

## COMMENTARIES



### JCI's Conversations with Giants in Medicine: Elias Zerhouni

Ushma Neill with the Journal of Clinical Investigation Series, Conversations with Giants in Medicine met Dr. Elias Zerhouni at the Lasker Awards in September of 2023 and jumped at the opportunity to be able to spend an hour with him. Zerhouni, who is Professor Emeritus at Johns Hopkins University and Vice Chairman and President of OPKO Health, is a radiologist by training, who focused much of his research on CT and MRI-based imaging methods to diagnose cancer and cardiovascular diseases. He notably served as the director of the US National Institutes of Health from 2002 to 2008 and later as president of global research and development at Sanofi.

[https://www.jci.org/articles/view/180284?utm\\_source=notices&utm\\_medium=email&utm\\_content=link&utm\\_campaign=JCI+-+April+1%2C+2024%2C+issue+published](https://www.jci.org/articles/view/180284?utm_source=notices&utm_medium=email&utm_content=link&utm_campaign=JCI+-+April+1%2C+2024%2C+issue+published)

Related video: [https://www.youtube.com/watch?v=x9vKZ\\_iwMcwi](https://www.youtube.com/watch?v=x9vKZ_iwMcwi)



### A fresh start for the African Academy of Sciences

New leadership is giving the academy a stronger voice for the continent's scientists, following one of its most testing periods.

<https://www.nature.com/articles/d41586-024-00814-1>

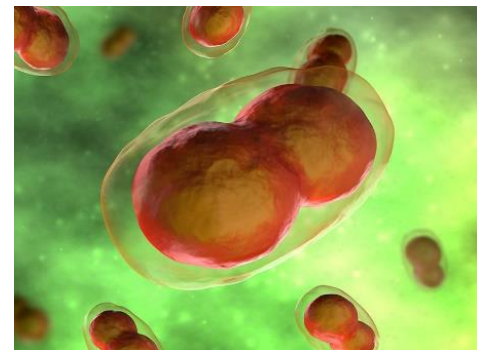
## SELECTED PUBLICATIONS

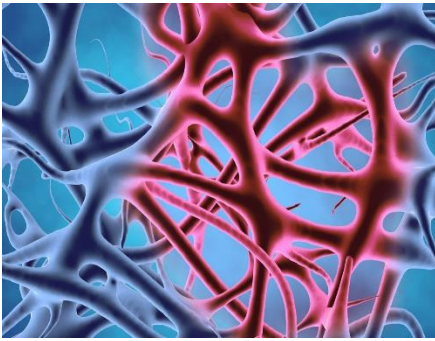
### A multivalent mRNA monkeypox virus vaccine (BNT166) protects mice and macaques from orthopoxvirus disease

**Adam Zuian et al., 2024**

[https://www.cell.com/cell/fulltext/S0092-8674\(24\)00054-0](https://www.cell.com/cell/fulltext/S0092-8674(24)00054-0)

- BNT166 is a multivalent mRNA orthopoxvirus vaccine encoding MPXV antigens A35, B6, M1, H3
- It elicits robust antibody and T cell responses to EV and MV antigens
- Immunization protects mice from VACV, clade I and IIb MPXV, and NHPs from clade I MPXV
- Clinical evaluation of BNT166 safety and immunogenicity is ongoing (NCT05988203)





## **IL-10 constrains sphingolipid metabolism to limit inflammation**

**York et al., 2024**

<https://www.nature.com/articles/s41586-024-07098-5>

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine that can limit immune cell activation and cytokine production in innate immune cell types<sup>1</sup>. Loss of IL-10 signalling results in life-threatening inflammatory bowel disease in humans and mice—however, the exact mechanism by which IL-10 signalling subdues inflammation remains unclear<sup>2,3,4,5</sup>. Here we find that increased saturated very long chain (VLC) ceramides are critical for the heightened inflammatory gene expression that is a hallmark of IL-10 deficiency.

## **Severe disease during both primary and secondary dengue virus infections in pediatric populations**

**Charu Aggarwal et al., 2024**

<https://www.nature.com/articles/s41591-024-02798-x>

Dengue is a global epidemic causing over 100 million cases annually. The clinical symptoms range from mild fever to severe hemorrhage and shock, including some fatalities. The current paradigm is that these severe dengue cases occur mostly during secondary infections due to antibody-dependent enhancement after infection with a different dengue virus serotype. India has the highest dengue burden worldwide, but little is known about disease severity and its association with primary and secondary dengue infections



## **The circadian molecular clock in the suprachiasmatic nucleus is necessary but not sufficient for fear entrainment**

**Bussi et al., 2024**

<https://doi.org/10.1073/pnas.231684112>

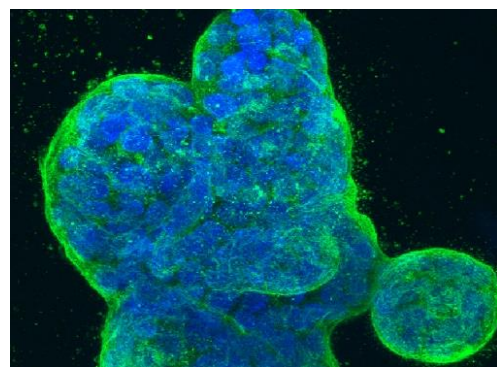
Cyclic fearful stimuli presented while mice are foraging and feeding outside of a safe nest can entrain circadian rhythms and lead to predominantly diurnal activity; this mistimed circadian behavior persists for days after the aversive stimulus is no longer present. Our results suggest that disrupted circadian rhythms and sleep typical of anxiety disorders, such as posttraumatic stress disorder, may represent the output of a previously entrained fear-entrained circadian clock whose output sustains a maladaptive timing of behavior and sleep in the absence of actual threats. We provide mechanistic insight into this fear-entrained clock, which could contribute to the elucidation of molecular mechanisms and neural circuitry that underlie anxiety disorders and provide broad avenues for their treatment.

## Activation of ER $\beta$ hijacks the splicing machinery to trigger R-loop formation in triple-negative breast cancer

Wang et al., 2024

<https://doi.org/10.1073/pnas.2306814121>

While accumulating evidence has proved the presence of ER $\beta$  (estrogen receptor  $\beta$ ) expression in TNBC (triple-negative breast cancer), the functional roles ER $\beta$  in TNBC have been controversial. Our study has demonstrated that the activation of ER $\beta$  hijacks the splicing machinery to modulate intron retention of 5-oxoprolinase (OPLAH), encoding a critical enzyme OPLAH involved in glutathione metabolism and oxidative stress. Altered splicing of OPLAH results in R-loop formation and DNA damage in TNBC cells. The identification of this molecular mechanism offers broad therapeutic avenues for future development of ER $\beta$  inhibitor and optimized combination therapies as treatment of TNBCs in the clinical setting.



## Engineering a nanoantibiotic system displaying dual mechanism of action

Xing et al., 2024

<https://doi.org/10.1073/pnas.2321498121>

The lack of new antibacterials has complicated our ability to deal with antimicrobial resistance. It is key to develop alternative approaches to combat pathogenic infections. Herein, we present a nanoantibacterial therapy that combines two molecules with orthogonal mechanism of action: a disruptor of cylindrical proteases (new mechanism of action) and a nanocarrier that damages the bacterial membrane. Notably, upon disassembly, the nanocarrier becomes an active component of the antimicrobial therapy, transforming the narrow-spectrum small molecule (limited permeation) into a broad-spectrum compound. Further, the antibacterial effect and cytotoxicity profile is altered based on how the therapy is formulated: coadministration of the molecule vs. encapsulation of the small molecule into the nanocarrier.

## Trends in rare disease drug development

Rui Chen et al., 2024

<https://doi.org/10.1038/d41573-023-00177-8>

Advances in the understanding of the biology underlying rare diseases, as well as progress with therapeutic platforms such as nucleic-acid agents, have enabled increased research and development (R&D) on drugs for rare diseases. Governmental incentives and regulatory initiatives have played a key role too, such as the Orphan Drug Act of 1983 in the USA



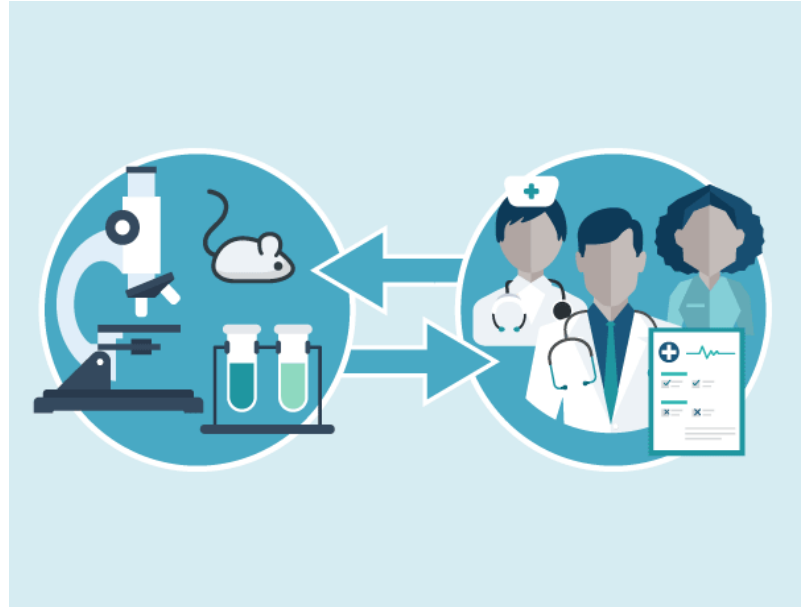
## RECOMMENDED EVENTS

### Cancer Immunotherapy: From bench to bedside and back

**June 10, 2024 – June 12, 2024**

**Dana-Farber Cancer Institute - Jimmy Fund Auditorium**

This meeting will bring together experts from across the cancer immunotherapy field to present the most striking biological, technological, translational and clinical advances. Discussions will focus on how fundamental knowledge can be translated to the clinic, with insights gained in the clinical setting brought back to the lab to inform the development of innovative cancer immunotherapy approaches for the benefit a wider group of patients.



<https://conferences.nature.com/event/7d8defc1-4522-41e2-955b-28844b576e6d/summary>

### Cell Symposia: Hallmarks of cancer



In partnership with Sun Yat-sen University Cancer Center and Guangdong Provincial Anticancer Association

**November 7–9, 2024**,  
Guangzhou, China

Abstract submission deadline:  
July 5, 2024

Early registration deadline:  
September 6, 2024

<https://www.cell-symposia.com/hallmarksofcancer-2024/index.html>