Capsule

Rejuvenating viral vectors

Adenoviral (Ad5) vaccine vectors elicit mixed responses: They induce protective CD8+ T cells, but these cells may be partially exhausted. Larocca et al. demonstrate that this exhausted phenotype may result from Ad5 vector-induced antigen-specific CD4+ T cells that express interleukin-10 (IL-10) and PD-1 in both mice and macaques. These IL-10+ CD4+ T cells suppress the vaccine-induced CD8+ T cell response, and their inhibitory function may depend in part on IL-27. Targeting this inhibitory pathway may thus enhance protection of viral vector-based vaccines.

Sci Immunol 2016; 1: eaaf7643

Eitan Israeli

Capsule

Ambulatory pediatric surveillance of hand, foot and mouth disease as signal of an outbreak of coxsackievirus A6 infections, France, 2014–2015

The clinical impact of enteroviruses associated with hand, foot and mouth disease (HFMD) is unknown outside Asia, and the prevalence of enterovirus A71 (EV-A71) in particular might be underestimated. To investigate the prevalence of enterovirus serotypes and the clinical presentations associated with HFMD in France, Mirand et al. conducted prospective ambulatory clinic-based surveillance of children during April 2014–March 2015. Throat or buccal swabs were collected from children with HFMD and tested for the enterovirus genome. Physical examinations were recorded on a standardized form. An enterovirus infection was detected in 523 (79.3%) of 659 children tested. Two epidemic waves occurred, dominated by coxsackievirus (CV) A6, which was detected in 53.9% of enterovirus-infected children. CV-A6 was more frequently related to atypical HFMD manifestations (eruptions extended to limbs and face). Early awareness and documentation of HFMD outbreaks can be achieved by syndromic surveillance of HFMD by ambulatory pediatricians and rapid enterovirus testing and genotyping.

Emerg Infect Dis 2016; 22: 1884

Eitan Israeli

Capsule

A touchy subject for neuroprostheses

Without tactile sensory input, amputees discern a firm handshake from a bone-crushing grip by visual cues and learned behavior. Next-generation prostheses aim to lend a more natural feel to artificial touch. Graczyk et al. looked at direct stimulation of the radial, ulnar and median nerves by implanted electrodes in two amputees. By modulating the number of nerve fibers stimulated and the frequency of stimulation, sensory information could be transmitted so that the amputees could distinguish distinct levels of tactile intensity.

Sci Transl Med 2016; 8: 362ra142

Eitan Israeli

Capsule

Integration of adult-born brain cells

Physical exercise or exploration of a novel environment greatly influences the production, maturation, and connectivity of adult-born neurons. Alvarez and co-authors investigated how experience affects the incorporation of adult-born neurons into the hippocampal network. A brief period of sensory enrichment when new neurons were 9 to 10 days old led to neurons having larger dendrites and more functional spine synapses. A disynaptic preexisting feedback circuit promoted the growth and integration of the new cells.

Science 2016; 354: 459

Eitan Israeli

Capsule

Plunging into a domain of silence

Female mammals have two X chromosomes. One must be silenced to "balance" gene dosage with male XY cells. The Xist long non-coding RNA coats the inactive X chromosome in female mammalian cells. Chen et al. show that the Xist RNA helps recruit the X chromosome to the internal rim of the cell nucleus, a region where gene expression is silenced. Xist is recruited to the domain through an interaction with the Lamin B receptor. This recruitment allows the Xist RNA to spread across the future inactive X chromosome, shutting down gene expression.

Science 2016; 354: 468

Eitan Israel

Capsule

Keeping white fat from expanding

Excess body fat caused by adipogenesis – the expansion of white adipose tissue – poses serious health risks. Wong et al. found that mice exposed to glucocorticoids or fed a high fat diet had decreased levels of the extracellular protein ADAMTS1 in white adipocytes, which was associated with increased adipogenesis. Increased caloric intake in human volunteers enhanced the expression of ADAMTS1 in adipose tissue. Mice that over-expressed Adamts1 had smaller white adipose deposits, suggesting that ADAMTS1 treatment could prevent diet- or glucocorticoid-induced obesity.

Sci Signal 2016; 9:ra103

Eitan Israeli

Capsule

Wreaking havoc while (growth-)arrested

Cells enter a state of senescence in response to certain stresses. Studying mouse models, Childs and team examined the role of senescent lipid-loaded macrophages (so-called foam cells) in the pathogenesis of atherosclerosis. At early stages of atherosclerosis, senescent foam cells promoted the expression of inflammatory cytokines. At later stages, they promoted the expression of matrix metalloproteases implicated in the rupture of atherosclerotic plaque, which can lead to blood clots. Experimental removal of the senescent cells had beneficial effects at both stages of the disease.

Science 2016; 354: 472

Eitan Israeli

Capsule

Group B *Streptococcus* circumvents neutrophils and neutrophil extracellular traps during amniotic cavity invasion and preterm labor

Preterm birth is a leading cause of neonatal morbidity and mortality. Although microbial invasion of the amniotic cavity (MIAC) is associated with most early preterm births, the temporal events that occur during MIAC and preterm labor are not known. Group B streptococci (GBS) are β-hemolytic, Gram-positive bacteria, which commonly colonize the vagina but have been recovered from the amniotic fluid in preterm birth cases. To understand temporal events that occur during MIAC, Boldenow et al. used a chronically catheterized non-human primate model that closely emulates human pregnancy. This model allows monitoring of uterine contractions, timing of MIAC, and immune responses during pregnancy-associated infections. The authors show that adverse outcomes such as preterm labor, MIAC, and fetal sepsis were observed more frequently during infection with hemolytic GBS when compared with non-hemolytic GBS. Although MIAC was associated with systematic progression in chorioamnionitis beginning with chorionic vasculitis and progressing to neutrophilic infiltration, the ability of the GBS hemolytic pigment toxin to induce neutrophil cell death and subvert killing by neutrophil extracellular traps (NETs) in placental membranes in vivo facilitated MIAC and fetal injury. Furthermore, compared with maternal neutrophils, fetal neutrophils exhibit decreased neutrophil elastase activity and impaired phagocytic functions to GBS. Collectively, these studies demonstrate how a bacterial hemolytic lipid toxin enables GBS to circumvent neutrophils and NETs in placental membranes to induce fetal injury and preterm labor.

Sci Immunol 2016; 1: doi: 10.1126/sciimmunol.aah4576

Eitan Israeli

Capsule

Keeping hearts and blood vessels young

Activation of the G protein-coupled receptor GPER is thought to confer cardiovascular benefits. Unexpectedly, Meyer et al. found that aged mice that were deficient in *Gper* did not develop as much cardiac fibrosis as aged mice in the control group and retained greater cardiovascular function. *Gper* deficiency was associated with reduced production of tissue-damaging superoxide in blood vessels and the myocardium. A GPER-blocking drug reduced blood pressure and superoxide production in hypertensive mice, suggesting that GPER inhibitors could be used to treat cardiovascular diseases caused by excessive superoxide generation.

Sci Signal 2016; 9: ra105

Eitan Israeli

Capsule

A global genetic suppression network

The genetic background of an organism can influence the overall effects of new genetic variants. Some mutations can amplify a deleterious phenotype, whereas others can suppress it. Starting with a literature survey and expanding into a genome-wide assay, van Leeuwen et al. generated a large-scale suppression network in yeast. The data set reveals a set of general properties that can be used to predict suppression interactions. Furthermore, the study provides a template for extending suppression studies to other genes or to more complex organisms.

Science 2106; 354: 599

Eitan Israeli

Capsule

Fulminant myocarditis with combination immune checkpoint blockade

Immune checkpoint inhibitors have improved clinical outcomes associated with numerous cancers, but high grade, immune related adverse events can occur, particularly with combination immunotherapy. Johnson et al. report the cases of two patients with melanoma in whom fatal myocarditis developed after treatment with ipilimumab and nivolumab. In both patients, there was development of myositis with rhabdomyolysis, early progressive and refractory cardiac electrical instability, and myocarditis with a robust presence of T cell and macrophage infiltrates. Selective clonal T cell populations infiltrating the myocardium were identical to those present in tumors and skeletal muscle. Pharmacovigilance studies show that myocarditis occurred in 0.27% of patients treated with a combination of ipilimumab and nivolumab, which suggests that our patients were having a rare, potentially fatal, T cell-driven drug reaction.

N Engl J Med 2016; 375: 1749

Eitan Israeli

Capsule

Assessing smoke damage in cancer genomes

We have known for over 60 years that smoking tobacco is one of the most avoidable risk factors for cancer. Yet the detailed mechanisms by which tobacco smoke damages the genome and creates the mutations that ultimately cause cancer are still not fully understood. Alexandrov and fellow-workers examined mutational signatures and DNA methylation changes in over 5000 genome sequences from 17 different cancer types linked to smoking. They found a complex pattern of mutational signatures. Only cancers originating in tissues directly exposed to smoke showed a signature characteristic of the known tobacco carcinogen benzo[a]pyrene. One mysterious signature was shared by all smoking-associated cancers but is of unknown origin. Smoking had only a modest effect on DNA methylation.

Science 2016; 354: 618

Eitan Israeli

Capsule

Benefits and risks of antiretroviral therapy for perinatal HIV prevention

Randomized trial data on the risks and benefits of antiretroviral therapy (ART) as compared with zidovudine and single-dose nevirapine to prevent transmission of the human immunodeficiency virus (HIV) in HIV-infected pregnant women with high CD4 counts are lacking. Fowler et al. found that the median CD4 count was 530 cells per mm^3 among 3490 primarily black African HIV-infected women enrolled at a median of 26 weeks of gestation (interquartile range 21–30). The rate of transmission was significantly lower with ART than with zidovudine alone (0.5% in the combined ART groups vs. 1.8%, difference -1.3 percentage points, repeated confidence interval -2.1 to -0.4). However, the rate of maternal grade 2 to 4 adverse events was significantly higher with zidovudine-based ART than with zidovudine alone (21.1% vs. 17.3%, $P = 0.008$), and the rate of grade 2 to 4 abnormal blood chemical values was higher with tenofovir-based ART than with zidovudine alone (2.9% vs. 0.8%, $P = 0.03$). Adverse events did not differ significantly between the ART groups ($P > 0.99$). A birth weight of less than 2500 g was more frequent with zidovudine-based ART than with zidovudine alone (23.0% vs. 12.0%, $P > 0.001$) and was more frequent with tenofovir-based ART than with zidovudine alone (16.9% vs. 8.9%, $P = 0.004$); preterm delivery before 37 weeks was more frequent with zidovudine-based ART than with zidovudine alone (20.5% vs. 13.1%, $P > 0.001$). Tenofovir-based ART was associated with higher rates than zidovudine-based ART of very preterm delivery before 34 weeks (6.0% vs. 2.6%, $P = 0.04$) and early infant death (4.4% vs. 0.6%, $P = 0.001$), but there were no significant differences between tenofovir-based ART and zidovudine alone ($P = 0.10$ and $P = 0.43$). The rate of HIV-free survival was highest among infants whose mothers received zidovudine-based ART.

N Engl J Med 2016; 375: 1726

Eitan Israeli

Capsule

Ebola virus glycoprotein with increased infectivity dominated the 2013–2016 epidemic

The magnitude of the 2013–2016 Ebola virus disease (EVD) epidemic enabled an unprecedented number of viral mutations to occur over successive human-to-human transmission events, increasing the probability that adaptation to the human host occurred during the outbreak. Diehl et al. investigated one non-synonymous mutation, Ebola virus (EBOV) glycoprotein (GP) mutant A82V, for its effect on viral infectivity. This mutation, located at the NPC1-binding site on EBOV GP, occurred early in the 2013–2016 outbreak and rose to high frequency. The authors found that GP-A82V had heightened ability to infect primate cells, including human dendritic cells. The increased infectivity was restricted to cells that have primate-specific NPC1 sequences at the EBOV interface, suggesting that this mutation was indeed an adaptation to the human host. GP-A82V was associated with increased mortality, consistent with the hypothesis that the heightened intrinsic infectivity of GP-A82V contributed to disease severity during the EVD epidemic.

Cell 2016; doi: http://dx.doi.org/10.1016/j.cell.2016.10.014

Eitan Israeli

Capsule

Quantifying the alarm from antibiotic resistance

Antibiotic resistance is a major global fear, but how fearful should we be? Multidrug resistance (MDR) is high among developing economies that are vulnerable to purveyors of substandard drugs and where over-the-counter sales are not controlled. Lim et al. collected mortality data on bacteremia from 10 public hospitals in northeast Thailand between 2004 and 2010. During this period, the incidence of bacteremia increased, and high case fatality rates were observed for MDR strains, especially hospital-acquired *Acinetobacter* spp. Extrapolating to the whole of Thailand for 2010 indicates that among patients with hospital-acquired MDR bacterial infection, 43% of deaths represented excess mortality caused by MDR – which is high compared with similar estimates for the United States or Europe.

eLife 2016; 10.7554/eLife.18082

Eitan Israeli

"It's no use going back to yesterday, because I was a different person then"

Lewis Carroll (1832-1898), English writer, mathematician, logician, Anglican deacon, and photographer. His most famous writings are *Alice's Adventures in Wonderland* and its sequel *Through the Looking-Glass*. He is noted for his facility at word play, logic and fantasy

Capsule

Risk factors for Middle East Respiratory syndrome coronavirus infection among health care personnel

Health care settings can amplify transmission of Middle East respiratory syndrome coronavirus (MERS-CoV), but knowledge gaps about the epidemiology of transmission remain. Alraddai et al. conducted a retrospective cohort study among health care personnel in hospital units that treated MERS-CoV patients. Participants were interviewed about exposures to MERS-CoV patients, use of personal protective equipment, and signs and symptoms of illness after exposure. Infection status was determined by the presence of antibodies against MERS-CoV. To assess risk factors, the authors compared infected and uninfected participants. Health care personnel caring for MERS-CoV patients were at high risk for infection, but infection most often resulted in a relatively mild illness that might be unrecognized. In the health care personnel cohort reported here, infections occurred exclusively among those who had close contact with MERS-CoV patients.

Emerg Infect Dis 2016; 22: 1915

Eitan Israeli

Capsule

Personalized medicine by another name

A vision of the Human Genome Project was that molecular profiling would enable identification of the molecular underpinnings of disease on an individual basis; "personalized medicine" became a watchword. However, a rebranding has been occurring since roughly 2012 in which the concept has been transmogrified into "precision medicine." Juengst and colleagues describe conclusions from interviews and case studies conducted since 2011 with 143 supporters of personalized genomic medicine. The terminology change may minimize unrealistic expectations. However, a shift from "personal" could mean a reversal of the trend toward patient autonomy in decision making. The need for population-level sequencing to identify groups with particular molecular profiles carries its own risks in terms of pressures to participate and the possibility of stigmatization.

Hastings Cent Rep 2016; 46: 21

Eitan Israeli

Capsule

Worms remodel immune responsiveness

Rural populations in less developed countries commonly show poor immunogenicity in vaccination programs. Helminth infestations remain common in some rural areas, and cellular immune hyporesponsiveness is a hallmark of chronic helminth infections. Community deworming programs are in general believed to be a good thing to reverse the morbidity that a large worm burden can impose on children. Wammes et al. set up a 2 year clinical trial to systematically test the immunological consequences of deworming in › 1000 villagers in Indonesia. After treatment, subjects showed significant immune remodeling, with reduced expression of CTLA-4 (cytotoxin T lymphocyte-associated antigen 4) and elevated pro-inflammatory cytokine responses to malaria parasite antigens. The challenge in the longer term could be that restored immune responsiveness might increase the prevalence of inflammatory diseases.

Proc Natl Acad Sci 2016; 10.1073/pnas.1604570113

Eitan Israeli

Capsule

Bidirectional intragraft alloreactivity drives the repopulation of human intestinal allografts and correlates with clinical outcome

One paradigm in transplantation is that graft-infiltrating T cells are largely non-alloreactive "bystander" cells. However, the origin and specificity of allograft T cells over time have not been investigated in detail in animals or humans. Zuber and co-researchers used polychromatic flow cytometry and high-throughput T cell receptor sequencing of serial biopsies to show that gut-resident T cell turnover kinetics in human intestinal allografts are correlated with the balance between intragraft host-versus-graft (HvG) and graft-versus-host (GvH) reactivities and with clinical outcomes. In the absence of rejection, donor T cells were enriched for GvH-reactive clones that persisted in the long term in the graft. Early expansion of GvH clones in the graft correlated with the rapid replacement of donor antigen-presenting cells by the recipient. Rejection was associated with transient infiltration by blood-like recipient D28^{+} NKG2D^{Hi} CD8^{+} $\alpha\beta$ T cells, marked predominance of HvG clones, and accelerated T cell turnover in the graft. Ultimately, these recipient T cells acquired a steady-state tissue-resident phenotype but regained CD28 expression during rejections. Increased ratios of GvH to HvG clones were seen in non-rejectors, potentially mitigating the constant threat of rejection posed by HvG clones persisting within the tissue-resident graft T cell population.

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Eitan Israeli