## Capsule

### How dying tumor cells get noticed

Besides killing tumor cells directly, some chemotherapies, such as anthracyclines, also activate the immune system to kill tumors. Vacchelli et al. discovered that in mice, anthracycline-induced antitumor immunity requires immune cells to express the protein formyl peptide receptor 1 (FPR1). Dendritic cells (DCs) near tumors expressed especially high amounts of FPR1. DCs normally capture fragments of dying tumor cells and use them to activate nearby T cells to kill tumors, but DCs lacking FPR1 failed to do this effectively. Individuals with breast or colon cancer expressing a variant of FPR1 and treated with anthracyclines showed poor metastasis-free and overall survival. Thus, FPR1 may affect anti-tumor immunity in people, too.

*Science* 2015; 350: 972
Eitan Israeli

## Capsule

### Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death

Inflammatory caspases (caspase-1, 4, 5 and 11) are critical for innate defenses. Caspase-1 is activated by ligands of various canonical inflammasomes, and caspase-4, 5 and 11 directly recognize bacterial lipopolysaccharide, both of which trigger pyroptosis. Despite the crucial role in immunity and endotoxic shock, the mechanism for pyroptosis induction by inflammatory caspases is unknown. Shi and team identify gasdermin D (*Gsdmd*) by genome-wide clustered regularly interspaced palindromic repeat (CRISPR)-Cas9 nuclease screens of caspase-11 and caspase-1 mediated pyroptosis in mouse bone marrow macrophages. GSDMD-deficient cells resisted the induction of pyroptosis by cytosolic lipopolysaccharide and known canonical inflammasome ligands. Interleukin-1β release was also diminished in *Gsdmd*$^{-/-}$ cells, despite intact processing by caspase-1. Caspase-1 and caspase-4, 5 and 11 specifically cleaved the linker between the amino-terminal gasdermin-N and carboxy-terminal gasdermin-C domains in GSDMD, which was required and sufficient for pyroptosis. The cleavage released the intramolecular inhibition on the gasdermin-N domain that showed intrinsic pyroptosis-inducing activity. Other gasdermin family members were not cleaved by inflammatory caspases but shared the autoinhibition; gain-of-function mutations in *Gsdma3* that cause alopecia and skin defects disrupted the autoinhibition, allowing its gasdermin-N domain to trigger pyroptosis. These findings offer insight into inflammasome-mediated immunity/diseases and also change our understanding of pyroptosis and programmed necrosis.

*Nature* 2015; 526: 660
Eitan Israeli

## Capsule

### Tumors evolve free of Darwinian constraints

Mutations help shape how tumors evolve. What constrains the diversity of these mutations is less clear. Ling et al. determined the spectrum of single-nucleotide variations in 286 samples from a single heptaocellular carcinoma tumor. They then modeled how mutations accumulated in tumors using population genetic theory. Their analysis predicted that the tumor harbored more than 100 million mutations. Such high genetic diversity suggests that the tumors evolve in a non-Darwinian manner, because Darwinian evolution generally reduces genetic diversity within a population. These results imply that microscopic tumors are likely to be highly diverse, suggesting that even these tumors could quickly develop resistance in the face of therapy.

*Proc Natl Acad Sci USA* 2015; 10.1073/pnas.1519556112

Eitan Israeli

## Capsule

### Novel antibody-antibiotic conjugate eliminates intracellular *S. aureus*

*Staphylococcus aureus* is considered to be an extracellular pathogen. However, survival of *S. aureus* within host cells may provide a reservoir relatively protected from antibiotics, thus enabling long-term colonization of the host and explaining clinical failures and relapses after antibiotic therapy. Lehar et al. confirm that intracellular reservoirs of *S. aureus* in mice comprise a virulent subset of bacteria that can establish infection even in the presence of vancomycin, and we introduce a novel therapeutic that effectively kills intracellular *S. aureus*. This antibody-antibiotic conjugate consists of an anti-*S. aureus* antibody conjugated to a highly efficacious antibiotic that is activated only after it is released in the proteolytic environment of the phagolysosome. The antibody-antibiotic conjugate is superior to vancomycin for treatment of bacteremia and provides direct evidence that intracellular *S. aureus* represents an important component of invasive infections.

*Nature* 2015; 527: 323

Eitan Israeli

Capsule

## Viral oncogenes remove the host's STING

Cancer-causing viruses, such as the human papillomavirus (HPV) that causes cervical cancer, account for 12% of human cancers. One way they can cause cancer is by targeting tumor suppressor proteins in the host. Lau et al. report that DNA tumor viruses can also thwart the host's immune system. Oncogenes from HPV and human adenovirus bound to the protein STING, a key component of the cGAS-STING pathway that senses and defends against intracellular DNA. In this way, the viruses subvert the host's antiviral immunity which eventually causes cancer.

*Science* 2015; 350: 568

Eitan Israeli

Capsule

## Pediatric outcome after maternal cancer diagnosed during pregnancy

In this multicenter case-control study, Amant and colleagues compared children whose mothers received a diagnosis of cancer during the pregnancy with matched children of women without a cancer diagnosis. All children were prospectively assessed (by means of a neurologic examination and the Bayley Scales of Infant Development) at 18 months, 36 months, or both. A cardiac assessment was performed at 36 months. A total of 129 children (median age 22 months, range 12–42) were included in the group whose mother had cancer (prenatal-exposure group) with a matching number in the control group. During pregnancy, 96 children (74.4%) were exposed to chemotherapy (alone or in combination with other treatments), 11 (8.5%) to radiotherapy (alone or in combination), 13 (10.1%) to surgery alone, 2 (1.6%) to other drug treatments, and 14 (10.9%) to no treatment. Birth weight was below the 10th percentile in 28 of 127 children (22.0%) in the prenatal-exposure group and in 19 of 125 children (15.2%) in the control group ($P = 0.16$). There was no significant between-group difference in cognitive development on the basis of the Bayley score ($P = 0.08$) or in subgroup analyses. The gestational age at birth was correlated with the cognitive outcome in the two study groups. Cardiologic evaluation among 47 children at 36 months of age showed normal cardiac findings. Prenatal exposure to maternal cancer with or without treatment did not impair the cognitive, cardiac, or general development of children in early childhood. Prematurity was correlated with a worse cognitive outcome, but this effect was independent of cancer treatment.

*N Engl J Med* 2015; 373: 1824

Eitan Israeli

Capsule

## When inhibitors don't mimic knockouts

The T helper 2 (TH2) subset of lymphocytes releases cytokines implicated in the pathogenesis of asthma, a process that requires the kinase ITK. ITK-knockout mice are resistant to airway inflammation, suggesting that ITK inhibitors might be used to treat human asthma. However, Sun et al. found that an ITK-specific inhibitor aggravated disease symptoms in a mouse model of asthma. The airways of these mice had more T cells and higher levels of cytokines that are typically released by TH2 lymphocytes. Thus, targeting ITK activity in asthma patients may exacerbate disease.

*Sci Signal* 2015; 8: ra122

Eitan Israeli

Capsule

## Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance

The role of epithelial-to-mesenchymal transition (EMT) in metastasis is a longstanding source of debate, largely owing to an inability to monitor transient and reversible EMT phenotypes in vivo. Fischer et al. established an EMT lineage-tracing system to monitor this process in mice, using a mesenchymal-specific Cre-mediated fluorescent marker switch system in spontaneous breast-to-lung metastasis models. The authors show that within a predominantly epithelial primary tumor, a small proportion of tumor cells undergo EMT. Notably, lung metastases mainly consist of non-EMT tumor cells that maintain their epithelial phenotype. Inhibiting EMT by overexpressing the microRNA miR-200 does not affect lung metastasis development. However, EMT cells significantly contribute to recurrent lung metastasis formation after chemotherapy. These cells survived cyclophosphamide treatment owing to reduced proliferation, apoptotic tolerance and increased expression of chemoresistance-related genes. Overexpression of miR-200 abrogated this resistance. This study suggests the potential of an EMT-targeting strategy, in conjunction with conventional chemotherapies, for breast cancer treatment.

*Nature* 2015; 527: 472

Eitan Israeli

## Capsule

### Mouse work may lead to male contraceptive

Unintended pregnancies are a major health issue worldwide. Although oral contraceptives were developed decades ago for use in women, there are no male oral contraceptives. Miyata and colleagues show that genetic deletion or drug inhibition of sperm-specific calcineurin enzymes in mice cause male sterility. Although calcineurin inhibitors resulted in male infertility within 2 weeks, fertility recovered 1 week after halting drug administration. Because the sperm-specific calcineuin complex is also found in humans, its inhibition may be a strategy for developing reversible male contraceptives.

*Science* 2015; 350: 442

Eitan Israeli

## Capsule

### Non-coding recurrent mutations in chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a frequent disease in which the genetic alterations determining the clinicobiological behavior are not fully understood. Puente and fellow researchers describe a comprehensive evaluation of the genomic landscape of 452 CLL cases and 54 patients with monoclonal B lymphocytosis, a precursor disorder. The authors extend the number of CLL driver alterations, including changes in *ZNF292*, *ZMYM3*, *ARID1A* and *PTPN11*. They also identify novel recurrent mutations in non-coding regions, including the 3' region of *NOTCH1*, which cause aberrant splicing events, increase NOTCH1 activity and result in a more aggressive disease. In addition, mutations in an enhancer located on chromosome 9p13 result in reduced expression of the B cell-specific transcription factor PAX5. The accumulative number of driver alterations (0 to $\geq 4$) discriminated between patients with differences in clinical behavior. This study provides an integrated portrait of the CLL genomic landscape, identifies new recurrent driver mutations of the disease, and suggests clinical interventions that may improve the management of this neoplasia.

*Nature* 2015; 526: 519

Eitan Israeli

## Capsule

### Establishing a long-time residency

Innate lymphoid cells (ILCs) are a subset of immune cells that promote barrier immunity in tissues such as the gut and lungs and help to maintain immune homeostasis. Gasteiger et al. investigated how the body maintains its pools of ILCs in such peripheral tissues, as well as in immune tissues such as the lymph nodes and the spleen. In mice surgically joined to share their bloodstreams, unlike lymphocytes, most ILCs did not circulate through the blood. Instead, ILCs resided long term in tissues, even in the face of inflammation or infection.

*Science* 2015; 350: 981

Eitan Israeli

## Capsule

### Gut microbes affect immunotherapy

The unleashing of antitumor T cell responses has ushered in a new era of cancer treatment. Although these therapies can cause dramatic tumor regressions in some patients, many patients inexplicably see no benefit. Mice have been used in two studies to investigate what might be happening. Specific members of the gut microbiota influence the efficacy of this type of immunotherapy. Vétizou et al. (*Science* 2015; 350: 1079) found that optimal responses to anticytotoxic T lymphocyte antigen blockade required specific *Bacteroides* spp. Similarly, Sivan et al. (*Science* 2015; 350: 1084) discovered that *Bifidobacterium* spp. enhanced the efficacy of anti-programmed cell death ligand 1 therapy.

Eitan Israeli

## Capsule

### A perisinusoidal niche for extramedullary hematopoiesis in the spleen

Hematopoietic stresses mobilize hematopoietic stem cells (HSCs) from the bone marrow to the spleen and induce extramedullary hematopoiesis (EMH). However, the cellular nature of the EMH niche is unknown. Inra et al. assessed the sources of the key niche factors, SCF (also known as KITL) and *CXCL12*, in the mouse spleen after EMH induction by myeloablation, blood loss, or pregnancy. In each case, *Scf* was expressed by endothelial cells and *Tcf21*$^+$ stromal cells, primarily around sinusoids in the red pulp, while *Cxcl12* was expressed by a subset of *Tcf21*$^+$ stromal cells. EMH induction markedly expanded the Scf-expressing endothelial cells and stromal cells by inducing proliferation. Most splenic HSCs were adjacent to *Tcf21*$^+$ stromal cells in red pulp. Conditional deletion of *Scf* from spleen endothelial cells, or of Scf or *Cxcl12* from *Tcf21*$^+$ stromal cells, severely reduced spleen EMH and reduced blood cell counts without affecting bone marrow hematopoiesis. Endothelial cells and *Tcf21*$^+$ stromal cells thus create a perisinusoidal EMH niche in the spleen, which is necessary for the physiological response to diverse hematopoietic stresses.

*Nature* 2015; 527: 466

Eitan Israeli

Capsule

## Neutrophil aging is regulated by the microbiome

Blood polymorphonuclear neutrophils provide immune protection against pathogens, but may also promote tissue injury in inflammatory diseases. Although neutrophils are generally considered to be a relatively homogeneous population, evidence for heterogeneity is emerging. Under steady-state conditions, neutrophil heterogeneity may arise from aging and replenishment by newly released neutrophils from the bone marrow. Aged neutrophils upregulate CXCR4, a receptor allowing their clearance in the bone marrow, with feedback inhibition of neutrophil production via the IL-17/G-CSF axis, and rhythmic modulation of the hematopoietic stem cell niche. The aged subset also expresses low levels of L-selectin. Previous studies have suggested that in vitro-aged neutrophils exhibit impaired migration and reduced pro-inflammatory properties. Zhang et al., using in vivo aging analyses in mice, show that neutrophil pro-inflammatory activity correlates positively with their aging while in circulation. Aged neutrophils represent an overly active subset exhibiting enhanced $\alpha M\beta 2$ integrin activation and neutrophil extracellular trap formation under inflammatory conditions. Neutrophil aging is driven by the microbiota via Toll-like receptor and myeloid differentiation factor 88-mediated signaling pathways. Depletion of the microbiota significantly reduces the number of circulating aged neutrophils and dramatically improves the pathogenesis and inflammation-related organ damage in models of sickle cell disease or endotoxin-induced septic shock. These results identify a role for the microbiota in regulating a disease-promoting neutrophil subset.

*Nature* 2015; 525: 528

Eitan Israeli

Capsule

## A change of heart mitochondria

Mitochondria provide an essential source of energy to drive cellular processes and are particularly important in heart muscle cells. After birth, the availability of oxygen and nutrients to organs and tissues changes. This invokes changes in metabolism. Gong et al. studied the developmental transitions in mouse heart mitochondria soon after birth. Mitochondria were replaced wholesale via mitophagy in cardiomyocytes over the first 3 weeks after birth. Preventing this turnover by interfering with parkin-mediated mitophagy specifically in cardiomyocytes prevented the normal metabolic transition and caused heart failure. Thus, the heart has co-opted a quality-control pathway to facilitate a major developmental transition after birth. Wai et al. examined the role of mitochondrial fission and fusion in mouse cardiomyocytes. Disruption of these processes led to "middle-aged" death from a form of dilated cardiomyopathy. Mice destined to develop cardiomyopathy were protected by feeding with a high-fat diet, which altered cardiac metabolism.

*Science* 2015; 350: p. 10.1126/*science*.aad2459, p. 10.1126/*science*.aad0116

Eitan Israeli

Capsule

## Treatment during a vulnerable developmental period rescues a genetic epilepsy

The nervous system is vulnerable to perturbations during specific developmental periods. Insults during such susceptible time windows can have long-term consequences, including the development of neurological diseases such as epilepsy. Marguet et al. report that a pharmacological intervention timed during a vulnerable neonatal period of cortical development prevents pathology in a genetic epilepsy model. By using mice with dysfunctional Kv7 voltage-gated K+ channels, which are mutated in human neonatal epilepsy syndromes, they demonstrated the safety and efficacy of the sodium-potassium-chloride co-transporter NKCC1 antagonist bumetanide, which was administered during the first two postnatal weeks. In Kv7 current-deficient mice, which normally display epilepsy, hyperactivity and stereotypies as adults, transient bumetanide treatment normalized neonatal in vivo cortical network and hippocampal neuronal activity, prevented structural damage in the hippocampus, and restored wild-type adult behavioral phenotypes. Furthermore, bumetanide treatment did not adversely affect control mice. These results suggest that in individuals with disease susceptibility, timing prophylactically safe interventions to specific windows during development may prevent or arrest disease progression.

*Nature Med* 2015; 21: 1436

Eitan Israeli

Capsule

## Aging: all in the head – and the gut

The effects of hypoxia and caloric restriction, both of which extend life span in *Caenorhabditis elegans*, converge on the activation of an enzyme in cells of the intestine. Leiser et al show that the life-extending effects of hypoxia begin in neurons with transcriptional activation by hypoxia-inducible factor-1 and increased serotonergic signaling. These effects led to increased production of flavin-containing monooxygenase-2 (FMO-2) in the intestine, which increased longevity. Finding the relevant targets of FMO-2, which also accumulates in mammals under conditions that promote longevity, may elucidate further mechanisms that promote healthy aging.

*Science* 2015; 350: 1375

Eitan Israeli

Capsule

## Putting both heart and brain at risk

For reasons that are unclear, newborns with congenital heart disease (CHD) have a high risk of neurodevelopmental disabilities. Homsy et al. performed exome sequence analysis of 1200 CHD patients and their parents to identify spontaneously arising (de novo) mutations. Patients with both CHD and neurodevelopmental disorders had a much higher burden of damaging de novo mutations, particularly in genes with likely roles in both heart and brain development. Thus, clinical genotyping of patients with CHD may help to identify those at greatest risk of neurodevelopmental disabilities, allowing surveillance and early intervention.

*Science* 2015; 350: 1262

Eitan Israeli

Capsule

## Inflammation improves insulin resistance

One of the hallmarks of diabetes is insulin resistance, a condition in which insulin accumulates because the body cannot effectively use it. Although insulin resistance occurs in both age- and obesity-associated diabetes, Bapat and fellow researchers now report that the underlying cellular mechanisms that drive these diseases differ. An overzealous inflammatory response contributes to obesity-associated insulin resistance. In contrast, an immunosuppressive subset of T cells, called regulatory T cells (Tregs), promoted insulin resistance in aging mice. Aged but not obese mice that lacked these cells experienced improvement in multiple metabolic parameters. Scientists will need to determine whether Tregsin adipose tissue contributes to age-associated insulin resistance in humans and how they may do so.

*Nature* 2015; 10.1038/*nature*16151

Eitan Israeli

Capsule

## Growing blood vessels in gliomas

Aggressive gliomas have a high density of abnormal blood vessels that enables tumor growth and damages the brain. Zhang et al. analyzed patient data and correlated increased levels of a secreted factor called pleiotrophin with more aggressive grades of glioma and decreased survival. When implanted in mice, glioma cells that released pleiotrophin formed larger tumors with more blood vessels. Mice developed smaller gliomas and survived longer when treated with inhibitors of ALK, a receptor for pleiotrophin.

*Sci Signal* 2015; 8: ra125

Eitan Israeli

Capsule

## T regulatory cells transfer for diabetes

In patients with type 1 diabetes (T1D), immune cells destroy the insulin-producing beta cells of the pancreas. Consequent prolonged exposure to high blood sugar can damage organs and lead to heart disease and kidney failure. Regulatory T cells ($T_{regs}$) are known to be defective in autoimmune diseases, such as type 1 diabetes. Bluestone and group report a phase 1 trial of adoptive Treg immunotherapy to repair or replace these cells in type 1 diabetics. The cultured $T_{regs}$ were long-lived after transfer and retained a broad Treg phenotype. Moreover, the trial showed that transfer therapy was safe, endorsing efficacy testing in further trials.

*Sci Transl Med* 2015; 7: 315ra189

Eitan Israeli

Capsule

## Stalking a universal flu vaccine

A universal flu vaccine has been a Sisyphean trial. Despite successful seasonal vaccines, the immune system must start over when meeting newly mutated influenza strains. Andrews and colleagues took an in-depth look, over time, at the B cell response to the pandemic 2009 H1N1 vaccine. People with low titers of preexisting antibodies were more likely to generate a broadly reactive response that targets the more conserved hemagglutinin (HA) stalk region, whereas those with higher levels of preexisting antibodies responded by targeting the more variable HA head. The preexisting head antibodies were immunodominant and prevented clear access to the stalk. These data suggest that recipients' exposure history will be critical in designing a universal flu vaccine.

*Sci Transl Med* 2015; 7: 316ra192

Eitan Israeli