Capsule

Adapting HIV-1 to infect monkeys

HIV-1 replicates well in humans but not in monkeys or mice. On the up side, this reduces the risk of cross-species transmissions, but it makes the study of HIV-1 and AIDS more difficult. Hatziioannou et al. overcame this hurdle by serially passaging HIV-1 in pigtailed macaques. Over time, the HIV-1 acquired mutations that allowed it to adapt to the monkeys. Depleting CD8+ T cells during acute infection resulted in a subset of animals developing an AIDS-like disease by the fourth passage. HIV-1 envelope protein gene selection and the acquisition of mutations in the HIV protein Vpu, which allowed HIV-1 to overcome host restriction by the macaque protein tetherin, accompanied the viral adaptation to the monkeys.

Science 2014; 344: 1401

Eitan Israeli

Capsule

Botulinum neurotoxin breaks through the epithelial barrier

Botulinum neurotoxin (BoNT) poisons its host when it crosses the intestinal epithelial barrier. To help it cross this barrier, the toxin forms a large complex with three bacterial proteins called hemagglutinins (HAs). To find out what happens when this complex binds to a cell-adhesion protein called E-cadherin, Lee et al. crystallized the bound complex and protein. Toxin binding disrupted the way E-cadherin maintains the epithelial barrier. When the researchers prevented the toxin complex from binding to E-cadherin, mice were protected from the toxin's deadly effects.

Science 2014; 344: 1405

Eitan Israeli

Capsule

The heart needs blood vessels, too

For the newborn heart to grow quickly, the heart's own blood vessels must grow as well. Researchers have assumed that preexisting fetal coronary vessels expand to cause this postnatal coronary vascular growth. Instead, Tian and collaborators show that, for the most part, brand-new blood vessels form within the neonatal heart (see the Perspective by Burns and Burns). This ability to produce new coronary blood vessels after birth may one day help researchers work out how to promote cardiovascular regeneration after injury or disease.

Science 2014; 345: 90

Eitan Israeli

Capsule

Comprehensive molecular profiling of lung adenocarcinoma

Adenocarcinoma of the lung is the leading cause of cancer death worldwide. The Cancer Genome Atlas Research Network report molecular profiling of 230 resected lung adenocarcinomas using messenger RNA, microRNA and DNA sequencing integrated with copy number, methylation and proteomic analyses. High rates of somatic mutation were seen (mean 8.9 mutations per megabase). Eighteen genes were statistically significantly mutated, including *RIT1* activating mutations and newly described loss-of-function MGAmutations which are mutually exclusive with focal MYC amplification. EGFR mutations were more frequent in female patients, whereas mutations in RBM10 were more common in males. Aberrations in *NF1*, *MET*, *ERBB2* and *RIT1* occurred in 13% of cases and were enriched in samples otherwise lacking an activated oncogene, suggesting a driver role for these events in certain tumors. DNA and mRNA sequence from the same tumor highlighted splicing alterations driven by somatic genomic changes, including exon 14 skipping in *MET* mRNA in 4% of cases. MAPK and PI(3)K pathway activity, when measured at the protein level, was explained by known mutations in only a fraction of cases, suggesting additional, unexplained mechanisms of pathway activation. These data establish a foundation for classification and further investigations of lung adenocarcinoma molecular pathogenesis.

Nature 2014; 511: 543

Eitan Israeli

Capsule

Ex vivo culture of circulating breast tumor cells for individualized testing of drug susceptibility

Circulating tumor cells (CTCs) are present at low concentrations in the peripheral blood of patients with solid tumors. It has been proposed that the isolation, ex vivo culture, and characterization of CTCs may provide an opportunity to noninvasively monitor the changing patterns of drug susceptibility in individual patients as their tumors acquire new mutations. In a proof-of-concept study, Yu et al. established CTC cultures from six patients with estrogen receptor-positive breast cancer. Three of five CTC lines tested were tumorigenic in mice. Genome sequencing of the CTC lines revealed preexisting mutations in the *PIK3CA*gene and newly acquired mutations in the estrogen receptor gene (*ESR1*), *PIK3CA* gene, and fibroblast growth factor receptor gene (*FGFR2*), among others. Drug sensitivity testing of CTC lines with multiple mutations revealed potential new therapeutic targets. With optimization of CTC culture conditions, this strategy may help identify the best therapies for individual cancer patients over the course of their disease.

Science 2014; 345: 216

Eitan Israeli

Capsule

HIV needs to be fit to transmit

Although you might not think it, it's hard to catch HIV. Less than 1% of unprotected sexual exposures result in infection. What then leads to transmission? Carlson et al. determined the amino acid sequence of viruses infecting 137 Zambian heterosexual couples in which one partner infected the other. The authors then used statistical modeling and found that transmitted viruses are typically the most evolutionarily fit. That is, compared to other viral variants in the infected person, the transmitted virus most closely matches the most common viral sequence found in the Zambian population.

Science 2014; 345: 10.1126/science.1254031

Eitan Israeli

Capsule

The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response

Assembly of the NLRP3 inflammasome activates caspase-1 and mediates the processing and release of the leaderless cytokine IL-1β and thereby serves a central role in the inflammatory response and in diverse human diseases. Baroja-Mazo et al. found that upon activation of caspase-1, oligomeric NLRP3 inflammasome particles were released from macrophages. Recombinant oligomeric protein particles composed of the adaptor ASC or the p.D303N mutant form of NLRP3 associated with cryopyrin-associated periodic syndromes (CAPS) stimulated further activation of caspase-1 extracellularly, as well as intracellularly after phagocytosis by surrounding macrophages. The authors found oligomeric ASC particles in the serum of patients with active CAPS but not in that of patients with other inherited autoinflammatory diseases. These findings support a model whereby the NLRP3 inflammasome, acting as an extracellular oligomeric complex, amplifies the inflammatory response.

Nature Immunol 2014; 15: 738

Eitan Israeli

Capsule

Citrulline-specific Th1 cells are increased in rheumatoid arthritis and their frequency is influenced by disease duration and therapy

Rheumatoid arthritis (RA) is thought to be a T cell-mediated disease, based on its strong association with HLA class II alleles, clinical responsiveness to T cell-directed therapies, and the presence of CD4+ T cells in rheumatoid joints. The presence of anti-citrullinated protein antibodies (ACPAs) in RA serum and the association of these antibodies with HLA-DR4 alleles implicate citrulline-specific autoreactive T cells in the development and progression of RA. To determine the characteristics and specificity of autoreactive T cell responses in RA. James et al. developed a panel of HLA-DRB1*04:01 tetramers, selecting citrullinated peptides from synovial antigens and verifying their immunogenicity in DRB1*04:01-transgenic mice. Seven tetramers were used to examine the ex vivo frequency and surface phenotype of citrulline-specific (Cit-specific) T cells in patients with RA and healthy subjects with DRB1*04:01 haplotypes, using a magnetic enrichment procedure. Cit-specific T cells were detectable in peripheral blood samples from both healthy subjects and RA patients. Compared to healthy subjects, RA patients had significantly higher frequencies of Cit-specific T cells, and a greater proportion of these cells displayed a Th1 memory phenotype. Among RA patients, the frequency of Cit-specific T cells was highest within the first 5 years after diagnosis of RA and was decreased in patients taking biologic agents, irrespective of disease duration. These findings link the presence of ACPAs in RA with Th1 cells specific for citrullinated epitopes and provide tools for disease-specific immuno-monitoring of autoreactive T cells.

Arthritis Rheum 2014; 66: 1712

Eitan Israeli

Capsule

Changing skin cells in development with TGF-β

Transforming growth factor-β (TGF-β) makes some cells stop dividing, separate from one another, and start migrating. This process, called the epithelial-to-mesenchymal transition, occurs during normal development and can help cancers progress. D'Souza and co-workers cultured skin cells and measured changes in their proteins as they underwent this process. TGF-β caused thousands of protein changes that varied depending on how long cells were exposed to TGF-β. The protein changes correlated with changes in cell behavior. The authors modeled the network of interacting proteins affected by TGF-β, creating a road map that can explain how TGF-β influences cell behavior.

Sci Signal 2014; 7: rs5

Eitan Israeli

Capsule

Targeting transcription regulation in cancer with a covalent CDK7 inhibitor

Tumor oncogenes include transcription factors that co-opt the general transcriptional machinery to sustain the oncogenic state, but direct pharmacological inhibition of transcription factors has so far proven difficult. However, the transcriptional machinery contains various enzymatic cofactors that can be targeted for the development of new therapeutic candidates, including cyclin-dependent kinases (CDKs). Kwiatkowski et al. present the discovery and characterization of a covalent CDK7 inhibitor, THZ1, which has the unprecedented ability to target a remote cysteine residue located outside of the canonical kinase domain, providing an unanticipated means of achieving selectivity for CDK7. Cancer cell-line profiling indicates that a subset of cancer cell lines, including human T cell acute lymphoblastic leukemia (T-ALL), have exceptional sensitivity to THZ1. Genome-wide analysis in Jurkat T-ALL cells shows that THZ1 disproportionally affects transcription of RUNX1 and suggests that sensitivity to THZ1 may be due to vulnerability conferred by the RUNX1 super-enhancer and the key role of RUNX1 in the core transcriptional regulatory circuitry of these tumor cells. Pharmacological modulation of CDK7 kinase activity may thus provide an approach to identify and treat tumor types that are dependent on transcription for maintenance of the oncogenic state.

Nature 2014; 511: 616

Eitan Israeli

Capsule

In CF, two drugs are no better than one

Cystic fibrosis (CF), a disabling lung disease, is caused by mutations in a protein called CFTR, which acts as a channel to move chloride ions into and out of cells. Ivacaftor, the only targeted drug available, does not work well for the severest, most common form of disease. Cholon et al. and Veit et al. explain why efforts to improve CF treatment by combining ivacaftor with new drugs have failed. Ivacaftor increases mutant CFTR activity, but it only works when CFTR is on the cell surface. The new drugs under development bring mutant CFTR to the surface, but combining the two types of drugs has not been effective because ivacaftor also makes CFTR less stable, so cells remove it quickly from their membranes.

Sci Transl Med 2014; 6: 246ra96, 246ra97

Eitan Israeli

Capsule

Macrophages help food move through

Food needs a complex array of cellular interactions to move through the body. Neurons, muscle cells, and interstitial cells all cooperate to ease it through the gastrointestinal (GI) tract. Now Muller and colleagues report intestinal muscularis macrophages, a type of immune cell that resides in the smooth muscles that surround the GI tract, participate, too. These macrophages secrete a substance called bone morphogenetic protein 2 (BMP2), which binds to enteric neurons and directs them to coordinate the muscle cell contractions that squeeze food through. The neurons, in turn, produce a growth factor required by the macrophages. Macrophage-neuron crosstalk is essential: When mice don't have enough of the growth factor, BMP2, or muscularis macrophages, they have defects in gut muscle contractions.

Cell 2014; 10.1016/j.cell.2014.04.050

Eitan Israeli

Capsule

Problems making proteins kills nerve cells

Neurodegeneration is associated with a variety of different diseases, but its cellular roots are often obscure. Ishimura and co-authors found that mutant mice whose brain cells start to die rapidly soon after birth have lost the function of two vital cellular components. The first is a protein that releases stalled ribosomes stuck on messenger RNA (mRNA); the second is a transfer RNA (tRNA), which reads the code for arginine in the mRNA. This tRNA is expressed predominantly in the central nervous system. The lack of the tRNA leads to increased ribosomal stalling at arginine codons, which, when left uncorrected, blocks protein synthesis and proves fatal.

Science 2014; 345: 455

Eitan Israeli

Capsule

Parasites make it hard to fight viruses

Microbial co-infections challenge the immune system – different pathogens often require different flavors of immune responses for their elimination. Two teams studied what happens when parasitic worms and viruses infect mice at the same time. Reese et al. (Science 2014; 345: 73) found that parasite co-infection woke up a dormant virus. Osborne et al. (Science p. 517) found that mice already infected with parasitic worms were worse at fighting off viruses. In both cases, worms skewed the immune response so that the immune cells and the molecules they secreted created an environment favorable for the worm at the expense of antiviral immunity.

Eitan Israeli

Capsule

The long and short of hair growth

The length of your eyelashes probably differs from the length of the hair on your head – and unlike your hair, your eyelashes can never reach your shoulders. What controls how long hair can get? To find out, Higgins et al. studied people with a rare disorder called familial trichomegaly, who have very long eyelashes and longer hair on the arms. They found that these people had a mutation in the gene that encodes fibroblast growth factor 5 (FGF5). When human hair follicles produce FGF5, they stop growing hair. Targeting FGF5 could potentially control the growth and rest phases of hair follicles, preventing unwanted hair from sprouting or growing longer lashes and locks.

Proc Natl Acad Sci USA 2014;10.1073/pnas.1402862111

Eitan Israeli

Capsule

Mycobacterium make not-so-painful ulcers

Buruli ulcer disease causes extensive skin lesions and can be deadly, but the lesions themselves don't hurt, which can stop patients from seeking the appropriate care. The pathogen Mycobacterium ulcerans causes Buruli ulcers and also alleviates the pain. Although many scientists studying this disease thought the pathogen caused nerve damage that blocked the pain, Marion et al. show that the mycobacteria produce the mycolactone toxin, which causes analgesia by blocking the function of pain-responsive nerves. The findings could potentially help researchers develop a whole new class of painkillers.

Cell 2014;157: 1565

Eitan Israeli

Capsule

A neuropeptide kills patient's motivation

Chronic pain is not only extremely disturbing and unpleasant, it can also make people depressed and demotivated. What causes these effects? Schwartz and co-researchers discovered that chronic pain causes changes in the way a neuropeptide called galanin affects certain neurons in a brain region called the nucleus accumbens. Galanin influences a variety of behaviors, including feeding and certain aspects of pain. In this case, it depresses synaptic transmission at specific excitatory synapses. It does so, in part, by changing the ratio of subunits of an important receptor protein.

Science 2014; 345: 535

Eitan Israeli

Capsule

A vitamin's dark side in liver disease

Too much of a good thing can be bad for the liver. Chen et al. found that mice with high levels of thiamine (vitamin B1) in their livers develop fatty liver disease, a metabolic disorder that affects one-third of adults in the United States. A protein called organic cation transporter 1 (*OCT1*) carries dietary thiamine into the liver. When the researchers deleted the Oct1 gene in mice or fed mice a diet low in thiamine, the mice did not develop the disease. OCT1 also carries the diabetes drug metformin into the liver, which might explain why metformin decreases symptoms of fatty liver disease: By competing with thiamine for OCT1, metformin reduces the amount of dietary thiamine that reaches the liver.

Proc Natl Acad Sci USA 2014;10.1073/pnas.1314939111

Eitan Israeli

Capsule

Reprogrammed heart cells set the pace

Pacemakers have revolutionized the care of patients with slow or abnormal heart rhythms, but these devices can break or become infected. With these patients in mind, Hu et al. created biological pacemakers to provide temporary, hardware-free support until a damaged electronic device can be replaced. They inserted a gene for a human transcription factor into heart muscle cells. This gene reprogrammed the cells to become pacemakers – cells that emit rhythmic electrical impulses to drive the beating heart. These biological pacemaker cells restored normal heart rate in pigs with complete heart block, a problem with the heart's electrical system.

Sci Transl Med 2014; 6: 245ra94

Eitan Israeli

Capsule

The latent reservoir of HIV

HIV-infected cells linger even in the face of therapy, and this persistence, termed the latent reservoir, is a major hurdle for curing HIV. HIV integrates itself into the DNA of its host cells. Could that affect the latent reservoir? To find out, Maldarelli and collaborators drew blood from five HIV patients on antiretroviral therapy and analyzed sites where HIV had inserted itself into the blood cells' DNA. In many cases, these sites were not random; HIV often weaseled its way into genes that help cells grow and proliferate. Where HIV integrates into the host genome may thus determine the size of the latent reservoir.

Science 2014; 345; 1790

Eitan Israeli

Capsule

Regulation of the hepatitis C virus RNA replicase by endogenous lipid peroxidation

Oxidative tissue injury often accompanies viral infection, yet there is little understanding of how it influences virus replication. Yamane et al. show that multiple hepatitis C virus (HCV) genotypes are exquisitely sensitive to oxidative membrane damage, a property distinguishing them from other pathogenic RNA viruses. Lipid peroxidation, regulated in part through sphingosine kinase-2, severely restricts HCV replication in Huh-7 cells and primary human hepatoblasts. Endogenous oxidative membrane damage lowers the 50% effective concentration of direct-acting antivirals in vitro, suggesting critical regulation of the conformation of the NS3-4A protease and the NS5B polymerase, membrane-bound HCV replicase components. Resistance to lipid peroxidation maps genetically to transmembrane and membrane-proximal residues within these proteins and is essential for robust replication in cell culture, as exemplified by the atypical JFH1 strain of HCV. Thus, the typical, wild-type HCV replicase is uniquely regulated by lipid peroxidation, providing a mechanism for attenuating replication in stressed tissue and possibly facilitating long-term viral persistence.

Nature Med 2014; 20: 927

Eitan Israeli

Capsule

Two signals for maximal T cell activation

T cell activation requires increased intracellular calcium and the activity of various enzymes, such as the kinase Itk. Wang et al. report that two signals, calcium and lipids, converged on Itk for maximal activation of T cells. The same region of the Itk protein bound to the signaling lipid PI(3,4,5)P3 and to the calcium-binding protein calmodulin. PI(3,4,5)P3 and calmodulin enhanced the binding of each other to Itk. The binding of both PI(3,4,5)P3 and calmodulin was necessary so that T cells produced maximal levels of an inflammatory cytokine, interleukin-17A.

Sci Signal 2014; 7: ra74

Eitan Israeli

Capsule

Putative cis-regulatory drivers in colorectal cancer

The cis-regulatory effects responsible for cancer development have not been as extensively studied as the perturbations of the protein coding genome in tumorigenesis. To better characterize colorectal cancer (CRC) development Ongen et al. conducted an RNA-sequencing experiment of 103 matched tumor and normal colon mucosa samples from Danish CRC patients, 90 of which were germline-genotyped. By investigating allele-specific expression (ASE) the authors show that the germline genotypes remain important determinants of allelic gene expression in tumors. Using the changes in ASE in matched pairs of samples they discovered 71 genes with excess of somatic cis-regulatory effects in CRC, suggesting a cancer driver role. The authors correlated genotypes and gene expression to identify expression quantitative trait loci (eQTLs) and found 1693 and 948 eQTLs in normal samples and tumors, respectively. They estimate that 36% of the tumor eQTLs are exclusive to CRC and show that this specificity is partially driven by increased expression of specific transcription factors and changes in methylation patterns. They also show that tumor-specific eQTLs are more enriched for low CRC genome-wide association study (GWAS) P values than shared eQTLs, which suggests that some of the GWAS variants are tumor-specific regulatory variants. Importantly, tumor-specific eQTL genes also accumulate more somatic mutations when compared to the shared eQTL genes, raising the possibility that they constitute germline-derived cancer regulatory drivers. Collectively the integration of genome and the transcriptome reveals a substantial number of putative somatic and germline cis-regulatory cancer changes that may have a role in tumorigenesis.

Nature 2014; 512: 87

Eitan Israeli

Capsule

Hearing sounds can improve your vision

Sounds can draw our attention to a specific location and make us aware of something that we may otherwise overlook. But do auditory cues improve the function of other senses, such as sight? To find out, Feng et al. recorded the electrical activity in people's brains when they were seeing and hearing stimuli. The researchers played a sound from one side and then quickly flashed a visual stimulus either on the same side as the sound or on the opposite side. When the sound and the visual stimulus came on the same side, electrical activity in the brain increased and people correctly identified the visual stimulus more often. This suggests that sound helps the brain process co-localized visual input.

J Neurosci 2014; 34: 9817

Eitan Israeli

Capsule

Tumorigenicity and genetic profiling of circulating tumor cells in small-cell lung cancer

Small-cell lung cancer (SCLC), an aggressive neuroendocrine tumor with early dissemination and dismal prognosis, accounts for 15–20% of lung cancer cases and ~200,000 deaths each year. Most cases are inoperable, and biopsies to investigate SCLC biology are rarely obtainable. Circulating tumor cells (CTCs), which are prevalent in SCLC, present a readily accessible 'liquid biopsy'. Hodgkinson et al. show that CTCs from patients with either chemosensitive or chemorefractory SCLC are tumorigenic in immune-compromised mice, and the resultant CTC-derived explants (CDXs) mirror the donor patient's response to platinum and etoposide chemotherapy. Genomic analysis of isolated CTCs revealed considerable similarity to the corresponding CDX. Most marked differences were observed between CDXs from patients with different clinical outcomes. These data demonstrate that CTC molecular analysis via serial blood sampling could facilitate delivery of personalized medicine for SCLC. CDXs are readily passaged, and these unique mouse models provide tractable systems for therapy testing and understanding drug resistance mechanisms.

Nature Med 2014; 20: 897

Eitan Israeli

Capsule

Bad cholesterol: Bad for bacteria, too?

Why do viral infections, such as the common cold, leave people more susceptible to bacterial pneumonia? One reason is that type I interferons, secreted proteins that initiate antiviral immune responses, suppress other inflammatory molecules that protect against bacterial infection. Reboldi et al. investigated how this suppression occurs on a molecular level in mice. Interferons stimulated expression of a particular enzyme that catalyzes the production of the oxysterol 25-hydroxycholesterol (25-HC). 25-HC inhibits the function of the transcription factor SREBP, which normally drives expression of the gene that encodes interleukin-1, a secreted inflammatory protein with wide-ranging antibacterial functions.

Science 2014; 345: 679

Eitan Israeli

Capsule

A not so random integration for HIV

Even in the face of a cocktail of antiretroviral drugs, HIV manages to hang on. It does so by integrating its own genome into those of host cells, where it persists in a latent state. To better understand this process, Wagner et al. determined the sites where HIV integrated into three HIV-infected patients treated with antiretroviral drugs for more than a decade. They found an over-representation of sites where HIV integrated into genes associated with cancer and cell proliferation. Also, multiple cells in the same individual harbored the same integration sites. This suggests that integration into specific genes may drive cell proliferation and viral persistence.

Science 2014; 345: 570

Eitan Israeli

Capsule

Better blood thinner, without bleeding

Blood thinners prevent heart attacks and strokes by making it harder for blood to clot, but these drugs can put patients at risk of dangerous bleeding. Now Moeckle et al. describe an enzyme that can prevent clots without this perilous side effect. They engineered the enzyme apyrase to remove the pro-clotting molecule ADP from the blood quickly. In dogs and mice with heart attacks, apyrase stopped blood cells from aggregating, the first step in forming a clot. At the highest dose, the animals suffered less heart damage and did not bleed excessively. In comparison, clopidogrel, a blood thinner used currently in patients, protected the heart less well and did cause excessive bleeding.

Sci Transl Med 2014; 6: 248ra105

Eitan Israeli