identify the conserved ER membrane protein TMEM161B as a regulator of cytosolic labile heme. Cryo-EM structures reveal monomeric and dimeric TMEM161B assemblies that form linear arrays through two oligomerization interfaces. Within each dimer, cytosolic loops form a pseudo-C2-symmetric clamp capable of binding up to 8–9 heme molecules. TMEM161B overexpression decreases cytosolic labile heme, whereas knockdown increases it and alters heme-responsive transcription. Loss of the TMEM161 ortholog in *C. elegans* produces a consistent heme-responsive phenotype. Together, these findings support a conserved role for TMEM161B assemblies as a membrane-associated heme-buffering platform.

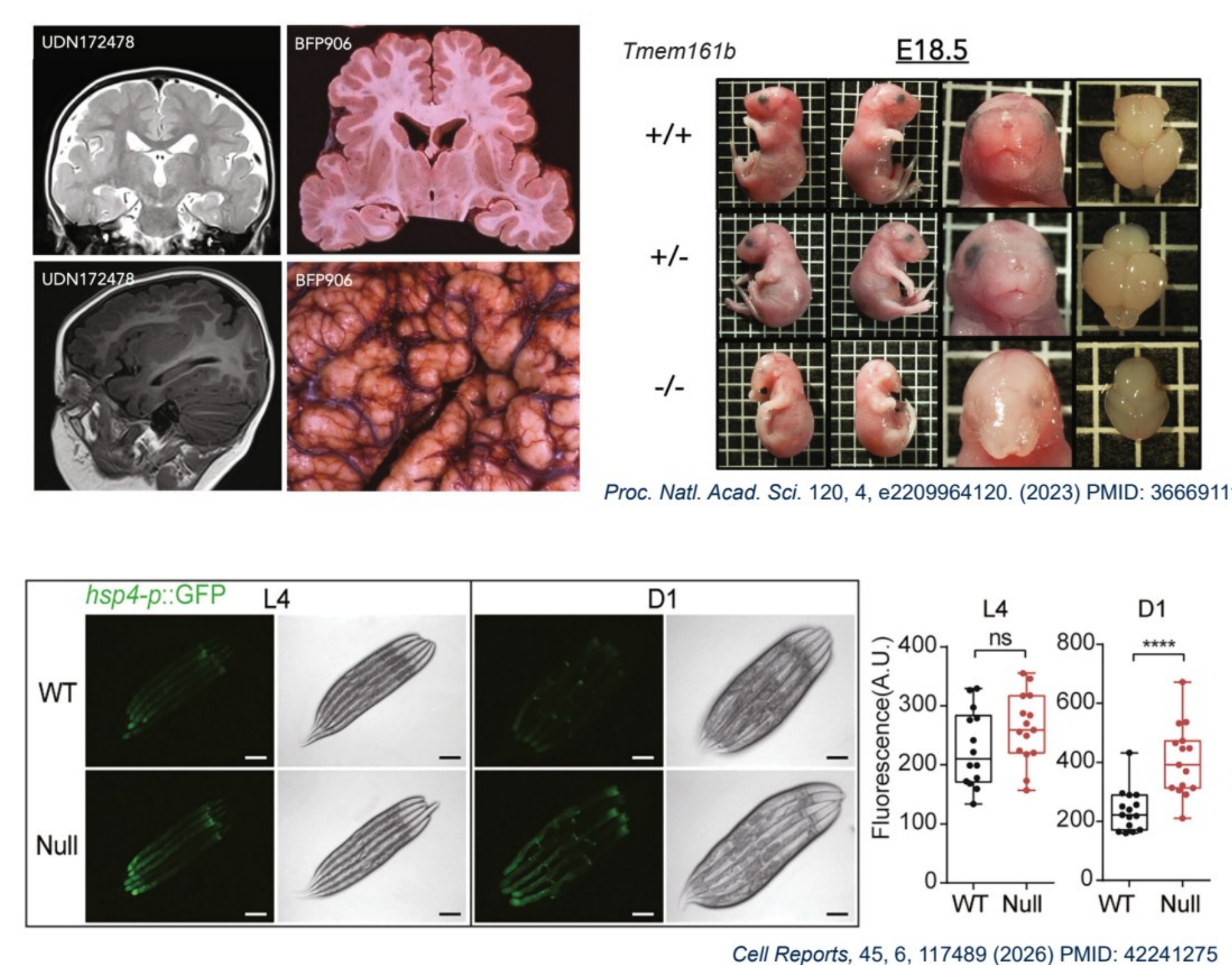
TMEM161B forms heme-associated monomers and linear filaments



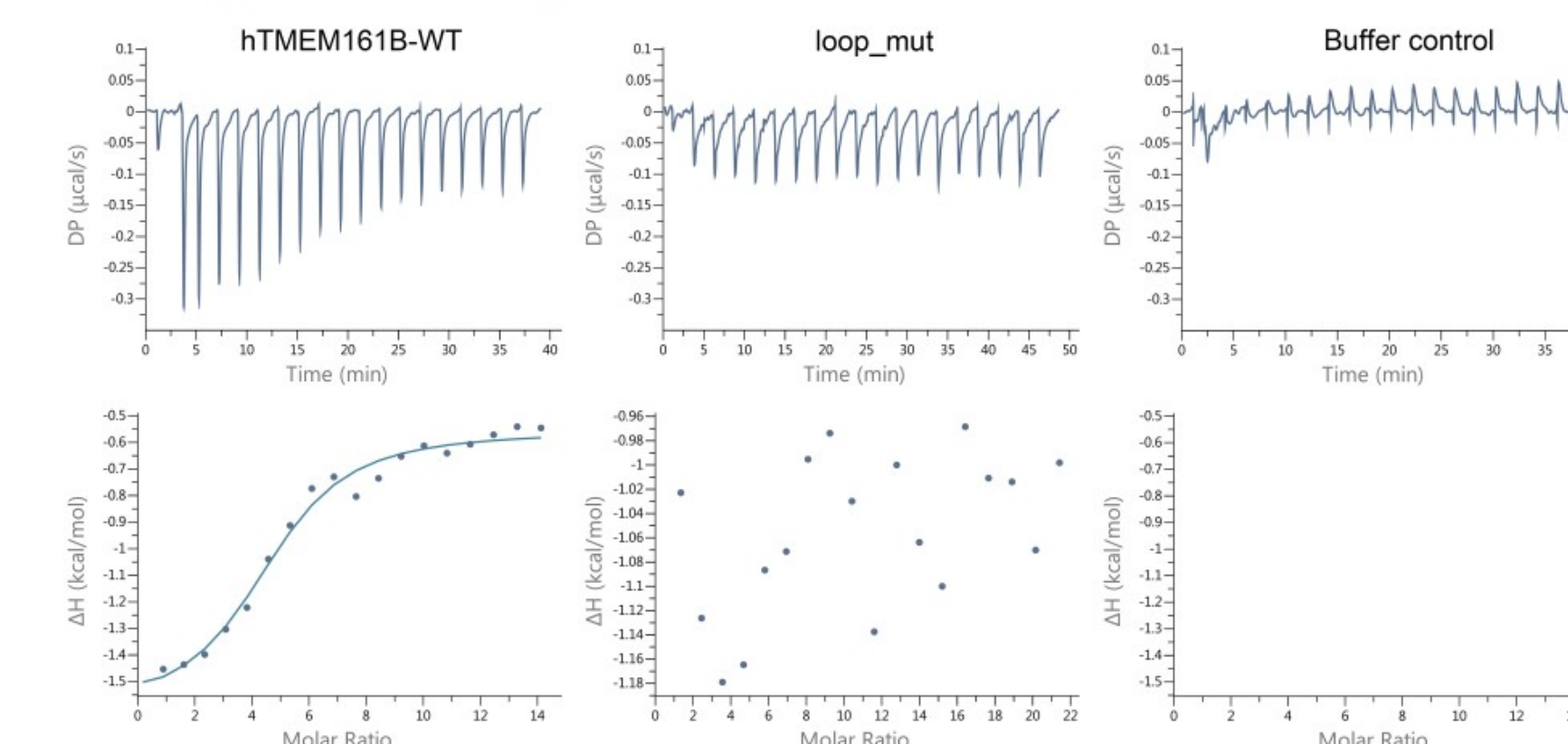
Structural basis of TMEM161B heme binding, dimerization, and filament assembly



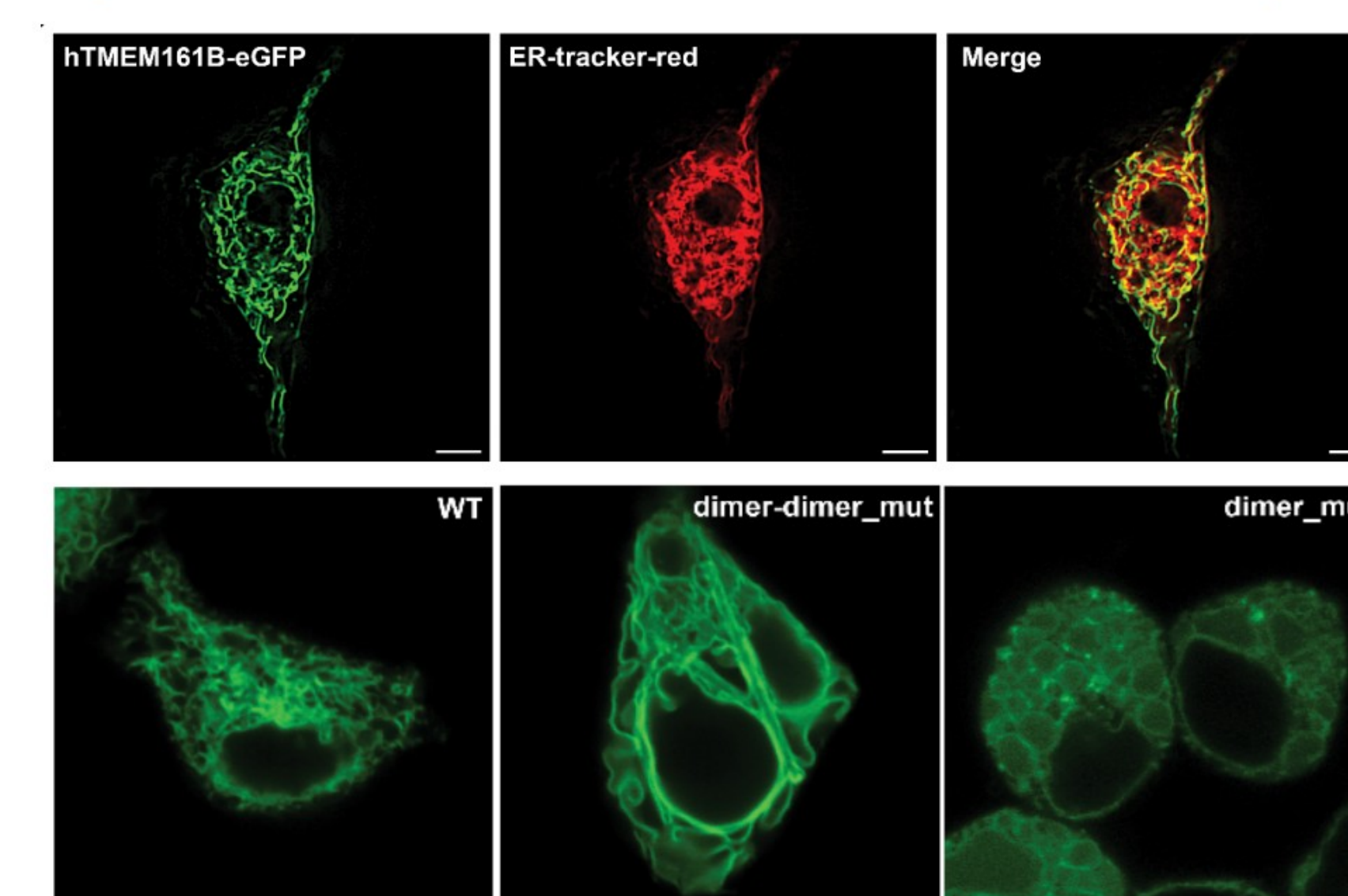
TMEM161B is evolutionarily conserved and essential for development



The cytosolic loop mediates multivalent heme binding

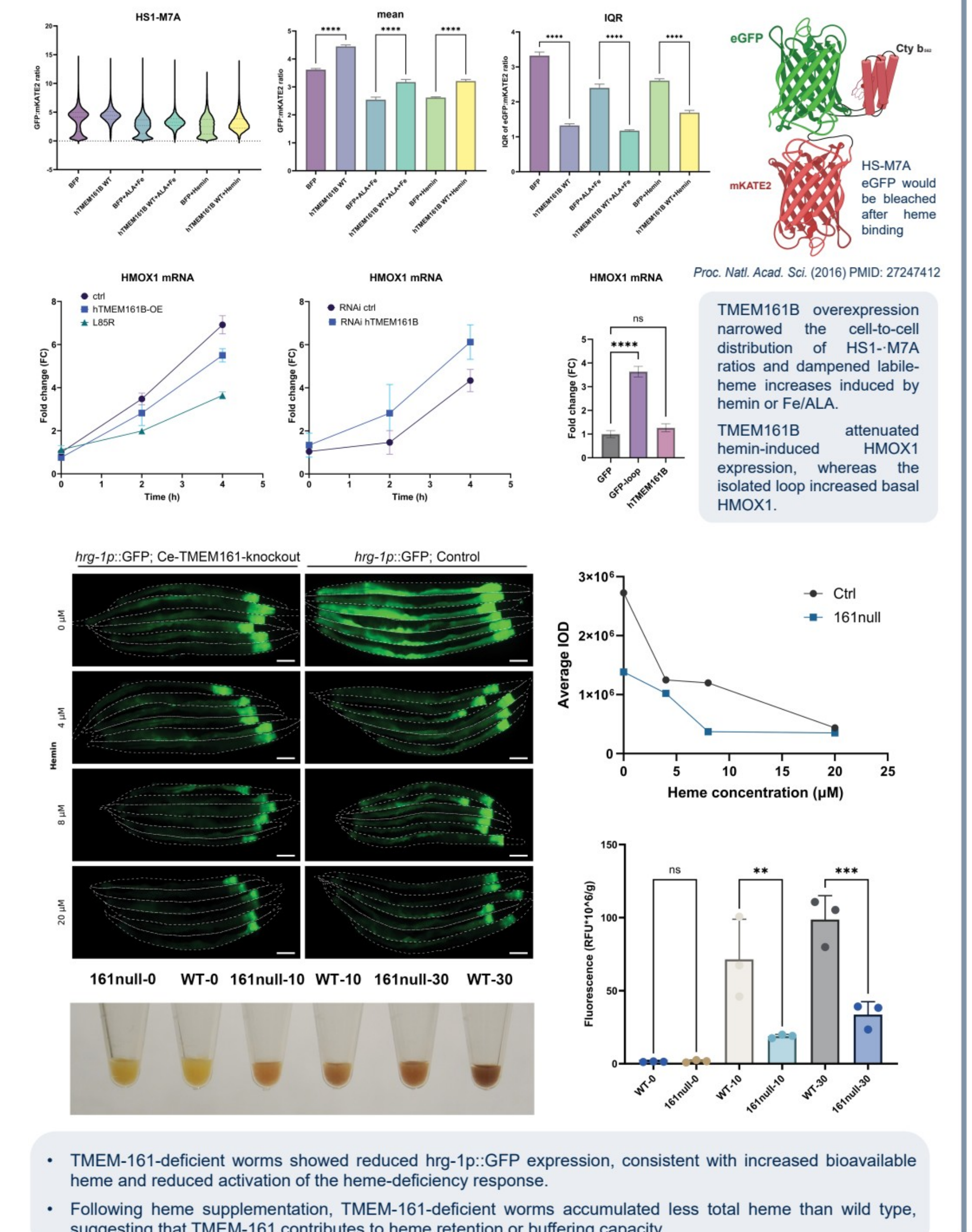


The oligomeric state of TMEM161B influences ER morphology



TMEM161B localizes to the ER. Mutations of aromatic residues at the dimerization interface, or polar residues at the dimer-dimer interface, caused severe disruption of ER morphology.

TMEM161B buffers labile heme



Summary

- TMEM161B dimers assemble into ER-associated linear filaments.
- A cytosolic loop clamp binds approximately nine hemin molecules per dimer.
- Cellular and *C. elegans* data support a conserved role for TMEM161B in buffering labile heme.