

Progress toward an effective malaria vaccine

The history of efforts to develop a malaria vaccine has been long and difficult. Raj et al. probed for molecules produced by this blood parasite that are recognized by natural immune responses of people living in malaria-endemic areas of Africa. One, PfSEA-1, blocked parasite exit from red blood cells. Vaccination experiments with mouse malaria showed almost fourfold reduction in parasitemia;

moreover, passive transfer of PfSEA-1 antibodies transferred protection from mouse to mouse. Encouragingly, the presence of PfSEA-1 antibodies correlates with significant protection from severe malaria in children and adolescents from Kenya and Tanzania.

Science 2014; 344: 871

Eitan Israeli

Another way of growing strong bones

To stay strong, bones are constantly rebuilding themselves. Thyroid hormones regulate this process by entering cells and binding to nuclear receptors, which travel to the nucleus where they change gene expression. However, these hormones also stimulate rapid cellular changes that do not require gene regulation. Kalyanaraman et al. found a different form of nuclear receptor in bone cells. When bound

to thyroid hormones, this receptor increased the numbers of bone cells and protected them from death. When the researchers treated mice lacking thyroid hormones with a compound that mimicked the effects of this receptor, their bone cells grew normally.

Sci Signal 2014; 7: ra48

Eitan Israeli

Celecoxib, familiar remedies for arthritis as a new anti-cancer drug

Cancer researchers have been trying to develop drugs that inhibit angiogenesis, the formation of new blood vessels that nourish a tumor and allow it to grow. A few drugs that fight angiogenesis are now used for some cancers, but they are not always effective. Xu et al. report a potential addition to the anti-angiogenic armamentarium: non-steroidal anti-inflammatory agents such as celecoxib,

familiar remedies for arthritis. In mice, celecoxib inhibits blood vessel growth by a mechanism different from existing angiogenesis inhibitors. A combination of the two types of drugs was particularly effective in reducing tumor growth and spread.

Sci Transl Med 2014; 6: 242ra84

Eitan Israeli

Breaking down the blood-brain barrier in stroke

Ischemic stroke, one of the most common causes of death and disability, occurs when a blood vessel supplying oxygen and nutrients to the brain becomes obstructed. Besides injuring brain cells, a stroke disrupts the function of endothelial cells in the blood-brain barrier (BBB), which exacerbates brain damage. The cellular mechanisms underlying BBB breakdown during a stroke are poorly understood. To study this, Knowland et al. created transgenic mice expressing a fluorescent reporter gene in endothelial cells and then, with the help of fluorescent dyes, used two-photon microscopy to image BBB function in the mice after an experimentally induced stroke. In contrast

to a prevailing theory emphasizing the primary role played by a diffusion barrier called the tight junction, the imaging study revealed that the initial cause of BBB breakdown (occurring 6 hours after the stroke) was aberrant upregulation of transcytosis, a process by which molecules are transported across the endothelial cell. It was not until 24 to 48 hours after the stroke that tight junctions showed structural defects. Understanding this sequence of events may lead to therapies that limit the brain damage caused by a stroke.

Neuron 2014;10.1016/j.neuron.2014.03.003

Eitan Israeli

Evaluation of safety of A/H1N1 pandemic vaccination during pregnancy

Trotta et al. assessed the risk of maternal, fetal, and neonatal outcomes associated with the administration of an MF59 adjuvanted A/H1N1 vaccine during pregnancy. Of the 86,171 eligible pregnancies, 6246 women were vaccinated: 3615 (57.9%) in the third trimester and 2557 (40.9%) in the second. No difference was observed regarding spontaneous deliveries (adjusted odds ratio 1.02, 95% confidence interval 0.96–1.08) or admissions to intensive care units (0.95, 0.47–1.88), whereas a limited increase in the prevalence of gestational diabetes (1.26, 1.04–1.53) and eclampsia (1.19, 1.04–1.39) was seen in vaccinated women. Rates of fetal and neonatal outcomes

were similar in vaccinated and non-vaccinated women. A slight increase in congenital malformations, although not statistically significant, was present in the exposed cohort (1.14, 0.99–1.31). These findings add relevant information about the safety of the MF59 adjuvanted A/H1N1 vaccine in pregnancy. Residual confounding may partly explain the increased risk of some maternal outcomes. Meta-analysis of published studies should be conducted to further clarify the risk of infrequent outcomes, such as specific congenital malformations.

BMJ 2014; 348: g3361

Eitan Israeli

Human oocytes reprogram adult somatic nuclei of a type 1 diabetic to diploid pluripotent stem cells

The transfer of somatic cell nuclei into oocytes can give rise to pluripotent stem cells that are consistently equivalent to embryonic stem cells, holding promise for autologous cell replacement therapy. Although methods to induce pluripotent stem cells from somatic cells by transcription factors are widely used in basic research, numerous differences between induced pluripotent stem cells and embryonic stem cells have been reported, potentially affecting their clinical use. Because of the therapeutic potential of diploid embryonic stem-cell lines derived from adult cells of diseased human subjects, Yamada and team systematically investigated the parameters affecting efficiency of blastocyst development and stem-cell derivation. They show that improvements to the oocyte activation protocol, including the use of both kinase and translation inhibitors, and cell culture in the presence of histone deacetylase inhibitors,

promote development to the blastocyst stage. Developmental efficiency varied between oocyte donors and was inversely related to the number of days of hormonal stimulation required for oocyte maturation, whereas the daily dose of gonadotropin or the total number of metaphase II oocytes retrieved did not affect developmental outcome. Because the use of concentrated Sendai virus for cell fusion induced an increase in intracellular calcium concentration, causing premature oocyte activation, the authors used diluted Sendai virus in calcium-free medium. With this modified nuclear transfer protocol, they derived diploid pluripotent stem-cell lines from somatic cells of a newborn and, for the first time, an adult, a female with type 1 diabetes.

Nature 2014; 510: 533

Eitan Israeli

A role for mom's genes in Prader-Willi syndrome

Prader-Willi syndrome, a genetic disorder characterized by intellectual impairment, behavioral and learning disabilities, and other features, occurs in about 1 in 15,000 to 25,000 births. In most cases, the syndrome results when cells fail to express a part of chromosome 15 inherited from the father, but Steltzer et al. now show a maternal contribution as well. Cells taken from patients, they found, expressed higher amounts of genes from a specific section of chromosome 14, but only those genes

inherited from the mother. The cells turned on those maternal genes by suppressing a long non-coding RNA and by modifying histones – proteins that regulate gene expression. Understanding what makes genes turn on and off inappropriately in individuals with Prader-Willi syndrome may help illuminate the causes of this disease and point the way toward treatments.

Nat Genet 2014; 10: 1038/ng.2968

Eitan Israeli

Aspergillomarasmine A overcomes metallo- β -lactamase antibiotic resistance

The emergence and spread of carbapenem-resistant gram-negative pathogens is a global public health problem. The acquisition of metallo- β -lactamases (MBLs) such as NDM-1 is a principle contributor to the emergence of carbapenem-resistant gram-negative pathogens that threatens the use of penicillin, cephalosporin and carbapenem antibiotics to treat infections. To date, a clinical inhibitor of MBLs that could reverse resistance and re-sensitize resistant gram-negative pathogens to carbapenems has not been found. King et al. have identified a fungal natural product, aspergillomarasmine A (AMA), a rapid and potent inhibitor of the

NDM-1 enzyme, and another clinically relevant MBL, VIM-2. AMA also fully restored the activity of meropenem against Enterobacteriaceae, Acinetobacter spp. and Pseudomonas spp. possessing either VIM or NDM-type alleles. In mice infected with NDM-1-expressing *Klebsiella pneumoniae*, AMA efficiently restored meropenem activity, demonstrating that a combination of AMA and a carbapenem antibiotic has therapeutic potential to address the clinical challenge of MBL-positive carbapenem-resistant gram-negative pathogens.

Nature 2014; 510: 503

Eitan Israeli

Capsule

Taking a broader view of cancer imaging

Many people think the best way to visualize tumors is to target imaging agents to specific cancers at the molecular level. Kuo et al. feel differently: They developed a new class of small molecules, called alkylphosphocholine (APC) analogs, which are broadly taken up by nearly all cancers, without such molecular specificity. Compared to normal cells, cancer cells have a strong taste for APC analogs. By attaching fluorescent labels or radiolabels to the

APC analogs, the researchers could image more than 50 different human cancers in animal models, as well as brain, lung and liver tumors in human patients. These broadly applicable APC-based agents for imaging – and possibly for treatment – are now poised for further translation to clinical trials.

Sci Transl Med 2014; 6: 240ra75

Eitan Israeli

Capsule

Skin may hold the key for Parkinson's

In Parkinson's disease, a degenerative movement disorder of the central nervous system, a protein called phosphorylated alpha-synuclein builds up in neurons, damaging the brain. The disease is hard to diagnose early or monitor over time because the protein builds up so slowly and so deep inside the brain. Doppler et al. report that patient skin samples hold key insights. The authors detected phosphorylated alpha-synuclein

in autonomic and sensory nerves found in the skin samples in 16 of 31 people diagnosed with Parkinson's disease and in 0 of 35 healthy volunteers. Because skin is far more accessible than brain tissue, these observations could lead to diagnostic tests to identify and follow the progression of Parkinson's disease.

Acta Neuropathol 2014; 10: 1007/s00401-014-1284-0

Eitan Israeli

Broad-spectrum bug biofilm buster

Imagine slime growing on your heart valves. Such infections, which happen all too often and are often deadly, can be eradicated by blocking stress responses in biofilm-producing bacteria – that is, fighting the bacteria's defenses. Unfortunately, however, there are no approved biofilm-busting drugs yet, so Fuente-Núñez et al. went looking for one. They knew that small positively charged synthetic peptides can stop biofilm formation in many antibiotic-resistant bacterial pathogens, such as *Staphylococcus aureus*, *Escherichia*

coli, and *Salmonella*. When they performed a screening assay of small peptides, they found a candidate that acts on an important stress pathway. Bacteria use the pathway to synthesize the signaling nucleotide ppGpp. Without ppGpp, the bacteria have trouble forming biofilms and even staying alive. The candidate, peptide 1018, binds directly to ppGpp and degrades it, stopping deadly pathogens in their tracks.

PLOS Biol 2014; 10: e1004152

Eitan Israeli

Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the USA

In assessing the association between serum 25-hydroxyvitamin D concentrations (25(OH)D) and mortality in a large consortium of cohort studies (with particular attention to potential age, gender, season, and country differences), Schöttker and team found that 25(OH)D concentrations varied strongly by season (higher in summer), country (higher in the USA and northern Europe) and gender (higher in men), but no consistent trend with age was observed. During follow-up, 6695 study participants died: 2624 from cardiovascular diseases and 2227 from cancer. For each cohort and analysis, 25(OH)D quintiles were defined with cohort and subgroup specific cutoff values. Comparing bottom versus top quintiles resulted in a pooled risk ratio of 1.57 (95% confidence interval 1.36–1.81) for all-cause mortality. Risk ratios for cardiovascular mortality were similar in magnitude to that for all-cause mortality in subjects both with and without a

history of cardiovascular disease at baseline. With respect to cancer mortality, an association was only observed among subjects with a history of cancer (risk ratio 1.70, 1.00–2.88). Analyses using all quintiles suggest curvilinear, inverse, dose-response curves for the aforementioned relationships. No strong differences specific for age, gender, season, or country were detected. Heterogeneity was low in most meta-analyses. Despite levels of 25(OH)D strongly varying with country, gender, and season, the association between 25(OH)D level and all-cause and cause-specific mortality was remarkably consistent. Results from a long-term randomized controlled trial addressing longevity are being awaited before vitamin D supplementation can be recommended in most individuals with low 25(OH)D levels.

Metformin's recipe for a long life

Metformin, a drug commonly prescribed to treat type 2 diabetes, has side effects, but some of these are beneficial, such as fighting certain cancers and increasing longevity. By studying the worm *Caenorhabditis elegans*, a model of aging, De Haes and fellow researchers discovered the molecular basis for how metformin may prolong lives. In treated worms, metformin promoted mitochondrial respiration, a process that converts nutrients into energy for the cell. Mitochondrial respiration also produces byproducts

called reactive oxygen species (ROS), which can react with proteins, harming them. When the worms produced limited amounts of ROS, however, the life span of worms increased. The increase in life span required a protein called peroxiredoxin-2, which is oxidized by ROS and may then activate other enzymes to produce effects that promote longevity.

Proc Natl Acad Sci USA 2014; 10: 1073/pnas.1321776111

Eitan Israeli

Dietary protein sources in early adulthood and breast cancer incidence

Investigating the association between dietary protein sources in early adulthood and risk of breast cancer, Farvid et al. documented 2830 cases of breast cancer during 20 years of follow-up. Higher intake of total red meat was associated with an increased risk of breast cancer overall (relative risk 1.22, 95% confidence interval 1.06–1.40; $P_{\text{trend}}=0.01$, for highest fifth v lowest fifth of intake). However, higher intakes of poultry, fish, eggs, legumes, and nuts were not related to breast cancer overall. When the association was evaluated by menopausal status, higher intake of poultry was associated with a lower risk of breast cancer in postmenopausal women (0.73, 0.58–0.91; $P_{\text{trend}} = 0.02$, for highest fifth v lowest fifth of intake) but not in premenopausal women (0.93, 0.78–1.11; $P_{\text{trend}} = 0.60$, for highest fifth v lowest fifth of intake). In estimating the effects of exchanging different protein sources, substituting one serving/day of legumes for one serving/day of red meat was associated

with a 15% lower risk of breast cancer among all women (0.85, 0.73–0.98) and a 19% lower risk among premenopausal women (0.81, 0.66–0.99). Also, substituting one serving/day of poultry for one serving/day of red meat was associated with a 17% lower risk of breast cancer overall (0.83, 0.72–0.96) and a 24% lower risk of postmenopausal breast cancer (0.76, 0.59–0.99). Furthermore, substituting one serving/day of combined legumes, nuts, poultry, and fish for one serving/day of red meat was associated with a 14% lower risk of breast cancer overall (0.86, 0.78–0.94) and premenopausal breast cancer (0.86, 0.76–0.98). The authors conclude that higher red meat intake in early adulthood may be a risk factor for breast cancer, and replacing red meat with a combination of legumes, poultry, nuts and fish may reduce the risk of breast cancer.

BMJ 2014; 348: g3437

Eitan Israeli

Toward safer bone marrow transplants

People who receive bone marrow transplants often develop graft-versus-host disease, where immune cells from the transplanted bone marrow attack the patient's body. To understand this serious complication, Nalle and co-workers mimicked common human transplantations in mice. Before a transplant, human patients – and the experimental mice – are irradiated to kill their own bone marrow. In the mice, however,

this irradiation promoted gut “leakiness,” allowing immune activating bacteria to enter the body. That made graft-versus-host disease worse. If medics can find a way around this sort of complication in humans, they should be on their way to safer transplants.

Sci Transl Med 2014; 6: 243ra87

Eitan Israeli

Capsule

Stem cell plasticity: the versatility of epithelial stem cells

Stem cells are crucial to the maintenance of our bodies' tissues and organs. Blanpain and Fuchs review how different populations of naturally lineage-restricted epithelial stem cells and committed progenitors can also display remarkable plasticity. These cells can reacquire long-term self-renewing capacities and multilineage differentiation potential during physiological and

regenerative conditions. These abilities depend on whether the stem cell remains within its resident niche or has been mobilized to repair a wound. Such cellular plasticity has implications for regenerative medicine and for cancer.

Science 2014; 344: 10.1126/science.1242281

Eitan Israeli

Capsule

A surprising culprit attacks the brain

The brain deterioration in mice with a multiple sclerosis (MS)-like disease is exacerbated by a signaling molecule called interleukin-17 (IL-17), raising hopes that MS patients could be treated with drugs that target this cytokine. In an unexpected twist, however, Noster and team found that in humans the culprit is a different cytokine, GM-CSF, a small molecule that promotes

inflammation in many autoimmune diseases. What's more, in human patients IL-17 blocked GM-CSF production, a striking contrast to its effect in mice. These data suggest a new rationale for a therapeutic approach in MS patients: decreasing GM-CSF.

Sci Transl Med 2014; 6: 241ra80

Eitan Israeli

Capsule

Copper for breast cancer metastasis

Many patients with breast cancer die from metastases, when cancer cells spread from the primary tumor to other sites. Some of the intracellular proteins that help cells move from one location to another can be activated by a chemical modification called oxidation. MacDonald and co-scientists found that the enzyme Memo bound copper, enhancing the oxidation of

proteins involved in cell movement. Mice with tumors formed from breast cancer cells that lacked Memo had fewer lung metastases, and human patients with breast cancers that had high levels of Memo were more likely to develop metastases.

Sci Signal 2014; 7: ra56

Eitan Israeli

Capsule

Exploiting nervous paths already traveled

The parasympathetic nervous system helps regulate the functions of many tissues and organs, including the salivary glands and the esophagus. To do so, it needs to reach throughout the body, connecting central systems to peripheral ones. Dyachuk et al. and Espinosa-Medina et al. explored how these connections are established in mice (see the Perspective by Kalchauer and Rohrer). Progenitor cells that travel along with

the developing nerves can give rise to both myelin-forming Schwann cells and to parasympathetic neurons. That means the interacting nerves do not have to find each other. Instead, the beginnings of the connections are laid down as the nervous system develops.

Science 2014; 345: 82, 87

Eitan Israeli

Capsule

Can an airborne agent cause Kawasaki heart disease?

Kawasaki disease is the most common cause of acquired heart disease in children, but even now – 40 years after its discovery – doctors still don't know its cause. Infectious and environmental agents are both possibilities. Rodó and co-authors compared daily Kawasaki disease case records in Japan with models of regional air trajectories. They found that spikes in disease incidence occurred when the wind blew from an agricultural region in northeastern China. Aerosol samples

identified a high abundance of *Candida*, a fungus. Although the results are only a correlation, they support an existing model suggesting that genetically susceptible children may develop the disease when a windborne toxin or environmental agent triggers an aberrant immune response.

Proc Natl Acad Sci USA 2014; 110: 1073/pnas.1400380111

Nat Genet 2014; 46: 1038/ng.2982

Eitan Israeli

Blocking DDX5 enzyme for cancer treatment

Cancer chemotherapy is infamous for harming healthy cells. This collateral damage causes the side effects that range from unpleasant (such as hair loss) to life-threatening (e.g., increased susceptibility to infection). They can be particularly devastating for elderly patients. Promising new data may one day lead to a safer treatment for a type of acute myeloid leukemia, which first strikes patients at age 66, on average. Mazurek and colleagues found that when

they blocked mouse genes from expressing an enzyme called DDX5, the leukemia cells died, but healthy bone marrow cells were unharmed. DDX5 made the cancer cells proliferate; inhibiting DDX5 made the cells accumulate toxic molecules called reactive oxygen species, which contributed to cancer cell death.

Cell Rep 2014; 7: 10.1016/j.celrep.2014.05.010

Eitan Israeli

Improving stroke recovery by timing treatment

Patients recovering from strokes often fight a long uphill battle, with mixed results. Studying the effect of physical training on regeneration from damaged nerves in a model of stroke in rats, Wahl et al. show that timing matters. First, the researchers gave the rats a stroke, which damaged their ability to reach for food pellets with their forelimbs. The researchers then gave them physical training and treated

them with an antibody to encourage neural regeneration. The rats improved more when the researchers waited until after the antibody treatment to start the training. Damaged circuits, it seems, need a little time to regrow before being called into action.

Science 2014; 344: 1250

Eitan Israeli