Capsule

Structure of the toxic core of α-synuclein from invisible crystals

The protein α-synuclein is the main component of Lewy bodies, the neuron-associated aggregates seen in Parkinson disease and other neurodegenerative pathologies. An 11-residue segment, termed NACore, appears to be responsible for amyloid formation and cytotoxicity of human α-synuclein. Rodriguez et al. describe crystals of NACore that have dimensions smaller than the wavelength of visible light and thus are invisible by optical microscopy. As the crystals are thousands of times too small for structure determination by synchrotron X-ray diffraction, the authors used micro-electron diffraction to determine the structure at atomic resolution. The 1.4 Å resolution structure demonstrates that this method can determine previously unknown protein structures and yields the highest resolution achieved by any cryo-electron microscopy method to date. The structure exhibits protofibrils built of pairs of face-to-face β-sheets. X-ray fiber diffraction patterns show the similarity of NACore to toxic fibrils of full-length α-synuclein. The NACore structure, together with that of a second segment, inspires a model for most of the ordered portion of the toxic, full-length α-synuclein fibril, presenting opportunities for the design of inhibitors of α-synuclein fibrils.

Nature 2015; 525: 486

Eitan Israeli

Capsule

CTLA-4 as a genetic determinant in autoimmune Addison's disease

In common with several other autoimmune diseases, autoimmune Addison's disease (AAD) is thought to be caused by a combination of deleterious susceptibility polymorphisms in several genes, together with undefined environmental factors and stochastic events. To date, the strongest genomic association with AAD has been with alleles at the HLA locus, DR3–DQ2 and DR4. The contribution of other genetic variants has been inconsistent. Wolff et al. studied the association of 16 single-nucleotide polymorphisms (SNPs) within the CD28–CTLA-4–ICOS genomic locus, in a cohort comprising 691 AAD patients of Norwegian and UK origin with matched controls. The authors also performed a meta-analysis including 1002 patients from European countries. The G-allele of SNP rs231775 in *CTLA-4* is associated with AAD in Norwegian patients (odds ratio 1.35) but not in UK patients. The same allele is associated with AAD in the total European population (OR 1.37). A three-marker haplotype, comprising *PROMOTER_1661*, *rs231726* and *rs1896286*, was found to be associated with AAD in the Norwegian cohort only (OR 2.43). This study points to the *CTLA-4* gene as a susceptibility locus for the development of AAD, and refines its mapping within the wider genomic locus.

Genes Immunity 2015; 16: 430

Eitan Israeli

Capsule

Adaptive servo-ventilation for central sleep apnea in systolic heart failure

Central sleep apnea is associated with poor prognosis and death in patients with heart failure. Adaptive servo-ventilation is a therapy that uses a non-invasive ventilator to treat central sleep apnea by delivering servo-controlled inspiratory pressure support on top of expiratory positive airway pressure. Cowie et al. investigated the effects of adaptive servo-ventilation in patients who had heart failure with reduced ejection fraction and predominantly central sleep apnea. The authors randomly assigned 1325 patients with a left ventricular ejection fraction of 45% or less, an apnea-hypopnea index (AHI) of 15 or more events (occurrences of apnea or hypopnea) per hour, and a predominance of central events to receive guideline-based medical treatment with adaptive servo-ventilation or guideline-based medical treatment alone (control). The primary endpoint in the time-to-event analysis was the first event of death from any cause, life-saving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate life-saving shock), or unplanned hospitalization for worsening heart failure. In the adaptive servo-ventilation group, the mean AHI at 12 months was 6.6 events per hour. The incidence of the primary endpoint did not differ significantly between the adaptive servo-ventilation group and the control group (54.1% and 50.8%, respectively; hazard ratio, 1.13). All-cause mortality and cardiovascular mortality were significantly higher in the adaptive servo-ventilation group than in the control group (hazard ratio for death from any cause 1.28, and hazard ratio for cardiovascular death 1.34).

N Engl J Med 2015; 373: 1095

Eitan Israeli

Capsule

Restraining plasma cells and multiple myeloma

Plasma cells are specialized B cells that secrete antibodies. People with multiple myeloma have too many plasma cells. Mutations in the gene encoding the adaptor TRAF3 are associated with some cases of multiple myeloma. Lin et al. thus characterized mice that lacked TRAF3 in B cells. These mice had more plasma cells, and their B cells were more responsive to interleukin-6 (IL-6), a key cytokine for the development and survival of plasma cells. In normal mouse B cells, TRAF3 promoted the inactivation of a transcription factor downstream of the IL-6 receptor, suggesting that TRAF3 limits plasma cell numbers by inhibiting IL-6 signaling.

Sci Signal 2015; 8: ra88

Eitan Israeli

Capsule

Exercise capacity and muscle strength and risk of vascular disease and arrhythmia in 1.1 million young Swedish men: cohort study

Andersen and colleagues investigated the associations of exercise capacity and muscle strength in late adolescence with risk of vascular disease and arrhythmia. The subjects – 1.1 million men in Sweden in mandatory military conscription between 1 August 1972 and 31 December 1995, at a median age of 18.2 years – were followed until 31 December 2010. During a median follow-up of 26.3 years, 26,088 vascular disease events and 17,312 arrhythmia events were recorded. Exercise capacity was inversely associated with risk of vascular disease and its subgroups. Muscle strength was also inversely associated with vascular disease risk, driven by associations of higher muscle strength with lower risk of heart failure and cardiovascular death. Exercise capacity had a U-shaped association with risk of arrhythmia, driven by a direct association with risk of atrial fibrillation and a U-shaped association with bradyarrhythmia. Higher muscle strength was associated with lower risk of arrhythmia (specifically, lower risk of bradyarrhythmia and ventricular arrhythmia). The combination of high exercise capacity and high muscle strength was associated with a hazard ratio of 0.67 (95% confidence interval 0.65–0.70) for vascular events and 0.92 (0.88–0.97) for arrhythmia compared with the combination of low exercise capacity and low muscle strength.

BMJ 2015; 351: h4543

Eitan Israeli

Capsule

Percutaneous implantation of an entirely intracardiac leadless pacemaker

Cardiac pacemakers are limited by device-related complications, notably infection and problems related to pacemaker leads. Reddy et al. studied a miniaturized, fully self-contained leadless pacemaker that is non-surgically implanted in the right ventricle with the use of a catheter. In this multicenter study, the authors implanted an active-fixation leadless cardiac pacemaker in patients who required permanent single-chamber ventricular pacing. The primary efficacy endpoint was both an acceptable pacing threshold (≤ 2.0 V at 0.4 msec) and an acceptable sensing amplitude (R wave ≥ 5.0 mV, or a value equal to or greater than the value at implantation) for 6 months. The primary safety endpoint was freedom from device-related serious adverse events for 6 months. In this ongoing study, the prespecified analysis of the primary endpoints was performed on data from the first 300 patients who completed 6 months of follow-up (primary cohort). The rates of the efficacy endpoint and safety endpoint were compared with performance goals (based on historical data) of 85% and 86%, respectively. Additional outcomes were assessed in all 526 patients who were enrolled as of June 2015 (the total cohort). The leadless pacemaker was successfully implanted in 504 of the 526 patients in the total cohort (95.8%). The intention-to-treat primary efficacy endpoint was met in 270 of the 300 patients in the primary cohort (90.0%, 95% confidence interval 86.0–93.2, $P = 0.007$), and the primary safety endpoint was met in 280 of the 300 patients (93.3%, 95%CI 89.9–95.9, $P < 0.001$). At 6 months, device-related serious adverse events were observed in 6.7% of the patients; events included device dislodgement with percutaneous retrieval (in 1.7%), cardiac perforation (in 1.3%), and pacing-threshold elevation requiring percutaneous retrieval and device replacement (in 1.3%).

N Engl J Med 2015; 373: 1125

Eitan Israeli

Capsule

Targeting CD38 with daratumumab monotherapy in multiple myeloma

Multiple myeloma cells uniformly over-express CD38. Lokhorst and co-authors studied daratumumab, a CD38-targeting, human IgG1κ monoclonal antibody, in a phase 1–2 trial involving patients with relapsed myeloma or relapsed myeloma that was refractory to two or more prior lines of therapy. In part 1, the dose-escalation phase, the authors administered daratumumab at doses of 0.005 to 24 mg/kg body weight. In part 2, the dose-expansion phase, 30 patients received 8 mg/kg daratumumab and 42 received 16 mg/kg, administered once weekly (8 doses), twice monthly (8 doses), and monthly for up to 24 months. Endpoints included safety, efficacy, and pharmacokinetics. No maximum tolerated dose was identified in part 1. In part 2, the median time since diagnosis was 5.7 years. Patients had received a median of four prior treatments; 79% of the patients had disease that was refractory to the last therapy received (64% had disease refractory to proteasome inhibitors and immunomodulatory drugs and 64% had disease refractory to bortezomib and lenalidomide), and 76% had received autologous stem cell transplants. Infusion-related reactions in part 2 were mild (71% of patients had an event of any grade, and 1% had an event of grade 3), with no dose-dependent adverse events. The most common adverse events of grade 3 or 4 (in ≥ 5% of patients) were pneumonia and thrombocytopenia. The overall response rate was 36% in the cohort that received 16 mg/kg (15 patients had a partial response or better, including 2 with a complete response and 2 with a very good partial response) and 10% in the cohort that received 8 mg/kg (3 had a partial response). In the cohort that received 16 mg/kg, the median progression-free survival was 5.6 months (95% confidence interval 4.2–8.1), and 65% (95%CI 28–86) of the patients who had a response did not have progression at 12 months.

N Engl J Med 2015; 373: 1207

Eitan Israeli

Capsule

CD47 blockade triggers T cell-mediated destruction of immunogenic tumors

Macrophage phagocytosis of tumor cells mediated by CD47-specific blocking antibodies has been proposed to be the major effector mechanism in xenograft models. Using syngeneic immunocompetent mouse tumor models, Liu et al. reveal that the therapeutic effects of CD47 blockade depend on dendritic cell but not macrophage cross-priming of T cell responses. The therapeutic effects of anti-CD47 antibody therapy were abrogated in T cell-deficient mice. In addition, the anti-tumor effects of CD47 blockade required expression of the cytosolic DNA sensor STING, but neither MyD88 nor TRIF, in CD11c+ cells, suggesting that cytosolic sensing of DNA from tumor cells is enhanced by anti-CD47 treatment, further bridging the innate and adaptive responses. Notably, the timing of administration of standard chemotherapy markedly impacted the induction of anti-tumor T cell responses by CD47 blockade. Together, our findings indicate that CD47 blockade drives T cell-mediated elimination of immunogenic tumors.

Nature Med 2015; 21: 1209

Eitan Israeli

Capsule

Randomized trial of reduced-nicotine standards for cigarettes

The Food and Drug Administration can set standards that reduce the nicotine content of cigarettes. Donny and group conducted a double-blind, parallel, randomized clinical trial between June 2013 and July 2014 at 10 sites. Eligibility criteria included age 18 years or older, smoking of five or more cigarettes per day, and no current interest in quitting smoking. Participants were randomly assigned to smoke for 6 weeks either their usual brand of cigarettes or one of six types of investigational cigarettes, provided free. The investigational cigarettes had nicotine content ranging from 15.8 mg/g tobacco (typical of commercial brands) to 0.4 mg/g. The primary outcome was the number of cigarettes smoked per day during week 6. A total of 840 participants underwent randomization, and 780 completed the 6 week study. During week 6, the average number of cigarettes smoked per day was lower for participants randomly assigned to cigarettes containing 2.4, 1.3, or 0.4 mg of nicotine per gram tobacco (16.5, 16.3, and 14.9 cigarettes, respectively) than for participants randomly assigned to their usual brand or to cigarettes containing 15.8 mg/g (22.2 and 21.3 cigarettes, respectively, $P < 0.001$). Participants assigned to cigarettes with 5.2 mg/g smoked an average of 20.8 cigarettes per day, which did not differ significantly from the average number among those who smoked control cigarettes. Cigarettes with lower nicotine content, as compared with control cigarettes, reduced exposure to and dependence on nicotine, as well as craving during abstinence from smoking, without significantly increasing the expired carbon monoxide level or total puff volume, suggesting minimal compensation.

N Engl J Med 2015; 373: 1340

Eitan Israeli

Capsule

Epicardial FSTL1 reconstitution regenerates the adult mammalian heart

The elucidation of factors that activate the regeneration of the adult mammalian heart is of major scientific and therapeutic importance. Wei and co-workers found that epicardial cells contain a potent cardiogenic activity identified as follistatin-like 1 (Fstl1). Epicardial Fstl1 declines following myocardial infarction and is replaced by myocardial expression. Myocardial Fstl1 does not promote regeneration, either basally or upon transgenic over-expression. Application of the human Fstl1 protein (FSTL1) via an epicardial patch stimulates cell cycle entry and division of pre-existing cardiomyocytes, improving cardiac function and survival in mouse and swine models of myocardial infarction. The data suggest that the loss of epicardial FSTL1 is a maladaptive response to injury, and that its restoration would be an effective way to reverse myocardial death and remodeling following myocardial infarction in humans.

Nature 2015; 525: 479

Eitan Israeli

Capsule

Human infection with *Ehrlichia muris*-like pathogen, United States, 2007–2013

An *Ehrlichia muris*-like (EML) pathogen was detected in four patients in Minnesota and Wisconsin in 2009. Johnson et al. characterized additional cases clinically and epidemiologically. During 2004–2013, blood samples from 75,077 patients from all 50 states in the USA were tested by polymerase chain reaction from the *groEL* gene for *Ehrlichia* spp. and *Anaplasma phagocytophilum*. During 2007–2013, samples from 69 patients (0.1%) were positive for the EML pathogen; patients were from five states: Indiana (1), Michigan (1), Minnesota (33), North Dakota (3), and Wisconsin (31). Most patients (64%) were male; median age was 63 years (range 15–94), and all 69 patients reported likely tick exposure in Minnesota or Wisconsin. Fever, malaise, thrombocytopenia and lymphopenia were the most common symptoms. Sixteen patients (23%) were hospitalized (median 4 days); all recovered, and 96% received doxycycline. Infection with the EML pathogen should be considered for persons reporting tick exposure in Minnesota or Wisconsin.

http://wwwnc.cdc.gov/eid/article/21/10/15-0143_article

Eitan Israeli

Capsule

Cardiometabolic risks and severity of obesity in children and young adults

Skiner et al. performed a cross-sectional analysis of data on overweight or obese children and young adults (age 3–19 years) participating in the National Health and Nutrition Examination Survey from 1999 through 2012 to assess the prevalence of multiple cardiometabolic risk factors according to the severity of obesity. Weight status was classified on the basis of measured height and weight. Among 8579 children and young adults with a body mass index at the 85th percentile or higher (according to the Centers for Disease Control and Prevention growth charts), 46.9% were overweight, 36.4% had class I obesity, 11.9% class II obesity, and 4.8% class III obesity. Mean values for some, but not all, cardiometabolic variables were higher with greater severity of obesity in both male and female participants, and higher values in male than female participants; for HDL-cholesterol, the mean values were lower with greater severity of obesity. Multivariable models that controlled for age, race or ethnic group, and gender showed that the greater the severity of obesity the higher the risks of a low HDL-cholesterol level, high systolic and diastolic blood pressures, and high triglyceride and glycated hemoglobin levels.

N Engl J Med 2015; 373: 1307

Eitan Israeli

Capsule

Function of the nucleus accumbens in motor control during recovery after spinal cord injury

Motivation facilitates recovery after neuronal damage, but its mechanism is elusive. It is generally thought that the nucleus accumbens (NAc) regulates motivation-driven effort but is not involved in the direct control of movement. Using causality analysis, Sawada et al. identified the flow of activity from the NAc to the sensorimotor cortex (SMC) during the recovery of dexterous finger movements after spinal cord injury at the cervical level in macaque monkeys. Furthermore, reversible pharmacological inactivation of the NAc during the early recovery period diminished high frequency oscillatory activity in the SMC, which was accompanied by a transient deficit of amelioration in finger dexterity obtained by rehabilitation. These results demonstrate that during recovery after spinal damage, the NAc up-regulates the high frequency activity of the SMC and is directly involved in the control of finger movements.

Science 2015; 350: 98

Eitan Israeli

Capsule

Anticoagulant "morfs" into pneumonia therapy

Pneumonia can cause lung cell death, yet the mechanisms by which infection reduces cell viability are unclear. Zou et al. found that a poorly described protein, Morf4l1, triggers cell death in mice with pneumonia. The half-life of Morf4l1 – normally a short-lived protein – was increased in the context of pneumonia. The anticoagulant drug argatroban blocked half-life extension as well as the injurious actions of Morf4l1, thus prolonging the survival of mice with experimental pneumonia.

Sci Transl Med 2015; 7: 311ra171

Eitan Israeli

Capsule

Patching up the injured heart

During a heart attack, heart muscle is deprived of oxygen and nutrients and dies as a result. Because heart muscle cells, or cardiomyocytes, have a limited capacity to divide, this damage is often permanent. Wei and colleagues describe an intervention that may help minimize the damage. Working with mice, they applied a collagen patch containing a protein called follistatin-like 1 to the heart immediately after a heart attack. Four weeks later, they saw signs of cardiomyocyte division, new blood vessel growth, and reduced scarring, which are consistent with heart muscle regeneration. Mysteriously, follistatin-like 1 has this beneficial activity only when it is synthesized by cells in the epicardium (a membrane layer surrounding the heart); myocardial-derived follistatin-like 1 was inactive.

Nature 2015; 525: 479

Eitan Israeli

Capsule

Therapeutic clearance of amyloid by antibodies to serum amyloid P component

The amyloid fibril deposits that cause systemic amyloidosis always contain the non-fibrillar normal plasma protein, serum amyloid P component (SAP). The drug (R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid (CPHPC) efficiently depletes SAP from the plasma but leaves some SAP in amyloid deposits that can be specifically targeted by therapeutic IgG anti-SAP antibodies. In murine amyloid A type amyloidosis, the binding of these antibodies to the residual SAP in amyloid deposits activates complement and triggers the rapid clearance of amyloid by macrophage-derived multinucleated giant cells. Richards et al. conducted an open-label, single-dose-escalation, phase 1 trial involving 15 patients with systemic amyloidosis. After first using CPHPC to deplete circulating SAP, the authors infused a fully humanized monoclonal IgG1 anti-SAP antibody. Patients with clinical evidence of cardiac involvement were not included for safety reasons. Organ function, inflammatory markers, and amyloid load were monitored. There were no serious adverse events. Infusion reactions occurred in some of the initial recipients of larger doses of antibody; reactions were reduced by slowing the infusion rate for later patients. At 6 weeks, patients who had received a sufficient dose of antibody in relation to their amyloid load had decreased liver stiffness, as measured by transient elastography. These patients also had improvements in liver function in association with a substantial reduction in hepatic amyloid load, as shown by SAP scintigraphy and measurement of extracellular volume by magnetic resonance imaging. A reduction in kidney amyloid load and shrinkage of an amyloid-laden lymph node were also observed.

N Engl J Med 2015; 373: 1106

Eitan Israeli

Capsule

Three antibiotics to fight MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a worldwide threat to human health, because it is resistant to a large class of β-lactams (penicillins) and to second-generation penicillins, including methicillin. However, Gonzales et al. report that combining different classes and generations of these drugs could be effective in fighting MRSA. A 1:1:1 mix of three compounds – a β-lactam, a carbapenem, and a β-lactamase inhibitor – synergistically targeted bacterial cell wall synthesis and was bactericidal against 73 different clinical isolates of MRSA. The drug combination prevented MRSA from acquiring resistance to the mix and cleared infection in a mouse model of lethal MRSA. The finding opens the prospect of using already clinically approved drugs to treat multidrug-resistant infections.

Nat Chem Biol 2015; 10.1038/nchembio.1911

Eitan Israeli

Capsule

Control of peripheral tolerance by regulatory T cell-intrinsic Notch signaling

Receptors of the Notch family direct the differentiation of helper T cell subsets, but their influence on regulatory T cell (T_{reg} cell) responses is obscure. Charbonnier et al. found that lineage-specific deletion of components of the Notch pathway enhanced T_{reg} cell–mediated suppression of type 1 helper T cell (TH1 cell) responses and protected against their TH1 skewing and apoptosis. In contrast, expression in T_{reg} cells of a gain-of-function transgene encoding the Notch1 intracellular domain resulted in lymphoproliferation, exacerbated TH1 responses and autoimmunity. Cell-intrinsic canonical Notch signaling impaired T_{reg} cell fitness and promoted the acquisition by T_{reg} cells of a TH1 cell-like phenotype, whereas non-canonical Notch signaling dependent on the adaptor Rictor activated the kinase AKT-transcription factor Foxo1 axis and impaired the epigenetic stability of Foxp3. These findings establish a critical role for Notch signaling in controlling peripheral T_{reg} cell function.

Nature Immunol 2015; 16: 1162

Eitan Israeli

Capsule

Efficacy and long-term safety of a dengue vaccine in regions of endemic disease

A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian Pacific and Latin American countries. Hadinegoro et al. report the results of long-term follow-up interim analyses and integrated efficacy analyses. The authors are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety endpoint during follow-up in years 3–6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. They estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15. Follow-up data were available for 10,165 of 10,275 participants (99%) in CYD14 and 19,898 of 20,869 participants (95%) in CYD15. Data were available for 3203 of the 4002 participants (80%) in the CYD23 trial included in CYD57. During year 3 in the CYD14, CYD15, and CYD57 trials combined, hospitalization for virologically confirmed dengue occurred in 65 of 22,177 participants in the vaccine group and 39 of 11,089 participants in the control group. Pooled relative risks of hospitalization for dengue were 0.84 among all participants, 1.58 among those ‹ 9 years old, and 0.50 among those ≥ 9 years. During year 3, hospitalization for severe dengue, as defined by the independent data monitoring committee criteria, occurred in 18 of 22,177 participants in the vaccine group and 6 of 11,089 participants in the control group. Pooled rates of efficacy for symptomatic dengue during the first 25 months were 60.3% for all participants, 65.6% for those ≥ 9 years, and 44.6% for those ‹ 9 years old. Although the unexplained higher incidence of hospitalization for dengue in year 3 among children ‹ 9 years of age needs to be carefully monitored during long-term follow-up, the risk among children 2–16 years old was lower in the vaccine group than in the control group.

N Engl J Med 2015; 373: 1195

Eitan Israeli

Capsule

Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits

Tauopathies, including frontotemporal dementia (FTD) and Alzheimer's disease (AD), are neurodegenerative diseases in which tau fibrils accumulate. Recent evidence supports soluble tau species as the major toxic species. How soluble tau accumulates and causes neurodegeneration remains unclear. Min and co-researchers identify tau acetylation at Lys174 (K174) as an early change in AD brains and a critical determinant in tau homeostasis and toxicity in mice. The acetyl-mimicking mutant K174Q slows tau turnover and induces cognitive deficits in vivo. Acetyltransferase p300-induced tau acetylation is inhibited by salsalate and salicylate, which enhance tau turnover and reduce tau levels. In the PS19 transgenic mouse model of FTD, administration of salsalate after disease onset inhibited p300 activity, lowered levels of total tau and tau acetylated at K174, rescued tau-induced memory deficits and prevented hippocampal atrophy. The tau-lowering and protective effects of salsalate were diminished in neurons expressing K174Q tau. Targeting tau acetylation could be a new therapeutic strategy against human tauopathies.

Nature Med 2015; 21: 1154

Eitan Israeli

Capsule

Virome analysis of transfusion recipients: novel human virus sharing genomic features with hepaciviruses and pegiviruses

To investigate the transmission of novel infectious agents by blood transfusion, Kappor et al. studied changes in the virome composition of blood transfusion recipients pre- and post-transfusion. Using this approach, they detected and genetically characterized a novel human virus, human hepegivirus 1 (HHpgV-1), that shares features with hepatitis C virus (HCV) and human pegivirus (HPgV; formerly called GB virus C or hepatitis G virus). HCV and HPgV belong to the genera Hepacivirus and Pegivirus of the family *Flaviviridae*. HHpgV-1 was found in serum samples from two blood transfusion recipients and two hemophilia patients who had received plasma-derived clotting factor concentrates. In the former, the virus was detected only in the post-transfusion samples, indicating blood-borne transmission. Both hemophiliacs were persistently viremic over periods of at least 201 and 1981 days. Phylogenetic analysis of non-structural genes (*NS3* and *NS5B*) showed that HHpgV-1 forms a branch within the pegivirus clade distinct from HPgV and homologs infecting other mammalian species. In common with some pegivirus variants infecting rodents and bats, the HHpgV-1 genome encodes a short, highly basic protein upstream of E1, potentially possessing a core-like function in packaging RNA during assembly. Identification of this new human virus, HHpgV-1, expands our knowledge of the range of genome configurations of these viruses and may lead to a reevaluation of the original criteria by which the genera Hepacivirus and Pegivirus are defined.

mBio 6(5):e01466-15. doi:10.1128/mBio.01466-15

Eitan Israeli

Capsule

Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence

Noury et al. re-analyzed SmithKline Beecham's Study 329 (published by Keller and colleagues in 2001), the primary objective of which was to compare the efficacy and safety of paroxetine and imipramine with placebo in the treatment of adolescents with unipolar major depression. The re-analysis under the restoring invisible and abandoned trials (RIAT) initiative was performed to determine whether access to and re-analysis of a full dataset from a randomized controlled trial would have clinically relevant implications for evidence-based medicine. The study, a double-blind randomized placebo-controlled trial, was conducted in 12 North American academic psychiatry centers from 20 April 1994 to 15 February 1998. The participants were 275 adolescents with major depression of at least 8 weeks duration. Exclusion criteria included a range of comorbid psychiatric and medical disorders and suicidality. Participants were randomized to 8 weeks double-blind treatment with paroxetine (20–40 mg), imipramine (200–300 mg), or placebo. The efficacy of paroxetine and imipramine was not statistically or clinically significantly different from placebo for any pre-specified primary or secondary efficacy outcome. HAM-D scores decreased by 10.7 (least squares mean) (95% confidence interval 9.1–12.3), 9.0 (7.4–10.5) and 9.1 (7.5–10.7) points, respectively, for the paroxetine, imipramine and placebo groups (P = 0.20). There were clinically significant increases in harms, including suicidal ideation and behavior and other serious adverse events in the paroxetine group and cardiovascular problems in the imipramine group. The authors concluded that neither paroxetine nor high dose imipramine showed efficacy for major depression in adolescents, and there was an increase in harms with both drugs. Access to primary data from trials has important implications for both clinical practice and research, including that published conclusions about efficacy and safety should not be read as authoritative. The re-analysis of Study 329 illustrates the necessity to make primary trial data and protocols available to increase the rigor of the evidence base.

BMJ 2015; 351: h4320

Eitan Israeli

Capsule

A close up view of retrovirus spreading

Viral infections typically begin with a small number of viral particles gaining access to the host at a specific tissue site. But how do viruses that cause systemic infections, such as HIV, spread more widely? Sewald et al. visualized how the retroviruses murine leukemia virus (MLV) and HIV spread within lymph nodes in mice. Specific macrophages that line the lymph-draining sinuses in lymph nodes first captured the virus using the carbohydrate-binding protein CD169. These macrophages subsequently transferred virus to the B1 subclass of B lymphocytes, which migrated further into the lymph node, disseminating the virus more widely.

Science 2015; 350: 563

Eitan Israeli