Capsule

Cancer and nerves: A tuf(t) partnership

Stomach tumor growth is accompanied by an expansion of surrounding nerves. Whether and how these two events are functionally related has been unclear. Studying mouse models, Hayakawa et al. showed that a molecular conversation occurs between nerves and the epithelial cells that give rise to cancer. This cross-talk relies in part on tuft cells, a mysterious cell type in the epithelial lining of the gastrointestinal tract. Tuft cells and nerves produce the neurotransmitter acetylcholine, which stimulates expression of nerve growth factor (NGF) in the gastric epithelium. NGF in turn acts to promote neuronal expansion and aberrant growth of gastric epithelial cells, which ultimately leads to cancer. Drugs that block NGF signaling inhibited gastric tumor growth in mice.

Cancer Cell 2017; 10.1016/j.ccell.2016.11.005
Eitan Israeli

Capsule

This antiplatelet agent is just right

Antiplatelet drugs are commonly used to prevent stroke in high-risk patients. Unfortunately, a frequent side effect of these drugs is excessive bleeding. To improve the safety margin of antiplatelet agents, Wong et al. identified a new target for treatment, a platelet receptor called PAR4. They developed a small-molecule drug and evaluated its efficacy and safety in animal models. The new drug was no less effective and had a much larger therapeutic window than the widely used antiplatelet agent clopidogrel.

Sci Transl Med 2016; 9: eaaf5294
Eitan Israeli

Capsule

Chronic sleep deprivation suppresses the immune system

Researchers took blood samples from 11 pairs of identical twins with different sleep patterns and discovered that the twin with shorter sleep duration had a depressed immune system, compared with his or her sibling. The immune system functions best when it gets enough sleep. Seven or more hours of sleep are recommended for optimal health. A unique feature of this study was using identical twins in order to control for the large genetic determinant to humans' sleep duration. Researchers say genetics account for 31–55% of sleep duration, and behavior and environment account for the remainder. Existing data show that curtailing sleep – for a limited time in the laboratory setting – can increase inflammatory markers and activate immune cells. Little is known, though, about the effects of longstanding short sleep duration under natural conditions. This study employed real-world conditions and showed for the first time that chronic short sleep shuts down programs involved in immune response of circulating white blood cells. The results are consistent with studies that show when sleep-deprived people are given a vaccine there is a lower antibody response and if sleep-deprived people are exposed to a rhinovirus they are more likely to get the virus. This study provides further evidence of the importance of sleep to overall health and well-being, particularly immune health.

Sleep 2017 https://www.eurekalert.org/pub_releases/2017-01/uowh-csd012617.php
Eitan Israeli

Capsule

Regulator loop enabling cancer cell growth

It is not easy being a cancer cell, so such cells may need help from factors other than oncogenes that contribute to the cancer cell phenotype. Bublik et al. identified such a factor in protein fibroblast growth factor 13 (FGF13). FGF13 does not function like a regular growth factor. Instead, it acts in the nucleolus to repress transcription of ribosomal RNA and inhibit protein synthesis. Furthermore, it is tightly linked to the action of the tumor suppressor p53. The p53 protein inhibits expression of the *FGF13* gene, which also encodes a microRNA that in turn down-regulates p53, forming a negative feedback loop. FGF13 may help cancer cells avoid the toxic effects of excessive protein synthesis and could therefore be targeted for cancer therapy.

Proc Natl Acad Sci USA 2016; 10.1073/pnas.1614876114

Eitan Israeli

Capsule

Menopausal factors are associated with seronegative RA in large prospective cohorts: results from the Nurses' Health Studies

Bengtsson and colleagues investigated whether menopausal factors are associated with development of serologic rheumatoid arthritis (RA) phenotypes. Data were analyzed from the Nurses' Health Studies (NHS 1976–2010, NHSII 1989–2011). In the NHS 120,700 female nurses aged 30–55 and in NHSII 116,430 female nurses aged 25–42 were followed via biennial questionnaires on lifestyle and disease outcomes. In total, 1096 incident RA cases were confirmed by questionnaire and chart review. Seropositive RA was defined as +RF or ACPA+; seronegative RA as -RF and ACPA. Postmenopausal women had a twofold increased risk of seronegative RA, compared with premenopausal women (NHS: HR 1.8, 95%CI 1.1–3.0; NHSII: HR 2.4, 95%CI 1.4–3.9; pooled HR 2.1, 95%CI 1.4–3.0). Natural menopause at early age (≤ 44) was associated with an increased risk of seronegative RA (pooled HR 2.4, 95%CI 1.5–4.0). None of the menopausal factors was significantly associated with seropositive RA. We observed no association between PMH use and the risk of seronegative or seropositive RA, except that PMH use for ≥ 8 years was associated with increased risk of seropositive RA (pooled HR 1.4, 95%CI 1.1–1.9).

Arthritis Care Res 2017; doi: 10.1002/acr.23194

Eitan Israeli

Capsule

A non-toxic pain killer designed by modeling of pathological receptor conformations

Indiscriminate activation of opioid receptors provides pain relief but also has severe central and intestinal side effects. Spahn and colleagues hypothesized that exploiting pathological (rather than physiological) conformation dynamics of opioid receptor-ligand interactions might yield ligands without adverse actions. By computer simulations at low pH, a hallmark of injured tissue, the authors designed an agonist that, because of its low acid dissociation constant, selectively activates peripheral μ-opioid receptors at the source of pain generation. Unlike the conventional opioid fentanyl, this agonist showed pH-sensitive binding, heterotrimeric guanine nucleotide binding protein (G protein) subunit dissociation by fluorescence resonance energy transfer, and adenosine 3',5'-monophosphate inhibition in vitro. It produced injury-restricted analgesia in rats with different types of inflammatory pain without exhibiting respiratory depression, sedation, constipation, or addiction potential.

Science 2017; 355: 966

Eitan Israeli

Capsule

Romania: Anti-vaxxer movement results in huge measles surge in 2016

Romania saw 15 measles cases in 2015. Since 2016, this number has exploded to 2165, including 13 fatalities. This is largely due to bogus claims from anti-vaccination campaigns in the country, according to a report in *La Vanguardia*. President of the Romanian Society of Microbiology, Alexandru Rafila, directly points a finger at the anti-vaxx movement: "Incorrect information, often tendentious, not based on scientific methods or real data should end so that they do not affect the health of our children." Among the arguments forwarded by the anti-vaccination movement are: vaccines contain mercury, introduce foreign elements, and cause asthma. This misinformation has resulted in vaccination rates of the measles-mumps-rubella (MMR) vaccine falling from 95% of children in 2013 to 80% in 2016, and the rates continue to drop. Campaigns led by the Christian Orthodox Pro Vita Federation; Christei Todea-Gross, author of the 2012 book *Vaccines: Prevention or Illness*; and the Coalition for the Family have spread the anti-vaccination message through a number of outlets. The Ministry of Health has been denouncing "the irresponsible campaigns against the vaccination of children" for months; however, there are many parents who do not vaccinate their children because they lack confidence in the authorities.

http://outbreaknewstoday.com/romania-anti-vaxxer-movement-results-huge-measles-surge-2016/

Eitan Israeli

Capsule

Vitamin B3 protects mice from glaucoma

Glaucoma is the most common cause of age-related blindness in the United States. There is currently no cure, and once vision is lost the condition is irreversible. Williams et al. report that vitamin B3 (also known as niacin) prevents eye degeneration in glaucoma-prone mice. Supplementing the diets of young mice with vitamin B3 averted early signs of glaucoma. Vitamin B3 also halted further glaucoma development in aged mice that already showed signs of the disease. Thus, healthy intake of vitamin B3 may protect eyesight.

Science 2017; 355: 756

Eitan Israeli

Capsule

Interspecies organogenesis generates autologous functional islets

Islet transplantation is an established therapy for diabetes. Yamaguchi and team previously showed that rat pancreata can be created from rat pluripotent stem cells (PSCs) in mice through interspecies blastocyst complementation. Although they were functional and composed of rat-derived cells, the resulting pancreata were of mouse size, rendering them insufficient for isolating the numbers of islets required to treat diabetes in a rat model. Now, by performing the reverse experiment – injecting mouse PSCs into Pdx-1-deficient rat blastocysts – the authors generated rat-sized pancreata composed of mouse-PSC-derived cells. Islets subsequently prepared from these mouse–rat chimeric pancreata were transplanted into mice with streptozotocin-induced diabetes. The transplanted islets successfully normalized and maintained host blood glucose levels for over 370 days in the absence of immunosuppression (excluding the first 5 days after transplant). These data provide proof-of-principle evidence for the therapeutic potential of PSC-derived islets generated by blastocyst complementation in a xenogeneic host.

Nature 2017; 542: 191

Eitan Israeli

Capsule

Stem cells on a mission

Healthy neural stem cells can infiltrate and help treat brain tumors because they naturally migrate toward gliomas in response to tumor-derived chemotactic signals. Obtaining neural stem cells from a patient can be difficult, however, and donor stem cells pose a risk of immune rejection and other safety concerns. Bagó and co-authors discovered a way to avoid these risks by taking normal human skin fibroblasts and trans-differentiating them into neural stem cells. The entire process took only 4 days to complete, yielding autologous patient-derived neural stem cells. The authors engineered these stem cells to infiltrate and effectively treat brain tumors in multiple mouse models.

Sci Transl Med 2017; 9: eaah6510

Eitan Israeli

Capsule

HIV immunity

For rapidly mutating viruses such as HIV, antibodies that can neutralize more than one strain may have real therapeutic potential. Williams et al. examined the origin of broadly neutralizing antibodies (bnAbs) that recognize a part of the membrane-proximal external region (MPER) of HIV-1 gp41. They found similar clonal lineages of a MPER bnAb from both memory B cells and plasma, highlighting the viability of plasma as a source of bnAbs. These lineages shared an autoreactive unmutated common ancestor, suggesting that tolerance must be overcome for bnAb induction. The authors then engineered chimeric antibodies from the plasma and memory B cells that successfully neutralized most HIV-1 strains.

Sci Immunol 2017; 2: eaal2200

Eitan Israeli

Capsule

Postprandial macrophage-derived IL-1β stimulates insulin, and both synergistically promote glucose disposal and inflammation

The deleterious effect of chronic activation of the IL-1β system on type 2 diabetes and other metabolic diseases is well documented. However, a possible physiological role for IL-1β in glucose metabolism has remained unexplored. Dror et al. found that feeding induced a physiological increase in the number of peritoneal macrophages that secreted IL-1β, in a glucose-dependent manner. Subsequently, IL-1β contributed to the postprandial stimulation of insulin secretion. Accordingly, lack of endogenous IL-1β signaling in mice during refeeding and obesity diminished the concentration of insulin in plasma. IL-1β and insulin increased the uptake of glucose into macrophages, and insulin reinforced a pro-inflammatory pattern via the insulin receptor, glucose metabolism, production of reactive oxygen species, and secretion of IL-1β mediated by the NLRP3 inflammasome. Postprandial inflammation might be limited by normalization of glycemia since it was prevented by inhibition of the sodium–glucose co-transporter SGLT2. These findings identify a physiological role for IL-1β and insulin in the regulation of both metabolism and immunity.

Nat Immunol 217; 18: 283

Eitan Israeli

Capsule

Targeting nitric oxide to treat aneurysm

Aneurysms are the abnormal enlargement of arteries and can lead to death if the artery wall bursts. Oller and team studied patients with Marfan syndrome, an inherited genetic condition in which individuals are prone to cardiac aneurysms. They discovered lower levels of ADAMTS1 in the heart tissue of Marfan syndrome patients compared with that of organ transplant donors. Genetic inactivation of ADAMTS1 in mice resulted in a Marfan syndrome-like disease, which included low blood pressure, aortic dilation, and aneurysm development. These effects were driven by enhanced activity of nitric oxide, and treatment with a nitric oxide inhibitor reduced blood vessel size and reversed the clinical signs of aneurysm formation.

Nat Med 2017; 10.1038/nm.4266

Eitan Israeli

Capsule

Defining the tree rings of T cells

T cell function declines with age. What does T cell aging look like at the molecular level? To understand the transcriptional programs that regulate T cell differentiation and aging, Moskowitz and co-authors generated genome-wide maps of chromatin accessibility in CD8+ T cells from young and old individuals. In naive CD8+ T cells in the elderly, promoters that recruit nuclear respiratory factor 1 (NRF1), which controls expression of mitochondrial proteins, were less accessible. Thus, loss of NRF1 binding could contribute to lower metabolic activity in aged T cells. The transcriptional circuits uncovered by this study set the stage for designing approaches to modulate T cell function in the elderly.

Sci Immunol 2017; 2: eaag0192

Eitan Israeli

Capsule

Bacterial battles on your skin

Normal human skin is colonized by a variety of normally harmless bacteria. However, one such bacterium, *Staphylococcus aureus*, can aggravate symptoms of atopic dermatitis. Nakatsuji et al. reported that other strains of *Staphylococcus* residing on the skin of healthy individuals produce an antimicrobial peptide that can inhibit *S. aureus* growth. Colonization of pigskin or mouse skin with these protective commensals reduced *S. aureus* replication. Furthermore, autologous bacterial transplant in a small number of atopic dermatitis patients drastically reduced *S. aureus* skin burden. This commensal skin transplant has already been approved by the U.S. Food and Drug Administration, and a clinical trial is underway.

Sci Transl Med 2017; 9: eaah4680

Eitan Israeli

Capsule

An encephalitis-boosting microRNA

Japanese encephalitis virus (JEV), which is related to the Zika and West Nile viruses, targets the central nervous system. The encephalitis induced by JEV inflicts neurological damage and can be fatal. Hazra and colleagues found that JEV infection in mouse and human neuronal cells reduced the production of antiviral cytokines through the microRNA miR-301a. Treating JEV-infected mice with a miR-301a inhibitor increased antiviral cytokine production, decreased viral replication, and improved survival. Thus, targeting miR-301a may be an effective therapy against JEV infection.

Sci Signal 2017; 10: eaaf5185

Eitan Israeli

Capsule

Withaferin A is a leptin sensitizer with strong antidiabetic properties in mice

The increasing global prevalence of obesity and its associated disorders points to an urgent need for the development of novel and effective therapeutic strategies that induce healthy weight loss. Obesity is characterized by hyperleptinemia and central leptin resistance. In an attempt to identify compounds that could reverse leptin resistance and thus promote weight loss, Lee and colleagues analyzed a library of small molecules that have mRNA expression profiles similar to that of celastrol, a naturally occurring compound that we previously identified as a leptin sensitizer. Through this process, the authors identified another naturally occurring compound, withaferin A, (from *Withania somnifera*, known commonly as *ashwagandha*, Indian ginseng, poison gooseberry or winter cherry) that also acts as a leptin sensitizer. They found that withaferin A treatment of mice with diet-induced obesity (DIO) resulted in a 20–25% reduction of body weight while also decreasing obesity-associated abnormalities, including hepatic steatosis. Withaferin A treatment marginally affected the body weight of *ob/ob* and *db/db* mice, both of which are deficient in leptin signaling. In addition, withaferin A, unlike celastrol, has beneficial effects on glucose metabolism that occur independently of its leptin-sensitizing effect. These results show that the metabolic abnormalities of DIO can be mitigated by sensitizing animals to endogenous leptin, and they indicate that withaferin A is a potential leptin sensitizer with additional antidiabetic actions.

Nat Med 2016; 22: 1023

Eitan Israeli

Capsule

Touchdown for gut pathogen virulence

Escherichia coli is transformed from a commensal organism into a pathogen by acquisition of genetic elements called pathogenicity islands (PAIs). Katsowich and colleagues investigated how the PAI virulence genes of enteropathogenic *E. coli* (EPEC) respond when the bacterium attaches to a host gut cell. EPEC first sticks to the host by means of pili and then uses a PAI-encoded type 3 secretion system (T3SS) to inject multiple effectors into the host cell. But not all virulence mediators are injected. For example, CesT, a bacterial chaperone, delivers virulence effectors into the T3SS apparatus. Then, within the bacterial cytoplasm, it interacts with a gene repressor called CsrA, which reprograms bacterial gene expression to help the bacteria to adapt to epithelial cell-associated life.

Science 2017; 355: 735

Eitan Israel

Capsule

Peak HIV viremia pushes CD8+ T cells

Human immunodeficiency virus (HIV) induces widespread immune dysfunction. Animal studies with simian immunodeficiency virus have suggested that early CD8+ T cell responses may reduce viral burden. Takata et al. examined a large cohort of HIV patients given antiretroviral therapy (ART). They evaluated T cell activation and HIV viral load over time, which allowed them to parse out immune function on the basis of acute stages of infection. CD8+ T cell responses were a little slow to ramp up, but activated CD8+ T cells present after ART initiation reduced the viral reservoir. Thus, targeting CD8+ T cells early in infection could lead to viral eradication.

Sci Transl Med 2017; 9: eaag1809

Eitan Israeli

Capsule

Interfering with bad cholesterol

Over the past few decades, the number of deaths from cardiovascular disease has declined substantially in developed countries. Statins, drugs that lower serum levels of low density lipoprotein cholesterol (LDL-C), have been instrumental in this trend. Not everyone responds to statins, however, and new types of cholesterol-lowering drugs are attracting great interest. Fitzgerald et al. tested inclisiran, a drug based on small interfering RNA technology, in a small phase 1 trial. Inclisiran induces degradation of the mRNA encoding PCSK9, a liver-derived protease whose activity increases serum LDL-C levels. Subcutaneous injection of inclisiran durably reduced PCSK9 levels by as much as 83% and LDL-C levels by as much as 59% without serious toxicities.

N Engl J Med 2017; 376: 41

Eitan Israeli

Capsule

How red berries reduce inflammation

Members of the interleukin-17 (IL-17) family of pro-inflammatory cytokines are important in the immune response to infections. However, too much IL-17 signaling is associated with autoimmune inflammatory diseases, such as asthma, psoriasis, and rheumatoid arthritis. Liu et al. performed small-molecule screening to look for compounds that could bind to the IL-17 receptor. They found that cyanidin, a flavonoid found in red berries and other fruits, bound to the IL-17 receptor and blocked the binding of IL-17A. In several mouse models of inflammatory disease, cyanidin alleviated the inflammation induced by IL-17A-producing T cells.

Sci Signal 2017; 10: eaaf8823

Eitan Israeli

Capsule

Whole-genome landscape of pancreatic neuroendocrine tumors

The diagnosis of pancreatic neuroendocrine tumors (PanNETs) is increasing owing to more sensitive detection methods, and this increase is creating challenges for clinical management. Scarpa et al. performed whole-genome sequencing of 102 primary PanNETs and defined the genomic events that characterize their pathogenesis. They describe the mutational signatures they harbor, including a deficiency in G:C›T:A base excision repair due to inactivation of *MUTYH*, which encodes a DNA glycosylase. Clinically sporadic PanNETs contain a larger than expected proportion of germline mutations, including previously unreported mutations in the DNA repair genes *MUTYH*, *CHEK2* and *BRCA2*. Together with mutations in *MEN1* and *VHL*, these mutations occur in 17% of patients. Somatic mutations, including point mutations and gene fusions, were commonly found in genes involved in four main pathways: chromatin remodeling, DNA damage repair, activation of mTOR signaling (including previously undescribed *EWSR*1 gene fusions), and telomere maintenance. In addition, our gene expression analyses identified a subgroup of tumors associated with hypoxia and HIF signaling.

Nature 2017; 543: 65

Eitan Israeli

Capsule

Blockade to pathological remodeling of infarcted heart tissue using a porcupine antagonist

The secreted Wnt signaling molecules are essential to the coordination of cell-fate decision making in multicellular organisms. In adult animals, the secreted Wnt proteins are critical for tissue regeneration and frequently contribute to cancer. Small molecules that disable the Wnt acyltransferase Porcupine (Porcn) are candidate anticancer agents in clinical testing. Moon et al. have systematically assessed the effects of the Porcn inhibitor (WNT-974) on the regeneration of several tissue types to identify potentially unwanted chemical effects that could limit the therapeutic utility of such agents. An unanticipated observation from these studies is pro-regenerative responses in heart muscle induced by systemic chemical suppression of Wnt signaling. Using in vitro cultures of several cell types found in the heart, the authors delineate the Wnt signaling apparatus supporting an anti-regenerative transcriptional program that includes a subunit of the non-fibrillar collagen VI. Similar to observations seen in animals exposed to WNT-974, deletion of the collagen VI subunit, *COL6A1*, has been shown to decrease aberrant remodeling and fibrosis in infarcted heart tissue. The authors demonstrated that WNT-974 can improve the recovery of heart function after left anterior descending coronary artery ligation by mitigating adverse remodeling of infarcted tissue. Injured heart tissue exposed to WNT-974 exhibits decreased scarring and reduced Col6 production. These findings support the development of Porcn inhibitors as anti-fibrotic agents that could be exploited to promote heart repair following injury.

PNAS 2017; early edition doi: 10.1073/pnas.1621346114

Eitan Israeli

Capsule

A target for intracranial aneurysms

Surgery is the only therapeutic option currently available for intracranial aneurysms. Aoki et al. delineated a self-amplifying signaling pathway in macrophages that could be pharmacologically targeted to limit the inflammation that initiates intracranial aneurysms and causes them to enlarge. Stimulation of EP2 (prostaglandin E receptor subtype 2) in macrophages increased the levels of COX-2, the enzyme that synthesizes the ligand for EP2, and MCP-1, an attractant for macrophages. Administering an EP2 antagonist to rats prevented the formation and progression of intracranial aneurysms.

Sci Signal 2017; 10: eaah6037

Eitan Israeli