Capsule

Rituximab, SLE and reduction of steroids

Rituximab, a chimeric anti-CD20 antibody that efficiently depletes CD20-positive B cells, has been used in the last decade as off-label treatment for lupus nephritis. To date, data of more than 400 patients have been reported regarding the clinical effects of rituximab for lupus nephritis, including a randomized controlled LUNAR study population. Despite promising results from observational studies and registries, the LUNAR trial failed to achieve the primary endpoint. The lack of evidence from randomized controlled trials may explain why rituximab is not approved as treatment for lupus nephritis. However, as often occurs in rheumatic disease, the data from observational studies are powerful. Hickman et al. recently reported the findings of their study assessing the safety and efficacy of rituximab in 15 refractory SLE patients (mean age 38 years, mean disease duration 8.5 years); all patients received at least one course of rituximab for systemic lupus erythematosus (SLE) refractory to corticosteroids and at least two cytotoxic agents. British Isles Lupus Assessment Group (BILAG) index, anti-DNA antibodies and complement levels were used to measure disease activity. The results of the study showed that repeated treatments until the fourth course appear safe and efficacious in providing many months of remission in previously severe refractory SLE. Globally, according to BILAG scores, there was improvement in steroid reduction, levels of complement and anti-DNA, and both clinical and serological outcome. Twelve patients responded by 6 months; 6 did not experience a major flare for › 1 year. Complete absence of disease activity (BILAG D/E) lasted for 5.5 months and 4.8 months after the first and second rituximab course, respectively. Notably, the mean 6 month reduction in daily prednisolone was 10.4 mg/day and 10.7 mg/day from baseline after the first and second course, respectively; moreover, patients with low C3/C4 normalized their C3 by 6 months and most patients with high anti-dsDNA normalized after rituximab courses. These data concur with previous results showing that repeated rituximab courses were safe and efficacious. The noteworthy finding of this study in the evaluation of steroid reduction was that repeated courses of rituximab improved disease control. Globally, safety profile was acceptable, with serious adverse events occurring only after more than four courses of rituximab.

Clin Rheumatol 2015; 34: 263-71

Luca Cantarini

Capsule

Antibiotics in fetal and early life and subsequent childhood asthma

Örtqvist and co-authors examined the association between exposure to antibiotics in fetal and early life and asthma in childhood, with adjustment for confounding factors. A nationwide prospective population-based cohort study in Sweden, including a sibling control design, identified from national demographic and health registers 493,785 children born in 2006-2010; of these, 180,894 eligible for sibling analyses participated. Antibiotic exposure in fetal life was associated with an increased risk of asthma in cohort analyses (hazard ratio 1.28, 95% confidence interval 1.25 to 1.32), but not in sibling analyses (0.99, 0.92–1.07). In cohort analyses, antibiotics used to treat respiratory infections in childhood were associated with a more pronounced increased risk of asthma (4.12, 3.78–4.50) than antibiotics used for urinary tract and skin infections (1.54, 1.24–1.92). In sibling analyses, the excess risks after exposure to antibiotics for respiratory infections decreased (2.36, 1.78–3.13) and disappeared for antibiotics for urinary tract and skin infections (0.85, 0.47–1.55). Previous positive associations between exposure to antibiotics in fetal and early life and subsequent childhood asthma could have been due to confounding by shared familial factors, in addition to confounding by respiratory infections.

BMJ 2014; 349: g6979

Eitan Israeli

Capsule

Smoking is associated with mosaic loss of chromosome Y

Tobacco smoking is a risk factor for numerous disorders, including cancers affecting organs outside the respiratory tract. Epidemiological data suggest that smoking is a greater risk factor for these cancers in males compared to females. This observation, together with the fact that males have a higher incidence of and mortality from most non-sex-specific cancers, remains unexplained. Loss of chromosome Y (LOY) in blood cells is associated with increased risk of no-hematological tumors. Dumanski et al. demonstrated that smoking is associated with LOY in blood cells in three independent cohorts [TwinGene: odds ratio (OR) 4.3, 95%CI 2.8–6.7; ULSAM: OR 2.4, 95%CI 1.6–3.6; and PIVUS: OR 3.5, 95%CI 1.4–8.4] encompassing a total of 6014 men. The data also suggest that smoking has a transient and dose-dependent mutagenic effect on LOY status. The finding that smoking induces LOY thus links a preventable risk factor with the most common acquired human mutation.

Science 2014; DOI: 10.1126/science.1262092

Eitan Israeli

Capsule

Antigen modification regulates competition of broad and narrow neutralizing HIV antibodies

Some HIV-infected individuals develop broadly neutralizing antibodies (bNAbs), whereas most develop antibodies that neutralize only a narrow range of viruses (nNAbs). bNAbs, but not nNAbs, protect animals from experimental infection and are likely a key component of an effective vaccine. nNAbs and bNAbs target the same regions of the viral envelope glycoprotein (Env), but for reasons that remain unclear only nNAbs are elicited by Env immunization. McGuire et al. show that in contrast to germline-reverted (gl) bNAbs, glnNAbs recognized diverse recombinant Envs. Moreover, owing to binding affinity differences, nNAb B cell progenitors had an advantage in becoming activated and internalizing Env compared with bNAb B cell progenitors. We then identified an Env modification strategy that minimized the activation of nNAb B cells targeting epitopes that overlap those of bNAbs.

Science 2014; 346: 1380

Eitan Israeli

Capsule

Chronic enrichment of hepatic endoplasmic reticulum-mitochondria contact leads to mitochondrial dysfunction in obesity

Proper function of the endoplasmic reticulum (ER) and mitochondria is crucial for cellular homeostasis, and dysfunction at either site has been linked to pathophysiological states, including metabolic diseases. Although the ER and mitochondria play distinct cellular roles, these organelles also form physical interactions with each other at sites defined as mitochondria-associated ER membranes (MAMs), which are essential for calcium, lipid and metabolite exchange. Arruda et al. show that in the liver, obesity leads to a marked reorganization of MAMs resulting in mitochondrial calcium overload, compromised mitochondrial oxidative capacity and augmented oxidative stress. Experimental induction of ER-mitochondria interactions results in oxidative stress and impaired metabolic homeostasis, whereas down-regulation of PACS-2 or IP3R1, proteins important for ER-mitochondria tethering or calcium transport, respectively, improves mitochondrial oxidative capacity and glucose metabolism in obese animals. These findings establish excessive ER-mitochondrial coupling as an essential component of organelle dysfunction in obesity that may contribute to the development of metabolic pathologies such as insulin resistance and diabetes.

Nature Med 2014; 20: 1427

Eitan Israeli

Capsule

CD8+ T cells prevent antigen-induced antibody-dependent enhancement of dengue disease in mice

Dengue virus (DENV) causes pathologies ranging from the febrile illness dengue fever to the potentially lethal severe dengue disease. A major risk factor for developing severe dengue disease is the presence of sub-protective DENV-reactive antibodies from a previous infection (or from an immune mother), which can induce Ab-dependent enhancement of infection (ADE). However, infection in the presence of sub-protective anti-DENV antibodies does not always result in severe disease, suggesting that other factors influence disease severity. Zellweger et al. investigated how CD8(+) T cell responses influence the outcome of antibody-mediated severe dengue disease. Mice were primed with aluminum hydroxide-adjuvanted UV-inactivated DENV prior to challenge with DENV. Priming failed to induce robust CD8(+) T cell responses, and it induced non-neutralizing antibody responses that increased disease severity upon infection. Transfer of exogenous DENV-activated CD8(+) T cells into primed mice prior to infection prevented antibody-dependent enhancement and dramatically reduced viral load. These results suggest that in the presence of sub-protective anti-DENV antibodies, efficient CD8(+) T cell responses reduce the risk of antibody-mediated severe dengue disease.

J Immunol 2014; 193: 4117

Eitan Israeli

Capsule

Coffee or tea consumption and the risk of rheumatoid arthritis: a meta-analysis

Lee et al. investigated the evidence for a relationship between coffee or tea consumption and the development of RA by performing a meta-analysis of the published results. Five studies (three cohort and two case-control studies) including 134,901 participants (1279 cases of RA and 133,622 non-cases) were considered. Meta-analysis of the cohort studies revealed a trend of an association between total coffee intake and RA incidence (relative risk [RR] of the highest versus the lowest group = 4.148, 95% confidence interval [CI] = 0.792–21.73, $P = 0.092$). Meta-analysis of case-control studies showed a significant association between total coffee intake and RA incidence (RR = 1.201, 95%CI = 1.058–1.361, $P = 0.005$). Combining the data of the cohort and case-control studies showed a significant association between total coffee intake and RA incidence (RR = 2.426, 95%CI = 1.060–5.554, $P = 0.036$). Meta-analysis stratified by seropositivity indicated a significant association between coffee consumption and seropositive RA risk (RR = 1.329, 95%CI = 1.162–1.522, $P = 3.5 \times 10–5$), but not seronegative RA risk (RR = 1.093, 95%CI = 0.884–1.350, $P = 0.411$). No association was found between tea intake and RA incidence (RR = 0.880, 95%CI = 0.624–1.239, $P = 0.463$). This meta-analysis of 134,901 participants (most of the participants were controls) suggests that high coffee consumption is associated with an elevated risk of RA development. The association between coffee and RA was found in seropositive RA, but not in seronegative RA.

Clin Rheumatol 2014; 33: 1575

Eitan Israeli

Capsule

Glycemic control in diabetes is restored by therapeutic manipulation of cytokines that regulate beta cell stress

In type 2 diabetes, hyperglycemia is present when an increased demand for insulin, typically due to insulin resistance, is not met as a result of progressive pancreatic beta cell dysfunction. This defect in beta cell activity is typically characterized by impaired insulin biosynthesis and secretion, usually accompanied by oxidative and endoplasmic reticulum (ER) stress. Hasnain et al. demonstrated that multiple inflammatory cytokines elevated in diabetic pancreatic islets induce beta cell oxidative and ER stress, with interleukin-23 (IL-23), IL-24 and IL-33 being the most potent. Conversely, the authors show that islet-endogenous and exogenous IL-22, by regulating oxidative stress pathways, suppresses oxidative and ER stress caused by cytokines or glucolipotoxicity in mouse and human beta cells. In obese mice, antibody neutralization of IL-23 or IL-24 partially reduced beta cell ER stress and improved glucose tolerance, whereas IL-22 administration modulated oxidative stress regulatory genes in islets, suppressed ER stress and inflammation, promoted secretion of high quality efficacious insulin and fully restored glucose homeostasis followed by restitution of insulin sensitivity. Thus, therapeutic manipulation of immune regulators of beta cell stress reverses the hyperglycemia central to diabetes pathology.

Nature Med 2014; 29: 1417

Eitan Israeli

Capsule

Dietary modulation of the microbiome affects autoinflammatory disease

The incidences of chronic inflammatory disorders have increased considerably over the past three decades. Recent shifts in dietary consumption may have contributed importantly to this surge, but how dietary consumption modulates inflammatory disease is poorly defined. *Pstpip2*^{cmo} mice, which express a homozygous Leu98Pro missense mutation in the Pombe Cdc15 homology family protein *PSTPIP2* (proline-serine-threonine phosphatase interacting protein 2), spontaneously develop osteomyelitis that resembles chronic recurrent multifocal osteomyelitis in humans. Recent reports demonstrated a crucial role for interleukin-1β (IL-1β) in osteomyelitis, but deletion of the inflammasome components caspase-1 and NLRP3 failed to rescue *Pstpip2*^{cmo} mice from inflammatory bone disease. Thus, the upstream mechanisms controlling IL-1β production in *Pstpip2*^{cmo} mice remain to be identified. In addition, the environmental factors driving IL-1β-dependent inflammatory bone erosion are unknown. Lukens et al. have shown that the intestinal microbiota of diseased Pstpip2cmo mice was characterized by an outgrowth of Prevotella. Notably, *Pstpip2*^{cmo} mice that were fed a diet rich in fat and cholesterol maintained a normal body weight, but were markedly protected against inflammatory bone disease and bone erosion. Diet-induced protection against osteomyelitis was accompanied by marked reductions in intestinal Prevotella levels and significantly reduced pro-IL-1β expression in distant neutrophils. Furthermore, pro-IL-1β expression was also decreased in *Pstpip2*^{cmo} mice treated with antibiotics, and in wild-type mice that were kept under germ-free conditions. The authors further demonstrate that combined deletion of caspases 1 and 8 was required for protection against IL-1β-dependent inflammatory bone disease, whereas the deletion of either caspase alone or of elastase or neutrophil proteinase 3 failed to prevent inflammatory disease. Collectively, this work reveals diet-associated changes in the intestinal microbiome as a crucial factor regulating inflammasome- and caspase-8-mediated maturation of IL-1β and osteomyelitis in *Pstpip2*^{cmo} mice.

Nature 2014: 516: 246

Eitan Israeli

Capsule

Biocontainment of genetically modified organisms by synthetic protein design

Genetically modified organisms (GMOs) are increasingly deployed at large scales and in open environments. Genetic biocontainment strategies are needed to prevent unintended proliferation of GMOs in natural ecosystems. Existing biocontainment methods are insufficient because they impose evolutionary pressure on the organism to eject the safeguard by spontaneous mutagenesis or horizontal gene transfer, or because they can be circumvented by environmentally available compounds. Mandell and team computationally redesigned essential enzymes in the first organism possessing an altered genetic code (*Escherichia coli* strain C321.ΔA) to confer metabolic dependence on non-standard amino acids for survival. The resulting GMOs could not metabolically bypass their biocontainment mechanisms using known environmental compounds, and exhibited unprecedented resistance to evolutionary escape through mutagenesis and horizontal gene transfer. This work provides a foundation for safer GMOs that are isolated from natural ecosystems by a reliance on synthetic metabolites.

Nature 2015; 518: 55

Eitan Israeli

Capsule

Aberrant epithelial *GREM1* expression initiates colonic tumorigenesis from cells outside the stem cell niche

Hereditary mixed polyposis syndrome (HMPS) is characterized by the development of mixed-morphology colorectal tumors and is caused by a 40 kb genetic duplication that results in aberrant epithelial expression of the gene encoding mesenchymal bone morphogenetic protein antagonist, *GREM1*. Davis et al. used HMPS tissue and a mouse model of the disease to show that epithelial *GREM1* disrupts homeostatic intestinal morphogen gradients, altering cell fate that is normally determined by position along the vertical epithelial axis. This promotes the persistence and/or reacquisition of stem cell properties in Lgr5-negative progenitor cells that have exited the stem cell niche. These cells form ectopic crypts, proliferate, accumulate somatic mutations and can initiate intestinal neoplasia, indicating that the crypt base stem cell is not the sole cell of origin of colorectal cancer. Furthermore, the authors show that epithelial expression of *GREM1* also occurs in traditional serrated adenomas, sporadic premalignant lesions with a hitherto unknown pathogenesis, and these lesions can be considered the sporadic equivalents of HMPS polyps.

Nature Med 2015; 21: 62

Eitan Israeli

Capsule

Divergent reprogramming routes lead to alternative stem-cell states

Pluripotency is defined by the ability of a cell to differentiate to the derivatives of all the three embryonic germ layers: ectoderm, mesoderm and endoderm. Pluripotent cells can be captured via the archetypal derivation of embryonic stem cells or via somatic cell reprogramming. Somatic cells are induced to acquire a pluripotent stem cell (iPSC) state through the forced expression of key transcription factors, and in the mouse these cells can fulfil the strictest of all developmental assays for pluripotent cells by generating completely iPSC-derived embryos and mice. However, it is not known whether there are additional classes of pluripotent cells, or what the spectrum of reprogrammed phenotypes encompasses. Tonge et al. explored alternative outcomes of somatic reprogramming by fully characterizing reprogrammed cells independent of preconceived definitions of iPSC states. They demonstrated that by maintaining elevated reprogramming factor expression levels, mouse embryonic fibroblasts go through unique epigenetic modifications to arrive at a stable, Nanog-positive, alternative pluripotent state. In doing so, they prove that the pluripotent spectrum can encompass multiple, unique cell states.

Nature 2014; 516: 192

Eitan Israeli

Capsule

Chemical corrector treatment ameliorates increased seizure susceptibility in a mouse model of familial epilepsy

Epilepsy is one of the most common and intractable brain disorders. Mutations in the human gene *LGI1*, encoding a neuronal secreted protein, cause autosomal dominant lateral temporal lobe epilepsy (ADLTE). However, the pathogenic mechanisms of *LGI1* mutations remain unclear. Yokoi et al. classified 22 reported *LGI1* missense mutations as either secretion defective or secretion competent, generated and analyzed two mouse models of ADLTE encoding mutant proteins representative of the two groups. The secretion-defective LGI1^{E383A} protein was recognized by the ER quality-control machinery and prematurely degraded, whereas the secretable *LGI1*^{S473L} protein abnormally dimerized and was selectively defective in binding to one of its receptors, ADAM22. Both mutations caused a loss of function, compromising intracellular trafficking or ligand activity of *LGI1* and converging on reduced synaptic LGI1-ADAM22 interaction. A chemical corrector, 4-phenylbutyrate (4PBA), restored *LGI1*^{E383A} folding and binding to ADAM22 and ameliorated the increased seizure susceptibility of the LGI1^{E383A} model mice. This study establishes *LGI1*-related epilepsy as a conformational disease and suggests new therapeutic options for human epilepsy.

Nature Med 2015; 21: 19

Eitan Israeli

Capsule

Embryonic intraventricular exposure to autism-specific maternal autoantibodies produces alterations in autistic-like stereotypical behaviors in offspring mice

Multiple studies have implicated a role of maternal autoantibodies reactive against fetal brain proteins specific to autism in the etiology of autism spectrum disorders (ASD). In the current study, we examined the impact of brain-reactive maternal autoantibodies of mothers of children with autism (MAU) on offspring behavior in mice compared to offspring exposed to non-reactive immunoglobulin G (IgG) of mothers of typically developing children (MTD). Embryonic offspring were exposed to a single intraventricular injection of MAU or MTD IgG on embryonic day 14. Offspring were allowed to mature to adulthood and were subsequently tested for sociability and stereotypic behaviors using a three-chambered social approach task, marble-burying task, and assessment of spontaneous grooming behaviors in response to a novel environment. Results indicate that MAU offspring display autistic-like stereotypical behavior in both marble burying and spontaneous grooming behaviors. Additionally, small alterations in social approach behavior were also observed in MAU offspring compared to MTD offspring. This report demonstrates for the first time the effects of a single, low dose intraventricular exposure of IgG derived from individual MAU samples on offspring behavior.

Behav Brain Res 2014; 266: 46

Eitan Israeli

Capsule

Myeloid-derived growth factor (C19orf10) mediates cardiac repair following myocardial infarction

Paracrine-acting proteins are emerging as a central mechanism by which bone marrow cell-based therapies improve tissue repair and heart function after myocardial infarction (MI). Korf-Klingebiel et al. carried out a bioinformatic secretome analysis in bone marrow cells from patients with acute MI to identify novel secreted proteins with therapeutic potential. Functional screens revealed a secreted protein encoded by an open reading frame on chromosome 19 (C19orf10) that promotes cardiac myocyte survival and angiogenesis. The authors show that bone marrow-derived monocytes and macrophages produce this protein endogenously to protect and repair the heart after MI, and they named it myeloid-derived growth factor (MYDGF). Whereas Mydgf-deficient mice develop larger infarct scars and more severe contractile dysfunction compared to wild-type mice, treatment with recombinant Mydgf reduces scar size and contractile dysfunction after MI. This study is the first to assign a biological function to MYDGF, and it may serve as a prototypical example for the development of protein-based therapies for ischemic tissue repair.

Nature Med 2015; 21: 140

Eitan Israeli

Capsule

Escape from bacterial iron piracy through rapid evolution of transferrin

Iron sequestration provides an innate defense, termed nutritional immunity, leading pathogens to scavenge iron from hosts. Although the molecular basis of this battle for iron is established, its potential as a force for evolution at host-pathogen interfaces is unknown. Barber & Elde have shown that the iron transport protein transferrin is engaged in ancient and ongoing evolutionary conflicts with TbpA, a transferrin surface receptor from bacteria. Single substitutions in transferrin at rapidly evolving sites reverse TbpA binding, providing a mechanism to counteract bacterial iron piracy among great apes. Furthermore, the C2 transferrin polymorphism in humans evades TbpA variants from *Haemophilus influenzae*, revealing a functional basis for standing genetic variation. These findings identify a central role for nutritional immunity in the persistent evolutionary conflicts between primates and bacterial pathogens.

Science 2014; 346: 1362

Eitan Israeli

Capsule

Biocontainment of genetically modified organisms by synthetic protein design

Genetically modified organisms (GMOs) are increasingly deployed at large scales and in open environments. Genetic biocontainment strategies are needed to prevent unintended proliferation of GMOs in natural ecosystems. Existing biocontainment methods are insufficient because they impose evolutionary pressure on the organism to eject the safeguard by spontaneous mutagenesis or horizontal gene transfer, or because they can be circumvented by environmentally available compounds. Mandell and team computationally redesigned essential enzymes in the first organism possessing an altered genetic code (*Escherichia coli* strain C321.ΔA) to confer metabolic dependence on non-standard amino acids for survival. The resulting GMOs could not metabolically bypass their biocontainment mechanisms using known environmental compounds, and exhibited unprecedented resistance to evolutionary escape through mutagenesis and horizontal gene transfer. This work provides a foundation for safer GMOs that are isolated from natural ecosystems by a reliance on synthetic metabolites.

Nature 2015; 518: 55

Eitan Israeli