Capsule

An oncohistone deranges inhibitory chromatin

Missense mutations (that change one amino acid for another) in histone H3 can produce a so-called oncohistone and are found in a number of pediatric cancers. For example, the lysine-36–to-methionine (K36M) mutation is seen in almost all chondroblastomas. Lu et al. show that K36M mutant histones are oncogenic, and they inhibit the normal methylation of this same residue in wild-type H3 histones. The mutant histones also interfere with the normal development of bone-related cells and the deposition of inhibitory chromatin marks.

Science 2016; 352: 844

Eitan Israeli

Capsule

A role for PKCα in Alzheimer's disease

The neurodegeneration that occurs in Alzheimer's disease is thought to be due to the accumulation of a protein called amyloid-β (Aβ). Alfonso et al. identified activating mutations in protein kinase Cα (PKCα) in a large cohort of families in which late-onset Alzheimer's disease was diagnosed. Pharmacologically inhibiting PKCα or deleting the gene encoding it prevented Aβ from impairing synaptic activity in mouse hippocampal tissue slices. Thus, PKCα variants may mediate the pathological effects of Aβ in some patients with late-onset Alzheimer's disease.

Sci Signal 2016; 9: ra47

Eitan Israeli

Capsule

A platform for the discovery of new macrolide antibiotics

The chemical modification of structurally complex fermentation products, a process known as semisynthesis, has been an important tool in the discovery and manufacture of antibiotics for the treatment of various infectious diseases. However, many of the therapeutics obtained in this way are no longer effective, because bacterial resistance to these compounds has developed. Seiple et al. describe a practical, fully synthetic route to macrolide antibiotics by the convergent assembly of simple chemical building blocks, enabling the synthesis of diverse structures not accessible by traditional semisynthetic approaches. More than 300 new macrolide antibiotic candidates, as well as the clinical candidate solithromycin, have been synthesized using this convergent approach. Evaluation of these compounds against a panel of pathogenic bacteria revealed that the majority of these structures had antibiotic activity, some efficacious against strains resistant to macrolides in current use. This chemistry provides a platform for the discovery of new macrolide antibiotics and may also serve as the basis for their manufacture.

Nature 2016; 533: 338

Eitan Israeli

Capsule

Periodontitis treatment improves systemic lupus erythematosus response to immunosuppressive therapy

Periodontal disease (POD) may affect rheumatic disease severity, but there are no data regarding the effect of its treatment on disease activity in SLE patients under immunosuppressive therapy. Fabbri et al. enrolled 49 consecutive SLE patients (SLEDAI ≥ 2) with POD and receiving corticosteroid and cyclophosphamide pulse therapy (IVCYC). Periodontal assessment included bleeding gingival index (BGI), probing depth (PD), and probing attachment level (PAL). At entry, POD was defined as BGI › 1 and patients were assigned to groups according to the availability of odontological intervention in TREATED (n = 32) and NOT TREATED (n = 17). SLEDAI and POD parameters were determined at entry and after 3 months. Age, female gender, and race were alike among TREATED and NOT TREATED. Both groups also had comparable disease duration, IVCYC number (5.8 ± 4.8 vs. 4.5 ± 4.8), and SLEDAI (5.9 ± 4.2 vs. 6.3 ± 4.3) as well as POD parameters [BGI (40.8 ± 31.0 vs. 40.7 ± 36.2 %), PD (1.7 ± 1.8 vs. 1.5 ± 0.60 mm, $P = 0.80$), and PAL (2.5 ± 1.9 vs. 1.9 ± 1.1 mm)]. At the end of the study, TREATED group had a significant improvement in SLEDAI (5.9 ± 4.2 vs. 3.4 ± 3.3) with a paralleled reduction in BGI (40.8 ± 31.0 vs. 15.2 ± 17.2 %), PD (1.7 ± 1.8 vs. 1.1 ± 0.3 mm), and PAL (2.5 ± 1.9 vs. 1.7 ± 0.9 mm). In contrast, SLEDAI (6.3 ± 4.3 vs. 6.0 ± 5.5) and POD parameters [BGI ($P = 0.33$), PD ($P = 0.91$), and PAL ($P = 0.39$)] remained largely unchanged in the NOT TREATED group. Since periodontal disease treatment seems to have a beneficial effect in controlling disease activity in SLE patients under immunosuppressive therapy, management of this modifiable risk factor is recommended.

Clin Rheumatol 2014; 33: 505

Eitan Israeli

Capsule

Insights into antibody therapy for HIV-1

Despite the success of antiretroviral therapy, HIV-1-infected individuals still harbor latent virus. Thus, other therapeutic strategies are needed. A single injection of a broad and potent monoclonal antibody targeting the HIV-1 envelope protein reduced viral loads in HIV-1-infected individuals, albeit only transiently. Lu et al. (*Science* 2016; 352: 1001) report that antibody treatment not only blocked free virus from infecting new cells, it also accelerated the clearance of infected cells. Furthermore, Schoofs et al. (*Science* 2016; 352: 997) demonstrated that therapeutic antibody treatment enhanced infected individuals' humoral response against the virus. Thus, neutralizing antibodies may be a promising therapy for HIV-1 because of their potential to reduce the viral reservoir.

Eitan Israeli

Capsule

Identification of an ideal adjuvant for receptor-binding domain-based subunit vaccines against Middle East respiratory syndrome coronavirus

Middle East respiratory syndrome (MERS), an emerging infectious disease caused by MERS coronavirus (MERS-CoV), has garnered worldwide attention as a result of its continuous spread and pandemic potential, making the development of effective vaccines a high priority. Naru et al. previously demonstrated that residues 377–588 of MERS-CoV spike (S) protein receptor-binding domain (RBD) is a very promising MERS subunit vaccine candidate, capable of inducing potent neutralization antibody responses. They sought to identify an adjuvant that optimally enhanced the immunogenicity of S377–588 protein fused with F*c* of human IgG (S377–588-F*c*). Specifically, they compared several commercially available adjuvants, including Freund's adjuvant, aluminum, Monophosphoryl lipid A, Montanide ISA51 and MF59 with regard to their capacity to enhance the immunogenicity of this subunit vaccine. In the absence of adjuvant, S377–588-F*c* alone induced readily detectable neutralizing antibody and T cell responses in immunized mice. However, incorporating an adjuvant improved its immunogenicity. Particularly, among the aforementioned adjuvants evaluated, MF59 is the most potent as judged by its superior ability to induce the highest titers of IgG, IgG1 and IgG2a subtypes, and neutralizing antibodies. The addition of MF59 significantly augmented the immunogenicity of S377–588-F*c* to induce strong IgG and neutralizing antibody responses as well as protection against MERS-CoV infection in mice, suggesting that MF59 is an optimal adjuvant for MERS-CoV RBD-based subunit vaccines.

Cell Molec Immunol 2016; 13: 180

Eitan Israeli

Capsule

Dengue model rises to the challenge

Human efficacy testing remains a major hurdle in bringing new vaccine candidates to the clinic. Without accepted correlates of protection, rounds of safety trials must be performed before efficacy can be tested in a large population in an endemic area. Kirkpatrick et al. developed a controlled human challenge model for dengue virus to assess the protective efficacy of the most clinically advanced dengue vaccine candidate. TV003, a live attenuated dengue vaccine that induces antibodies against all four dengue virus serotypes, protected against infection by an attenuated virus in 21 recipients when compared with 20 non-vaccinated controls. This model may serve as an early check for dengue vaccine candidates, limiting the risk of conducting large unsuccessful trials.

Sci Transl Med 2016; 8: 330ra36

Eitan Israeli

Capsule

A more complete look at the HIV-1 envelope

HIV-1 uses its envelope protein (Env), a large glycoprotein present on the viral surface, to enter target cells. Env forms trimers on the viral surface. Structural studies of solubilized Env trimers have provided important insights into viral entry and antibody binding, but soluble trimers lack several important insoluble regions of the native protein. Lee and collaborators used cryo-electron microscopy to solve the structure of a trimeric Env protein of HIV-1, missing only its cytoplasmic tail, in complex with broadly neutralizing antibodies. A more complete understanding of the Env structure may aid in vaccine design efforts.

Science 2016; 531: 1043

Eitan Israeli

Capsule

The cellular ancestry of tumor antigens

One contributing factor in antitumor immunity is the repertoire of neoantigens created by genetic mutations within tumor cells. Like the corresponding mutations, these neoantigens show intratumoral heterogeneity. Some are present in all tumor cells (clonal), and others are present in only a fraction of cells (subclonal). In a study of lung cancer and melanoma, McGranahan et al. found that a high burden of clonal tumor neoantigens correlated with improved patient survival, an increased presence of tumor-infiltrating lymphocytes, and a durable response to immunotherapy.

Science 2016; 351: 1463

Eitan Israeli

Capsule

The spread of bad neighborhoods

Our genomes have complex three-dimensional (3D) arrangements that partition and regulate gene expression. Cancer cells frequently have their genomes grossly rearranged, disturbing this intricate 3D organization. Hnisz et al. show that the disruption of these 3D neighborhoods can bring oncogenes under the control of regulatory elements normally kept separate from them. These novel juxtapositions can result in the inappropriate activation of oncogenes.

Science 2016; 351: 1454

Eitan Israeli

Capsule

A glucose balancing act

In autoimmune diseases, T cells engage their hyperdrive, both proliferating and secreting inflammatory cytokines at greater rates than normal. Little is known about the metabolic changes that fuel this process. Yang et al. report that a defect in reactive oxygen species (ROS) could boost pro-inflammatory T cells in rheumatoid arthritis. A defect in glycolytic flux led to increased ROS consumption, which bypassed a cell cycle checkpoint and contributed to hyperproliferation and pro-inflammatory cell differentiation. What's more, restoring intracellular ROS reduced proliferation and suppressed inflammation.

Sci Transl Med 2016; 8: 331ra38

Eitan Israeli

Capsule

Tuft cells help contain parasites

Trillions of microbes inhabit our guts, including worms and other parasites. Epithelial cells that line the gut orchestrate parasite-targeted immune responses. Howitt and co-authors identified a key cellular player in immunity to parasites: tuft cells. Tuft cells make up a small fraction of gut epithelial cells but expand when parasites colonize or infect the gut. Parasites cause tuft cells to secrete large amounts of interleukin-25, a key cytokine for parasite clearance that also indirectly feeds back on tuft cells to expand their numbers. Tuft cells express chemosensory signaling machinery: disrupting this blocked parasite-triggered tuft cell expansion and weakened the ability of mice to control a parasitic infection.

Science 2016; 351: 1329

Eitan Israeli

Capsule

Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the Finnish Maternity Cohort

Vitamin D has been associated with a decreased risk of multiple sclerosis (MS) in adulthood; however, some, but not all, previous studies have suggested that in utero vitamin D exposure may be a risk factor for MS later in life. Munger et al. questioned whether serum 25-hydroxyvitamin D (25[OH]D) levels in early pregnancy are associated with risk of MS in offspring. They measured maternal serum 25(OH)D levels with a chemiluminescence assay. The risk of MS among offspring and association with maternal 25(OH)D levels were the main outcomes. Conditional logistic regression was used and further adjusted for sex of the child, gestational age at the time of sample collection, and season of sample collection to estimate the relative risks and 95% CI. Of the 193 cases 163 were female, and of the 331 controls 218 were female. Seventy percent of serum samples were collected during the first trimester of pregnancy. The mean (SD) maternal vitamin D levels were in the insufficient vitamin D range, but higher in maternal control than case samples (15.02 [6.41] ng/ml vs 13.86 [5.49] ng/ml [to convert to nanomoles per liter, multiply by 2.496]). Maternal vitamin D deficiency (25[OH]D levels < 12.02 ng/ml) during early pregnancy was associated with a nearly twofold increased risk of MS in the offspring (relative risk 1.90; 95%CI 1.20–3.01, $P = 0.006$) compared with women who did not have deficient 25(OH)D levels. There was no statistically significant association between the risk of MS and increasing serum 25(OH)D levels ($P = 0.12$). The authors concluded that insufficient maternal 25(OH)D during pregnancy may increase the risk of MS in offspring.

JAMA Neurol 2016. doi:10.1001/jamaneurol.2015.4800

Eitan Israeli

Capsule

Sticking it to T cells

The cytokine TGFβ is abundant in the tumor microenvironment, where it inhibits T cells that could attack and destroy tumors. However, targeting TGFβ throughout the body would interfere with other immune responses. Newman et al. found that T cells without the adhesion molecule PECAM-1 were less sensitive to inhibition by TGFβ. Furthermore, mice lacking PECAM-1 had smaller tumors than those in control mice. Thus, targeting PECAM-1 may enhance the antitumor activity of T cells.

Sci Signal 2016; 9: ra27

Eitan Israeli

Capsule

Lymphocytes force target cells to die

The ability of cytotoxic T lymphocytes (CTLs) to kill target cells is essential for immune system function and recent cancer therapies. Basu et al. show that CTLs induce cell death in part by tugging on the target cell. Stimulating CTLs caused increased force generation that was associated with increased formation of pores in target cells, which result from release of the perforin protein from CTLs. Enhanced pore formation and the resultant lysis of target cells were diminished if force generation was limited by growing cells on soft hydrogels. Local activation of pore formation in this manner may help protect neighboring cells from cytolytic secretions.

Cell 2016; 10.1016/j.cell.2016.01.021

Eitan Israeli

Capsule

Sleep loss, brain structure, and learning

Sleep loss is bad for memory formation; however, it affects some of us more than others. Saleti et al. combined memory tests, brain imaging, and sleep EEG recordings to study the interaction between brain structure, sleep loss, and cognitive performance. Individual differences in the anatomy of the human hippocampus explained many of the differences in learning impairment after sleep loss. These structural differences also predicted the subsequent EEG slow-wave activity during recovery sleep and the restoration of learning after sleep. The anatomical structure of the brain may thus represent a biomarker that predicts vulnerability to sleep loss and how easily an individual will recover.

J Neurosci 2016; 36: 235

Eitan Israeli

Capsule

Controlling T cell access to the brain

Although immune cells fight infections, given their potential to cause damage, the brain must carefully regulate their entry. Cupovic et al. sought to better understand this process in mice infected with a neurotrophic coronavirus. They found that in response to infection, pockets of stromal cells in the brain rapidly expressed high amounts of the chemokines CCL19 and CCL21, secreted proteins that can attract virus-fighting T cells. Disrupting this important molecular circuitry increased the susceptibility of mice to the virus, and for the few T cells that could enter the brain, reduced their antiviral capabilities. Viral clearance led to reduced chemokine expression by stromal cells, indicating that the brain quickly rebuilds its barriers once an infection runs its course.

Immunity 2016; 10.1016/j.immuni.2015.12.022

Eitan Israeli

Capsule

Cost-effectiveness of ward closure to control outbreaks of Norovirus

Norovirus is the most common cause of outbreaks of acute gastroenteritis in National Health Service hospitals in the United Kingdom. Wards (units) are often closed to new admissions to stop the spread of the virus, but there is limited evidence describing the cost-effectiveness of ward closure. Sadique et al. conducted an economic analysis based on the results from a large, prospective, active-surveillance study of gastroenteritis outbreaks in hospitals and from an epidemic simulation study and compared alternative ward closure options evaluated at different time points since first infection, assuming different efficacies of ward closure. A total of 232 gastroenteritis outbreaks occurring in 14 hospitals over a 1 year period were analyzed. The risk of a new outbreak in a hospital is significantly associated with the number of admissions, general medical, and long-stay wards that are concurrently affected but is less affected by the level of community transmission. Ward closure leads to higher costs but reduces the number of new outbreaks by 6%–56% and the number of clinical cases by 1%–55%, depending on the efficacy of the intervention. The incremental cost per outbreak averted varies from £10,000 ($14,000) to £306,000 ($428,000), and the cost per case averted varies from £500 ($700) to £61,000 ($85,000). The cost-effectiveness of ward closure decreases as the efficacy of the intervention increases, and the cost-effectiveness increases with the timing of the intervention. The efficacy of ward closure is critical from a cost-effectiveness perspective. The authors conclude that ward closure may be cost-effective, particularly if targeted to high-throughput units.

J Infect Dis 2016; 213 (Suppl 1): S19-26

Eitan Israeli

Capsule

Reelin in leukocytes for atherosclerosis

In the circulation, the secreted protein Reelin acts to stem bleeding after injury. Receptors for Reelin are found on the endothelial cells that line blood vessels. Ding et al. questioned whether Reelin contributes to atherosclerosis: plaque buildup in arteries. Mice that lacked Reelin in the circulation were protected from diet-induced atherosclerosis. Reelin deficiency prevented leukocytes from sticking to endothelial cells, a critical first step in the inflammatory response that promotes atherosclerosis.

Sci Signal 2015; 9: ra29

Eitan Israeli