

## Capsule

### Influenza HA needs stability to spread

Influenza pandemics occur every few decades, but scientists still do not understand why only some strains cause pandemics. To enter host cells, the virus' hemagglutinin (HA) protein must undergo a pH-driven conformational change. During the 2009 pandemic, a swine H1N1 virus jumped to humans. Russier et al. now report that for swine H1N1, the HA conformational switch occurs at pH 5.5 to 6.0. In viruses isolated from hu-

mans, the pH of the switch changed from 5.5 to 5.6 early in the pandemic to 5.0 to 5.4 later in the pandemic. A swine H1N1 with HA mutated to switch at pH 6 was less pathogenic in mice and ferrets. The lower-pH switching probably increases HA stability in the upper respiratory tract.

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Eitan Israeli

## Capsule

### Cancer therapy by entrapment

Mutations in the *KRAS* oncogene occur at high frequency in several of the most lethal human cancers, including lung and pancreatic cancer. Substantial effort has thus been directed toward developing *KRAS* inhibitors. *KRAS* encodes an enzyme that binds the nucleotide GTP and hydrolyzes it to GDP. It had been thought that oncogenic mutations disable this hydrolytic activity, locking *KRAS* in the GTP-bound, active state. Surpris-

ingly, Lito et al. found that a certain *KRAS* mutant (G12C) retains hydrolytic activity and continues to cycle between its active and inactive states. They describe a compound that inhibits *KRAS*(G12C) signaling and tumor cell growth by binding to the GDP bound form of *KRAS*, trapping it in its inactive state.

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Eitan Israeli

## Capsule

### Timing the attack on cancer cells

Cell regulatory systems have dynamic properties that will need to be taken into account when planning therapeutic strategies. Chen and team found that the timing of a radiation treatment of human breast cancer-derived cells in culture determined whether cell survival was enhanced or reduced. Depletion of the oncogene product MDMX caused an initial burst of expression of the tumor suppressor protein p53

within the first 24 hours, and then oscillations of lower amplitude. When the radiation treatment coincided with the first phase, 95% of the cells died, but if radiation was applied in the second phase, fewer than 20% of the cells died.

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Eitan Israeli

## The microRNA miR-148a functions as a critical regulator of B cell tolerance and autoimmunity

Autoreactive B cells have critical roles in a large diversity of autoimmune diseases, but the molecular pathways that control these cells remain poorly understood. Gonzalez-Martin et al. performed an in vivo functional screen of a lymphocyte-expressed microRNA library and identified miR-148a as a potent regulator of B cell tolerance. Elevated miR-148a expression impaired B cell tolerance by promoting the survival of immature B cells after engagement of the B cell antigen receptor by suppressing the expression of the autoimmune

suppressor Gadd45 $\alpha$ , the tumor suppressor PTEN and the pro-apoptotic protein Bim. Furthermore, increased expression of miR-148a, which occurs frequently in patients with lupus and lupus-prone mice, facilitated the development of lethal autoimmune disease in a mouse model of lupus. These studies demonstrate a function for miR-148a as a regulator of B cell tolerance and autoimmunity.

*Nature Immunol* 2016; 17: 433

Eitan Israeli

## Potassium loss stresses out kidney cells

African-Americans are five times more likely than Caucasians to develop advanced kidney disease. Two sequence variants in a gene called *APOL1* confer most of this elevated risk. Scientists think that the prevalence of these sequence variants in people of African descent probably arose because they also confer protection against parasite infection. The *APOL1* gene encodes the protein apolipoprotein L1, which forms ion pores in the kidney cell membrane, but how the risk variants

cause kidney disease remains a mystery. Studying cultured kidney cells, Olabisi et al. found that the *APOL1* risk variants cause excessive loss of potassium from the cells. This in turn activates stress-activated enzymes called kinases, which ultimately leads to kidney cell death.

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Eitan Israeli

### Colonization of germ-free mice with a mixture of three *Lactobacillus* strains enhances the integrity of gut mucosa and ameliorates allergic sensitization

Increasing numbers of clinical trials and animal experiments have shown that probiotic bacteria are promising tools for allergy prevention. Kozakova et al. analyzed the immunomodulatory properties of three selected *Lactobacillus* strains and the impact of their mixture on allergic sensitization to Bet v 1 using a gnotobiotic mouse model. The authors showed that *Lactobacillus rhamnosus* LOCK0900, *L. rhamnosus* LOCK0908 and *L. casei* LOCK0919 are recognized via Toll-like receptor 2 (TLR2) and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) receptors and stimulate bone marrow-derived dendritic cells to produce cytokines in species- and strain-dependent manners. Colonization of germ-free (GF) mice with a mixture of all three strains (Lmix) improved the intestinal barrier by strengthening the apical junctional complexes of enterocytes and restoring the structures of microfilaments extending into the terminal web. Mice colonized with Lmix and sensitized to the Bet

v 1 allergen showed significantly lower levels of allergen-specific IgE, IgG1 and IgG2a and an elevated total IgA level in the sera and intestinal lavages as well as an increased transforming growth factor-beta (TGF $\beta$ ) level compared with the sensitized GF mice. Splenocytes and mesenteric lymph node cells from the Lmix-colonized mice showed the significant upregulation of TGF $\beta$  after in vitro stimulation with Bet v 1. These results show that Lmix colonization improved the gut epithelial barrier and reduced allergic sensitization to Bet v 1. Furthermore, these findings were accompanied by the increased production of circulating and secretory IgA and the regulatory cytokine TGF $\beta$ . Thus, this mixture of three *Lactobacillus* strains shows potential for use in the prevention of increased gut permeability and the onset of allergies in humans.

*Cell Molec Immunol* 2016; 13: 251

Eitan Israeli

### “It’s not what you look at that matters, it’s what you see”

Henry David Thoreau (1817-1862), American author, poet, philosopher, abolitionist, naturalist, tax resister, development critic, surveyor, and historian. A leading transcendentalist, Thoreau is best known for his book *Walden*, a reflection upon simple living in natural surroundings

## A scavenger that protects the heart

Coronary heart disease is a tale of two forms of plasma cholesterol. In contrast to the well-established effects of “bad” cholesterol (LDL-C), the role of “good” cholesterol (HDL-C) is mysterious. Elevated HDL-C correlates with a lower risk of heart disease, yet drugs that raise HDL-C levels do not reduce risk. Zannoni et al. found that some people with exceptionally high levels of HDL-C carry a rare sequence

variant in the gene encoding the major HDL-C receptor, scavenger receptor BI. This variant destroys the receptor's ability to take up HDL-C. Interestingly, people with this variant have a higher risk of heart disease despite having high levels of HDL-C.

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Eitan Israeli

## Tumors put in a vulnerable position

Cancer cells often display alterations in metabolism that help fuel their growth. Such metabolic “rewiring” may also work against the cancer cells, however, by creating new vulnerabilities that can be exploited therapeutically. A variety of human tumors show changes in methionine metabolism caused by loss of the gene coding for 5-methylthioadenosine phosphorylase (MTAP). Mavrakis et al. and Kryukov et al. found

that the loss of MTAP renders cancer cell lines sensitive to growth inhibition by compounds that suppress the activity of a specific arginine methyltransferase called PRMT5. Conceivably, drugs that inhibit PRMT5 activity could be developed into a tailored therapy for MTAP-deficient tumors.

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Eitan Israeli

## “There can be no keener revelation of a society’s soul than the way in which it treats its children”

Nelson Mandela (1918-2013), South African anti-apartheid revolutionary, politician and philanthropist, who served as President of South Africa from 1994 to 1999. He was the country's first black chief executive, and the first elected in a fully representative democratic election. His government focused on dismantling the legacy of apartheid through tackling institutionalized racism and fostering racial reconciliation

## Have cancer stem cells MET their match?

Solid tumors have been hypothesized to contain a subset of highly aggressive cells that fuel tumor growth and metastasis. The search is on for drugs that selectively kill or diminish the malignant properties of these tumor-initiating cells (TICs; previously called “cancer stem cells”). Pattabiraman et al. hypothesized that compounds that induce TICs to undergo a phenotypic change called the mesenchymal-to-epithelial

transition (MET) would therefore cause TICs to lose their tumor-initiating ability. Indeed, drugs activating the protein kinase A signaling pathway triggered an epigenetic reprogramming of TICs that resulted in the cells acquiring a more benign epithelial-like phenotype.

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Eitan Israeli

## Making the right cut in the right location in $\beta$ -amyloid

In Alzheimer’s disease, pathogenic  $\beta$ -amyloid ( $A\beta$ ) accumulates in the brain. Two enzymes,  $\gamma$ - and  $\beta$ -secretase, produce  $A\beta$  by cleaving amyloid precursor protein. Therapeutically, the  $\beta$ -secretase cleavage reaction would be a good one to target, but inhibiting the enzyme also inhibits the cleavage of other key substrates, and so it can be harmful. Ben Halima et al. exploited the fact that  $A\beta$  cleavage occurs within an endocytic compartment, whereas  $\gamma$ - and  $\beta$ -secretase cleave other impor-

tant substrates at the cell surface. They targeted a  $\beta$ -secretase inhibitor to endosomes and successfully inhibited  $A\beta$  production in a variety of different cells. These encouraging findings may help in the search for an Alzheimer’s disease therapy with minimal off-target side effects.

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Eitan Israeli

### Diversity reigns in antibody responses

During the course of an immune response, B cells specific for an invading pathogen divide. The antibodies they produce increase in affinity via somatic mutation in specialized lymph node structures called germinal centers. Tas et al. used multiphoton microscopy and sequencing to determine how different B cell clones compete with one another within mouse germinal centers. Multiple B cell clones can seed indi-

vidual germinal centers, and germinal centers lose diversity at disparate rates. Such heterogeneity suggests that manipulating minor clonal populations to gain an advantage during vaccination may one day be possible.

*Science* 2016; 351: 1048

Eitan Israeli

**“It had long since come to my attention that people of accomplishment rarely sat back and let things happen to them. They went out and happened to things”**

Leonardo da Vinci (1452-1519), Italian polymath whose talents included invention, painting, sculpting, architecture, science, music, mathematics, engineering, literature, anatomy, geology, astronomy, botany, writing, history, and cartography. He has been called the father of paleontology and architecture, and is thought to be one of the greatest painters of all time. His genius epitomized the Renaissance humanist ideal

## Capsule

### Toxic tenant promotes bad bugs

There are many benefits to a good roommate, but the wrong choice can be toxic. Cohen et al. found that alpha toxin produced by *Staphylococcus aureus* worsened lung co-infection by Gram-negative bacteria. The alpha toxin prevented acidification of bacteria-containing phagosomes, thus increasing bacterial proliferation, spread, and lethality. However, early

treatment or prophylaxis with a neutralizing antibody to alpha toxin prevented this effect and promoted *S. aureus* clearance in a humanized mouse model.

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Eitan Israeli

## Capsule

### Profiling the antibody response to Ebola

The recent Ebola virus outbreak in West Africa illustrates the need not only for a vaccine but for potential therapies as well. One promising therapy is monoclonal antibodies that target Ebola's membrane-anchored glycoprotein (GP). Bornholdt and co-workers isolated and characterized 349 antibodies from a survivor of the 2014 outbreak. A large fraction showed some

neutralizing activity and several were quite potent. Structural analysis revealed an important site of vulnerability on the membrane stalk region of GP. Antibodies targeting this area were therapeutically effective in Ebola virus-infected mice.

*Science* 2016; 351: 1078

Eitan Israeli

### Gastric tissue makes insulin

Diabetics lack insulin-producing pancreatic beta cells. One therapeutic strategy involves generating these cells from other sources and then transplanting them into patients. To withstand the pathological diabetic environment, a renewable source of beta cells is crucial. Ariyachet and group show that stomach cells fit the bill. Like the pancreas, the stomach arises from the endoderm and harbors many stem and progenitor cells. Introducing the trio of proteins into mouse endocrine

cells from the lower stomach reprograms them into insulin-producing beta cells. Transplanting reprogrammed stomach mini-organs into diabetic mice allowed them to control their hyperglycemia, suggesting a viable gastric source for the production of insulin.

*Cell Stem Cell* 2016; 10.1016/j.stem.2016.01.003

Eitan Israeli

### “When dictatorship is a fact, revolution becomes a right”

Victor Hugo (1802-1885), French poet, novelist and dramatist of the Romantic movement and considered one of the greatest and best-known French writers. His best-known works are *Les Misérables* and *The Hunchback of Notre-Dame*. He was also a campaigner for social causes such as the abolition of capital punishment



### Regulatory use of endogenous retroviruses

Mammalian genomes contain many endogenous retroviruses (ERVs), which have a range of evolutionary ages. The propagation and maintenance of these genetic elements have been attributed to their ability to contribute to gene regulation. Chuong et al. demonstrated that some ERV families are enriched in regulatory elements, so that they act as independently evolved enhancers for immune genes in both humans

and mice. The analysis revealed a primate-specific element that orchestrates the transcriptional response to interferons. Selection can therefore act on selfish genetic elements to generate novel gene networks.

*Science* 2016; 531: 1083

Eitan Israeli

**“Conscience is a man’s compass, and though the needle sometimes deviates, though one often perceives irregularities when directing one’s course by it, one must still try to follow its direction”**

Vincent van Gogh (1853-1890), Dutch post-Impressionist painter whose work had far-reaching influence on 20<sup>th</sup> century art. His output includes portraits, self portraits, landscapes, still lifes, olive trees and cypresses, wheat fields and (the famous) sunflowers. He is the quintessential misunderstood genius

## Capsule

### A GRK2 peptide prevents heart failure

During cardiac hypertrophy, sustained high blood pressure causes the heart walls to thicken to deal with the increased load. If left unchecked, cardiac hypertrophy leads to heart failure. A particular part of the kinase and scaffolding protein GRK2 inhibits a G protein that promotes cardiac hypertrophy. Schumacher et al. generated mice that over-

expressed a peptide of this inhibitory region of GRK2 in the heart. Under conditions that cause heart failure, these mice developed less cardiac hypertrophy and retained greater cardiac function.

*Sci Signal* 2016; 9: ra30

Eitan Israeli

**“If you have knowledge, let others light their candles in it”**

Margaret Fuller (1810-1850), American journalist, critic, and women's rights advocate

### Steps toward bNAbs for HIV

Some HIV-infected individuals develop heavily mutated, broadly neutralizing antibodies (bNAbs) that target HIV. Scientists aim to design vaccines that would elicit such antibodies. Jardine and fellow researchers report an important step toward this goal. They engineered an immunogen that could engage B cells from HIV-uninfected individuals that express the germline versions of the immunoglobulin genes harbored by

a particular class of bNAbs. The frequencies of these B cells, their affinities for the immunogen, and structural analysis suggest that the immunogen is a promising candidate. Further shaping of the B cell response with subsequent immunogens may eventually elicit bNAbs in people.

*Science* 2016; 351: 1458

Eitan Israeli

**“One good thing about music, when it hits you, you feel no pain”**

Bob Marley (1945-1981), Jamaican reggae singer, songwriter, musician, and guitarist who achieved international fame

### Mom's bugs shape offspring immunity

In utero, babies are relatively microbe-free but are quickly colonized at birth. These early microbial residents help to shape our immune systems. Gomez de Agüero et al. wondered whether the maternal microbiome also affects the offsprings' immune system during gestation. To do this, they transiently colonized otherwise microbe-free pregnant mice.

Compared to those born to microbe-free moms, pups born to colonized moms had increased numbers of certain innate immune cells and different patterns of gene expression in their guts.

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Eitan Israeli