Capsule

A beneficial role of some prions

Prions are the causative agent in fatal neurological diseases affecting humans and animals. Prions adopt a particular conformation that induces self-perpetuating protein aggregation, which can lead to devastating effects. Recent evidence suggests that not all prions are bad, however, and now Hou et al. show that effective antiviral immunity may depend on the formation of prion-like aggregates of the protein MAVS. MAVS functions downstream of RIG-I, an RNA helicase important for detecting viruses. RIG-I induced formation of MAVS prion-like fibrils in response to viral infection. These fibrils were resistant to detergent and protease and were able to "infect" endogenous MAVS proteins – that is, convert native MAVS into fibrils. These characteristics are all hallmarks of prions, which suggest that organisms can also use prions to their own advantage.

Cell 2011; 146: 448

Eitan Israeli

Capsule

The role of *HLA-DR-DQ* haplotypes in variable antibody responses to anthrax vaccine adsorbed

Host genetic variation, particularly within the human leukocyte antigen (HLA) loci, reportedly mediates heterogeneity in immune response to certain vaccines; however, no large study of genetic determinants of anthrax vaccine response has been described. Pajewski et al. searched for associations between the immunoglobulin G antibody to protective antigen (AbPA) response to anthrax vaccine adsorbed (AVA) in humans, and polymorphisms at HLA class I (*HLA-A*, *-B*, and *-C*) and class II (*HLA-DRB*1, *-DQA*1, *-DQB*1, *-DPB*1) loci. The study included 794 European Americans and 200 African Americans participating in a 43 month, double-blind and placebo-controlled clinical trial of AVA (clinicaltrials.gov identifier NCT00119067). Among European Americans, genes from tightly linked *HLA-DRB*1,*-DQA*1,*-DQB*1 haplotypes displayed significant overall associations with longitudinal variation in AbPA levels at 4, 8, 26 and 30 weeks from baseline in response to vaccination with three or four doses of AVA (global $P = 6.53 \times 10^{-4}$). In particular, carriage of the DRB1-DQA1-DQB1 haplotypes *1501-*0102-*0602 ($P = 1.17 \times 10^{-5}$), *0101-*0101-*0501 ($P = 0.009$) and *0102-*0101-*0501 ($P = 0.006$) was associated with significantly lower AbPA levels. In carriers of two copies of these haplotypes, lower AbPA levels persisted following subsequent vaccinations. No significant associations were observed among African Americans or for any HLA class I allele/haplotype. Further studies will be required to replicate these findings and to explore the role of host genetic variation outside of the HLA region.

Genes Immunity 2011; 12: 457

Eitan Israeli

Capsule

Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women

Anal cancer remains rare (incidence about 1.5/100,000 women yearly), but rates are increasing in many countries. Human papillomavirus (HPV) 16 and 18 infections cause most cases of anal cancer. Kreimer and team assessed the efficacy of an AS04-adjuvanted HPV 16 and HPV 18 vaccine against anal infection with HPV 16, HPV 18, or both (HPV 16/18). This randomized double-blind controlled trial, conducted in Costa Rica between 28 June 2004 and 21 December 2005, was designed to assess vaccine efficacy against persistent cervical HPV 16/18 infections and associated precancerous lesions. Eligible women were 18–25 years old, residents of Guanacaste and selected areas of Puntarenas, Costa Rica, in good general health, willing to provide informed consent, and not pregnant or breast-feeding. Participants were randomly assigned (1:1) to receive an HPV vaccine (Cervarix®, GlaxoSmithKline, Rixensart, Belgium) or a control hepatitis A vaccine (modified preparation of Havrix®, GlaxoSmithKline). All women who attended the final blinded study visit and consented to anal specimen collection were included in the analysis (4210 of 6352 eligible women). In the full cohort, vaccine efficacy against prevalent HPV 16/18 infection measured once, 4 years post-vaccination, was lower at the anus (62.0%) compared with the cervix (76.4%). In the restricted cohort, vaccine efficacy against anal HPV 16/18 infection was 83·6%, which was similar to vaccine efficacy against cervical HPV 16/18 infection (87.9%). Safety issues were not addressed in the current analysis. Additional safety data will be published later. The authors conclude that the AS04-adjuvanted vaccine affords strong protection against anal HPV infection, particularly among women more likely to be HPV naive at enrollment.

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Eitan Israeli

"A problem well stated is a problem half solved"

Charles F. Kettering (1876-1958), American inventor and engineer, businessman and the holder of 140 patents

Capsule

FADD prevents RIP3-mediated epithelial cell necrosis and chronic intestinal inflammation

Intestinal immune homeostasis depends on a tightly regulated cross-talk between commensal bacteria, mucosal immune cells and intestinal epithelial cells (IECs). Epithelial barrier disruption is considered to be a potential cause of inflammatory bowel disease; however, the mechanisms regulating intestinal epithelial integrity are poorly understood. Simon Welz and co-workers have shown that mice with IEC-specific knockout of FADD ($FADD^{IEC\text{-}KO}$), an adaptor protein required for death-receptor-induced apoptosis, spontaneously developed epithelial cell necrosis, loss of Paneth cells, enteritis and severe erosive colitis. Genetic deficiency in RIP3, a critical regulator of programmed necrosis, prevented the development of spontaneous pathology in both the small intestine and colon of $FADD^{IEC\text{-}KO}$ mice, demonstrating that intestinal inflammation is triggered by RIP3-dependent death of FADD-deficient IECs. Epithelial-specific inhibition of CYLD, a deubiquitinase that regulates cellular necrosis, prevented colitis development in $FADD^{IEC\text{-}KO}$ but not in $NEMO^{IEC\text{-}KO}$ mice, showing that different mechanisms mediated death of colonic epithelial cells in these two models. In $FADD^{IEC\text{-}KO}$ mice, tumor necrosis factor (TNF) deficiency ameliorated colon inflammation, whereas MYD88 deficiency and also elimination of the microbiota prevented colon inflammation, indicating that bacteria-mediated Toll-like-receptor signalling drives colitis by inducing the expression of TNF and other cytokines. However, neither CYLD, TNF or MYD88 deficiency nor elimination of the microbiota could prevent Paneth cell loss and enteritis in $FADD^{IEC\text{-}KO}$ mice, showing that different mechanisms drive RIP3-dependent necrosis of FADD-deficient IECs in the small and large bowel. Therefore, by inhibiting RIP3-mediated IEC necrosis, FADD preserves epithelial barrier integrity and antibacterial defense, maintains homeostasis and prevents chronic intestinal inflammation. Collectively, these results show that mechanisms preventing RIP3-mediated epithelial cell death are critical for the maintenance of intestinal homeostasis and indicate that programmed necrosis of IECs might be implicated in the pathogenesis of inflammatory bowel disease, in which Paneth cell and barrier defects are thought to contribute to intestinal inflammation.

Nature 2011; 477: 330

Eitan Israeli

"Every man possesses three characters: that which he exhibits, that which he really has, and that which he believes he has"

Jean-Baptiste Alphonse Karr (1808-1890), French critic, journalist, and novelist

Capsule

A draft genome of *Yersinia pestis* from victims of the Black Death

Bos et al. report a reconstructed ancient genome of *Yersinia pestis* at 30-fold average coverage from Black Death victims securely dated to episodes of pestilence-associated mortality in London, England, 1348–1350. Genetic architecture and phylogenetic analysis indicate that the ancient organism is ancestral to most extant strains and sits very close to the ancestral node of all *Y. pestis* commonly associated with human infection. Temporal estimates suggest that the Black Death of 1347–1351 was the main historical event responsible for the introduction and widespread dissemination of the ancestor to all currently circulating *Y. pestis* strains pathogenic to humans, and further indicates that contemporary *Y. pestis* epidemics have their origins in the medieval era. Comparisons against modern genomes reveal no unique derived positions in the medieval organism, indicating that the perceived increased virulence of the disease during the Black Death may not have been due to bacterial phenotype. These findings support the notion that factors other than microbial genetics, such as environment, vector dynamics and host susceptibility, should be at the forefront of epidemiological discussions regarding emerging *Y. pestis* infections.

Nature 2011; doi:10.1038/nature10549

Eitan Israeli

Capsule

Matrix-embedded cells control osteoclast formation

Osteoclasts resorb the mineralized matrices formed by chondrocytes or osteoblasts. The cytokine receptor activator of nuclear factor-κB ligand (RANKL) is essential for osteoclast formation and is thought to be supplied by osteoblasts or their precursors, thereby linking bone formation to resorption. However, RANKL is expressed by a variety of cell types, and it is unclear which of them are essential sources for osteoclast formation. Xiong and team used a mouse strain in which RANKL can be conditionally deleted and a series of Cre-deleter strains to demonstrate that hypertrophic chondrocytes and osteocytes, both of which are embedded in matrix, are essential sources of the RANKL that controls mineralized cartilage resorption and bone remodeling, respectively. Moreover, osteocyte RANKL is responsible for the bone loss associated with unloading. Contrary to the current paradigm, RANKL produced by osteoblasts or their progenitors does not contribute to adult bone remodeling. These results suggest that the rate-limiting step of matrix resorption is controlled by cells embedded within the matrix itself.

Nature Med 2011; 17: 1235

Eitan Israeli

Capsule

Israeli start-up offers minty solution for bad breath

A Jerusalem-based start-up has come up with a mint candy that may be a breath of fresh air for millions of people around the world who suffer from halitosis. According to one of the developers, "It showed around 60% success in all the individuals tested and is guaranteed to last for hours, unlike mouthwash and similar products." The lollipop-shaped candy scrapes the bacteria that causes bad breath off the tongue. The candy, named Like, is sugarless and works using microcapsules that scrub the bacteria off and release active agents that eliminate the remaining bacteria. The company, Breezy, is also working on other products to ward off oral bacteria, including mouth sores and oral fungus, to eliminate smoker's breath, as well as a product to prevent cavities.

Israel High-Tech & Investment Report

Capsule

Peripheral education of the immune system by colonic commensal microbiota

The instruction of the immune system to be tolerant of self, thereby preventing autoimmunity, is facilitated by the education of T cells in a specialized organ, the thymus, in which self-reactive cells are either eliminated or differentiated into tolerogenic Foxp3+ regulatory T (T_{reg}) cells. However, it is unknown whether T cells are also educated to be tolerant of foreign antigens, such as those from commensal bacteria, to prevent immunopathology such as inflammatory bowel disease. Lathrop et al. have shown that encounter with commensal microbiota results in the peripheral generation of T_{reg} cells rather than pathogenic effectors. The authors observed that colonic T_{reg} cells used T cell antigen receptors (TCRs) different from those used by T_{reg} cells in other locations, implying an important role for local antigens in shaping the colonic T_{reg} cell population. Many of the local antigens seemed to be derived from commensal bacteria, on the basis of the in vitro reactivity of common colon T_{reg} TCRs. These TCRs did not facilitate thymic T_{reg} cell development, implying that many colonic T_{reg} cells arise instead by means of antigen-driven peripheral T_{reg} cell development. Further analysis of two of these TCRs by the creation of retroviral bone marrow chimeras and a TCR transgenic line revealed that microbiota indigenous to a mouse colony was required for the generation of colonic T_{reg} cells from otherwise naive T cells. If T cells expressing these TCRs fail to undergo T_{reg} cell development and instead become effector cells, they have the potential to induce colitis, as evidenced by adoptive transfer studies. These results suggest that the efficient peripheral generation of antigen-specific populations of T_{reg} cells in response to an individual's microbiota provides important post-thymic education of the immune system to foreign antigens, thereby providing tolerance to commensal microbiota.

Nature 2011; doi:10.1038/nature10434

Eitan Israeli

Capsule

The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus

Inflammasomes are large cytoplasmic complexes that sense microbial infections/danger molecules and induce caspase-1 activation-dependent cytokine production and macrophage inflammatory death. The inflammasome assembled by the NOD-like receptor (NLR) protein NLRC4 responds to bacterial flagellin and a conserved type III secretion system (TTSS) rod component. How the NLRC4 inflammasome detects the two bacterial products and the molecular mechanism of NLRC4 inflammasome activation are not understood. Zhao and collaborators have shown that NAIP5, a BIR-domain NLR protein required for *Legionella pneumophila* replication in mouse macrophages, is a universal component of the flagellin-NLRC4 pathway. NAIP5 directly and specifically interacted with flagellin, which determined the inflammasome-stimulation activities of different bacterial flagellins. NAIP5 engagement by flagellin promoted a physical NAIP5-NLRC4 association, rendering full reconstitution of a flagellin-responsive NLRC4 inflammasome in non-macrophage cells. The related NAIP2 functioned analogously to NAIP5, serving as a specific inflammasome receptor for TTSS rod proteins such as Salmonella PrgJ and Burkholderia BsaK. Genetic analysis of *Chromobacterium violaceum* infection revealed that the TTSS needle protein CprI can stimulate NLRC4 inflammasome activation in human macrophages. Similarly, CprI is specifically recognized by human NAIP, the sole NAIP family member in humans. The finding that NAIP proteins are inflammasome receptors for bacterial flagellin and TTSS apparatus components further predicts that the remaining NAIP family members may recognize other unidentified microbial products to activate NLRC4 inflammasome-mediated innate immunity.

Nature 2011; doi:10.1038/nature10510

Eitan Israeli

Capsule

Exome sequencing strategy and brain tumors

Oligodendrogliomas are common adult brain tumors with a poor prognosis. A characteristic chromosomal aberration in these tumors has led to speculation that chromosomes 19q and 1p harbor tumor suppressor genes that, when inactivated, contribute to tumorigenesis. Bettegowda and co-researchers applied an exome sequencing strategy to these cancers and found recurrent somatic mutations in the *CIC* gene on chromosome 19q and the *FUBP1* gene on chromosome 1p, indicating that these are the long-sought-after tumor suppressors in oligodendrogliomas. *CIC* is the homolog of the *capicua* gene in the fruit fly Drosophila, where it encodes a transcriptional repressor whose inactivation produces embryos that have head and tail structures but no intervening segments. *FUBP1* codes for a protein that binds DNA, including the regulatory region of the *MYC* oncogene.

Science 2011; 333: 1453

Eitan Israeli

Capsule

Broad neutralization coverage of HIV by multiple highly potent antibodies

Broadly neutralizing antibodies against highly variable viral pathogens are much sought after to treat or protect against global circulating viruses. Walker and co-authors probed the neutralizing antibody repertoires of four human immunodeficiency virus (HIV)-infected donors with remarkably broad and potent neutralizing responses and rescued 17 new monoclonal antibodies that neutralize broadly across clades. Many of the new monoclonal antibodies are almost tenfold more potent than the recently described PG9, PG16 and VRC01 broadly neutralizing monoclonal antibodies and 100-fold more potent than the original prototype HIV broadly neutralizing monoclonal antibodies. The monoclonal antibodies largely recapitulate the neutralization breadth found in the corresponding donor serum and many recognize novel epitopes on envelope (Env) glycoprotein gp120, illuminating new targets for vaccine design. Analysis of neutralization by the full complement of anti-HIV broadly neutralizing monoclonal antibodies now available reveals that certain combinations of antibodies should offer markedly more favorable coverage of the enormous diversity of global circulating viruses than others and these combinations might be sought in active or passive immunization regimes. Overall, the isolation of multiple HIV broadly neutralizing monoclonal antibodies from several donors that, in aggregate, provide broad coverage at low concentrations is a highly positive indicator for the eventual design of an effective antibody-based HIV vaccine.

Nature 2011; 477: 466

Eitan Israeli

Capsule

Risk alleles for chronic hepatitis B are associated with decreased mRNA expression of *HLA-DPA1* and *HLA-DPB1* in normal human liver

A genome-wide association study identified single nucleotide polymorphisms (SNPs) rs3077 and rs9277535 located in the 3' untranslated regions of human leukocyte antigen (HLA) class II genes *HLA-DPA1* and *HLA-DPB1*, respectively, as the independent variants most strongly associated with chronic hepatitis B. O'Brien and group examined whether these SNPs are associated with mRNA expression of *HLA-DPA1* and *HLA-DPB1*. The authors identified gene expression-associated SNPs (eSNPs) in normal liver samples obtained from 651 individuals of European ancestry by integrating genotype (~650 000 SNPs) and gene expression (› 39 000 transcripts) data from each sample. They used the Kruskal-Wallis test to determine associations between gene expression and genotype. To confirm findings, they measured allelic expression imbalance (AEI) of complementary DNA compared with DNA in liver specimens from subjects who were heterozygous for rs3077 and rs9277535. On a genome-wide basis, rs3077 was the SNP most strongly associated with *HLA-DPA1* expression ($P = 10^{-48}$), and rs9277535 was strongly associated with *HLA-DPB*1 expression ($P = 10^{-15}$). Consistent with these gene expression associations, we observed AEI for both rs3077 ($P = 3.0 \times 10^{-7}$; 17 samples) and rs9277535 ($P = 0.001$; 17 samples). The authors conclude that the variants previously associated with chronic hepatitis B are also strongly associated with mRNA expression of *HLA-DPA1* and *HLA-DPB1*, suggesting that expression of these genes is important in control of HBV.

Genes Immun 2011; 12: 428

Eitan Israeli

Capsule

Glutamate release by primary brain tumors induces epileptic activity

Epileptic seizures are a common and poorly understood comorbidity for individuals with primary brain tumors. To investigate peritumoral seizure etiology, Buckingham et al. implanted human-derived glioma cells into severe combined immunodeficient mice. Within 14–18 days glioma-bearing mice developed spontaneous and recurring abnormal electroencephalogram events consistent with progressive epileptic activity. Acute brain slices from these mice showed marked glutamate release from the tumor mediated by the system x_c^- cystine-glutamate transporter (encoded by *Slc7a11*). Biophysical and optical recordings showed glutamatergic epileptiform hyperexcitability that spread into adjacent brain tissue. The authors inhibited glutamate release from the tumor and the ensuing hyperexcitability by sulfasalazine (SAS), a U.S. Food and Drug Authority-approved drug that blocks system x_c^-. We found that acute administration of SAS at concentrations equivalent to those used to treat Crohn's disease in humans reduced epileptic event frequency in tumor-bearing mice compared with untreated controls. SAS should be considered as an adjuvant treatment to ameliorate peritumoral seizures associated with glioma in humans.

Nature Med 2011; 17: 1269

Eitan Israeli

Capsule

Monoclonal antibodies against influenza viruses

An important goal in public health is the development of a universal influenza vaccine. Broadly neutralizing antibodies against group 1 influenza A virus have been described; however, a broadly neutralizing antibody against group 2 viruses has not. Ekiert and team (*Science* 2011; 333: 843) describe the isolation and characterization of a human monoclonal antibody, CR8020, with broadly neutralizing activity against group 2 viruses, which recognizes a region distinct from that recognized by the group 1 antibodies. In a separate study, Corti et al. (p. 850) report the isolation of an antibody from an influenza-infected individual that shows neutralizing activity against both group 1 and group 2 influenza A viruses. The antibody binds to a conserved region in the influenza hemagglutinin. Administration of the antibody protected both mice and ferrets against infection with a group 1 or group 2 influenza A virus.

Eitan Israeli

Capsule

Ebola virus entry requires the cholesterol transporter Niemann-Pick C1

Infections by the Ebola and Marburg filoviruses cause a rapidly fatal hemorrhagic fever in humans for which no approved antivirals are available. Filovirus entry is mediated by the viral spike glycoprotein (GP), which attaches viral particles to the cell surface, delivers them to endosomes and catalyses fusion between viral and endosomal membranes. Additional host factors in the endosomal compartment are probably required for viral membrane fusion; however, despite considerable efforts, these critical host factors have defied molecular identification. Carette et al. describe a genome-wide haploid genetic screen in human cells to identify host factors required for Ebola virus entry. The screen uncovered 67 mutations disrupting all six members of the homotypic fusion and vacuole protein-sorting (HOPS) multisubunit tethering complex, which is involved in the fusion of endosomes to lysosomes, and 39 independent mutations that disrupt the endo/lysosomal cholesterol transporter protein Niemann-Pick C1 (NPC1). Cells defective for the HOPS complex or NPC1 function, including primary fibroblasts derived from human Niemann-Pick type C1 disease patients, are resistant to infection by Ebola virus and Marburg virus, but remain fully susceptible to a suite of unrelated viruses. We show that membrane fusion mediated by filovirus glycoproteins and viral escape from the vesicular compartment require the NPC1 protein, independent of its known function in cholesterol transport. These findings uncover unique features of the entry pathway used by filoviruses and indicate potential antiviral strategies to combat these deadly agents.

Nature 2011; 477: 340

Eitan Israeli

Capsule

Non-invasive not even skin-deep treatment and monitoring

Fixing electronics onto skin typically involves the attachment of bulk electrodes using adhesive tapes, mechanical clamps or straps, or penetrating needles. Kim et al. have designed filamentary serpentine electronic circuits that encompass very thin functional components encased in a flexible polymer that can be attached to the skin by using non-invasive van der Waals contacts. As a result of this technology, components and devices were produced for physiological status monitoring, wound measurement and treatment, human-machine interfaces, and covert communications.

Science 2011; 333: 838

Eitan Israeli

Capsule

A recombinant *Mycobacterium smegmatis* induces potent bactericidal immunity against *Mycobacterium tuberculosis*

Sweeney and colleagues report the involvement of an evolutionarily conserved set of mycobacterial genes, the *esx*-3 region, in evasion of bacterial killing by innate immunity. Whereas high dose intravenous infections of mice with the rapidly growing mycobacterial species *Mycobacterium smegmatis* bearing an intact *esx*-3 locus were rapidly lethal, infection with an *M. smegmatis* Δ*esx*-3 mutant (here designated as the IKE strain) was controlled and cleared by a MyD88-dependent bactericidal immune response. Introduction of the orthologous *Mycobacterium tuberculosis esx*-3 genes into the IKE strain resulted in a strain, designated IKEPLUS, that remained susceptible to innate immune killing and was highly attenuated in mice but had a marked ability to stimulate bactericidal immunity against challenge with virulent *M. tuberculosis*. Analysis of these adaptive immune responses indicated that the highly protective bactericidal immunity elicited by IKEPLUS was dependent on $CD4^+$ memory T cells and involved a distinct shift in the pattern of cytokine responses by $CD4^+$ cells. These results establish a role for the *esx*-3 locus in promoting mycobacterial virulence and also identify the IKE strain as a potentially powerful candidate vaccine vector for eliciting protective immunity to *M. tuberculosis*.

Nature Med 2011; 17: 1261

Eitan Israeli

Capsule

The ubiquitin ligase Peli1 negatively regulates T cell activation and prevents autoimmunity

T cell activation is subject to tight regulation to avoid inappropriate responses to self-antigens. Chang et al. show that genetic deficiency in the ubiquitin ligase Peli1 caused hyperactivation of T cells and rendered T cells refractory to suppression by regulatory T cells and transforming growth factor-β (TGF-β). As a result, Peli1-deficient mice spontaneously developed autoimmunity characterized by multiorgan inflammation and autoantibody production. Peli1 deficiency resulted in the nuclear accumulation of c-Rel, a member of the NF-κB family of transcription factors with pivotal roles in T cell activation. Peli1 negatively regulated c-Rel by mediating its Lys48 (K48) ubiquitination. These results identify Peli1 as a critical factor in the maintenance of peripheral T cell tolerance and demonstrate a previously unknown mechanism of c-Rel regulation.

Nature Immunol 2011; 12: 1002

Eitan Israeli

Capsule

Unraveling neuropathic pain

Neuropathic pain results from nerve damage and is evoked by trauma in conditions ranging from shingles and diabetes to cancer chemotherapy, but the mechanisms remain poorly understood. By using gene knockouts in animal models, Emery et al. found that a member of the HCN ion channel family is important in both inflammatory and neuropathic pain. This discovery opens up the possibility of developing specific antagonists to treat neuropathic pain.

Science 2011; 333: 1462

Eitan Israeli

Capsule

Expression of a mutant HSP110 sensitizes colorectal cancer cells to chemotherapy and improves disease prognosis

Heat shock proteins (HSPs) are necessary for cancer cell survival. Dorard and colleagues identified a mutant of HSP110 (HSP110ΔE9) in colorectal cancer showing microsatellite instability (MSI CRC), generated from an aberrantly spliced mRNA and lacking the HSP110 substrate-binding domain. This mutant was expressed at variable levels in almost all MSI CRC cell lines and primary tumors tested. HSP110ΔE9 impaired both the normal cellular localization of HSP110 and its interaction with other HSPs, thus abrogating the chaperone activity and anti-apoptotic function of HSP110 in a dominant-negative manner. HSP110ΔE9 overexpression caused the sensitization of cells to anticancer agents such as oxaliplatin and 5-fluorouracil, which are routinely prescribed in the adjuvant treatment of people with CRC. The survival and response to chemotherapy of subjects with MSI CRC was associated with the tumor expression level of HSP110ΔE9. HSP110 may thus constitute a major determinant for both prognosis and treatment response in CRC.

Nature Med 2011; 17: 1283

Eitan Israeli

"A decent provision for the poor is the true test of civilization"

Samuel Johnson (1709-1784), British lexicographer