Patient Wellness First

BioSciTech biweekly NEWS

Issue: October 15th, 2024

NEWS & COMMENTARIES

2024 Nobel Prize

Physiology -Medicine

Victor Ambros and Gary Ruvkun:

Discovery of microRNA and its role in post-transcriptional gene regulation.

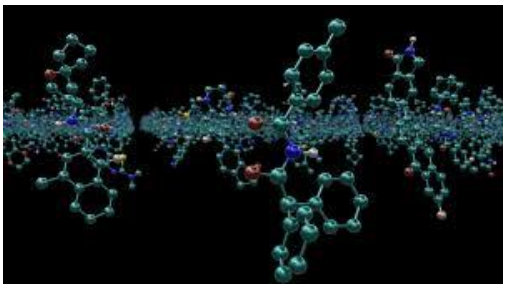
Warm Congratulation

Chemistry

David Baker for computational protein design" and the other half jointly to **Demis Hassabis** and **John M. Jumper** "for protein structure prediction."

Wellcome Sanger Institute-Sanger spin-out Microbiotica , a clinical-stage biopharma company, announced earlier this week that the first patient has received treatment in its advanced melanoma (MELODY-1) trial. A feat that deserves to be celebrated as microbiome research advances to positively impact human lives.

https://www.sanger.ac.uk/innovation/spin-outs/



TxGNN: Zero-shot prediction of therapeutic use with geometric deep learning and human centered design

Excited to share TxGNN, a model that identifies potential therapies from existing medicines for thousands of diseases. Trained across 17,080 diseases, TxGNN predicts drug candidates for conditions with limited or no treatment options, including rare diseases

https://github.com/mims-harvard/TxGNN?tab=readme-ov-file

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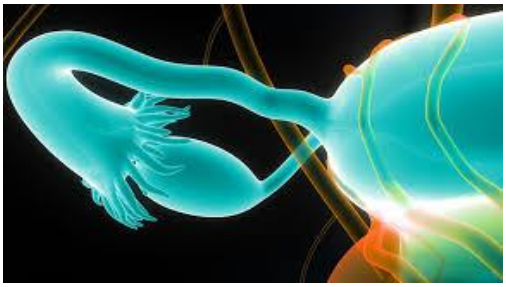
Flagship's AI biotech Generate lands $65M upfront in Novartis deal, as first clinical readouts near

Generate:Biomedicines announced Tuesday another pharma partnership, just the latest indicator of Big Pharma's growing appetite for deals with AI-focused biotechs. Novartis will pay $65 million upfront — $50 million in cash and $15 million for an equity stake — to work with Generate on certain, undisclosed targets.

https://endpts.com/flagships-ai-biotech-generate-lands-65m-upfront-in-novartis-deal-as-first-clinical-readouts-near/



Cancer Research UK awarded researchers at the University of Oxford up to £600,000 to create the world's first vaccine to prevent ovarian cancer. OvarianVax is a vaccine that will teach the immune system to recognize and attack the earliest stages of ovarian cancer developed by **Prof. Ahmed Ahmed**,

https://www.ox.ac.uk/news/2024-10-04-oxford-researchers-secure-funding-worlds-first-ovarian-cancer-prevention-vaccine

Dupixent approved in China as the first-ever biologic medicine for patients with COPD

https://www.sanofi.com/en/media-room/press-releases/2024/2024-09-27-11-00-00-2954416

Dupixent approved in China as the first-ever biologic medicine for patients with COPD. Approval follows EU approval of Dupixent for adults with COPD with raised blood eosinophils, and is based on two landmark phase 3 studies showing Dupixent significantly reduced exacerbations, improved lung function, and also improved health-related quality of life

JCI 100th Anniversary Viewpoints: October 1, 2024

Elizabeth M. McNally reflects on the 100th anniversary of the Journal of Clinical Investigation, major breakthroughs in medicine in the last century, and emerging areas of innovation.

https://www.jci.org/134/19?utm_source=notices&utm_medium=email&utm_content=link&utm_campaign=JCI+-+October+1%2C+2024%2C+issue+published

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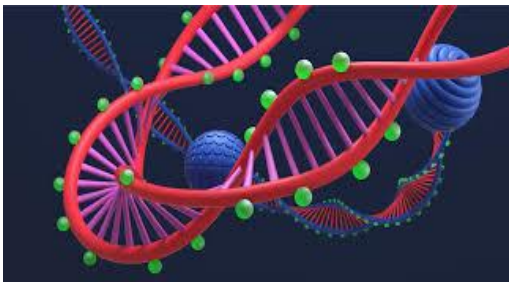
SELECTED PUBLICATIONS

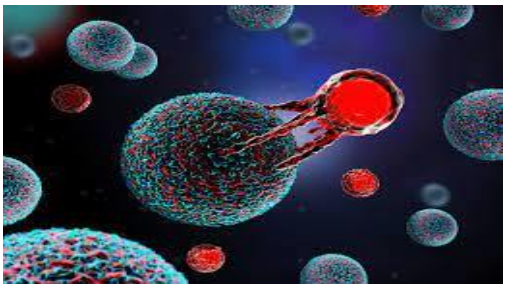


DNA methylation as a new tool for the differential diagnosis between T-LBL and lymphocyte-rich thymoma.

M Latiri, M Belhocine et al, 2024

http://dx.doi.org/10.1002/path.6346

T-lymphoblastic lymphoma (T-LBL) and thymomas are rare thymic tumors that can be hard to differentiate, especially in needle biopsies, due to similar T-cell precursors. To clarify, DNA methylation profiles were analyzed using MeDIP and EPIC arrays, showing distinct separation between T-LBL and thymoma samples. Several differentially methylated genes, including ZIC1 and MACROD2, were identified. A classifier using MS-MLPA showed significant methylation differences, with MACROD2 as the key marker distinguishing thymomas from T-LBLs.

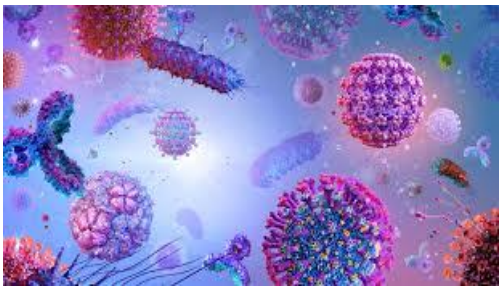


Engineered CD4 T cells for in vivo delivery of therapeutic proteins

Harikrishnan Radhakrishnan et al., 2024

https://doi.org/10.1073/pnas.231868712

Researchers have developed CD4 T cells that deliver therapeutic proteins directly to disease sites, offering safer, more effective treatment than conventional methods. This approach, demonstrated with IFNβ for antitumor therapy, boasts superior transduction, faster expansion, and higher protein production compared to CD8 T cells. With reduced cytotoxicity, CD4 T cells also allow for higher dosing in clinical trials.

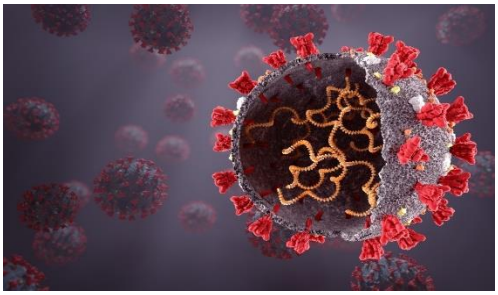


Animal and bacterial viruses share conserved mechanisms of immune evasion

Samuel J. Hobbs et al., 2024

https://www.cell.com/cell/abstract/S0092-8674(24)00889-4

New research reveals that animal and bacterial viruses use similar strategies to evade host immune systems. Structural analysis shows that animal poxvirus proteins share homology with bacteriophage enzymes, both targeting and degrading host nucleotide.



Viral DNA polymerase structures reveal mechanisms of antiviral drug resistance

Sundaresh Shankar et al., 2024

https://www.cell.com/cell/fulltext/S0092-8674(24)00842-0

Cryo-EM structures of herpes simplex virus polymerase have uncovered how antiviral drugs interact with the enzyme, revealing mechanisms behind drug resistance. These findings show that certain mutations alter the enzyme's conformational dynamics, impacting drug selectivity rather than direct binding. This insight is crucial for developing more effective antiviral treatments.

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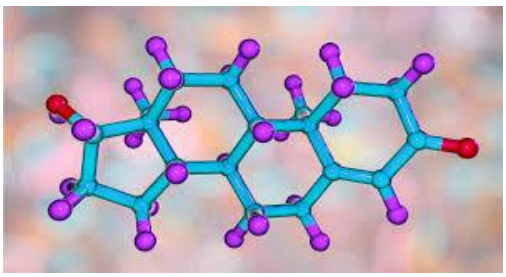


Genomic and transcriptomic features of androgen receptor signaling inhibitor resistance in metastatic castration-resistant prostate cancer

Zhu et al., 2024

https://doi.org/10.1172/JCI178604

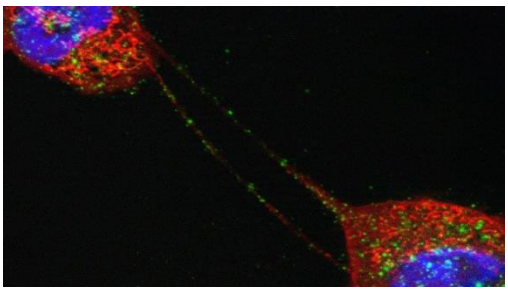
Researchers have uncovered key genomic and transcriptomic changes driving resistance to androgen receptor signaling inhibitors (ARSIs) in metastatic castration-resistant prostate cancer (mCRPC). The study highlights increased AR signaling and transcriptional heterogeneity, along with downregulation of SSTR1, which is linked to reduced therapy effectiveness. Notably, the FDA-approved drug pasireotide was found to suppress tumor cell proliferation.

Natural TCRs targeting KRASG12V display fine specificity and sensitivity to human solid tumors

Bear et al., 2024

https://doi.org/10.1172/JCI175790.

This study reveals the fine specificity of natural TCRs targeting the KRASG12V mutation in solid tumors. These TCRs demonstrated strong sensitivity to mutated KRAS with no cross-reactivity to the wild-type protein, offering high precision in targeting cancer cells. CD8+ and CD4+ T cells redirected with KRASG12V-specific TCRs showed potent anti-tumor activity, highlighting their potential for developing targeted TCR-T cell therapies.



Intercellular nanotube-mediated mitochondrial transfer enhances T cell metabolic fitness and antitumor efficacy

Baldwin et al., 2024

https://doi.org/10.1016/j.cell.2024.08.029

A groundbreaking platform that transfers mitochondria from bone marrow stromal cells to T cells has been shown to enhance T cell metabolism and improve their antitumor efficacy. Through nanotubular connections, mitochondria are delivered to CD8+ T cells, boosting their respiration and reducing exhaustion.

Non-pathogenic E. coli displaying decoy-resistant IL18 mutein boosts anti-tumor and CAR NK cell responses

Yang et al., 2024

https://doi.org/10.1038/s41587-024-02418-6

The tumor microenvironment can hinder cancer therapies by impairing immune cell function. To overcome this, we used non-pathogenic *Escherichia coli* (E. coli) K-12 DH5α, known for its safety and tumor-targeting abilities, to deliver immune-activating cytokines directly to tumors. E. coli expressing a decoy-resistant IL18 mutein (DR18) triggered strong CD8+ T and NK cell responses, slowing tumor growth in colorectal carcinoma and melanoma mouse models.

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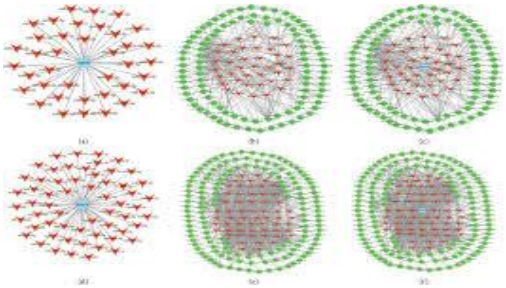
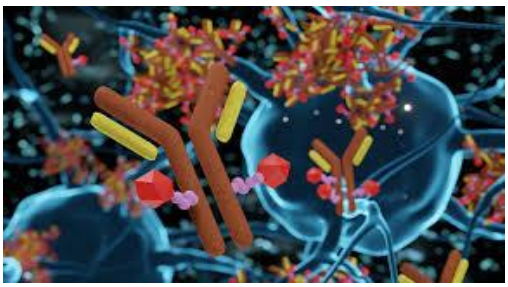


A tripartite circRNA/mRNA/miRNA interaction regulates glutamatergic signaling in the mouse brain

Silenzi et al., 2024

https://www.cell.com/cell-reports/fulltext/S2211-1247(24)01117-3

Functional studies on circular RNAs (circRNAs) are still in their early stages, with limited in vivo data. We created a knockout mouse model to investigate circDlc1(2), a circRNA highly expressed in the prefrontal cortex and striatum. Loss of circDlc1(2) led to increased expression of glutamatergic-response genes in the striatum, enhanced excitatory synaptic transmission, and hyperactivity in mice. Mechanistically, circDlc1(2) interacts with mRNAs related to glutamate receptor signaling and miR-130b-5p, which regulates these transcripts. Unlike typical miRNA sponges, circDlc1(2) cooperates with miR-130b-5p to repress gluRNA expression by localizing it to synaptic regions, ensuring precise gene regulation.

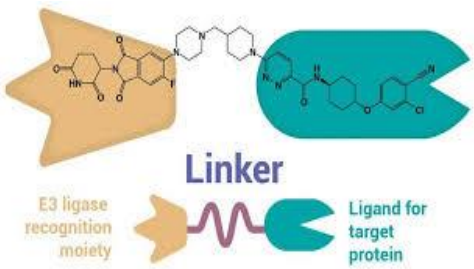


BCL-XL–targeting antibody-drug conjugates are active in preclinical models and mitigate on-mechanism toxicity of small-molecule inhibitors

Judd et al., 2024

https://doi.org/10.1126/sciadv.ado7120

Overexpression of the antiapoptotic protein BCL-XL is linked to drug resistance and cancer progression, making it a key therapeutic target. While selective small-molecule BCL-XL inhibitors showed promise in preclinical models, they caused severe cardiovascular toxicity in higher species. To address this, antibody-drug conjugates were developed using modified BCL-XL-targeting warheads, unique linkers, and therapeutic antibodies. The AM1-15 conjugate, targeting the epidermal growth factor receptor, effectively inhibited tumor growth without causing cardiovascular toxicity or thrombocytopenia in monkeys. However, BCL-XL toxicity in monkey kidneys was observed, which was mitigated by modifying the drug-linker to create AM1-AAA, incorporated into mirzotamab clezutoclax, now in clinical trials.



Precise Modulation of Protein Degradation by Smart PROTACs

Cheng et al., 2024

https://doi.org/10.1002/cbic.202400682

Proteolysis-targeting chimera (PROTAC) is gaining attention as a promising approach in drug discovery. These bifunctional molecules target proteins of interest (POIs) for degradation by linking them to E3 ubiquitin ligases, leading to proteasome-mediated degradation. However, conventional PROTAC degraders face challenges such as systemic toxicity from non-specific targeting. To overcome this, smart PROTACs activated by specific stimuli have been developed to allow precise, spatiotemporal control of protein degradation. This review highlights recent advancements in smart PROTACs, including those responsive to tumor microenvironments, light, and X-ray radiation, discussing their design, applications, and challenges.

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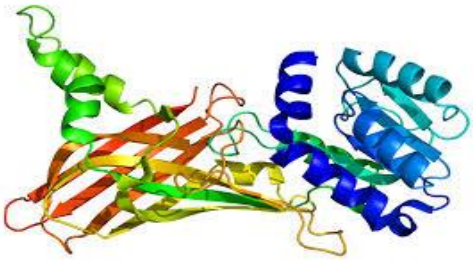
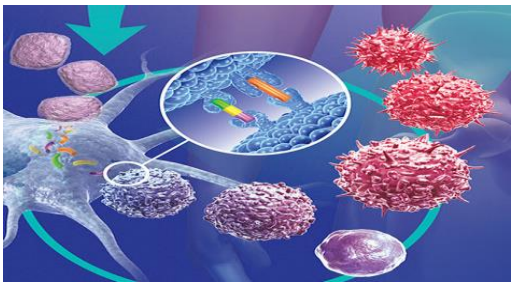


Towards the Targeted Protein Degradation of PRMT1

Martin, et al., 2024

https://doi.org/10.1002/cmdc.202400269

Targeting protein arginine methyltransferase 1 (PRMT1) has shown potential in cancer therapy. However, the first PRMT1 inhibitor to reach clinical trials, GSK3368715, was discontinued due to lack of efficacy and significant side effects. These issues were likely linked to the need for high, sustained inhibitor levels. A better approach may involve using proteolysis-targeting chimeras (PROTACs), which degrade PRMT1 through catalytic, low-dose mechanisms. Researchers synthesized PROTACs incorporating the same pharmacophore as GSK3368715, recruiting either VHL or CRBN E3-ligase. Despite showing cell permeability and target engagement, these candidates did not induce PRMT1 degradation. This study provides valuable insights for future PROTAC design targeting PRMT1 and other proteins.



Proteolysis Targeting Chimeras (PROTACs) in Breast Cancer Therapy

Yerim Jin, Yeongju Lee, 2024

https://doi.org/10.1002/cmdc.202400267

Breast cancer (BC) represents 30% of cancer cases among women globally, highlighting the urgent need for targeted therapies. Proteolysis-targeting chimera (PROTAC) has emerged as a promising strategy for targeting BC. PROTACs are chimeric molecules consisting of a target protein ligand, an E3 ligase ligand, and linkers, which bring the target protein and E3 ligase into proximity for degradation. By catalytically degrading cancer-causing proteins with lower doses, PROTACs offer high therapeutic efficacy. This review discusses the currently developed PROTACs for various BC subtypes, explores their limitations, and examines future perspectives in BC treatment.

RECOMMENDED EVENTS

The Protein Science and Production Week the premier conference dedicated to advancing biotherapeutic discovery and development. With over two decades of experience, PepTalk provides comprehensive programming and innovative solutions that bridge biotherapeutic research and practical application. **https://www.chi-peptalk.com/**

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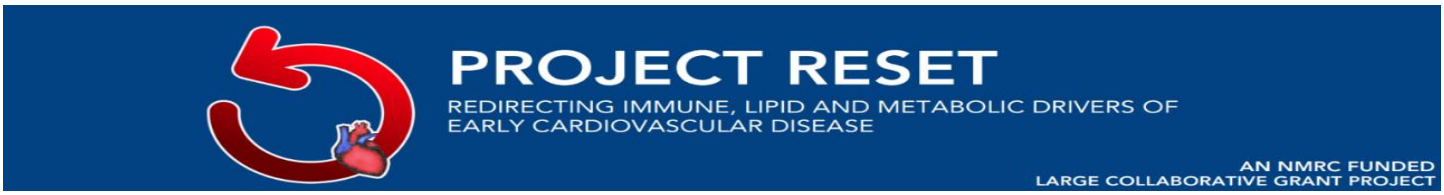


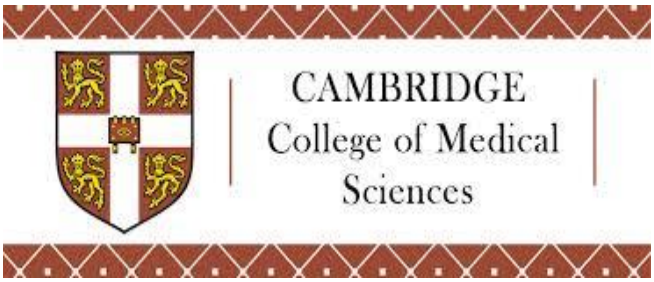
What is Project RESET? is a 5-year government-funded research initiative. It aims to gain a deeper understanding about the population's metabolism, heart, and liver health as well as lifestyle behaviour to prevent heart diseases, including heart attack and stroke.

You may be eligible if you are 40-70 years old, and have any of the following:

- High blood pressure.
- High cholesterol.
- Fatty liver.
- Family history of heart diseases or stroke.

https://medicine.nus.edu.sg/reset_landing/

JOBS CORNER



Fully funded PhD Program for Health Professionals

As a clinical professional, you can study and have a successful academic career. This program is fully-funded. Open on **3 September and the deadline is 5 November 2024**.

https://www.postgraduate.study.cam.ac.uk/courses/directory/cvcbpdwtc

VIB.AIVIB.AI Is actively recruiting junior and senior group leaders at both locations to help define and drive the VIB.AI research agenda. Successful candidates will be appointed as professor at KU Leuven or UGent, two leading universities with top-notch infrastructure and world-class research.

Application deadline: November 1st

https://vib.ai/en

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Scientific Junior Group Leaders
Location: Basel, Basel-city, Switzerland

The Institute of Human Biology (IHB), If you have recently completed a successful postdoctoral appointment and are eager to launch your career as a principal investigator, we encourage you to apply. These roles come with a highly competitive funding package to support your research.

https://institutehumanbiology.com/about-the-ihb/careers/scientific-junior-group-leaders/

Research Assistant (Immunology)
Babraham Institute

We are looking to welcome a new member to our team, with a research assistant position available to work on the mechanisms that underpin successful immune responses

Informal enquiries can be addressed **to Louise Webb, louise.webb@babraham.ac.uk or Michelle Linterman, michelle.linterman@babraham.ac.uk**

https://babrahaminstitute.livevacancies.co.uk/#/job/details/468

EMBL-EBI-AstraZeneca postdoctoral fellowships

https://www.ebi.ac.uk/research/postdocs/eazpods

The EMBL-EBI–AstraZeneca Postdoctoral (EAZPOD) Program builds on the collaborative relationship between EMBL-EBI and AstraZeneca, offering projects that push the boundaries of cutting-edge computational biology in oncology. EAZPOD fellows will be awarded salary funding for three years to carry out a research project between a group at EMBL-EBI and Computational Oncology at AstraZeneca.

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