Antibody Therapy to Limit the Spread of Ebola Virus

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Antibody therapy for viral infections in the form of immunoglobulin G (IVIG) has been successfully used over the past century [1,2]. IVIG is a major source for antibody therapy due to the diverse repertoire of antibodies against bacterial and viral infections that it contains.

We and others used IVIG for the prophylactic and therapeutic treatment of mice infected with West Nile virus (WNV) and showed that pooled IVIG from donors protected the mice from the development of a fatal WNV disease [3]. No protection of WNV-infected mice was obtained when they were treated with pooled IVIG prepared from American donors in the pre-WNV era. The protective efficacy of the pooled Israeli IVIG preparation was attributed to the fact that WNV is endemic in Israel and many people have been exposed to the virus or even suffered from mild infections. The efficacy was improved with the treatment of West Nile hyperimmune IVIG (WIVIG). The success of these treatments was time and dose dependent. It was noted that prophylactic therapy was always better than the therapeutic treatment [4].

There is good evidence that antibody therapy can be effective in protecting against Ebola infection; nonetheless, as in other diseases it is probably also time and dose dependent [5]. Since in most cases exposure to Ebola patients can be detected before clinical symptoms appear, it may be more efficacious to treat these human contacts – including health workers – in addition to the patients, with hyperimmune Ebola serum or IVIG prepared from recovered individuals.

In order to control the pandemic, prophylactic treatment should be given. That is, prevention should become the central strategy, and IVIG prepared from convalescent patients should be used at earlier stages before clinical symptoms emerge.

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References

Capsule
Cancer cell-autonomous contribution of type I interferon signaling to the efficacy of chemotherapy

Some of the anti-neoplastic effects of anthracyclines in mice originate from the induction of innate and T cell-mediated anticancer immune responses. Sistigu et al. have demonstrated that anthracyclines stimulate the rapid production of type I interferons (IFNs) by malignant cells after activation of the endosomal pattern recognition receptor Toll-like receptor 3 (TLR3). By binding to IFNα and IFNβ receptors (IFNARs) on neoplastic cells, type I IFNs trigger autocrine and paracrine circuitries that result in the release of chemokine (C–X–C motif) ligand 10 (CXCL10). Tumors lacking Tlr3 or Ifnar failed to respond to chemotherapy unless type I IFN or Cxcl10, respectively, was artificially supplied. Moreover, a type I IFN-related signature predicted clinical responses to anthracycline-based chemotherapy in several independent cohorts of patients with breast carcinoma characterized by poor prognosis. These data suggest that anthracycline-mediated immune responses mimic those induced by viral pathogens. The authors surmise that such ‘viral mimicry’ constitutes a hallmark of successful chemotherapy.

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References

Capsule
Rapid fucosylation of intestinal epithelium sustains host-commensal symbiosis in sickness

Systemic infection induces conserved physiological responses that include both resistance and ‘tolerance of infection’ mechanisms. Temporary anorexia associated with an infection is often beneficial, reallocating energy from food foraging towards resistance to infection or depriving pathogens of nutrients. However, it imposes a stress on intestinal commensals, as they also experience reduced substrate availability; this affects host fitness owing to the loss of caloric intake and colonization resistance (protection from additional infections). Pickard et al. hypothesized that the host might utilize internal resources to support the gut microbiota during the acute phase of the disease. The authors show that systemic exposure to Toll-like receptor (TLR) ligands causes rapid α(1,2)-fucosylation of small intestine epithelial cells (IECs) in mice, which requires the sensing of TLR agonists, as well as the production of interleukin (IL)-23 by dendritic cells, activation of innate lymphoid cells, and expression of fucosyltransferase 2 (Fut2) by IL-22-stimulated IECs. Fucosylated proteins are shed into the lumen and fucose is liberated and metabolized by the gut microbiota, as shown by reporter bacteria and community-wide analysis of microbial gene expression. Fucose affects the expression of microbial metabolic pathways and reduces the expression of bacterial virulence genes. It also improves host tolerance of the mild pathogen Citrobacter rodentium. Thus, rapid IEC fucosylation appears to be a protective mechanism that utilizes the host’s resources to maintain host-microbial interactions during pathogen-induced stress.

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from aspartic acid to asparagine. This site is involved in the contact area between alpha1 and beta2 globins. The effect manifests as a stabilization of the T state and lowering the affinity of the hemoglobin to oxygen [Figure 1A]. Interestingly, mutations in the beta globin, involving the same contact area, have also been described, including Hb Kansas [8] and Hb Beth Israel [9], both involving residue 102 of the beta globin. Asn102, in the beta globin, is connected to asp94 in the alpha globin by a hydrogen bond. Thus, Hb Kansas, Hb Beth Israel and Hb Titusville all cause an interruption to the alpha1-beta2 interface. Similarly, in Hb F-Sarajevo, amino acid 102 of the gamma globin is involved [10], leading to cyanosis appearing early in life and subsiding after the neonatal period. All of the described cases of Hb Titusville are heterozygous to the mutation, and no known homozygotes have been found as this is most likely a lethal defect.

In Hb Titusville, as in other hemoglobinopathies causing low oxygen affinity, the oxygen dissociation curve is shifted to the right [Figure 1B] and the oxygen extraction to the tissues is enhanced [7]. The p50 of Hb Titusville is higher than normal. Oxygen saturation measured by pulse oximetry is low; however, the partial pressure of oxygen in the arterial blood is normal. The diagnosis can be made by hemoglobin electrophoresis and confirmed by DNA sequencing. A bedside test that can rule out the presence of methemoglobin, sulfhemoglobin and hemoglobin M can be performed by exposing the blood of the patient to oxygen. In low oxygen affinity hemoglobinopathies, blood will turn from purple to bright red upon exposure to oxygen, while the color will not change in methemoglobinemia, sulfhemoglobinemia and hemoglobin M disease. This test cannot, however, rule out cardiopulmonary diseases that will give the same effect.

In summary, low affinity hemoglobin variants are usually benign, causing no or mild symptoms. However, they should be considered in the differential diagnosis of any patient with unexplained low oxygen saturation, dyspnea or cyanosis, especially when there is no evidence of cardiopulmonary abnormalities. Correct diagnosis of low oxygen affinity hemoglobinopathies is important, as it can eliminate the need for an expensive and invasive workup and is relatively simple, when these abnormalities are properly considered in the differential diagnosis.

Capsule

How the common cold can worsen asthma

Rhinoviruses – the main cause of the common cold – can make asthma attacks worse. Now Beale and co-workers report that one reason may be because rhinoviruses cause lung epithelial cells to make the cytokine interleukin-25 (IL-25). More IL-25 is produced in people with asthma than in those who are healthy. In mice with allergic “asthma,” rhinovirus infection triggered IL-25 production, and blocking the IL-25 receptor eased the increased asthma symptoms. Thus, as the cold season approaches, blocking IL-25 may be a promising therapeutic strategy in asthmatics.

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**Capsule**

**A new approach for treating colon cancer?**

Most patients with colon cancer have a mutation that results in the Wnt/β-catenin pathway being "on" all the time. But inhibitors of this pathway interfere with the continuous renewal of the epithelial cells lining the intestinal tract. Phesse et al. discovered that the signaling pathway involving the receptor gp130, its associated Jak kinases, and the transcription factor Stat3 enhanced the growth of intestinal tumors in mice. Inhibiting this pathway stopped cell proliferation and reduced tumor growth. Drugs targeting the Jak-Stat3 pathway are currently in clinical trials for treating hematological malignancies; hopefully they will also be useful for treating colon cancer. *Sci Signal* 2014; 7: ra92

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**Capsule**

**A microRNA for retinal regeneration**

Damage to the retina causes blindness in humans but not in zebrafish. Müller glia, a cell type shared by both mammals and zebrafish, helps zebrafish retinas regenerate. Rajaram et al. sought to better understand how this process works and identified miR-203, a microRNA (small RNA molecules that regulate gene expression) as a key player. Light-induced retina damage causes Müller glia cells to kick into action to generate progenitor cells, which then proliferate to help repair the retina. Under normal conditions, miR-203 blocked this, but retina damage caused miR-203 levels to decrease. miR-203 levels also decrease when mouse skin or the caudal fin in zebrafish regenerates, suggesting similarities in the molecular control of cellular replacement. *Dev Biol* 2014; 392: 393

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**Capsule**

**How to stop after copying the genome**

Replication is highly regulated: failure to copy any part of the genome or copying parts of it more than once can cause genome instability with potentially disastrous consequences. Maric et al. show that the DNA replication machinery, which stably encircles DNA during the duplication process, is actively disassembled once replication is complete. The protein ring encircling the DNA is covalently modified, which allows it to be opened and the whole replication complex to be removed from DNA by a special disassembly complex.

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**Capsule**

**Excess signaling is bad for the aging brain**

Preventing antiviral-like responses may protect function in the aging brain. Baruch and colleagues monitored messenger RNA production in the choroid plexus, the interface between the blood and cerebrospinal fluid, in young and old mice. They detected an inflammatory response in older mice not present in the brain of young mice that was also seen in old aged human samples postmortem. Preventing signaling by the cytokine interferon-1, which normally helps in the antiviral response of the immune system, helped prevent the decrease in cognitive function seen in aged mice.

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“*If you are neutral in situations of injustice, you have chosen the side of the oppressor. If an elephant has its foot on the tail of a mouse and you say that you are neutral, the mouse will not appreciate your neutrality*”

Desmond Tutu (born 1931), South African social rights activist and retired Anglican bishop who rose to worldwide fame during the 1980s as an opponent of apartheid
organdy cardiovascular disease. The diagnostic clue leading to the correct diagnosis in this case was rather a non- sophisticated determination of blood gases and oxygen saturation which remained low under various conditions. These findings strongly suggested a low oxygen affinity hemoglobinopathy as the leading cause of his complaints. Prior to his most recent admission to our ward this patient underwent an extensive diagnostic workup in search of pulmonary and/or cardiac abnormalities, which were not found. Nevertheless, a normal PaO₂ and low oxygen saturation were evident. This combination is highly suggestive of hemoglobinopathy. Thus, the delayed diagnosis in this case was most probably due to improper interpretation of these two simple key diagnostic clues and to the well-recognized tendency to perform complex diagnostic procedures.

In conclusion, we present here, to the best of our knowledge, the first case description in Israel of a young adult patient with TV hemoglobinopathy presenting as effort dyspnea. Clinical awareness and relatively simple diagnostic measures can provide accurate diagnosis in similar patients.

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References

Resident memory T cells sound the alarm

Immunological memory protects against reinfection. Resident memory T cells (TRM) are long-lived and remain in the tissues where they first encountered a pathogen. Schenkel et al. and Ariotti et al. (Science 2014; 346: 98, 101) found that CD8+ TRM cells act like first responders in the female reproductive tissue or the skin of mice upon antigen reencounter. By secreting inflammatory proteins, TRM cells rapidly activated local immune cells to respond, so much so that they protected against infection with an unrelated pathogen. Iijima and Iwasaki (Science 2014; 346: 83) found that CD4+ TRM cells protected mice against reinfection with intravaginal herpes simplex virus 2.

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Overcoming Staph infections is hardwired

Several evolutionarily conserved components of anti-staphylococcal immunity have been identified, using Drosophila as a model organism. However, no vertebrate ortholog has been identified for the Toll ligand Spaetzle, which plays a key role in controlling gram-positive infection in flies. Hepburn and group have now identified NGF-β as a functional equivalent to Spaetzle in vertebrates. NGF-β acts as a paracrine “alarmin” orchestrating macrophage and neutrophil responses to S. aureus infection. People with deleterious mutations in genes encoding NGF-β or its high-affinity receptor TRKA are predisposed to recurrent and severe Staph infections. S. aureus proteins selectively trigger macrophage production of NGF-β, which enhances uptake and superoxide-dependent killing of S. aureus, stimulates pro-inflammatory cytokine production, and promotes neutrophil recruitment. Moreover, TrKA silencing in vivo increases susceptibility to S. aureus. Thus, the NGF-β-TRKA pathway is a critical, evolutionarily conserved component of vertebrate immunity to S. aureus infection.

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classified as having asymptomatic Candida isolated from ascites. None of the patients received antifungal therapy. Within 1 year of diagnosis all patients with spontaneous Candida peritonitis died, compared with 54.5% in the asymptomatic group. Ascitic fluid PMN > 315 cells/µl demonstrated 100% sensitivity in diagnosing spontaneous Candida peritonitis [4].

In a recently published study, spontaneous fungal peritonitis was found in 15 of 416 patients (3.6%) diagnosed with spontaneous peritonitis; all of them had a neutrophil count of at least 250 cells/µl. Sixty percent of the patients received antibiotic therapy 90 days prior to the fungal infection. Nosocomial spontaneous peritonitis was significantly more common in the spontaneous fungal peritonitis cohort than in the spontaneous bacterial peritonitis cohort (80% versus 35%, P = 0.0009). Only five patients were treated with appropriate antifungal therapy, and only one of them improved. Patients with spontaneous fungal peritonitis had significantly higher 30 days mortality than spontaneous bacterial peritonitis patients (73% vs. 29%) [5].

Previously published data included patients with a higher ascitic neutrophil count than in our patient, and most of the patients did not receive antifungal treatment. Our case is unique because the patient was treated appropriately although she had a very low neutrophil count, her condition improved substantially and the culture became negative, suggesting that in her case it was truly an infection rather than colonization alone. Unfortunately, she died a few days later due to septic shock and bacteremia.

Candida peritonitis is a rare complication in cirrhotic patients. The definition of an infection versus colonization and its clinical significance and need for appropriate treatment is under debate. After reviewing the literature, we believe that primary fungal peritonitis is under-diagnosed. We suggest that in patients at high risk for fungal peritonitis (prolonged antibiotic therapy, recent hospitalization, and no improvement with empirical antibiotic therapy) [5] fungal cultures from ascitic fluid should be sent to the microbiology laboratory, regardless of neutrophil count. Empiric antifungal therapy should be considered in selected severely ill patients.

Patients with this disorder are rare and the diagnosis is difficult to ascertain, but our case raises the possibility that positive fungal cultures from ascitic fluid in cirrhotic patients are an indication of infection and not simply a harmless colonization, and the appropriate treatment should be administered. Therefore, larger scale studies are needed to determine both diagnostic and treatment guidelines for this condition. It seems, however, that regardless of treatment, Candida peritonitis is associated with a poor prognosis in cirrhotic patients.

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Capsule

Pulmonary macrophage transplantation therapy

Bone marrow transplantation is an effective cell therapy but requires myeloablation, which increases infection risk and mortality. Recent lineage-tracing studies documenting that resident macrophage populations self-maintain independently of hematological progenitors prompted us to consider organ-targeted, cell-specific therapy. Suzuki et al., using granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor-β-deficient (Csf2rb−/−) mice that develop a myeloid cell disorder identical to hereditary pulmonary alveolar proteinosis (hPAP) in children with CSF2RA or CSF2RB mutations, show that pulmonary macrophage transplantation (PMT) of either wild-type or Csf2rb-gene-corrected macrophages without myeloablation was safe and well-tolerated. They showed that one administration corrected the lung disease, secondary systemic manifestations and normalized disease-related biomarkers, and prevented disease-specific mortality. PMT-derived alveolar macrophages persisted for at least one year, as did therapeutic effects. These findings identify mechanisms regulating alveolar macrophage population size in health and disease, indicate that GM-CSF is required for phenotypic determination of alveolar macrophages, and support translation of PMT as the first specific therapy for children with hPAP.

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“It’s not what you look at that matters but what you see”

Henry David Thoreau (1817-1862), American author, poet, philosopher, polymath, abolitionist, naturalist, tax resister, development critic, surveyor, historian and leading transcendentalist. He is best known for his book Walden, a reflection upon simple living in natural surroundings, and his essay Civil Disobedience, an argument for disobedience to an unjust state order.
evidence of vegetations but a thrombus was seen in the left auricle. Similar to our case, their patient also developed a splenic infarction. Furthermore, urine culture in their case grew Streptococcus, 1000 colony-forming units (CFU)/ml. No antibiotic treatment was given prior to or following the ESWL procedure in that case.

Fever and urosepsis following ESWL have been reported since 1985, when Wickham and team [3] described the first series of 50 patients treated with ESWL, many of whom developed fever despite antibiotic prophylaxis following the procedure. In 1986 Matlow and Goldberg [4] reviewed the data of 80 patients treated with ESWL, focusing on the risk for bacteremia in a population of patients with no history of UTI, whose urine cultures were sterile and who did not receive prophylactic antibiotic before the procedure. Within the first 24 hours after lithotripsy 4% of this group became febrile. Although many authors stressed the need for antibiotic prophylaxis following genitourinary procedures during the last 25 years, in 2008 the National Institute for Clinical Excellence (NICE) and the American Heart Association (AHA) guidelines for prevention of IE have recommended cessation of routine prophylactic therapy for most patients undergoing urological procedures. Indeed, this was accepted due to the evidence of scarce reports of secondary IE following such procedures. Similarly, the 2009 new version of the European Society of Cardiology (ESC) guidelines on prevention, diagnosis and treatment of IE reduced the number of indications for prophylactic therapy and recommends it only for patients with the highest risk for endocarditis, such as those with prosthetic valves, patients with previous IE history, and patients with a complex congenital heart disease [5].

In conclusion, despite the absence of known risk factors for IE in our patient and despite the rarity of this kind of complications, IE following ESWL may occur. Therefore, a thorough clinical evaluation should be performed before the procedure in order to consider the benefits of possible prophylactic antimicrobial therapy. This is especially important in patients with an existing urinary tract infection.

## Capsule

### A dendritic cell target for immunotherapy

Cancer immunotherapies work by activating T cells to kill tumors. Antigen-presenting cells (APCs), such as dendritic cells and macrophages, activate T cells by engaging protein receptors on the T cell surface. This then tells the T cells to attack the tumors. But T cells typically cannot attack tumors because the immunosuppressive microenvironment of tumors keeps APCs from turning these signals on. Broz and fellow researchers report, however, that low numbers of dendritic cells capable of activating T cells exist in tumors in mice. T cell-mediated clearance of tumors depended on these cells. In humans, an increased genetic signature of these cells correlated with better outcomes in a variety of tumor types.  

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### Cancer’s deadly mutational tug of war

As cancers grow, they mutate, which allows their continued growth and metastasis. Mutations are either driver mutations (required for tumors to progress) or passenger mutations (additional random mutations that result from such rapid adaptation). How do passenger mutations affect tumors? McFarland and team found that passenger mutations are 100 times more common than driver mutations and have smaller effects on tumors, but the effects are often deleterious. Thus driver and passenger mutations are in a “tug of war” that determines whether a tumor will progress. A better understanding of how passenger mutations accumulate could explain the success of current treatments or provide additional avenues to explore for therapeutic benefit.  

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