Capsule

Blood and brain intertwined during development

During brain development, blood vasculature grows rapidly to keep up with growing brain tissue. Studying the mouse hindbrain, Tata and collaborators show how these events are coordinated. Peak angiogenesis during embryonic development correlates with a surge in mitotic activity of neural progenitor cells. Processes from these cells wrap around developing vessels or tag the perineural vascular plexus. The interaction depends on neuropilin-1 (NRP1), a cell surface receptor that is expressed in endothelial cells of the developing vasculature. Without NRP1, neural progenitor cells fail to proliferate normally, resulting in fewer than normal progenitors and compromising hindbrain growth.

Proc Natl Acad Sci USA 2016; 113: 13414

Eitan Israeli

Capsule

The aryl hydrocarbon receptor AhR links atopic dermatitis and air pollution via induction of the neurotrophic factor artemin

Atopic dermatitis is increasing worldwide in correlation with air pollution. Various organic components of pollutants activate the transcription factor AhR (aryl hydrocarbon receptor). Through the use of AhR-CA mice, whose keratinocytes express constitutively active AhR and that develop atopic-dermatitis-like phenotypes, Hidaka et al. identified *Artn* as a keratinocyte-specific AhR target gene whose product (the neurotrophic factor artemin) was responsible for epidermal hyper-innervation that led to hypersensitivity to pruritus. The activation of AhR via air pollutants induced expression of artemin, alloknesis, epidermal hyper-innervation and inflammation. AhR activation and *ARTN* expression were positively correlated in the epidermis of patients with atopic dermatitis. Thus, AhR in keratinocytes senses environmental stimuli and elicits an atopic-dermatitis pathology. The authors propose a mechanism of air-pollution-induced atopic dermatitis via activation of AhR.

Nature Immunol 2017; 18: 64

Eitan Israeli

Capsule

Regulation of autoantibody activity by the IL-23–T_H17 axis determines the onset of autoimmune disease

The checkpoints and mechanisms that contribute to autoantibody-driven disease are as yet incompletely understood. Pfeifle et al. identified the axis of interleukin 23 (IL-23) and the T_H17 subset of helper T cells as a decisive factor that controlled the intrinsic inflammatory activity of autoantibodies and triggered the clinical onset of autoimmune arthritis. By instructing B cells in an IL-22- and IL-21-dependent manner, T_H17 cells regulated the expression of β-galactoside α2,6-sialyltransferase 1 in newly differentiating antibody-producing cells and determined the glycosylation profile and activity of immunoglobulin G (IgG) produced by the plasma cells that subsequently emerged. Asymptomatic humans with rheumatoid arthritis (RA)-specific autoantibodies showed identical changes in the activity and glycosylation of autoreactive IgG antibodies before shifting to the inflammatory phase of RA; thus, these results identify an IL-23–T_H17 cell-dependent pathway that controls autoantibody activity and unmasks a preexisting breach in immunotolerance.

Nature Immunol 2017; 18: 104

Eitan Israeli

Capsule

The signaling adaptor TRAF1 negatively regulates Toll-like receptor signaling and this underlies its role in rheumatic disease

TRAF1 is a signaling adaptor known for its role in tumor necrosis factor receptor-induced cell survival. Abdul-Sater and fellow-researchers show that monocytes from healthy human subjects with a rheumatoid arthritis-associated single-nucleotide polymorphism (SNP) in the *TRAF*1 gene express less TRAF1 protein but greater amounts of inflammatory cytokines in response to lipopolysaccharide (LPS). The TRAF1 MATH domain binds directly to three components of the linear ubiquitination (LUBAC) complex, SHARPIN, HOIP and HOIL-1, to interfere with the recruitment and linear ubiquitination of NEMO. This results in decreased NF-κB activation and cytokine production, independently of tumor necrosis factor. Consistent with this, *Traf*1-/- mice show increased susceptibility to LPS-induced septic shock. These findings reveal an unexpected role for TRAF1 in negatively regulating Toll-like receptor signaling, providing a mechanistic explanation for the increased inflammation seen with a disease-associated *TRAF*1 SNP.

Nature Immunol 2017;1 8: 26

Eitan Israeli

Capsule

Neuron development in human embryos

Mammalian fertility depends on the secretion of gonadotropin-releasing hormone (GnRH) from a population of specialized neurons residing in the hypothalamus. During embryogenesis, these neurons develop at the olfactory placodes, and they subsequently migrate to the brain. Very little is known about the process in humans, however. Casoni et al. studied this in depth by using donated human embryonic tissue. They tracked the differentiation and migration of GnRH neurons through the first trimester of gestation by examining samples at different developmental stages and identified important differences between humans and rodents. Unexpectedly, they also found that some of these neurons migrate to extra-hypothalmic regions of the brain, suggesting that they play roles in other processes not linked to fertility.

Development 2016; 10.1242/dev.139444

Eitan Israeli

Capsule

Increased activity of TNAP compensates for reduced adenosine production and promotes ectopic calcification in the genetic disease ACDC

ACDC (arterial calcification due to deficiency of CD73) is an autosomal recessive disease resulting from loss-of-function mutations in *NT5E*, which encodes CD73, a 5'-ectonucleotidase that converts extracellular adenosine monophosphate to adenosine. ACDC patients display progressive calcification of lower extremity arteries, causing limb ischemia. Tissue non-specific alkaline phosphatase (TNAP), which converts pyrophosphate (PPi) to inorganic phosphate (Pi), and extracellular purine metabolism play important roles in other inherited forms of vascular calcification. Jin et al. showed that compared to cells from healthy subjects, induced pluripotent stem cell-derived mesenchymal stromal cells (iMSCs) from ACDC patients displayed accelerated calcification and increased TNAP activity when cultured under conditions that promote osteogenesis. TNAP activity generated adenosine in iMSCs derived from ACDC patients but not in iMSCs from control subjects, which have CD73. In response to osteogenic stimulation, ACDC patient-derived iMSCs had decreased amounts of the TNAP substrate PPi, an inhibitor of extracellular matrix calcification, and exhibited increased activation of AKT, mechanistic target of rapamycin (mTOR), and the 70 kDa ribosomal protein S6 kinase (p70S6K), a pathway that promotes calcification. In vivo, teratomas derived from ACDC patient cells showed extensive calcification and increased TNAP activity. Treating mice bearing these teratomas with an A2b adenosine receptor agonist, the mTOR inhibitor rapamycin, or the bisphosphonate etidronate reduced calcification. These results show that an increase of TNAP activity in ACDC contributes to ectopic calcification by disrupting the extracellular balance of PPi and Pi and identify potential therapeutic targets for ACDC.

Sci Signal 2016: 9: ra121

Eitan Israeli

Capsule

Genomic hallmarks of localized, non-indolent prostate cancer

Prostate tumors are highly variable in their response to therapies, but clinically available prognostic factors can explain only a fraction of this heterogeneity. Fraser et al. analyzed 200 whole-genome sequences and 277 additional whole-exome sequences from localized, non-indolent prostate tumors with similar clinical risk profiles, and carried out RNA and methylation analyses in a subset. These tumors had a paucity of clinically actionable single nucleotide variants, unlike those seen in metastatic disease. Rather, a significant proportion of tumors harbored recurrent non-coding aberrations, large-scale genomic rearrangements, and alterations in which an inversion repressed transcription within its boundaries. Local hypermutation events were frequent and correlated with specific genomic profiles. Numerous molecular aberrations were prognostic for disease recurrence, including several DNA methylation events, and a signature comprised of these aberrations outperformed well-described prognostic biomarkers. The authors suggest that intensified treatment of genomically aggressive localized prostate cancer may improve cure rates.

Nature 2017; 541: 359

Eitan Israeli

Capsule

Tracking extracellular space in the brain

Extracellular space takes up a large percentage of the brain. Its size changes with the sleep-wake cycle but also during brain development and normal aging, as well as under pathological conditions such as neurodegeneration. Godin et al. injected near-infrared luminescent carbon nanotubes into rat brains and tracked their diffusion in the extracellular space. This method revealed the dimensions of the extracellular space in live brain tissue. The extracellular space turned out to be a maze of interconnected compartments of multiple shapes that are structured in a wide range of different dimensions. This novel technique thus allows neuroscientists to observe fine structures of the extracellular space and provides insights into the flow of cerebrospinal fluid in the brain.

Nat Nanotech 2016; 10.1038/NNANO.2016.248

Eitan Israeli

Capsule

Initiating an antitumor attack

Cancer is notorious for relapsing after treatment. Such relapses are driven by tumor-initiating cells, a type of stem cell that gives rise to tumors. Damelin et al. determined that a protein called PTK7 is frequently present on tumor-initiating cells and developed an antibody-drug conjugate targeting it. In mouse models of several tumor types, the therapy reduced tumor-initiating cells and outperformed standard chemotherapy. The antibody-drug conjugate also reduced tumor angiogenesis and promoted antitumor immunity, possibly contributing to its effectiveness.

Sci Transl Med 2017; 9: eaag2611

Eitan Israeli

Capsule

Mobilization of neutrophils from the bone marrow

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 et al. 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

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 et al. 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

B cells safeguard against premature labor

Around one-third of cases of premature labor are caused by infection and inflammatory responses. B cells are specialized immune cells that should protect from pathogens, but their role in pregnancy is poorly defined. Huang et al. have identified a functionally distinct population of B cells in the choriodecidua (a specialized uterine lining that separates the mother from the fetus) that is associated with preterm labor in women. Mice lacking B cells had diminished levels of progesterone-induced blocking factor 1 (PIBF1) and were also more prone to premature labor after inflammation. But when B cell function was compensated by administering PIBF1, inflammation in the uterus and preterm labor were reduced in the B cell-deficient mice. The cytokine interleukin-33, which normally raises the alarm for inflammation, is responsible for stimulating B cell production of PIBF1. These insights provide therapeutic possibilities for maintaining term pregnancy.

Nat Med 2016;10.1038/nm.4244

Eitan Israeli

Capsule

Robots to assist heart beat

Ventricular assist devices help failing hearts function by pumping blood, but they require monitoring and anti-coagulant therapy to prevent blood clot formation. Roche et al. created a soft robotic device with material properties similar to those of native heart tissue that sits snugly around the heart and provides ventricular assistance without ever contacting the blood. The robotic sleeve uses compressed air to power artificial silicone muscles that compress and twist, mimicking the movements of the normal human heart. The device increased cardiac ejection volume in vitro and when implanted in adult pigs during drug-induced cardiac arrest.

Sci Transl Med 2017; 9: eaaf3925
Eitan Israeli

Capsule

TAMpering with tumors

Immunotherapeutic antibodies are a promising cancer therapy, but little is known about the non-targeted effects of these antibodies on immune cells through Fc receptor binding. Tumor-associated macrophages (TAMs) and neutrophils (TANs), which have been implicated in both promoting and inhibiting tumor growth, express abundant Fcγ receptors. Lehmann and team examined these cells in tumors growing in different sites (skin and lung). The organ environment determined which TAM and TAN subpopulations contributed to antibody-dependent tumor immunotherapy. These data may help fine-tune therapeutic strategies to target only cells that promote tumors.

Sci Immunol 2017; 2: eaah6413
Eitan Israeli

Capsule

In-house thymus protection squad

Circulating antibodies from bone marrow-resident plasma cells help to protect the thymus from infection. Nuñez and fellow-workers found that plasma cells that reside in the human thymus produce antibodies that are reactive to common viral proteins. These cells inhabit the thymic perivascular space between the thymic epithelial areas and circulation and may fortify the thymus against pathogen invasion. The plasma cells are maintained in aging individuals, presumably contributing to lifelong thymic protection.

Sci Immunol 2016; 1: eaah4447
Eitan Israeli

Capsule

Gut communities form a history of connection

An individual's gut microbial community is nested within a "cloud" of the shared microbiota of relatives, friends, and acquaintances. Unique combinations of selective pressures, including antibiotics and diet, shape an individual's microbiota. Using gnotobiotic mice as a lens for humans, Griffin and co-authors observed the effect of plant-rich, calorie-restricted diets on microbiota establishment and metabolic responses in fecal transplant experiments. The calorie-restricted participants had far richer and more diverse communities that even lean people on Western diets. Co-housing and cross-diet experiments in the mice showed the relative influences of microbial exchange and diet diversity on indicator species and the role a Western diet may play in extirpation of key microbiota taxa.

Cell Host Microbe 2017; 10.1016/j.chom.2016.12.006

Eitan Israeli

Capsule

Targeting metastasis-initiating cells through the fatty acid receptor CD3

The fact that the identity of the cells that initiate metastasis in most human cancers is unknown hampers the development of antimetastatic therapies. Pascual et al. describe a subpopulation of CD44^{bright} cells in human oral carcinomas that do not over-express mesenchymal genes, are slow-cycling, express high levels of the fatty acid receptor CD36 and lipid metabolism genes, and are unique in their ability to initiate metastasis. Palmitic acid or a high-fat diet specifically boosts the metastatic potential of CD36^{+} metastasis-initiating cells in a CD36-dependent manner. The use of neutralizing antibodies to block CD36 causes almost complete inhibition of metastasis in immunodeficient or immunocompetent orthotopic mouse models of human oral cancer, with no side effects. Clinically, the presence of CD36^{+} metastasis-initiating cells correlates with a poor prognosis for numerous types of carcinomas, and inhibition of CD36 also impairs metastasis, at least in human melanoma- and breast cancer-derived tumors. Together, these results indicate that metastasis-initiating cells particularly rely on dietary lipids to promote metastasis.

Nature 2017; 541: 41

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 and collaborators (*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.aaf6814) 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

Evading cancer drugs by identity fraud

Prostate cancer growth is fueled by male hormones called androgens. Drugs targeting the androgen receptor (AR) are initially efficacious, but most tumors eventually become resistant. Mu et al. found that prostate cancer cells escaped the effects of androgen deprivation therapy through a change in lineage identity. Functional loss of the tumor suppressors TP53 and RB1 promoted a shift from AR-dependent luminal epithelial cells to AR-independent basal-like cells. In related work, Ku et al. found that prostate cancer metastasis, lineage switching, and drug resistance were driven by the combined loss of the same tumor suppressors and were accompanied by increased expression of the epigenetic regulator Ezh2. Ezh2 inhibitors reversed the lineage switch and restored sensitivity to androgen deprivation therapy in experimental models.

Science 2016; 355: 84

Eitan Israeli

Capsule

DNA methylation in hematopoietic cascade

DNA methylation is well known for its role in repressing gene expression. However, analyzing patterns of this modification across the genome of pools of cells now reveals features of cell heterogeneity, cell differentiation, and cell lineage relationship. Farlik et al. examined DNA methylation dynamics of 17 hematopoietic cell types. They found that hematopoietic stem cells from different sources (fetal liver, cord blood, bone marrow, and peripheral blood), as well as lineage-specific progenitors, have different methylation characteristics. Using the DNA methylation profiling data, a computational model of human hematopoietic differentiation was derived, so that sorted cell populations could be placed in a developmental context. In addition to elucidating the hematopoietic cascade, this work has potential for understanding diseases of the blood.

Cell Stem Cell 2016; 19: 808

Eitan Israeli

Capsule

An intelligent little sniffer to detect diseases

From ancient medical tests to roadside sobriety tests to cancer-sniffing dogs, the analysis of compounds in a puff of breath has long been used for clinical diagnoses. When equipped with a targeted sensor, devices using nanosized materials can detect specific volatile organic compounds (VOCs) and thus be targeted to a single disease condition. Nakhleh and fellow-researchers follow a different approach, in which sensors based on modified gold nanoparticles and carbon nanotubes are used to identify 17 different disease conditions. Rather than searching for a single VOC, their sensors could identify a range of VOCs, albeit with less sensitivity, and were able to identify patterns of detection that correlated with each of the different diseases.

ACS Nano 2016; 10.1021/acsnano.6b04930

Eitan Israeli

Capsule

Brain cancer therapy

Glioblastoma multiforme (GBM) is a deadly brain cancer, and a major challenge to its treatment with radiation is that the approach often leads to an even more aggressive form of the cancer. Kegelman and team report that targeting a scaffolding protein called MDA-9 or syntenin (encoded by melanoma differentiation-associated gene 9) with a small-molecule inhibitor may prevent this outcome. The drug targets a protein interaction domain (PDZ1) in MDA-9, blocking key signaling pathways that promote invasiveness and proliferation in cultured glioblastoma cells. The drug also boosted tumor sensitivity to radiation and improved survival in a mouse model of GBM. The results suggest a possible path to targeted brain cancer therapy.

Prod Natl Acad Sci USA 2016; 10.1073/pnas.1616100114

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

Locking TNFR2 to kill ovarian cancer

The TNF (tumor necrosis factor) ligand family promotes tumor growth and progression. Torrey et al. developed an antibody that locks TNFR2, a TNF receptor found on immunosuppressive regulatory T cells and some tumor cells, in an inactive state. The antibody inhibited the proliferation of regulatory T cells while promoting the proliferation of effector T cells isolated from metastatic sites in ovarian cancer patients. The antibody had less of an effect on T cells from normal donors. Thus, this antibody may be more specific and less toxic than current antibodies against TNFRs.

Sci Signal 2017; 10: eaaf8608, eaal2328

Eitan Israeli

Capsule

Fast point-of-care detection of biomarkers

Many diseases can be diagnosed by detecting nucleic acid or protein biomarkers, but, with few exceptions, this detection requires complex and costly instruments. Du et al. adapted commercially available pregnancy kits for affordable and fast point-of-care diagnostics. In the detection method, nucleic acid is first amplified and then captured by a DNA oligonucleotide-human chorionic gonadotropin conjugate. The latter is detected by the commercial kits. The method allowed detection of just 20 copies of an Ebola virus template and could distinguish a melanoma-related biomarker from the wild-type sequence. It should be possible to adapt it for low cost detection of other biomarkers in clinical settings.

Angew Chem Int Ed Engl 2016: 10.1002/anie.201609108

Eitan Israeli

Capsule

Combining drugs as the doctor ordered for cancer immunotherapy

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

Chromosomal chaos and tumor immunity

Cancer immunotherapy produces durable clinical responses in only a subset of patients. Identification of tumor characteristics that correlate with responses could lead to predictive biomarkers and shed light on causal mechanisms. Davoli and co-authors found that human tumors with extensive aneuploidy – i.e., that display a highly abnormal number of chromosomes and chromosomal segments – express fewer markers of the immune cells responsible for tumor destruction. In a retrospective analysis of clinical trial data, they found that melanoma patients with highly aneuploid tumors were less likely to benefit from immune checkpoint blockade therapy than patients whose tumors had a more normal karyotype. Thus, aneuploidy appears to enhance the ability of tumors to evade the immune system.

Science 2017; 355: 10.1126/science.aaf8399

Eitan Israeli