Capsule

Vaccine protection against acquisition of neutralization-resistant SIV challenges in rhesus monkeys

Preclinical studies of human immunodeficiency virus type 1 (HIV-1) vaccine candidates have typically shown post-infection virological control, but protection against acquisition of infection has previously only been reported against neutralization-sensitive virus challenges. Barouch et al. demonstrate vaccine protection against acquisition of fully heterologous, neutralization-resistant simian immunodeficiency virus (SIV) challenges in rhesus monkeys. Adenovirus/poxvirus and adenovirus/adenovirus-vector-based vaccines expressing SIV_{SME543} Gag, Pol and Env antigens resulted in an 80% or greater reduction in the per-exposure probability of infection against repetitive, intrarectal SIV_{MAC251} challenges in rhesus monkeys. Protection against acquisition of infection showed distinct immunological correlates compared with post-infection virological control and required the inclusion of Env in the vaccine regimen. These data demonstrate the proof-of-concept that optimized HIV-1 vaccine candidates can block acquisition of stringent, heterologous, neutralization-resistant virus challenges in rhesus monkeys.

Nature 2012: doi:10.1038/nature10766

Eitan Israeli

Capsule

Melanopsin signalling in mammalian iris and retina

Non-mammalian vertebrates have an intrinsically photosensitive iris and thus a local pupillary light reflex (PLR). In contrast, it is thought that the PLR in mammals generally requires neuronal circuitry connecting the eye and the brain. Xue and collaborators report that an intrinsic component of the PLR is in fact widespread in nocturnal and crepuscular mammals. In mouse, this intrinsic PLR requires the visual pigment melanopsin; it also requires PLCβ4, a vertebrate homologue of the Drosophila NorpA phospholipase C which mediates rhabdomeric phototransduction. The *Plcb*4$^{-/-}$ genotype, in addition to removing the intrinsic PLR, also essentially eliminates the intrinsic light response of the M1 subtype of melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (M1-ipRGCs), which are by far the most photosensitive ipRGC subtype and also have the largest response to light. Ablating in mouse the expression of both TRPC6 and TRPC7, members of the TRP channel superfamily, also essentially eliminated the M1-ipRGC light response but the intrinsic PLR was not affected. Thus, melanopsin signaling exists in both iris and retina, involving a PLCβ4-mediated pathway that nonetheless diverges in the two locations.

Nature 2011; 479: 67

Eitan Israeli

Capsule

Clinical features, pathogenesis and treatment of juvenile and adult dermatomyositis

Juvenile and adult dermatomyositis have multiple commonalities, yet display differing prevalence of features, outcomes and comorbidities. In general, compared with the disease in adults, children with dermatomyositis have more vasculopathy and a greater likelihood of calcinosis, periungual and gingival telangiectasias, and ulceration, but have a better long-term prognosis with improved survival. Adults with the condition are more likely to have myositis-specific antibodies, develop interstitial lung disease, have amyopathic disease, and have a marked association with malignancy and other comorbidities. Both diseases have similar features on muscle biopsy and interferon gene signature, although subtle differences can exist in pathogenesis and pathology, such as more capillary loss and a greater degree of C5b-9 complement deposition in affected muscle of juvenile patients. Initiatives are underway to improve classification, markers of disease activity and ability to predict outcome of juvenile and adult dermatomyositis.

Nature Rev Rheumatol 2011; 7: 664

Eitan Israeli

"Forgive your enemies, but never forget their names"

John F. Kennedy (1917-1963), 35th President of the United States, serving from 1961 until his assassination in 1963

Capsule

Mast cells role to be reevaluated

Although the role of mast cells in allergic disease is well established, they have also been implicated in responses to bacterial infections, autoimmunity and cancer. Nearly all these studies relied on the use of mice containing mutations in the receptor tyrosine kinase Kit, which is important for mast cell development. Although these mice lacked mast cells, Kit is also expressed in other cell lineages and Kit mutant mice suffered from anemia, neutropenia, and impaired lymphocyte development, among other defects. Feyerabend and colleagues describe mice (called Cre-Master) with a selective deficiency in mast cells that were generated by the targeted insertion of Cre recombinase into the mast cell carboxypeptidase A3 locus. The insertion of Cre caused deletion of mast cells by genotoxic stress. Cre-Master mice were devoid of mast cells and, as expected, were unable to mount immunoglobulin E-mediated anaphylactic responses. In contrast to Kit mutant mice, Cre-Master mice were susceptible to antibody-induced autoimmune arthritis. Thus, the function of mast cells, one of the more enigmatic cells of the immune system, may need to be reevaluated.

Immunity 2011; 35: 832

Eitan Israeli

Capsule

Non-canonical inflammasome activation targets caspase-11

Caspase-1 activation by inflammasome scaffolds comprised of intracellular nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and the adaptor ASC is believed to be essential for production of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 during the innate immune response. Kayagaki et al. show, with C57BL/6 *Casp*11 gene-targeted mice, that caspase-11 (also known as caspase-4) is critical for caspase-1 activation and IL-1β production in macrophages infected with *Escherichia coli*, *Citrobacter rodentium* or *Vibrio cholerae*. Strain 129 mice, like *Casp*11−/− mice, exhibited defects in IL-1β production and harbored a mutation in the *Casp*11 locus that attenuated caspase-11 expression. This finding is important because published targeting of the *Casp*1 gene was done using strain 129 embryonic stem cells. *Casp*1 and *Casp*11 are too close in the genome to be segregated by recombination; consequently, the published *Casp*1−/− mice lack both caspase-11 and caspase-1. Interestingly, *Casp*11−/− macrophages secreted IL-1β normally in response to ATP and monosodium urate, indicating that caspase-11 is engaged by a non-canonical inflammasome. *Casp*1−/− *Casp*11$^{129mt/129mt}$ macrophages expressing caspase-11 from a C57BL/6 bacterial artificial chromosome transgene failed to secrete IL-1β regardless of stimulus, confirming an essential role for caspase-1 in IL-1β production. Caspase-11 rather than caspase-1, however, was required for non-canonical inflammasome-triggered macrophage cell death, indicating that caspase-11 orchestrates both caspase-1-dependent and -independent outputs. Caspase-1 activation by non-canonical stimuli required NLRP3 and ASC, but caspase-11 processing and cell death did not, implying that there is a distinct activator of caspase-11. Lastly, loss of caspase-11 rather than caspase-1 protected mice from a lethal dose of lipopolysaccharide. These data highlight a unique pro-inflammatory role for caspase-11 in the innate immune response to clinically significant bacterial infections.

Nature 2011; 479: 117

Eitan Israeli

Capsule

Uric acid: possible mediator of the adjuvant effect of alum in mice immunized with ovalbumin

One proposed mechanism by which alum enhances an immune response is by its ability to induce an inflammatory response that results in the release of uric acid from necrotic cells. Uric acid is thought to be a mediator in enhancing the immune response. A study from Lebanon investigated the immunopotentiating effect of uric acid. Groups of BALB/c mice were injected intraperitoneally with ovalbumin, ovalbumin + alum, ovalbumin + uric acid, uric acid, alum, or allopurinol. Two other groups were pretreated with allopurinol and were given ovalbumin + alum, or ovalbumin + uric acid 24 hours later. An additional two groups served as controls. On days 4, 7 and 10 post-injection, the numbers of interleukin 4 (IL-4) and interferon-gamma (IFNγ)-secreting spleen cells were determined by the ELISPOT assay. Serum uric acid levels were determined using an autoanalyser and nitric oxide using the Greiss reagent. The groups that received alum + ovalbumin or uric acid + ovalbumin had the highest numbers of IL-4 and IFNγ-secreting cells as compared to all the groups. Allopurinol administration one day prior to alum + ovalbumin or uric acid + ovalbumin resulted in a decrease in the number of IL-4 and IFNγ-secreting cells when compared to alum+ ovalbumin or uric acid + ovalbumin allopurinol-untreated groups. Groups that received alum, alum + ovalbumin, uric acid, and uric acid + ovalbumin had high serum uric acid levels as compared to all the groups. All groups that received alum had the highest levels of nitric oxide when compared to the groups that were not given alum. In conclusion, it appears that uric acid might be a mediator in the adjuvant effect of alum.

World J Vaccines 2011; 1: 148

Eitan Israeli

Capsule

The genetic basis of early T cell precursor acute lymphoblastic leukaemia

Early T cell precursor acute lymphoblastic leukemia (ETP ALL) is an aggressive malignancy of unknown genetic basis. Zhang and team performed whole-genome sequencing of 12 ETP ALL cases and assessed the frequency of the identified somatic mutations in 94 T cell acute lymphoblastic leukemia cases. ETP ALL was characterized by activating mutations in genes regulating cytokine receptor and RAS signaling (67% of cases; *NRAS*, *KRAS*, *FLT3*, *IL7R*, *JAK3*, *JAK1*, *SH2B3* and *BRAF*), inactivating lesions disrupting hematopoietic development (58%; *GATA3*, *ETV6*, *RUNX1*, *IKZF1* and *EP300*) and histone-modifying genes (48%; *EZH2*, *EED*, *SUZ12*, *SETD2* and *EP300*). The authors also identified new targets of recurrent mutation including *DNM2*, *ECT2L* and *RELN*. The mutational spectrum is similar to myeloid tumors and, moreover, the global transcriptional profile of ETP ALL was similar to that of normal and myeloid leukemia hematopoietic stem cells. These findings suggest that the addition of myeloid-directed therapies might improve the poor outcome of ETP ALL.

Nature 2012; 481: 157

Eitan Israeli

Capsule

NLRC4 inflammasomes in dendritic cells regulate non-cognate effector function by memory CD8+ T cells

Memory T cells exert antigen-independent effector functions, but how these responses are regulated is unclear. Kupz et al. discovered an in vivo link between flagellin-induced NLRC4 inflammasome activation in splenic dendritic cells (DCs) and host protective interferon-gamma (IFNγ) secretion by non-cognate memory CD8+ T cells, which could be activated by *Salmonella enterica* serovar Typhimurium, *Yersinia pseudotuberculosis* and *Pseudomonas aeruginosa*. The authors show that CD8α+ DCs were particularly efficient at sensing bacterial flagellin through NLRC4 inflammasomes. Although this activation released interleukin 18 (IL-18) and IL-1β, only IL-18 was required for IFNγ production by memory CD8+ T cells. Conversely, only the release of IL-1β, but not IL-18, depended on priming signals mediated by Toll-like receptors. These findings provide a comprehensive mechanistic framework for the regulation of non-cognate memory T cell responses during bacterial immunity.

Nature Immunol 2012; 13: 162

Eitan Israeli

Capsule

Towards a systems understanding of MHC class I and MHC class II antigen presentation

The molecular details of antigen processing and presentation by MHC class I and class II molecules have been studied extensively for almost three decades. Although the basic principles of these processes were laid out approximately 10 years ago, research in recent years has revealed many details and provided new insights into their control and specificity. MHC molecules use various biochemical reactions to achieve successful presentation of antigenic fragments to the immune system. Neefjes et al. present a timely evaluation of the biology of antigen presentation and a survey of issues that are considered unresolved. The continuing flow of new details into our understanding of the biology of MHC class I and class II antigen presentation builds a system involving several cell biological processes.

Nature Rev Immunol 2011; 11: 823

Eitan Israeli

Capsule

Langerhans cells may promote the transformation of skin epithelial cells

Several immune cell populations reside in the skin and are thought to provide a protective barrier against infections and to act as sentinels against malignant transformation. However, studies in mice that lack Langerhans cells, a subset of dendritic cells, have suggested that these cells may actually promote tumorigenesis. Using a mouse model of squamous cell carcinoma, Modi et al. reveal how Langerhans cells may promote the transformation of skin epithelial cells. In response to the carcinogen 7,12-dimethylbenz[α]anthracene (DMBA), Langerhans cells increased their expression of the cytochrome P-450 enzyme CYP1B1, which can metabolize DMBA to the mutagenic DMBA-*trans*-3,4-diol. Thus, besides their functions in regulating the adaptive immune response, Langerhans cells may participate in the metabolism of environmental carcinogens.

Science 2012: 335: 104

Eitan Israeli

Capsule

Safety of biologic therapy in rheumatoid arthritis

Biologic therapies have revolutionized the treatment of rheumatic diseases in the past decade. As with any drugs, however, a variety of important safety concerns affect the choice and use of these agents. Several issues, such as the risk of infection, malignancy, or administration reactions, apply to all of these compounds, although some conditions that affect patient selection and management within these categories seem to be specific to particular biologic treatments. Other safety concerns with biologic agents, such as congestive heart failure, demyelinating disease, and hyperlipidemia, are associated with individual agents. Despite all these concerns, the therapeutic indices for biologic agents remain fairly high in relation to non-biologic disease-modifying anti-rheumatic drugs. Available safety data for all biologic agents approved for the treatment of rheumatoid arthritis are reviewed by Woodrick and Ruderman. With careful patient selection and appropriate vigilance on the part of treating physicians and other care providers, these compounds can be safely integrated into the therapeutic plan.

Nature Rev Rheumatol 2011; 7: 639

Eitan Israeli

Capsule

A novel retinoblastoma therapy from genomic and epigenetic analyses

Retinoblastoma is an aggressive childhood cancer of the developing retina that is initiated by the biallelic loss of *RB*1. Tumors progress very quickly following *RB*1 inactivation but the underlying mechanism is not known. Zhang et al. show that the retinoblastoma genome is stable, but that multiple cancer pathways can be epigenetically deregulated. To identify the mutations that cooperate with *RB*1 loss, the authors performed whole-genome sequencing of retinoblastomas. The overall mutational rate was very low; *RB*1 was the only known cancer gene mutated. They then evaluated the role of *RB*1 in genome stability and considered non-genetic mechanisms of cancer pathway deregulation. For example, the proto-oncogene *SYK* is upregulated in retinoblastoma and is required for tumor cell survival. Targeting SYK with a small-molecule inhibitor induced retinoblastoma tumor cell death in vitro and in vivo. Thus, retinoblastomas may develop quickly as a result of the epigenetic deregulation of key cancer pathways as a direct or indirect result of *RB*1 loss.

Nature 2012; 481: doi:10.1038/nature10733

Eitan Israeli

"Middle age is when a narrow waist and a broad mind begin to change places"

Ogden Nash (1902-1971), American poet well known for his light verse

"Men shout to avoid listening to one another"

Miguel de Unamuno (1864-1936), Spanish essayist, novelist, poet, playwright and philosopher

Capsule

New targets for intervention in the treatment of postmenopausal osteoporosis

Postmenopausal osteoporosis is a disease of high bone remodeling, with an imbalance of bone resorption over bone formation, resulting in decreased bone mineral density and disruption of bone microarchitecture. With our improved understanding of the molecular and cellular regulators and mediators of bone remodeling, new targets for therapeutic intervention have been identified. Lewiecki reviewed the new approaches. Receptor activator of nuclear factor κB ligand (RANKL) is the principal regulator of osteoclast differentiation, activity, and survival; denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and is approved for the treatment of women with postmenopausal osteoporosis at high risk of fractures. Cathepsin K is a protease produced by activated osteoclasts that degrades the protein matrix of bone. An inhibitor of cathepsin K, odanacatib, is in phase III clinical trials for the treatment of postmenopausal osteoporosis; it decreases bone resorption while seeming to suppress bone formation less than other antiresorptive agents. Sclerostin is a cytokine produced by osteocytes that inhibits osteoblastic bone formation; investigational monoclonal antibodies to sclerostin, such as AMG 785, have osteoanabolic properties with the potential to improve clinical outcomes in patients with osteoporosis. These and other novel interventions that target newly recognized regulators of bone remodeling are promising agents for the treatment of osteoporosis.

Nature Rev Rheumatol 2011; 7: 631

Eitan Israeli

Capsule

Opoids as long-lasting pain killers

Opioids are among the most widely used and extensively studied drugs in the world. A continuous application of relatively low opioid doses is thought to be necessary to maintain synaptic depression in pain pathways. Drdla-Schutting and colleagues found that a single opioid application could produce lasting reversal of synaptic long-term potentiation in pain pathways. Chronic pain is often associated with synaptic potentiation in nociceptive pathways. A brief, high dose application of opioids depotentiated long-term potentiation in spinal pain pathways. The same dose also reversed hyperalgesia in behaving animals. Thus, opioids not only attenuate pain but may also eradicate a significant cause for chronic pain.

Science 2012; 335: 235

Eitan Israeli

"Do not resent growing old. Many are denied the privilege"

Irish proverb

Capsule

Uric acid: possible mediator of the adjuvant effect of alum in mice immunized with ovalbumin

One proposed mechanism by which alum enhances an immune response is by its ability to induce an inflammatory response that results in the release of uric acid from necrotic cells. Uric acid is thought to be a mediator in enhancing the immune response. A study from Lebanon investigated the immunopotentiating effect of uric acid. Groups of BALB/c mice were injected intraperitoneally with ovalbumin, ovalbumin + alum, ovalbumin + uric acid, uric acid, alum, or allopurinol. Two other groups were pretreated with allopurinol and were given ovalbumin + alum, or ovalbumin + uric acid 24 hours later. An additional two groups served as controls. On days 4, 7 and 10 post-injection, the numbers of interleukin 4 (IL-4) and interferon-gamma (IFNγ)-secreting spleen cells were determined by the ELISPOT assay. Serum uric acid levels were determined using an autoanalyser and nitric oxide using the Greiss reagent. The groups that received alum + ovalbumin or uric acid + ovalbumin had the highest numbers of IL-4 and IFNγ-secreting cells as compared to all the groups. Allopurinol administration one day prior to alum + ovalbumin or uric acid + ovalbumin resulted in a decrease in the number of IL-4 and IFNγ-secreting cells when compared to alum+ ovalbumin or uric acid + ovalbumin allopurinol-untreated groups. Groups that received alum, alum + ovalbumin, uric acid, and uric acid + ovalbumin had high serum uric acid levels as compared to all the groups. All groups that received alum had the highest levels of nitric oxide when compared to the groups that were not given alum. In conclusion, it appears that uric acid might be a mediator in the adjuvant effect of alum.

World J Vaccines 2011; 1: 148

Eitan Israeli

Capsule

Manufacturing an anti-malaria dug from tobacco

Combating malaria is one of the eight Millennium Development Goals described in the UN Millennium Declaration in 2000. Key to controlling malaria is prompt and effective use of artermisinin-based combination therapies. Artemisinin is a natural compound from *Artemisia annua* (sweet wormword) plants, but low cost artemisinin-based drugs are lacking because of the high cost of obtaining the natural or chemically synthesized drug. Despite extensive efforts during the last decade in metabolic engineering of the drug in both microbial and heterologous plant systems, production of artemisinin itself was never achieved.

Israel High-Tech & Investment Report, January 2012

"Mistakes are part of the dues that one pays for a full life"

Sophia Loren (b. 1934), Italian award-winning actress

Capsule

Acquisition of a multifunctional IgA+ plasma cell phenotype in the gut

The largest mucosal surface in the body is in the gastrointestinal tract, a location that is heavily colonized by microbes that are normally harmless. A key mechanism required for maintaining a homeostatic balance between this microbial burden and the lymphocytes that densely populate the gastrointestinal tract is the production and transepithelial transport of poly-reactive immunoglobulin A (IgA). Within the mucosal tissues, B cells respond to cytokines, sometimes in the absence of T cell help, undergo class switch recombination of their immunoglobulin receptor to IgA, and differentiate to become plasma cells. However, IgA-secreting plasma cells probably have additional attributes that are needed for coping with the tremendous bacterial load in the gastrointestinal tract. Fritz and co-workers report that mouse IgA+ plasma cells also produce the antimicrobial mediators tumor necrosis factor alpha (TNFα) and inducible nitric oxide synthase (iNOS), and express many molecules that are commonly associated with monocyte/granulocytic cell types. The development of iNOS-producing IgA+ plasma cells can be recapitulated in vitro in the presence of gut stroma, and the acquisition of this multifunctional phenotype in vivo and in vitro relies on microbial co-stimulation. Deletion of TNFα and iNOS in B-lineage cells resulted in a reduction in IgA production, altered diversification of the gut microbiota and poor clearance of a gut-tropic pathogen. These findings reveal a novel adaptation to maintaining homeostasis in the gut and extend the repertoire of protective responses exhibited by some B-lineage cells.

Nature 2012; 481: 199

Eitan Israeli

"Few things are more satisfying than seeing your children have teenagers of their own"

Doug Larson (b. 1926), American columnist

Capsule

Fine tuning neuronal networks

The double-stranded RNA-activated protein kinase (PKR) is widely present in vertebrates, and its activation leads to the phosphorylation of several substrates, the major known cytoplasmic target being the translation initiation factor eIF2α. PKR is activated in response to a variety of cellular stresses such as viral infection and status epilepticus, and in degenerating neurons in, among others, Huntington's, Parkinson's, Alzheimer's, and Creutzfeldt-Jakob's disease. At present, little is known about its role in normal neuronal function. Using transgenic mice, electrophysiology, immunohistochemistry, and behavioral analysis, Zhu and team discovered that loss of PKR or pharmacological blockade of PKR activity in mice promoted hyperexcitability in cortical and hippocampal networks and enhanced long-lasting synaptic potentiation and long-term memory. PKR regulated these processes via selective control of GABAergic synaptic transmission mediated by interferon-gamma (IFNγ). These findings thus uncovered a new molecular signaling pathway that regulates network rhythmicity, synaptic plasticity, and memory storage in the adult brain. PKR is activated in various neuropathies and may therefore be a potential therapeutic target.

Cell 2011; 147: 1384

Eitan Israeli

Capsule

Tegal invests in Israeli medtech start-up

Semiconductor equipment supplier Tegal Corporation (in California) made a strategic investment in NanoVibronix Inc, a private Israeli company that develops medical devices and products to implement its proprietary therapeutic ultrasound technology (low intensity surface acoustic wave, SAW). The company is developing a series of products aimed at the treatment of chronic non-healing wounds. Its first product, Painshield MD, for the treatment of tendonitis, muscle pain and trigeminal neuralgia, has received both U.S. Food and Drug Administration and Europe's CE Mark certification.

Israel High-Tech Investment Report, January 2012

"Some scientists work so hard there is no time left for serious thinking"

Francis Crick (1916-2004), English molecular biologist, biophysicist and neuroscientist, who with James Watson discovered the structure of the DNA molecule in 1953. He, Watson and Maurice Wilkins were jointly awarded the 1962 Nobel Prize for Physiology or Medicine