Capsule

Making aggregation of alpha-synuclein less aggravating

The accumulation of α-synuclein aggregates occurs in certain neurodegenerative disorders, including Parkinson's disease. Daniele and co-scientists found that α-synuclein aggregates activated the receptor complex TLR1/2 on primary mouse microglia, leading to the production of pro-inflammatory cytokines. TLR1/2 antagonists, including a drug approved for treating hypertension, prevented the activation of microglia and cytokine secretion in response to aggregated α-synuclein. Thus, repurposing of drugs that also inhibit TLR1/2 may be beneficial for patients with synucleinopathies.

Sci Signal 2015; 8: ra45

Eitan Israeli

Capsule

Sleeping while awake

Sleep deprivation affects our behavior and performance. Bernardi and co-workers demonstrate the connection between task-specific performance decrease and local sleep in relevant parts of the human brain. During 24 hours of wakefulness, individuals participated in driving simulations and executive function exercises. Their task-related abilities, such as visuo-motor control and response inhibition, were tested alongside electroencephalography (EEG) recordings and functional magnetic resonance imaging (fMRI). Local EEG theta waves, normally observed during sleep, coincided with times of slower movements, visual inaccuracies, and decreased impulse control. The fMRI scans exposed cognitive fatigue in the form of regional neuronal disconnections in the task-relevant brain areas in addition to the general deficiencies.

J Neurosci 2015; 35: 4487

Eitan Israeli

Capsule

Active Pin1 is a key target of all-*trans* retinoic acid in acute promyelocytic leukemia and breast cancer

A common key regulator of oncogenic signaling pathways in multiple tumor types is the unique isomerase Pin1. However, available Pin1 inhibitors lack the required specificity and potency for inhibiting Pin1 function in vivo. By using mechanism-based screening, Wei et al. find that all-*trans* retinoic acid (ATRA) – a therapy for acute promyelocytic leukemia (APL) that is considered the first example of targeted therapy in cancer, but whose drug target remains elusive – inhibits and degrades active Pin1 selectively in cancer cells by directly binding to the substrate phosphate- and proline-binding pockets in the Pin1 active site. ATRA-induced Pin1 ablation degrades the protein encoded by the fusion oncogene *PML–RARA* and treats APL in APL cell and animal models as well as in human patients. ATRA-induced Pin1 ablation also potently inhibits triple-negative breast cancer cell growth in human cells and in animal models by acting on many Pin1 substrate oncogenes and tumor suppressors. Thus, ATRA simultaneously blocks multiple Pin1-regulated cancer-driving pathways, an attractive property for treating aggressive and drug-resistant tumors.

Nature Med 2015; 21: 45

Eitan Israeli

Capsule

Inhibition and reversal of microbial attachment by an antibody with parasteric activity against the FimH adhesin of uropathogenic *E. coli*

Attachment proteins from the surface of eukaryotic cells, bacteria and viruses are critical receptors in cell adhesion or signaling and are primary targets for the development of vaccines and therapeutic antibodies. It is proposed that the ligand-binding pocket in receptor proteins can shift between inactive and active conformations with weak and strong ligand-binding capability, respectively. Using monoclonal antibodies against a vaccine target protein, fimbrial adhesin FimH of uropathogenic *Escherichia coli*, Kisiela et al. demonstrate that unusually strong receptor inhibition can be achieved by an antibody that binds within the binding pocket and displaces the ligand in a non-competitive way. The non-competitive antibody binds to a loop that interacts with the ligand in the active conformation of the pocket but is shifted away from ligand in the inactive conformation. The authors refer to this as a parasteric inhibition, where the inhibitor binds adjacent to the ligand in the binding pocket. They showed that the receptor-blocking mechanism of parasteric antibody differs from that of orthosteric inhibition where the inhibitor replaces the ligand, or allosteric inhibition where the inhibitor binds at a site distant from the ligand, and is very potent in blocking bacterial adhesion, dissolving surface-adherent biofilms and protecting mice from urinary bladder infection.

PLoS Path 2015; DOI: 10.1371/journal.ppat.1004857

Eitan Israeli

Capsule

Sequential cancer mutations in cultured human intestinal stem cells

Crypt stem cells represent the cells of origin for intestinal neoplasia. Both mouse and human intestinal stem cells can be cultured in medium containing the stem-cell-niche factors WNT, R-spondin, epidermal growth factor (EGF) and noggin over long time periods as epithelial organoids that remain genetically and phenotypically stable. Drost et al. utilized CRISPR/Cas9 technology for targeted gene modification of four of the most commonly mutated colorectal cancer genes – APC, P53 (also known as TP53), KRAS and SMAD4 – in cultured human intestinal stem cells. Mutant organoids can be selected by removing individual growth factors from the culture medium. Quadruple mutants grow independently of all stem-cell-niche factors and tolerate the presence of the P53 stabilizer nutlin-3. Upon xenotransplantation into mice, quadruple mutants grow as tumors with features of invasive carcinoma. Finally, combined loss of APC and P53 is sufficient for the appearance of extensive aneuploidy, a hallmark of tumor progression.

Nature 2015; 521: 43

Eitan Israeli

Capsule

Fibroblasts create a safe haven from drugs for tumor cells

Melanomas with certain mutations often respond dramatically to drugs inhibiting a protein kinase called BRAF. This is because BRAF is part of a signaling pathway that, when mutationally activated, drives melanoma growth. Unfortunately, the response is often short-lived because tumor cells develop resistance to the drugs. Hirata et al. made the surprising observation that melanoma cells do not acquire resistance to BRAF inhibition on their own but rather receive help from neighboring fibroblasts. BRAF inhibitors cause fibroblasts to remodel the extracellular matrix. Signals from the remodeled matrix then reactivate the growth signaling pathway in the melanoma cells. Thus, the tumor microenvironment can provide a safe haven for tumor cells that allows them to tolerate certain drugs.

Cancer Cell 2015; 27: 574

Eitan Israeli

Capsule

The microRNA-200 family regulates pancreatic beta cell survival in type 2 diabetes

Pancreatic beta cell death is a hallmark of type 1 (T1D) and type 2 (T2D) diabetes, but the molecular mechanisms underlying this aspect of diabetic pathology are poorly understood. Belgardt et al. report that expression of the microRNA (miR)-200 family is strongly induced in islets of diabetic mice and that beta cell-specific overexpression of miR-200 in mice is sufficient to induce beta cell apoptosis and lethal T2D. Conversely, mir-200 ablation in mice reduces beta cell apoptosis and ameliorates T2D. The authors show that miR-200 negatively regulates a conserved anti-apoptotic and stress-resistance network that includes the essential beta cell chaperone Dnajc3 (also known as p58IPK) and the caspase inhibitor Xiap. They also observed that mir-200 dosage positively controls activation of the tumor suppressor Trp53 and thereby creates a pro-apoptotic gene expression signature found in islets of diabetic mice. Consequently, miR-200-induced T2D is suppressed by interfering with the signaling of Trp53 and Bax, a pro-apoptotic member of the B cell lymphoma 2 protein family. These results reveal a crucial role for the miR-200 family in beta cell survival and the pathophysiology of diabetes.

Nature Med 2015; 21: 619

Eitan Israeli

Capsule

Trial of short-course antimicrobial therapy for intraabdominal infection

The successful treatment of intraabdominal infection requires a combination of anatomical source control and antibiotics. The appropriate duration of antimicrobial therapy remains unclear. Sawyer et al. randomly assigned 518 patients with complicated intraabdominal infection and adequate source control to receive antibiotics until 2 days after the resolution of fever, leukocytosis, and ileus, with a maximum of 10 days of therapy (control group), or to receive a fixed course of antibiotics (experimental group) for 4 ± 1 calendar days. The primary outcome was a composite of surgical site infection, recurrent intraabdominal infection, or death within 30 days after the index source-control procedure, according to treatment group. Secondary outcomes included the duration of therapy and rates of subsequent infections. Surgical site infection, recurrent intraabdominal infection, or death occurred in 56 of 257 patients in the experimental group (21.8%), as compared to 58 of 260 patients in the control group (22.3%). The median duration of antibiotic therapy was 4.0 days (interquartile range 4.0 –5.0) in the experimental group, as compared with 8.0 days (interquartile range 5.0–10.0) in the control group (absolute difference -4.0 days). No significant between-group differences were found in the individual rates of the components of the primary outcome or in other secondary outcomes.

N Engl J Med 2015; 372: 1996

Eitan Israeli

Capsule

Impact of chronic systemic inflammation such as rheumatoid arthritis on mortality following cancer

Emerging evidence links inflammation and immune competence to cancer progression and outcome. Few studies addressing cancer survival in the context of rheumatoid arthritis (RA) have reported reduced survival without accounting for the underlying mortality risk in RA. Whether this increased mortality is a cancer-specific phenomenon, an effect of the decreased lifespan in RA, or a combination of both remains unknown. Using Swedish register data (2001–2009), Simard et al. performed a cohort study of individuals with RA (N=34,930), matched to general population comparators (N=169,740), incident cancers (N=12,676) and deaths (N=14,291). Using stratified Cox models, the authors estimated the hazard ratio (HR) of death associated with RA in the presence and absence of cancer, by stage and time since cancer diagnosis, for all cancers and specific sites. In the absence of cancer, RA was associated with a doubled mortality rate (HR 2.1, 95% CI 2.0–2.2). In the presence of cancer, the relative effect of RA on mortality was varied by stage. For cancer (tumor, node, metastases) stages I and II at diagnosis, the relative effect of RA on mortality was the same as in the absence of cancer. For cancers diagnosed at advanced stages with absolute higher mortality, the effect decreased (HR 1.2, 95% CI 1.1–1.3). These associations remained across time since cancer diagnosis and were reasonably similar across cancer sites.

Ann Rheum Dis 2014; doi:10.1136

Eitan Israeli

Capsule

Inhibiting Hippo to mend broken hearts

Activation of the Hippo signaling pathway prevents organ overgrowth. The pathway inhibits the activity of the transcriptional coactivator Yap, which is important during development. However, this same activity limits the ability of some organs to regenerate after injury. Morikawa et al. found that Yap target genes not only included cell cycle genes but also genes encoding cytoskeletal remodeling proteins or proteins that link the cytoskeleton to the extracellular matrix. Cardiomyocytes from Hippo signaling-deficient mice formed cellular protrusions typical of migrating cells and more readily moved toward scar sites after cardiac injury. Thus, inhibiting the Hippo pathway could help with heart regeneration.

Sci Signal 2015; 8: ra41

Eitan Israeli

Capsule

Lung imaging for better TB treatments

Tuberculosis treatments typically take 6 months to complete. Although the success rate is high for full treatment, many patients do not complete the treatment course. Attempts to develop drugs with shorter treatment times have not been successful. Barry highlights the role that recent imaging advances can play in assessing the success of drug candidates. For example, serial computed tomography imaging can be used to map the lung at millimeter resolution and monitor changes in particular lung regions in response to treatment. This and other imaging methods have the potential to improve the quality of clinical trials by defining quantitative target outcomes.

Science 2015; 348: 633

Eitan Israeli

Capsule

A way to dissect malaria's secrets

Malaria has exerted a strong selective force on the human genome. However, efforts to identify host susceptibility factors have been hindered by the absence of a nucleus in red blood cells. Egan et al. developed an approach involving blood stem cells to discover host factors critical for *Plasmodium falciparum* infection of red blood cells. The authors identified an essential host receptor for parasite invasion that could provide a target for malaria therapeutics.

Science 2015; 348: 711

Eitan Israeli

Capsule

Studying clonal dynamics in response to cancer therapy using high complexity barcoding

Resistance to cancer therapies presents a significant clinical challenge. Recent studies have revealed intratumoral heterogeneity as a source of therapeutic resistance. However, it is unclear whether resistance is driven predominantly by preexisting or de novo alterations, in part because of the resolution limits of next-generation sequencing. To address this, Bhang et al. developed a high complexity barcode library, ClonTracer, which enables the high resolution tracking of more than 1 million cancer cells under drug treatment. In two clinically relevant models, ClonTracer studies showed that the majority of resistant clones were part of small, preexisting subpopulations that selectively escaped under therapeutic challenge. Moreover, the ClonTracer approach enabled quantitative assessment of the ability of combination treatments to suppress resistant clones. These findings suggest that resistant clones are present before treatment, which would make up-front therapeutic combinations that target non-overlapping resistance a preferred approach. Thus, ClonTracer barcoding may be a valuable tool for optimizing therapeutic regimens with the goal of curative combination therapies for cancer.

Nature Med 2014; 21: 440

Eitan Israeli

Capsule

Nanoformulation keeps vein grafts healthy

The MK2i peptide is now in clinical trials aimed at halting inflammation and fibrosis after vein grafting. However, low bioavailability and rapid degradation have slowed MK2i's clinical translation. Evans et al. formulated the MK2i peptide in electrostatically complexed nanoparticles. The resulting MK2i-nanopolyplexes entered both vascular smooth muscle and endothelial cells in human veins. Their delivery reduced pro-inflammatory cytokine levels, vascular smooth muscle cell migration, and neointima formation (i.e., vessel thickening). In rabbit vein grafts, treatment with MK2i-nanopolyplexes, but not free MK2i, prevented intimal hyperplasia for 1 month after transplant. Thus, nanopolyplexes might improve the utility of vein grafts in the longer term.

Sci Transl Med 2015; 7: 291ra95

Eitan Israeli

Capsule

The transcription factor GABP selectively binds and activates the mutant TERT promoter in cancer

Reactivation of telomerase reverse transcriptase (TERT) expression enables cells to overcome replicative senescence and escape apoptosis, which are fundamental steps in the initiation of human cancer. Multiple cancer types, including up to 83% of glioblastomas (GBMs), harbor highly recurrent TERT promoter mutations of unknown function but specific to two nucleotide positions. Bell et al. identified the functional consequence of these mutations in GBMs to be recruitment of the multimeric GA-binding protein (GABP) transcription factor specifically to the mutant promoter. Allelic recruitment of GABP is consistently observed across four cancer types, highlighting a shared mechanism underlying TERT reactivation. Tandem flanking native E26 transformation-specific motifs critically cooperate with these mutations to activate TERT, probably by facilitating GABP heterotetramer binding. GABP thus directly links TERT promoter mutations to aberrant expression in multiple cancers.

Science 2015; 348: 1036

Eitan Israeli

Capsule

Temperate and lytic bacteriophages programmed to sensitize and kill antibiotic-resistant bacteria

The increasing threat of pathogen resistance to antibiotics requires the development of novel antimicrobial strategies. Yosef et al. present a proof of concept for a genetic strategy that aims to sensitize bacteria to antibiotics and selectively kill antibiotic-resistant bacteria. The author used temperate phages to deliver a functional clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated (Cas) system into the genome of antibiotic-resistant bacteria. The delivered CRISPR-Cas system destroys both antibiotic resistance-conferring plasmids and genetically modified lytic phages. This linkage between antibiotic sensitization and protection from lytic phages is a key feature of the strategy. It allows programming of lytic phages to kill only antibiotic-resistant bacteria while protecting antibiotic-sensitized bacteria. Phages designed according to this strategy may be used on hospital surfaces and hand sanitizers to facilitate replacement of antibiotic-resistant pathogens with sensitive ones.

Proc Natl Assoc Sci USA 2015; doi: 10.1073/pnas.1500107112

Eitan Israeli

Capsule

Mechanisms of clonal evolution in childhood acute lymphoblastic leukemia

Childhood acute lymphoblastic leukemia (ALL) can often be traced to a preleukemic clone carrying a prenatal genetic lesion. Postnatally acquired mutations then drive clonal evolution toward overt leukemia. The enzymes RAG1-RAG2 and AID, which diversify immunoglobulin-encoding genes, are strictly segregated in developing cells during B lymphopoiesis and peripheral mature B cells, respectively. Swaminathan et al. identified small pre-BII cells as a natural subset with increased genetic vulnerability owing to concurrent activation of these enzymes. Consistent with epidemiological findings on childhood ALL etiology, susceptibility to genetic lesions during B lymphopoiesis at the transition from the large pre-BII cell stage to the small pre-BII cell stage was exacerbated by abnormal cytokine signaling and repetitive inflammatory stimuli. The authors demonstrated that AID and RAG1-RAG2 drove leukemic clonal evolution with repeated exposure to inflammatory stimuli, paralleling chronic infections in childhood. The authors also suggest that early age vaccinations against infectious diseases mitigate this path to malignancy driven by these enzymes, and as an example they mention HinfB vaccination which reduced ALL in 5–7 year old children by 20%.

Nature Immunol 2015: doi:10.1038/ni.3160

Eitan Israeli

Capsule

A gene therapy approach for diabetes

Gene therapy is being used with increasing success to treat a growing group of diseases. Akbarpour et al. used a lentiviral vector to express insulin in liver cells of a mouse model of type 1 diabetes. The therapy induced regulatory T cells specific for insulin and halted immune cell infiltration into the pancreatic islets. Moreover, when gene therapy was combined with a single dose of monoclonal antibody to CD3, it stopped disease progression in diabetic mice. Thus, expressing an autoantigen in liver cells can induce antigen-specific tolerance in autoimmune disease.

Sci Transl Med 2015; 7: 289ra81

Eitan Israeli

Capsule

Seeing stress signaling in living mice

Stress activates the eIF2α-ATF4 pathway to reduce global protein production while enhancing targeted gene expression, which helps cells adapt and survive. Activation of this pathway is associated with various pathologies, such as tissue fibrosis after injury. Chaveroux et al. developed transgenic mice in which the activation of this pathway could be monitored at the whole-animal level and at the tissue and cellular level. Activation was tissue-specific, depending on the initiating stress. Chemically induced liver fibrosis correlated with activation of the eIF2α-ATF4 pathway by a specific kinase.

Sci Signal 2015; 8: rs5

Eitan Israeli

Capsule

Rethinking the role of reactive T cells

In patients with multiple sclerosis (MS), damage to the nerve-insulating myelin sheath blocks the ability of neurons to conduct messages. Although the injury is thought to be caused by the body's own immune system, myelin-restricted immune cells exist in comparable numbers in MS patients and healthy controls. Cao and co-workers now report functional differences between myelin-reactive T cells from MS patients (which are pro-inflammatory) and those in healthy controls (which secrete more of the immunoregulatory cytokine interleukin-10). Thus, functional divergence in selected immune cells may contribute to disease development.

Sci Transl Med 2015; 7: 287ra74

Eitan Israeli

Capsule

Signaling at the heart of blood pressure regulation

Genetic variants, detected in large genome-wide association studies (GWAS) of blood pressure regulation in humans, account for only about 1% of the variability observed between individuals. Thus, better understanding of complex regulatory networks is necessary to find causal events and potential therapeutic targets. Huan and group used integrative analysis that included transcriptional profiling and co-expression network analysis, GWAS, and molecular network modeling to tease out "key driver" genes that are central to regulatory modules that control blood pressure. One of these was SH2B3, a cell signaling adaptor protein previously detected in GWAS studies. The analysis further suggested that SH2B3 may function by altering inflammatory responses and T cell functions.

Mol Syst Biol 2015; 10.15252/msb.20145399

Eitan Israeli

Capsule

Skirting quality control to treat cystic fibrosis

Patients with cystic fibrosis (CF) have fluid and mucus buildup in their lungs because of mutations that cause misfolding, intracellular retention, and degradation of the cystic fibrosis transmembrane conductance regulator (CFTR). Although drugs can improve the cell surface delivery of mutant CFTR proteins, which are usually partially functional, cells still degrade the mutant CFTR. Loureiro and co-scientists found that increasing the interaction between the scaffold protein NHERF1 and mutant CFTR prevented mutant CFTR from being marked for degradation. These manipulations increased the levels of partially functional CFTR on the surface of cultured lung epithelial cells from CF patients.

Sci Signal 2015; 8: ra48

Eitan Israeli

Capsule

Metabolic regulation of hepatitis B immunopathology by myeloid-derived suppressor cells

Infection with hepatitis B virus (HBV) results in disparate degrees of tissue injury: the virus can either replicate without pathological consequences or trigger immune-mediated necroinflammatory liver damage. Pallett et al. investigated the potential for myeloid-derived suppressor cells (MDSCs) to suppress T cell-mediated immunopathology in this setting. Granulocytic MDSCs (gMDSCs) expanded transiently in acute resolving HBV, decreasing in frequency prior to peak hepatic injury. In persistent infection, arginase-expressing gMDSCs (and circulating arginase) increased most in disease phases characterized by HBV replication without immunopathology, while L-arginine decreased. gMDSCs expressed liver-homing chemokine receptors and accumulated in the liver, their expansion supported by hepatic stellate cells. The authors provide in vitro and ex vivo evidence that gMDSCs potently inhibited T cells in a partially arginase-dependent manner. L-arginine-deprived T cells upregulated system L amino acid transporters to increase uptake of essential nutrients and attempt metabolic reprogramming. These data demonstrate the capacity of expanded arginase-expressing gMDSCs to regulate liver immunopathology in HBV infection.

Nature Med 2015; 21: 591

Eitan Israeli

Capsule

Irf5 deficiency in macrophages promotes beneficial adipose tissue expansion and insulin sensitivity during obesity

Accumulation of visceral adipose tissue correlates with elevated inflammation and increased risk of metabolic diseases. However, little is known about the molecular mechanisms that control its pathological expansion. Transcription factor interferon regulatory factor 5 (IRF5) has been implicated in polarizing macrophages towards an inflammatory phenotype. Dalmas et al. demonstrate that mice lacking Irf5, when placed on a high fat diet, show no difference in the growth of their epididymal white adipose tissue (epiWAT) but they show expansion of their subcutaneous white adipose tissue, as compared to wild-type (WT) mice on the same diet. EpiWAT from Irf5-deficient mice is marked by accumulation of alternatively activated macrophages, higher collagen deposition that restricts adipocyte size, and enhanced insulin sensitivity compared to epiWAT from WT mice. In obese individuals, IRF5 expression is negatively associated with insulin sensitivity and collagen deposition in visceral adipose tissue. Genome-wide analysis of gene expression in adipose tissue macrophages highlights the transforming growth factor β1 (TGFB1) gene itself as a direct target of IRF5-mediated inhibition. This study uncovers a new function for IRF5 in controlling the relative mass of different adipose tissue depots and thus insulin sensitivity in obesity, and it suggests that inhibition of IRF5 may promote a healthy metabolic state during this condition.

Nature Med 2015; 21: 610

Eitan Israeli

Capsule

The cyclophilin A-CD147 complex promotes the proliferation and homing of multiple myeloma cells

B cell malignancies frequently colonize the bone marrow. The mechanisms responsible for this preferential homing are incompletely understood. Zhu et al. studied multiple myeloma (MM) as a model of a terminally differentiated B cell malignancy that selectively colonizes the bone marrow. The authors found that extracellular CyPA (eCyPA), secreted by bone marrow endothelial cells (BMECs), promoted the colonization and proliferation of MM cells in an in vivo scaffold system via binding to its receptor, CD147, on MM cells. The expression and secretion of eCyPA by BMECs was enhanced by BCL9, a Wnt-β-catenin transcriptional coactivator that is selectively expressed by these cells. eCyPA levels were higher in bone marrow serum than in peripheral blood in individuals with MM, and eCyPA-CD147 blockade suppressed MM colonization and tumor growth in the in vivo scaffold system. eCyPA also promoted the migration of chronic lymphocytic leukemia and lymphoplasmacytic lymphoma cells, two other B cell malignancies that colonize the bone marrow and express CD147. These findings suggest that eCyPA-CD147 signaling promotes the bone marrow homing of B cell malignancies and offer a compelling rationale for exploring this axis as a therapeutic target for these malignancies

Nature Med 2015; 21: 572

Eitan Israeli

Capsule

Group 3 innate lymphoid cells mediate intestinal selection of commensal bacteria-specific CD4+ T cells

Inflammatory CD4+ T cell responses to self or commensal bacteria underlie the pathogenesis of autoimmunity and inflammatory bowel disease (IBD), respectively. Although selection of self-specific T cells in the thymus limits responses to mammalian tissue antigens, the mechanisms that control selection of commensal bacteria-specific T cells remain poorly understood. Hepworth and team demonstrate that group 3 innate lymphoid cell (ILC3)-intrinsic expression of major histocompatibility complex class II (MHCII) is regulated similarly to thymic epithelial cells and that MHCII+ ILC3s directly induce cell death of activated commensal bacteria-specific T cells. Further, MHCII on colonic ILC3s was reduced in pediatric IBD patients. Collectively, these results define a selection pathway for commensal bacteria-specific CD4+ T cells in the intestine and suggest that this process is dysregulated in human IBD.

Science 2015; 348: 1031

Eitan Israeli

Capsule

Reversible basal ganglia lesions in pediatric neuropsychiatric lupus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that may cause neurological and psychiatric symptoms in up to 75% of cases. This subgroup of SLE, termed neuropsychiatric SLE (NPSLE), is likely to be mediated by multiple factors including autoantibody production, vasculopathy and pro-inflammatory cytokines. Sato and fellow researchers describe three cases of pediatric NPSLE presenting with reversible basal ganglia lesions. All three, young girls aged 10–14 years, initially presented with mild to moderate SLE manifestations (malar rash, arthritis, oral ulcers, minimal kidney involvement), accompanied by antinuclear and anti-DNA antibodies. They were first treated with prednisone which led to some improvement. After tapering of the steroids, neuropsychiatric manifestations appeared, including headaches, tremors, memory and mood impairments, and in one case loss of consciousness. In addition, the patients had positive serum and cerebrospinal fluid (CSF) tests for anti-NR2 glutamate receptor (anti-NR2) and/or anti-ribosomal-P antibodies, and high levels of interleukin (IL)-6 in the CSF as well. Further workup including magnetic resonance imaging (MRI) demonstrated bilateral basal ganglia lesions. The patients were treated with pulse steroid therapy as well as various combinations of adjunctive treatments: plasmapharesis, cyclophosphamide, cyclosporine-A, intravenous immunoglobulin or mycophenolate mofetil. In all cases the treatment resulted in a gradual clinical, serological and radiographic resolution over several months.

Int J Rheum Dis 2014; 17: 274

Shaye Kivity