Capsule

Side effects for placebo poppers

Patients in clinical trials may see their conditions improve, sometimes dramatically, even when they are in the control arm of the study. Tétreault and collaborators used brain imaging to analyze the connectivity during placebo and pain relief treatment for arthritis-induced knee pain. Brain activity associated with the placebo effect was recorded in the right mid-frontal gyrus circuitry of about half of the participants. In contrast, duloxetine-induced analgesia stimulated activity deep in the right parahippocampbal gyrus. In some patients, duloxetine interfered adversely with the placebo effect. The responses of individuals can now be differentiated, and their exposure to ineffective therapies can be monitored.

PLOS Bio 2016; 10.1371/journal. *pbio.*1002570

Eitan Israeli

Capsule

Tau phosphorylation in Alzheimer's disease: not all bad

Alzheimer's disease presents with amyloid-β (Aβ) plaques and tau tangles. The prevailing idea in the field is that Aβ induces phosphorylation of tau, which in turn mediates neuronal dysfunction. Working with Alzheimer's disease mouse models, Ittner et al. found evidence for a protective role of tau in early Alzheimer's disease. This protection involves specific tau phosphorylation at threonine 205 at the postsynapse. A protective role of phosphorylated tau in disease challenges the dogma that tau phosphorylation only mediates toxic processes.

Science 2016; 354: 904

Eitan Israeli

Capsule

Glial cells contribute to pain

Pain hypersensitivity can spread to unaffected body regions immediately surrounding the initial insult. Sometimes it can even spread to the opposite site of the body or to large body areas and cause widespread pain. Kronschläger et al. discovered a form of synaptic plasticity in the spinal cord that may explain the spread of pain hypersensitivity. This plasticity was induced by the activation of glial cells. The spread was mediated by gliotransmitters that diffuse widely, even reaching the cerebrospinal fluid at biologically relevant concentrations.

Science 2016; 354: 1144

Eitan Israeli

Capsule

Transplanted embryonic neurons integrate into adult neocortical circuits

The ability of the adult mammalian brain to compensate for neuronal loss caused by injury or disease is very limited. Transplantation aims to replace lost neurons, but the extent to which new neurons can integrate into existing circuits is unknown. Using chronic in vivo two-photon imaging, Falkner et al. show that embryonic neurons transplanted into the visual cortex of adult mice mature into bona fide pyramidal cells with selective pruning of basal dendrites, achieving adult-like densities of dendritic spines and axonal boutons within 4–8 weeks. Monosynaptic tracing experiments reveal that grafted neurons receive area-specific afferent inputs matching those of pyramidal neurons in the normal visual cortex, including topographically organized geniculo-cortical connections. Furthermore, stimulus-selective responses refine over the course of many weeks and finally become indistinguishable from those of host neurons. Thus, grafted neurons can integrate with great specificity into neocortical circuits that normally never incorporate new neurons in the adult brain.

Nature 2016; 539: 248

Eitan Israeli

Capsule

Zika virus is fit to be tied

Zika virus (ZIKV) has been associated with fetal microcephaly and Guillain-Barre syndrome. Other mosquito-born flaviviruses, such as dengue virus, encode non-coding subgenomic flavivirus RNAs (sfRNAs) in their 3' untranslated region that accumulate during infection and cause pathology. Akiyama and co-researchers report that ZIKV also produces sfRNAs that resist degradation by host exonucleases in infected cells. The authors solved the structure of one of ZIKV's sfRNAs by X-ray crystallography and found that the multi-pseudoknot structure that it adopts underlies its exonuclease resistance.

Science 2016; 354: 1148

Eitan Israeli

Capsule

Protecting by changing the code

Live attenuated vaccines can be very potent, but their potential to revert to their pathogenic form limits their use. In an attempt to get around this, Si et al. expanded the genetic code of influenza A viruses. They propagated viruses that were mutated to encode premature termination codons (PTCs) in a cell line engineered to be able to express these flu proteins. Despite not being able to replicate in conventional cells, PTC-containing viruses were highly immunogenic and protected mice, guinea pigs, and ferrets against influenza challenge.

Science 2016; 354: 1170

Eitan Israeli

Capsule

A view to a kill, preventing collateral damage

Natural killer (NK) cells are immune cells that kill virally infected target cells. To do this, NK cells dock with their sickened targets and unleash on them the destructive contents of their cytotoxic lytic granules. Hsu et al. looked at the detailed cellular rearrangements involved in killing. They regulated signaling pathways and used acoustic trap microscopy to arrange NK and target cells in such a way that the lytic granules would be released in a directed fashion toward the targets or in a non-directed fashion. Perhaps unsurprisingly, when the NK cells had the chance to line up and release their lytic granules directly toward their targets, fewer bystander cells were damaged. Furthermore, killing of the target cells was more efficient. Inhibiting the microtubule motor dynein or blocking cell adhesion molecules interfered with targeted killing and increased non-directed granule release, thereby damaging more bystander cells.

J Cell Biol 2016; 10. 1083/jcb.201604136

Eitan Israeli

Capsule

For cell reprogramming, context matters

Differentiated cells in a culture dish can assume a new identity when manipulated to express four transcription factors. This "reprogramming" process has sparked interest because conceivably it could be harnessed as a therapeutic strategy for tissue regeneration. Mosteiro et al. used a mouse model to study the signals that promote cell reprogramming in vivo. They found that the factors that trigger reprogramming in vitro do the same in vivo; however, they also inflict cell damage. The damaged cells enter a state of senescence and begin secreting certain factors that promote reprogramming, including an inflammatory cytokine called interleukin-6. Thus, in the physiological setting, cell senescence may create a tissue context that favors reprogramming of neighboring cells.

Science 2016; 354: 10.1126/science.aaf4445

Eitan Israeli

Capsule

How bats spread viruses

Bats carry numerous viruses, such as rabies and Ebola, which they can transmit to humans. In a perspective, Hayman highlights recent genetic studies showing that male vampire bats are key to rabies dispersal and transmission in Peru. Rabies is more often transmitted between related species than between unrelated ones. For many other bat virus systems, little is known about how the virus is transmitted within and between species. Although challenging, further such studies of this and other bat virus systems are needed to inform public health efforts.

Science 2016; 354: 1099

Eitan Israeli

Capsule

A balance between staying and leaving

Mobilization of neutrophils from the bone marrow is determined by the balance between two opposing chemokines that either keep neutrophils in the bone marrow or recruit them to tissues. Both chemokines activate the small guanosine triphosphatase Rac. Campa and team found that the time that it took active Rac to return to baseline determined how long neutrophils stayed in the bone marrow. Mice lacking a Rac inhibitor had more neutrophils in the bone marrow and fewer circulating neutrophils than control mice had.

Sci Signal 2016; 9: ra124

Eitan Israeli

Capsule

SLE and atherosclerosis plaques

Patients with the autoimmune disease systemic lupus erythematosis (SLE) are more likely to develop atherosclerosis than healthy individuals. Smith and co-workers hypothesized that invariant natural killer T (iNKT) cells contribute to this process because of their connection to both immune responses and lipids. The authors found that iNKT cells from SLE patients with asymptomatic plaque (SLE-P) produced more of the Th2 cytokine interleukin-4 than those from SLE patients with no plaques. These SLE-P iNKT cells were associated with changes in lipid composition and monocyte skewing to the M2 phenotype. Thus, SLE-P iNKT cells may connect changes in lipids and the immune response, contributing to the development of cardiovascular disease in SLE patients.

Sci Immunol 2016; 1: eaah4081

Eitan Israeli

"In the depth of winter I finally learned that there was in me an invincible summer"

Albert Camus (1913-1960), French philosopher, author, and journalist

Capsule

Gamma frequency entrainment attenuates amyloid load and modifies microglia

Changes in gamma oscillations (20–50 Hz) have been observed in several neurological disorders. However, the relationship between gamma oscillations and cellular pathologies is unclear. Iaccarino et al. show reduced, behaviorally driven gamma oscillations before the onset of plaque formation or cognitive decline in a mouse model of Alzheimer's disease. Optogenetically driving fast-spiking parvalbumin-positive (FS-PV)-interneurons at gamma (40 Hz), but not other frequencies, reduces levels of amyloid-β $(A\beta)_{1-40}$ and $A\beta_{1-42}$ isoforms. Gene expression profiling revealed induction of genes associated with morphological transformation of microglia, and histological analysis confirmed increased microglia co-localization with Aβ. Subsequently, the authors designed a non-invasive 40 Hz light-flickering regime that reduced $A\beta_{1-40}$ and $A\beta_{1-42}$ levels in the visual cortex of pre-depositing mice and mitigated plaque load in aged, depositing mice. These findings uncover a previously unappreciated function of gamma rhythms in recruiting both neuronal and glial responses to attenuate Alzheimer's disease-associated pathology.

Nature 2016; 540: 230

Eitan Israeli

Capsule

Natural genetic variation profoundly regulates gene expression in immune cells and dictates susceptibility to CNS autoimmunity

Regulation of gene expression in immune cells is known to be under genetic control, and likely contributes to susceptibility to autoimmune diseases such as multiple sclerosis (MS). How this occurs in concert across multiple immune cell types is poorly understood. Using a mouse model that harnesses the genetic diversity of wild-derived mice, more accurately reflecting genetically diverse human populations, Bearoff et al. provide an extensive characterization of the genetic regulation of gene expression in five different naive immune cell types relevant to MS. The immune cell transcriptome is shown to be under profound genetic control, exhibiting diverse patterns: global, cell-specific and sex-specific. Bioinformatic analysis of the genetically controlled transcript networks reveals reduced cell type specificity and inflammatory activity in wild-derived PWD/PhJ mice, compared with the conventional laboratory strain C57BL/6J. Additionally, candidate MS-GWAS (genome-wide association study candidate genes for MS susceptibility) genes were significantly enriched among transcripts over-represented in C57BL/6J cells compared with PWD. These expression level differences correlate with robust differences in susceptibility to experimental autoimmune encephalomyelitis, the principal model of MS, and skewing of the encephalitogenic T cell responses. Taken together, these results provide functional insights into the genetic regulation of the immune transcriptome, and shed light on how this in turn contributes to susceptibility to autoimmune disease.

Genes Immunity 2016; 17: 386

Eitan Israeli

"Do unto those downstream as you would have those upstream do unto you"

Wendell Berry (born 1934), American novelist, poet, environmental activist, cultural critic, and farmer

Capsule

Combining drugs as the doctor ordered

Cancer immunotherapy is being used for a growing number of cancers. Chemotherapy is still the mainstay of cancer treatment, however, and it can be difficult to find good ways to combine the two approaches. Mathios et al. systematically evaluated the effectiveness of local or systemic chemotherapy before or after immune checkpoint inhibition in mouse models of glioblastoma. Local chemotherapy was particularly effective in combination with checkpoint inhibition, whereas systemic chemotherapy was too damaging to the immune system for the combination to be useful.

Sci Transl Med 2016; 8: 370ra180

Eitan Israeli

Capsule

A bacterium-induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis

A bacterial etiology of rheumatoid arthritis (RA) has been suspected since the beginnings of modern germ theory. Recent studies implicate mucosal surfaces as sites of disease initiation. The common occurrence of periodontal dysbiosis in RA suggests that oral pathogens may trigger the production of disease-specific autoantibodies and arthritis in susceptible individuals. Konig et al. used mass spectrometry to define the microbial composition and antigenic repertoire of gingival crevicular fluid in patients with periodontal disease and healthy controls. Periodontitis was characterized by the presence of citrullinated autoantigens that are primary immune targets in RA. The citrullinome in periodontitis mirrors patterns of hypercitrullination observed in the rheumatoid joint, implicating this mucosal site in RA pathogenesis. Proteomic signatures of several microbial species were detected in hypercitrullinated periodontitis samples. Among these, *Aggregatibacter actinomycetemcomitans* (*Aa*), but not other candidate pathogens, induced hypercitrullination in host neutrophils. The authors identified the pore-forming toxin leukotoxin A (LtxA) as the molecular mechanism by which *Aa* triggers dysregulated activation of citrullinating enzymes in neutrophils, mimicking membranolytic pathways that sustain autoantigen citrullination in the RA joint. Moreover, LtxA induced changes in neutrophil morphology mimicking extracellular trap formation, thereby releasing the hypercitrullinated cargo. Exposure to leukotoxic *Aa* strains was confirmed in patients with RA and was associated with both anticitrullinated protein antibodies and rheumatoid factor. The effect of human lymphocyte antigen-RB1 shared epitope alleles on autoantibody positivity was limited to RA patients who were exposed to *Aa*. These studies identify the periodontal pathogen *Aa* as a candidate bacterial trigger of autoimmunity in RA.

Sci Transl Med 2016; 8: 369ra176

Eitan Israeli

Capsule

Unleashing the power of precision medicine

Precision medicine promises the ability to identify risks and treat patients on the basis of pathogenic genetic variation. Two studies combined exome sequencing results for over 50,000 people with their electronic health records. Dewey et al. (*Science* 2016; 354: 10.1126/science.aaf6814) found that ~3.5% of individuals in their cohort had clinically actionable genetic variants. Many of these variants affected blood lipid levels that could influence cardiovascular health. Abul-Husn et al. (*Science* 2016; 354: 10.1126/science.aaf7000) extended these findings to investigate the genetics and treatment of familial hypercholesterolemia, a risk factor for cardiovascular disease, within their patient pool. Genetic screening helped identify at-risk patients who could benefit from increased treatment.

Eitan Israeli

Capsule

How to grow hair or sweat glands

Unlike other mammals that must pant or seek shade or water when overheated, humans are able to self-cool to tolerate extreme heat. Sweat glands, which enable humans to run in marathons, are instrumental for this remarkable feat. Lu and co-authors investigated skin appendage diversity during development of the furry backs and sweaty paws of mice. They also examined human skin, which is capable of making both hairs and sweat glands in the same area of the body. Epithelial mesenchymal interactions, with varied signaling pathways that act at specific times in development, are key to producing different skin appendages for adaptation to the environment.

Science 2016; 354: 10.1126/science.aah6102

Eitan Israeli

Capsule

The epigenetics of exhaustion

During cancer or chronic infection, T cells become dysfunctional, eventually acquiring an "exhausted" phenotype. Immunotherapies aim to reverse this state. Using a mouse model of chronic infection, two studies now show that the epigenetic profile of exhausted T cells differs substantially from those of effector and memory T cells, suggesting that exhausted T cells are a distinct lineage. Sen and group (*Science* 2016; 354: 1104) defined specific functional modules of enhancers that are also conserved in exhausted human T cells. Pauken et al. (*Science* 2016; 354: 1165) examined the epigenetic profile of exhausted T cells after immunotherapy. Although there was transcriptional rewiring, the cells never acquired a memory T cell phenotype. Thus, epigenetic regulation may limit the success of immunotherapies.

Eitan Israeli

Capsule

Gene signatures associated with adaptive humoral immunity following seasonal influenza A/H1N1 vaccination

Aiming to identify gene expression markers shared between both influenza hemagglutination inhibition (HAI) and virus-neutralization antibody (VNA) responses, Ovsyannikova et al. enrolled 158 older subjects who received the 2010–2011 trivalent inactivated influenza vaccine. Influenza-specific HAI and VNA titers and mRNA sequencing were performed using blood samples obtained on days 0, 3 and 28 post-vaccination. For antibody response at day 28 versus day 0, several gene sets were identified as significant in predictive models for HAI (n=7) and VNA (n=35) responses. Five gene sets (comprising the genes *MAZ*, *TTF*, *GSTM*, *RABGGTA*, *SMS*, *CA*, *IFNG* and *DOPEY*) were in common for both HAI and VNA. For response at day 28 versus day 3, many gene sets were identified in predictive models for HAI (n=13) and VNA (n =41). Ten gene sets (comprising biologically related genes, such as *MAN1B1*, *POLL*, *CEBPG*, *FOXP3*, *IL12A*, *TLR3*, *TLR7* and others) were shared between HAI and VNA. These identified gene sets demonstrated a high degree of network interactions and likelihood for functional relationships. Influenza-specific HAI and VNA responses demonstrated a remarkable degree of similarity. Although unique gene set signatures were identified for each humoral outcome, several gene sets were determined to be in common with both HAI and VNA response to influenza vaccine.

Genes Immunity 2016; 17: 371

Eitan Israeli

"The wisest man is he who does not fancy that he is so at all"

Nicolas Boileau-Despraux (1636-1711), French poet and critic

"One of the oldest human needs is having someone to wonder where you are when you don't come home at night"

Margaret Mead (1901-1978), American cultural anthropologist and often controversial academic who popularized the insights of anthropology in modern American and Western culture. Her reports detailing the attitudes towards sex in South Pacific and Southeast Asian traditional cultures influenced the 1960s sexual revolution. She was a proponent of broadening sexual mores within a context of traditional Western religious life

Capsule

Early dissemination seeds metastasis in breast cancer

Accumulating data suggest that metastatic dissemination often occurs early during tumor formation, but the mechanisms of early metastatic spread have not yet been addressed. By studying metastasis in a HER2-driven mouse breast cancer model, Hosseini and colleagues show that progesterone-induced signaling triggers migration of cancer cells from early lesions shortly after HER2 activation, but promotes proliferation in advanced primary tumor cells. The switch from migration to proliferation was regulated by increased HER2 expression and tumor-cell density involving microRNA-mediated progesterone receptor downregulation, and was reversible. Cells from early, low density lesions displayed more stemness features, migrated more and founded more metastases than cells from dense, advanced tumors. Notably, we found that at least 80% of metastases were derived from early disseminated cancer cells. Karyotypic and phenotypic analysis of human disseminated cancer cells and primary tumors corroborated the relevance of these findings for human metastatic dissemination.

Nature 2016; 540: 552

Eitan Israeli

Capsule

Birth defects among fetuses and infants of U.S. women with evidence of possible Zika virus infection during pregnancy

Understanding the risk of birth defects associated with Zika virus infection during pregnancy may help guide communication, prevention, and planning efforts. In the absence of Zika virus, microcephaly occurs in approximately 7 per 10,000 live births. Honein et al. tried to estimate the preliminary proportion of fetuses or infants with birth defects after maternal Zika virus infection by trimester of infection and maternal symptoms. Among 442 completed pregnancies in women (median age 28 years, range 15–50 years) with laboratory evidence of possible recent Zika virus infection, birth defects potentially related to Zika virus were identified in 26 (6%, 95%C, 4%–8%) fetuses or infants. There were 21 infants with birth defects among 395 live births and 5 fetuses with birth defects among 47 pregnancy losses. Birth defects were reported for 16 of 271 (6%, 95%CI 4%–9%) pregnant asymptomatic women and 10 of 167 (6%, 95%CI 3%–11%) symptomatic pregnant women. Of the 26 affected fetuses or infants, 4 had microcephaly and no reported neuroimaging, 14 had microcephaly and brain abnormalities, and 4 had brain abnormalities without microcephaly. Reported brain abnormalities included intracranial calcifications, corpus callosum abnormalities, abnormal cortical formation, cerebral atrophy, ventriculomegaly, hydrocephaly, and cerebellar abnormalities. Infants with microcephaly (18/442) represent 4% of completed pregnancies. Birth defects were reported in 9 of 85 (11%, 95%CI 6%–19%) completed pregnancies with maternal symptoms or exposure exclusively in the first trimester (or first trimester and periconceptional period), with no reports of birth defects among fetuses or infants with prenatal exposure to Zika virus infection only in the second or third trimester.

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doi:10.1001/jama.2016.19006

Eitan Israeli

Capsule

Shortened antimicrobial treatment for acute otitis media in young children

Limiting the duration of antimicrobial treatment constitutes a potential strategy to reduce the risk of antimicrobial resistance among children with acute otitis media. Hoberman et al. assigned 520 children, 6 to 23 months of age, with acute otitis media to receive amoxicillin-clavulanate either for a standard duration of 10 days or for a reduced duration of 5 days followed by placebo for 5 days. The authors measured rates of clinical response (in a systematic fashion, on the basis of signs and symptomatic response), recurrence, and nasopharyngeal colonization, and we analyzed episode outcomes using a non-inferiority approach. Symptom scores ranged from 0 to 14, with higher numbers indicating more severe symptoms. Among children 6 to 23 months of age with acute otitis media, reduced-duration antimicrobial treatment resulted in less favorable outcomes than standard-duration treatment; in addition, neither the rate of adverse events nor the rate of emergence of antimicrobial resistance was lower with the shorter regimen.

N Engl J Med 2016; 375: 2446

Eitan Israeli

Capsule

Persistent microbiome alterations modulate the rate of post-dieting weight regain

In tackling the obesity pandemic, considerable efforts are devoted to the development of effective weight reduction strategies, yet many dieting individuals fail to maintain a long-term weight reduction, and instead undergo excessive weight regain cycles. The mechanisms driving recurrent post-dieting obesity remain largely elusive. Thaiss et al. have identified an intestinal microbiome signature that persists after successful dieting of obese mice and contributes to faster weight regain and metabolic aberrations upon re-exposure to obesity-promoting conditions. Fecal transfer experiments show that the accelerated weight regain phenotype can be transmitted to germ-free mice. The authors developed a machine-learning algorithm that enables personalized microbiome-based prediction of the extent of post-dieting weight regain. Additionally, they found that the microbiome contributes to diminished post-dieting flavonoid levels and reduced energy expenditure, and demonstrated that flavonoid-based 'post-biotic' intervention ameliorates excessive secondary weight gain. Together, these data highlight a possible microbiome contribution to accelerated post-dieting weight regain, and suggest that microbiome-targeting approaches may help to diagnose and treat this common disorder.

Nature 2016; 540: 544

Eitan Israeli

"Humanity also needs dreamers, for whom the disinterested development of an enterprise is so captivating that it becomes impossible for them to devote their care to their own material profit. Without doubt, these dreamers do not deserve wealth, because they do not desire it. Even so, a well-organized society should assure to such workers the efficient means of accomplishing their task, in a life freed from material care and freely consecrated to research"

Marie Curie (1867-1934), Polish born French physicist and chemist who conducted pioneering research on radioactivity. She was the first woman to win a Nobel Prize, the first person and only woman to win twice, the only person to win a Nobel Prize in two different sciences, and was part of the Curie family legacy of five Nobel Prizes. She was also the first woman to become a professor at the University of Paris, and in 1995 became the first woman to be entombed on her own merits in the Panthéon in Paris