COMMENTARY

Interview with Dr. Yasmine Belkaid

President of Institut Pasteur, Université Paris-Saclay, Paris, Île-de-France, France

In an interview this morning with Ali Baddou on France Inter, I had the opportunity to share an often overlooked but fundamental perspective on microbes: their crucial role not only as pathogens but above all as allies. What if we explored the immune system together?

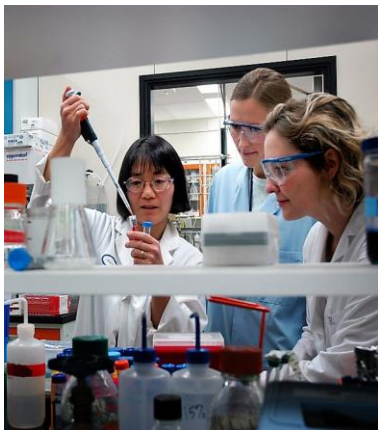
- Microbes can help us too!
- The regulatory role of the immune system
- The impact of pregnancy on future health
- The microbiota, this little-known conductor

I invite you to listen to this interview below and share your thoughts in the comments

https://www.youtube.com/watch?v=gcZpQn0c8sQ

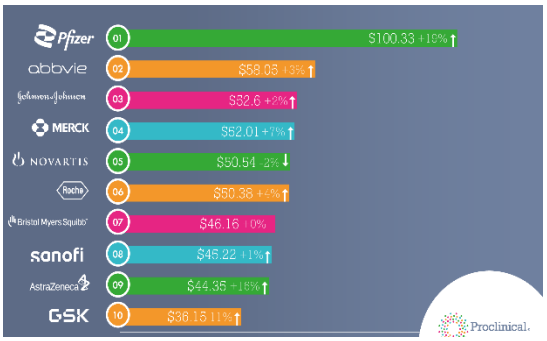
Biotech news from around the world

https://www.nature.com/articles/s41587-024-02216-0



The Ministry of Health and Welfare selects Johnson & Johnson's JLABS to operate the country's global accelerator platform. JLABS will engage with various local incubators and collaborators in the startup ecosystem to offer venture development programs, stimulate employment and encourage commercialization to enhance the global competitiveness of Korea's life sciences sector.

Costa Rica revises its biotech regulatory framework to ease restrictions on gene editing and other new breeding techniques.



Top companies and drugs by sales in 2023

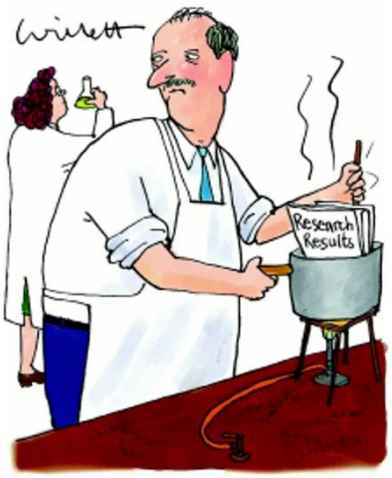
By Paul Verdin

https://www.nature.com/articles/d41573-024-00041-3

As anticipated, there was a shakeup at the top of the pharma industry rankings in 2023. Having sat at the top of the pile for several years as a result of huge sales of its COVID-19 vaccine Comirnaty (tozinameran), Pfizer dropped precipitously from the top spot to be replaced by Johnson & Johnson. The new market leader grew prescription pharmaceutical sales by almost US$3 billion year on year, the largest absolute growth in the cohort and second largest in percentage terms. Johnson & Johnson's growth is driven by a diversified mix of products, led by Darzelex (daratumumab) and Stelara (ustekinumab). Both of these products also feature in the top ten selling products in 2023.

Retractions are part of science, but misconduct isn't — lessons from a superconductivity lab

https://www.nature.com/articles/d41586-024-01174-6



Journals, funders and institutions that employ researchers all want to produce or disseminate rigorous scientific knowledge — and all can learn lessons from misconduct cases.
Research misconduct is hugely detrimental to science and to society. Defined as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results" by the US Office of Research Integrity, it violates trust in science and can do great harm to the wider public, scientific institutions and especially co-authors and students who had no part in the wrongdoing. In cases involving public funds, it squanders resources that could have been allocated to other research and it can erode lawmakers' support for science.

African Population and Health Research Center

http://www.aphrc.org is launching its Research Support Hub initiative with this webinar. This initiative aims to increase the number of African researchers successfully applying for grants from top science funders in the world. Taking a funnel approach, we will host a series of webinars in English and French to provide tips on successful grant writing - open to everyone.

The webinars will be followed by grant writing workshops in English and French for selected attendees. Out of these, a few participants will be given seed grants to flesh out and improve their ideas.

Use this link to register https://lnkd.in/dXQq_nui

SELECTED PUBLICATIONS

Life-saving effect of pulmonary surfactant in premature babies

Raj et al., 2024

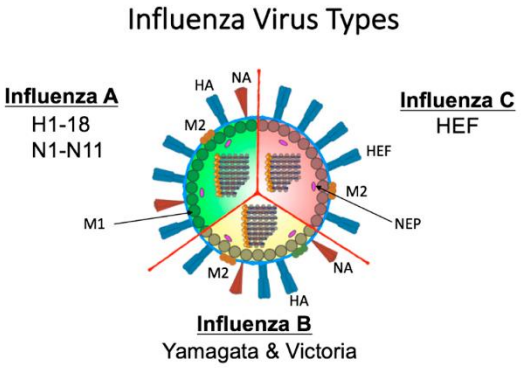
J Clin Invest. 2024;134(9):e179948. https://doi.org/10.1172/JCI179948.

In 1923, when the Journal of Clinical Investigation was founded, babies born prematurely with immature lungs rarely survived. Most of them died soon after birth, struggling to breathe, and no one knew why. Kurt von Neergaard recommended in a 1929 report that "Surface tension as a force counteracting the first breath of the newly born should be investigated further" .

Eliciting a single amino acid change by vaccination generates antibody protection against group 1 and group 2 influenza A viruses

Rashmi Ray, Faez Amokrane Nai et al., 2024

https://www.cell.com/immunity/fulltext/S1074-7613(24)00143-2

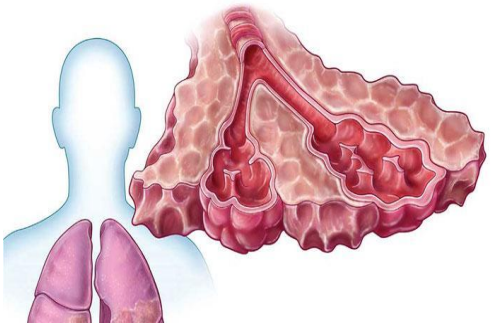


Broadly neutralizing antibodies (bnAbs) targeting the hemagglutinin (HA) stem of influenza A viruses (IAVs) tend to be effective against either group 1 or group 2 viral diversity. In rarer cases, intergroup protective bnAbs can be generated by human antibody paratopes that accommodate the conserved glycan differences between the group 1 and group 2 stems. We applied germline-engaging nanoparticle immunogens to elicit a class of cross-group bnAbs from physiological precursor frequency within a humanized mouse model. Cross-group protection depended on the presence of the human bnAb precursors within the B cell repertoire, and the vaccine-expanded antibodies enriched for an N55T substitution in the CDRH2 loop, a hallmark of the bnAb class. Structurally, this single mutation introduced a flexible fulcrum to accommodate glycosylation differences and could alone enable cross-group protection. Thus, broad IAV immunity can be expanded from the germline repertoire via minimal antigenic input and an exceptionally simple antibody development pathway.

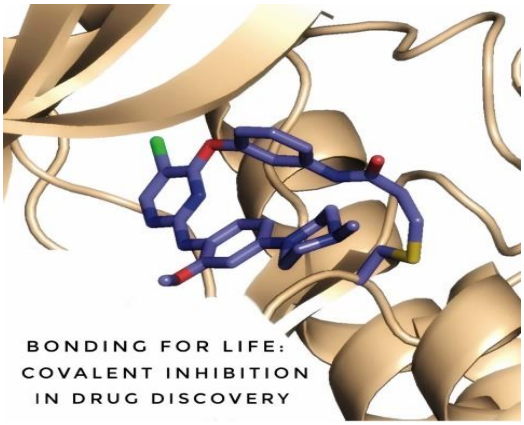
An in vivo screening platform identifies senolytic compounds that target p16INK4a+ fibroblasts in lung fibrosis

Lee et al., 2024

J Clin Invest. 2024;134(9):e173371.
https://doi.org/10.1172/JCI173371.



The appearance of senescent cells in age-related diseases has spurred the search for compounds that can target senescent cells in tissues, termed senolytics. However, a major caveat with current senolytic screens is the use of cell lines as targets where senescence is induced in vitro, which does not necessarily reflect the identity and function of pathogenic senescent cells in vivo. Here, we developed a new pipeline leveraging a fluorescent murine reporter that allows for isolation and quantification of p16Ink4a+ cells in diseased tissues. By high-throughput screening in vitro, precision-cut lung slice (PCLS) screening ex vivo, and phenotypic screening in vivo, we identified a HSP90 inhibitor, XL888, as a potent senolytic in tissue fibrosis. XL888 treatment eliminated pathogenic p16Ink4a+ fibroblasts in a murine model of lung fibrosis and reduced fibrotic burden. Finally, XL888 preferentially targeted p16INK4a-hi human lung fibroblasts isolated from patients with idiopathic pulmonary fibrosis (IPF), and reduced p16INK4a+ fibroblasts from IPF PCLS ex vivo. This study provides proof of concept for a platform where p16INK4a+ cells are directly isolated from diseased tissues to identify compounds with in vivo and ex vivo efficacy in mice and humans, respectively, and provides a senolytic screening platform for other age-related diseases.



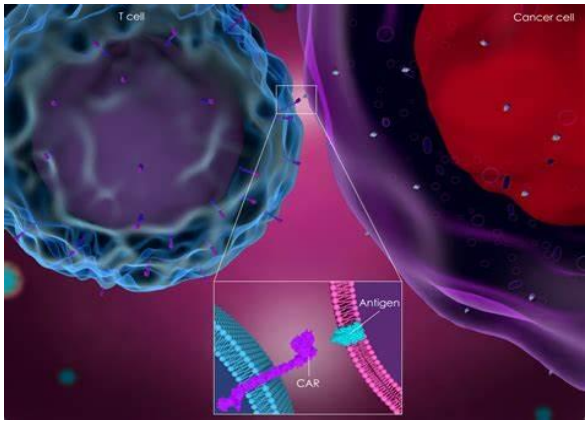
Chemoproteomic discovery of a covalent allosteric inhibitor of WRN helicase

Baltgalvis et al., 2024

https://www.nature.com/articles/s41586-024-07318-y

WRN helicase is a promising target for treatment of cancers with microsatellite instability (MSI) due to its essential role in resolving deleterious non-canonical DNA structures that accumulate in cells with faulty mismatch repair mechanisms1,2,3,4,5. Currently there are no approved drugs directly targeting human DNA or RNA helicases, in part owing to the challenging nature of developing potent and selective compounds to this class of proteins. Here we describe the chemoproteomics-enabled discovery of a clinical-stage, covalent allosteric inhibitor of WRN, VVD-133214. This compound selectively engages a cysteine (C727) located in a region of the helicase domain subject to interdomain movement during DNA unwinding. VVD-133214 binds WRN protein cooperatively with nucleotide and stabilizes compact conformations lacking the dynamic flexibility necessary for proper helicase function, resulting in widespread double-stranded DNA breaks, nuclear swelling and cell death in MSI-high (MSI-H), but not in microsatellite-stable, cells. The compound was well tolerated in mice and led to robust tumour regression in multiple MSI-H colorectal cancer cell lines and patient-derived xenograft models. Our work shows an allosteric approach for inhibition of WRN function that circumvents competition from an endogenous ATP cofactor in cancer cells, and designates VVD-133214 as a promising drug candidate for patients with MSI-H cancers.

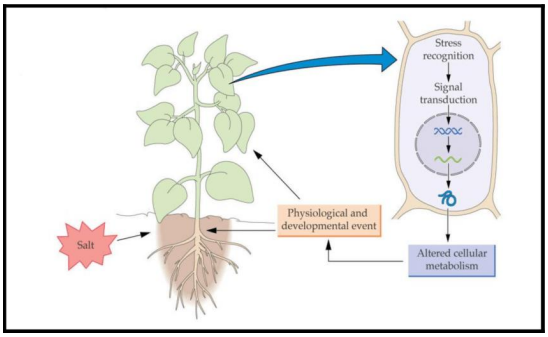
T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy



Guido Ghilardi, et al., 2024

https://www.nature.com/articles/s41591-024-02826-w

We report a T cell lymphoma (TCL) occurring 3 months after anti-CD19 chimeric antigen receptor (CAR) T cell immunotherapy for non-Hodgkin B cell lymphoma. The TCL was diagnosed from a thoracic lymph node upon surgery for lung cancer. The TCL exhibited $CD8^+$ cytotoxic phenotype and a *JAK3* variant, while the CAR transgene was very low. The T cell clone was identified at low levels in the blood before CAR T infusion and in lung cancer. To assess the overall risk of secondary primary malignancy after commercial CAR T (CD19, BCMA), we analyzed 449 patients treated at the University of Pennsylvania. At a median follow-up of 10.3 months, 16 patients (3.6%) had a secondary primary malignancy. The median onset time was 26.4 and 9.7 months for solid and hematological malignancies, respectively. The projected 5-year cumulative incidence is 15.2% for solid and 2.3% for hematological malignancies. Overall, one case of TCL was observed, suggesting a low risk of TCL after CAR T.



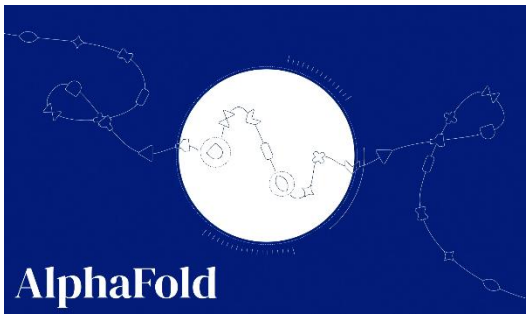
The plant immune system: From discovery to deployment

Jones et al., 2024.

https://www.cell.com/cell/fulltext/S0092-8674(24)00361-1

Plant diseases cause famines, drive human migration, and present challenges to agricultural sustainability as pathogen ranges shift under climate change. Plant breeders discovered Mendelian genetic loci conferring disease resistance to specific pathogen isolates over 100 years ago. Subsequent breeding for disease resistance underpins modern agriculture and, along with the emergence and focus on model plants for genetics and genomics research, has provided rich resources for molecular biological exploration over the last 50 years. These studies led to the identification of extracellular and intracellular receptors that convert recognition of extracellular microbe-encoded molecular patterns or intracellular pathogen-delivered virulence effectors into defense activation.

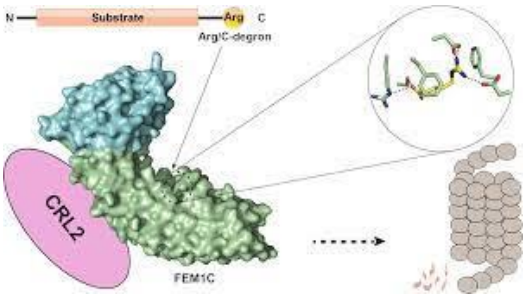
Accurate structure prediction of biomolecular interactions with AlphaFold 3



Abramson et al., 2024

https://www.nature.com/articles/s41586-024-07487-w

The introduction of AlphaFold 21 has spurred a revolution in modelling the structure of proteins and their interactions, enabling a huge range of applications in protein modelling and design2–6. In this paper, we describe our AlphaFold 3 model with a substantially updated diffusion-based architecture, which is capable of joint structure prediction of complexes including proteins, nucleic acids, small molecules, ions, and modified residues. The new AlphaFold model demonstrates significantly improved accuracy over many previous specialised tools: far greater accuracy on protein-ligand interactions than state of the art docking tools, much higher accuracy on protein-nucleic acid interactions than nucleic-acid-specific predictors, and significantly higher antibody-antigen prediction accuracy than AlphaFold-Multimer v2.37,8..



Probing the CRL4DCAF12 interactions with MAGEA3 and CCT5 di-Glu C-terminal degrons

Lima et al., 2024

https://doi.org/10.1093/pnasnexus/pgae153

Researchers from the Structural Genomics Consortium (SGC) Toronto and The Janssen Pharmaceutical Companies of Johnson & Johnson characterized the MAGEA3 and CCT5 C-terminal degron interactions with DCAF12 in proximity-based cellular Nano BRET assays and revealed the CryoEM structure of the DDB1–DCAF12–MAGEA3 ternary complex: These insights uncover the key DCAF12 residues responsible for C-terminal Degron recognition and binding. In addition, these results provide novel tools to enable Drug Discovery of Small Molecule handles targeting the WD40-repeat domain of DCAF12 for future proteolysis targeting chimera (PROTAC) Drug Design and Drug Development!

RECOMMENDED EVENTS

The transformative role of AI in revolutionising drug discovery? ELRIG

Our experts discussed how AI will impact your career in drug discovery and the steps you can take to stay ahead. Catch up on these valuable discussions and find answers to any questions you might have missed! NEW webinar recording now available! ▶ Watch the recording back now:

https://elrig.org/webinar-ai-at-the-frontier-empowering-early-career-professionals-in-drug-discovery/

The 2nd call for papers for the 12th European Workshop on Visual Information

Organized by Prof. Habib Zaidi, *Head of PET Instrumentation & Neuroimaging Laboratory (PINLab), Geneva University Hospital, Department of Diagnostics, Switzerland*

https://www.euvip2024.org/

Processing (EUVIP 2024) will be held on 8th-11th September 2024, in Geneva, Switzerland with a strong focus on medical imaging modalities including PET/SPECT, CT, MRI, US, optical and their combinations. Don't miss the opportunity to be there and present your work to an international team of leading experts from academia and industry interested in medical imaging, visual information processing, and their applications and performance assessment for all types of visual modalities.

Access Registration & Program:
https://www.euvip2024.org/

Reinventing Drug Discovery, from Retrospective to Perspectives
10th NovAliX Conference - Anniversary Edition

Brunnen, Switzerland June 2-4, 2024

The program is split into five Sessions:

- Unmet Therapeutic Needs: Current Challenges
- New Modalities as New Frontiers of Drug Discovery
- Present and Future Tools for Drug Discovery
- Vision for the Future of Drug Discovery
- Financial Perspectives on the Future of the Industry

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