ANSWERS for CME Questions # 1-50

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Explanations of answers to questions are divided by the issue in which the questions appeared.
1. In rodents, liver can regenerate after two-thirds partial hepatectomy (PHx), providing a model for organ regeneration. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2-13; DOI: 10.2353/ajpath.2010.090675; the author of the referenced article did not disclose any relevant financial relationship.]

   a. A drawback of the rodent PHx model system is that it is associated with necrosis, and regeneration of the residual lobes is affected by acute inflammatory processes. **This statement is NOT TRUE.** The removal of the resected tissue is not associated with massive necrosis and, therefore, is mediated by processes relevant only to liver tissue and not to necrosis or acute inflammation.

   b. Since PHx can be performed in a few minutes, liver regeneration can be precisely timed. **This statement is TRUE.** PHx stimulates the immediate initiation of regeneration, and the quickness of the procedure allows for a precise reference timepoint for the subsequent regeneration events.

   c. In human disease, regeneration is often coupled by innate immune responses. **This statement is TRUE.** Regeneration in human liver is also accompanied by wound healing. These responses will need to be considered when examining the regenerative response in human disease.

   d. Biochemical studies following PHx have identified key regulatory and signaling molecules involved in liver regeneration. **This statement is TRUE.** Molecules identified using biochemical studies of whole liver lysates include cyclin D1, stat3, and NF-kB.

   e. Performing PHx in mouse strains deficient for various molecules has clarified the role for these molecules in liver regeneration. **This statement is TRUE.** Although these molecules may not be mitogenic for hepatocytes per se, they play key role in the regenerative process.

2. Primary cultures of hepatocytes have been useful in deriving several aspects of hepatocyte biology. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2-13; DOI: 10.2353/ajpath.2010.090675; the author of the referenced article did not disclose any relevant financial relationship.]

   a. A 5- to 10-fold increase in DNA synthesis above control levels is considered a significant effect in hepatocyte culture. **This statement is TRUE.** A significant increase in DNA synthesis is most commonly seen by hepatocyte growth factor (HGF) and ligands of the epidermal growth factor receptor (EGFR), of which epidermal growth factor (EGF) and transforming growth factor alpha (TGFα) are the most commonly used.

   b. Norepinephrine and prostaglandins are also mitogenic stimuli for hepatocytes. **This statement is NOT TRUE.** Norepinephrine, prostaglandins, tumor necrosis factor alpha (TNFα), estrogens, and insulin are not significantly mitogenic by themselves but enhance the effects of HGF, EGF and TGFα.

   c. Complete mitogens are mitogenic in hepatocyte cultures in chemically defined (serum-free) media. In addition, they cause liver enlargement and hepatocyte DNA synthesis when injected in sufficient doses into whole animals. **This statement is TRUE.** Complete mitogens include HGF and ligands of the EGFR.
3. There is no single signal that alone drives the regenerative process. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2-13; DOI: 10.2353/ajpath.2010.090675; the author of the referenced article did not disclose any relevant financial relationship.]

a. Regeneration completes when the remnant lobes enlarge to the size of the original liver. This statement is TRUE. This process typically requires about 5 to 7 days in rat and mouse.

b. Elimination of the signals of either direct or auxiliary mitogens causes delays in regeneration; however, the regenerative process is eventually completed. This statement is TRUE. These delays can be measured by either delayed activation of transcription factors (STAT3, NF-kB) or delayed or diminished magnitude of hepatocyte DNA synthesis in the first 1 to 2 days.

c. Any signal whose deletion merely delays regeneration is of no importance. This statement is NOT TRUE. Regenerative delay is likely to have serious adverse effects to the life of the animal, as regeneration is critically needed to prevent loss of liver function and liver failure.

d. Studies on interference with specific signals tend to rely on mice with specific genetic deficiencies, which often demonstrate differences in liver histology. This statement is TRUE. Secondary gene expression changes deriving from the original signaling block often are not considered in these studies.

e. Acute elimination of specific signals so that there are no long term adaptive changes in gene expression or histologic changes should be a useful complementary approach to genetic knock-out studies. This statement is TRUE. As an example, targeted elimination of the HGF receptor from mouse hepatocytes leads to progressive fibro-fatty change in the livers. When these livers are subjected to partial hepatectomy, there is a dampening of the response in the first proliferative cycle, and hepatocyte proliferation is decreased but measurable, down to 1/3 of the control mice.

4. Failing kidneys approaching end-stage disease typically show tubular atrophy and interstitial fibrosis. Based on the referenced Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:22-24; DOI: 10.2353/ajpath.2010.090898; the author of the referenced article did not disclose any relevant financial relationship.]

a. In animal models, once the number of functioning nephrons falls below a critical level, there is an inevitable progression of further nephron loss, tubular atrophy, and interstitial fibrosis. This statement is TRUE. This also holds true for humans.

b. It has been hypothesized that tubular epithelial cells in the injured kidney undergo a phenotypic transition or can transdifferentiate into interstitial myofibroblasts by a process referred to as epithelial-mesenchymal transition (EMT). This statement is TRUE. However, there is now evidence that the process of EMT does not have a significant involvement in interstitial fibrosis.

c. The hypothesis that in glomerular disease, proteinuria is a major stimulus to alteration of epithelial cell function and leads to EMT and interstitial fibrosis is undisputed. This statement in NOT TRUE. Careful analysis of experimental glomerular injury suggests that, even with severe glomerular injury, the proximal tubule remains healthy unless the glomerular damage encroaches on the glomerulotubular junction.

d. Using the cre/lox technique to label cells, two types of mice were generated that were used to study injury and interstitial fibrosis. This statement is TRUE. The cre/lox technique depends on crossing mice that express the enzyme cre-recombinase under the control of a cell-lineage specific promoter with mice expressing a reporter gene that is activated by cre-recombinase.

e. The theory that some interstitial fibroblasts are derived from circulating cells of bone marrow origin has been called into question. This statement is TRUE. In a mouse model that expressed a reporter gene under the control of the promoter of the α-2 chain of type I collagen, no evidence was found that cells from the bone marrow could synthesize collagen in the kidney after unilateral ureteric obstruction (UOO). There is instead evidence that cells of metanephric mesenchymal origin expressing platelet-derived growth factor receptor β, consistent with pericytes, are the major source of interstitial fibroblasts in UOO.
5. Prostate cancer is the most prevalent noncutaneous malignancy in American men. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:518-527; DOI: 10.2353/ajpath.2010.090657; the author of the referenced article did not disclose any relevant financial relationship.]

a. The majority of patients with prostate cancer are clinically asymptomatic with early-stage, organ-confined disease. **This statement is TRUE.** More than 80% of men who reach the age of 80 develop this less aggressive type of prostate cancer. However, a subpopulation of patients with prostate cancer progress to highly invasive, androgen-independent metastatic disease, which is commonly fatal.

b. In males, the prostate develops in the presence of androgens from obligatory interactions between the urogenital sinus epithelium and the urogenital sinus mesenchyme. **This statement is TRUE.** Among the developmental pathways involved are the androgen receptor, fibroblast growth factor, transforming growth factor β, Hedgehog, Notch, and Wnt.

c. Developmentally important transcription factors such as sex-determining region Y-box 4 (SOX4), homeobox C6 (HOXC6), enhancer of zeste 2, and ETS-related gene are up-regulated in prostate cancers. **This statement is TRUE.** Both normal development of the prostate and progression of prostate cancer depend on key paracrine effects mediated by stromal-epithelial interactions.

d. The SOX4 transcription factor is a developmental transcription factor that contains a highly conserved high-mobility group DNA-binding domain related to the TCF/LEF family of transcription factors. **This statement is TRUE.** The TCF/LEF family of transcription factors play important roles in the Wnt pathway. However, the role of SOX4 in the Wnt pathway is still unclear.

e. Like SOX2, SOX4 is a stem cell marker. **This statement is NOT TRUE.** SOX4 is not a stem cell marker. However, like SOX2, it is expressed in intestinal stem cells and likely plays a role in the early differentiation and expansion of transit amplifying progenitor cells.

6. Notch signaling plays a key role in both normal development and carcinogenesis. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:518-527; DOI: 10.2353/ajpath.2010.090657; the author of the referenced article did not disclose any relevant financial relationship.]

a. After activation by its ligands JAK and STAT, the Notch receptor is proteolytically cleaved and translocates to the nucleus, where it regulates gene expression. **This statement is NOT TRUE.** The Notch receptor is activated by its ligands Jagged or Delta-like 1 prior to proteolytical cleavage and translocation to the nucleus, where it regulates gene expression.

b. In Notch-mediated neoplasias, Notch can act as an oncogene or as a tumor suppressor. **This statement is TRUE.** The function of Notch in neoplasias depends on the cellular context and differences in the strength and timing of Notch signals.

c. Notch signaling is a key cellular regulator during normal development of many organs, including the prostate and bone. **This statement is TRUE.** During prostate differentiation, Notch signaling is absent in stem cells and highest in the intermediate cells undergoing proliferation before terminal differentiation.

d. Inhibition of Notch signaling is effective at treating mouse models of medulloblastomas that are driven by the Sonic Hedgehog-Smootherned pathway. **This statement is TRUE.** This is particularly relevant to prostate cancer because Hedgehog signaling is activated in advanced prostate cancer and targeting of Hedgehog signals inhibits proliferation.

e. Notch inhibition reduces proliferation of primary prostate epithelial cells, suggesting that active Notch signaling is a key feature of prostate cancer. **This statement is TRUE.** Notch signaling is active in intermediate,
transit-amplifying prostate cells undergoing rapid proliferation, suggesting that prostate progenitor cells may be competent for cell-autonomous Notch1 signaling.

7. Wnt signaling plays critical roles in the development of breast, colon, and prostate cancers. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:518-527; DOI: 10.2353/ajpath.2010.090657; the author of the referenced article did not disclose any relevant financial relationship.]

   a. Ectopic expression of Wnt ligands can induce transformation of breast epithelial cells. This statement is TRUE. This transformation occurs through a Notch-dependent mechanism that requires expression of Notch ligands.

   b. Wnt ligand binding to HOXC6 inhibits the adenomatous polyposis coli (APC) complex, which plays a key role in initiating colorectal tumors. This statement is NOT TRUE. Wnt ligand binding to Frizzled-LRP6 co-receptors inhibits the APC complex, which plays a key role in initiating colorectal tumors.

   c. The canonical Wnt ligand Wnt3a can enhance activity of the androgen receptor and growth of LNCaP prostate cancer cells. This statement is TRUE. Suppression of Wnt signaling can inhibit proliferation of the PC-3 and DU145 prostate cancer cell lines.

   d. Expression of one negative regulator of Wnt signaling, dickkopf homolog 1 (DKK1), is reduced in bone metastases and may play a role in the osteoblastic properties of prostate cancer metastases. This statement is TRUE. Blocking Wnt activity via stable expression of DKK1 converts osteoblastic C4-2B prostate cancer cells to a highly osteolytic tumor.

   e. Inhibition of Wnt signaling using Wnt inhibitory factor 1 (WIF1) induces chemosensitivity in prostate cancer cells with mutations in the PTEN tumor suppressor. This statement is TRUE. Strongly reduced expression of WIF1 is highly correlated with Gleason score in prostate cancer.

8. Influenza A Virus (IAV) causes a respiratory illness that is often deadly in susceptible populations. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:536-541; DOI: 10.2352/ajpath.2010.090880 and Am J Pathol 2010, 176:800-811; DOI: 10.2352/ajpath.2010.090596; the authors of the referenced articles did not disclose any relevant financial relationship.]

   a. Annually, influenza causes between 3 and 5 million cases of severe illness worldwide. This statement is TRUE. In the United States, 5% to 20% of the population is infected annually.

   b. New IAV strains are formed as a result of frequent mutations in the viral genome. This statement is TRUE. New IAV strains can often evade the immune responses developed against prior strains.

   c. Antigenic drift occurs due to small mutations in the viral DNA of IAV. This statement is NOT TRUE. The genomic material of IAV is RNA. Antigenic drift occurs due to small mutations in the viral RNA of IAV, due to the low fidelity of the viral RNA polymerase.

   d. Antigenic shift occurs due to genetic reassortment between two or more IAV strains. This statement is TRUE. Major changes can result from the introduction of whole RNA genome segments from animal IAV strains.

   e. The innate immune response controls IAV replication during the first days after infection. This statement is TRUE. A unique adaptive immune response develops in response to each new strain of IAV.

9. IAV infection predisposes the lungs to secondary bacterial infection. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:536-541; DOI: 10.2352/ajpath.2010.090880 and Am J Pathol 2010, 176:800-811; DOI: 10.2352/ajpath.2010.090596; the authors of the referenced articles did not disclose any relevant financial relationship.]

   a. Mortality after IAV infection is often not the result of viral pneumonia. This statement is TRUE. Secondary bacterial infections cause significant morbidity, particularly in young children, the elderly, and immunocompromised individuals.

   b. During the 1918 influenza pandemic, although the virus alone could be lethal, the majority of deaths likely resulted from secondary bacterial pneumonia. This statement is TRUE. The 1918 influenza pandemic killed approximately 50 million people worldwide.

   c. Streptococcus pneumoniae, Staphylococcus aureus, and Haemophilus influenzae are the most common bacterial agents found in post-IAV-pneumonia. This statement is TRUE. S. pneumoniae and H. influenzae were found after the 1918 and subsequent pandemics; however, there have been recent reports of pneumonia and mortality due to methicillin-resistant staphylococcal infections in young subjects with IAV infection.

   d. IAV infection promotes other bacterial infections that enter through a respiratory route, including meningitis and otitis media. This statement is TRUE. H. influenzae is a common cause of otitis media, acute sinusitis, bronchitis, pneumonia, and exacerbations of chronic obstructive pulmonary disease.

   e. Antibiotics have virtually eliminated mortality from bacterial post-IAV infections. This statement is NOT TRUE. The mortality rate from bacterial pneumonia occurring in IAV-infected subjects remains high despite the use of antibiotics. The infections also have a high occurrence and mortality rate among otherwise young and healthy individuals.
10. Otherwise nonlethal IAV or *H. influenzae* infections cause high mortality rates when IAV infection precedes inoculation with *H. influenzae*. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:536-541; DOI: 10.2352/ajpath.2010.090880 and Am J Pathol 2010, 176:800-811; DOI: 10.2352/ajpath.2010.090596; the authors of the referenced articles did not disclose any relevant financial relationship.]

a. Infection of pigs with both influenza virus and *H. influenzae suis* resulted in severe disease or death, whereas the individual agents induced only mild infection. **This statement is TRUE.** Moreover, administration of both filtrates of nasal secretions from 1918 influenza patients and *H. influenzae* caused a lethal disease in guinea pigs, but there was no effect if either agent was administered alone.

b. *H. influenzae* synergizes with influenza virus to cause more severe disease in immunocompetent adult mice. **This statement is TRUE.** There is 100% lethality at doses that cause no mortality when the agents are given individually.

c. Lethality was dependent on the interval between introduction of the bacteria and the virus. **This statement is TRUE.** No synergistic effect was observed when both agents were administered at the same time or when the interval was extended beyond 7 days. Peak lethality occurred when the agents were administered 3 to 4 days apart.

d. The mechanism leading to disease exacerbation caused by IAV and *H. influenzae* co-infection requires both T and B cells. **This statement is NOT TRUE.** Disease exacerbation does not require T and B cells and therefore may be mediated by innate immunity.

e. Interleukin-6, tumor necrosis factor, and Toll-like receptor 4 are not required for disease exacerbation by dual IAV and *H. influenzae* co-infection. **This statement is TRUE.** Fas, CCR2, and CXCR3 are also not required.
11. In cells undergoing autophagy, cellular content and organelles are engulfed in membrane-bound vesicles and degraded. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:1065-1071; DOI: 10.2353/ajpath.2010.0090850; the authors of the referenced article did not disclose any relevant financial relationship.]

   a. In neurons, autophagy provides quality control to eliminate abnormal or dysfunctional proteins. **This statement is TRUE.** In neurons, autophagy is required to maintain neuronal function and viability.
   
   b. The autophagic process includes induction, vesicle nucleation, elongation, vesicle docking and lysozyme fusion, and vesicle content degradation. **This statement is TRUE.** In neurons, autophagy is not limited to a cellular response to nutrient stress but is also important in cellular housekeeping, maintaining genomic stability, and development.
   
   c. Autophagy is primarily mediated by autophagy-related genes (Atg). **This statement is TRUE.** Activation of the regulatory kinase TOR (target of rapamycin), an inhibitor of the Atg proteins, shuts off autophagy in response to nutrient-rich conditions.
   
   d. Autophagy is induced by positive upstream regulators of TOR. **This statement is NOT TRUE.** Autophagy is induced by negative upstream regulators of TOR; TOR induction inhibits Atg protein interactions.
   
   e. Vesicle nucleation in autophagy is negatively regulated by Bcl-2 family members. **This statement is TRUE.** Bcl-2 family members interact with beclin-1 (the mammalian ortholog of Atg6) and prevent formation of a complex that activates vesicle nucleation.

12. Methods to detect autophagy measure both steady-state levels and flux through the pathway. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:1065-1071; DOI: 10.2353/ajpath.2010.0090850; the authors of the referenced article did not disclose any relevant financial relationship.]

   a. Detecting steady-state levels of autophagy relies upon the detection of autophagosomes. **This statement is TRUE.** Both electron microscopy and detection of LC3-II via Western blot can be used to detect autophagosomes.
   
   b. Increased levels of autophagosomes directly reflect autophagy induction. **This statement is NOT TRUE.** Increased levels of autophagosomes do not necessarily reflect increased autophagy induction but instead may reflect blocked autophagosome fusion or degradation.
   
   c. Autophagic flux levels can be measured by protein degradation assays. **This statement is TRUE.** LC3-II turnover and lysosome-autophagosome colocalization can also be used to monitor autophagic flux levels.
   
   d. Rapamycin, an inhibitor of mTOR, can be used to induce autophagy. **This statement is TRUE.** Genetic approaches with targeted gene disruptions or RNA interference of key inhibitory proteins can also be used to induce autophagy.
   
   e. The phosphoinositide 3-kinase inhibitor 3-methyladenine can inhibit induction of autophagy. **This statement is TRUE.** Bafilomycin, an inhibitor of lysosomal vacuolar ATPase, can be used to inhibit degradation in autophagy.
13. Autophagy plays a key role in both physiological and pathological processes in neurons. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:1065-1071; DOI: 10.2353/ajpath.2010.0090850; the authors of the referenced article did not disclose any relevant financial relationship.]

a. In neurons, basal autophagy is required for maintenance of cellular homeostasis. This statement is TRUE. Neural-cell-specific Atg5−/− and Atg7−/− mice demonstrate a considerable loss of neurons (in a cell-autonomous fashion) as well as an accumulation of ubiquitin-positive aggregates in the brain despite the apparently normal function of proteasomes.

b. Oxidative stress-induced autophagy has been implicated in several neuropathological conditions. This statement is TRUE. Oxidative stress-induced autophagy has been implicated following cerebral ischemia-hypoxia or traumatic brain injury, in which significant autophagy is seen in neurites and is accompanied by rapid and massive neurite degeneration.

c. There is clear and definitive evidence that autophagy is required for cellular differentiation during nervous system development. This statement is NOT TRUE. The importance of autophagy in the ontogenesis of the central nervous system remains unclear. While Ambra 1Δp53 embryos display neural tube defects detected as midbrain/hindbrain exencephaly and/or spina bifida accompanied by excessive apoptosis, transgenic mice deficient in Atg5 or Atg7 specifically in the central nervous system demonstrate no developmental abnormalities.

d. A deficiency in autophagy induction can lead to aberrant accumulation of neuronal proteins with subsequent onset of neurodegenerative disorders. This statement is TRUE. Along with defects in autophagy induction, impairment of autophagy completion can also lead to onset of neurodegenerative disorders.

e. Levels of Atg proteins are significantly decreased in the neural tissues of older flies. This statement is TRUE. Enhanced Atg8 expression in older fly brains extends the average adult lifespan by 56% and promotes resistance to oxidative stress and the accumulation of ubiquitinated and oxidized proteins.


a. Cerebral malaria is associated with an encephalitic syndrome that includes ataxia, seizures, hemiplegia, and eventually coma and death. This statement is TRUE. These symptoms of severe malaria can progress very precipitously within hours from mild to severe.

b. Even with successful anti-parasitic treatment, residual neurological damage is common in patients with cerebral malaria. This statement is TRUE. More than 10% to 20% of the children who survive an episode of cerebral malaria are estimated to develop long-term cognitive deficits, which can include memory impairment, learning and language impairments, visuospatial and motor deficits, and psychiatric disorders.

c. The disrupted integrity of the cerebral vasculature may be an important contributing factor in the pathogenesis of cerebral malaria. This statement is TRUE. Both human and experimental animal cerebral malaria studies have demonstrated reduced cerebral blood flow, which may be an important factor in the progression to cerebral malaria.

d. Vasoconstriction plays a role in the setting of cerebral malaria. This statement is TRUE. Through the use of intravital microscopy, the pial microvasculature of the brain was directly visualized and correlated with progression of cerebral malaria. This highlights the importance of vascular dysfunction in the pathogenesis of cerebral malaria.

e. Disease progression was accelerated when vasculopathy was corrected with the calcium-channel blocker nimodipine. This statement is NOT TRUE. Disease progression was reversed when vasculopathy was corrected the calcium-channel blocker nimodipine.
15. Bone marrow-derived cells (BMDCs) play an important role in regulating tumor angiogenesis. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:1564-1576; DOI: 10.2352/ajpath.2010.090786; the authors of the referenced article did not disclose any relevant financial relationships.]

a. Myeloid-lineage BMDCs have been shown to be proangiogenic in mouse tumor studies. This statement is TRUE. These cell types include monocytes/macrophages, dendritic cell (DC) precursors, mast cells, neutrophils, and the so-called myeloid-derived suppressor cells (MDSCs or CD11b^Gr-1^ cells).

b. Myeloid BMDCs promote tumor angiogenesis by expressing factors that promote widening and thickening of existing blood vessels. This statement is NOT TRUE. BMDCs are thought to promote tumor angiogenesis by expressing factors that promote the growth and expansion of new blood vessels from the pre-existing vasculature.

c. Myeloid BMDC-secreted factors may encourage tumor angiogenesis through direct stimulation of endothelial cells. This statement is TRUE. BMDC-secreted factors may also lead to remodeling of the extra-cellular matrix during tumor angiogenesis.

d. Tumor-infiltrating myeloid BMDCs are heterogeneous and functionally redundant, and these cell types often express overlapping phenotypic markers. This statement is TRUE. These qualities make it difficult to identify the exact roles that distinct cell types play in tumor angiogenesis.

e. In addition to classic myeloid cells, other BMDCs have been implicated in tumor angiogenesis. This statement is TRUE. These cell types include various progenitor or precursor cell populations, such as hematopoietic stem/progenitor cells (HS/PCs), endothelial progenitor cells (EPCs), pericyte precursor cells (PPCs), and mesenchymal stem/stromal cells (MSCs).

16. Different myeloid cell types have distinct functions in tumor angiogenesis. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:1564-1576; DOI: 10.2352/ajpath.2010.090786; the authors of the referenced article did not disclose any relevant financial relationships.]

a. Tumor-associated macrophages (TAMs) express multiple proangiogenic factors such as vascular endothelial growth factor (VEGF)-A and matrix metalloproteinase (MMP)-9. This statement is TRUE. Inhibition of tumor-derived TAM chemoattractants, ablation of TAMs by DNA vaccination, or pharmacological neutralization of TAM-produced proangiogenic molecules impaired tumor angiogenesis in various tumor models.

b. Tie2-expressing monocytes (TEMs) express the angiopoietin receptor Tie2 and play an important role in angiogenesis. This statement is TRUE. TEMs also express a wide array of monocyte/macrophage markers.

c. Elimination of neutrophils with anti-Gr-1 antibodies reduces the levels of MMP-9 in the tumors, which in turn inhibits the association of VEGF with VEGF receptor-2 (VEGFR-2) on endothelial cells, thus suppressing angiogenesis. This statement is TRUE. Neutrophils can either express a protumoral or antitumoral phenotype according to the levels of transforming growth factor (TGF)-β present in the tumor.
d. While MDSCs are believed to promote tumor progression through immunosuppression and other mechanisms, these cells may also influence angiogenesis. **This statement is TRUE.** This effect is mediated, at least in part, by the release of proangiogenic factors by MDSCs.

e. Mast cells have direct antiangiogenic activity due to their secretion of antiangiogenic molecules such as basic fibroblast growth factor (FGF) and interleukin (IL)-8. **This statement is NOT TRUE.** Mast cells have direct proangiogenic activity due to their production of MMPs, particularly MMP-9, and secretion of other proangiogenic molecules such as FGF, VEGF, and IL-8.

17. The most common phenotypic markers used to identify myeloid cells are expressed by more than one myeloid cell type, making it difficult to distinguish between cell types. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:1564-1576; DOI: 10.2352/ajpath.2010.090786; the authors of the referenced article did not disclose any relevant financial relationships.]

a. CD45 (leukocyte common antigen) is a transmembrane protein broadly expressed by hematopoietic-lineage cells. **This statement is TRUE.** CD45 is expressed on both myeloid and lymphoid cells.

b. CD11b is expressed on myeloid cells as well as lymphocyte and NK cell subsets, depending on their activation status. **This statement is TRUE.** CD11b is also known as MAC-1.

c. F4/80, which is regularly used to identify murine TAMs, is broadly expressed on both tissue-resident and tumor-infiltrating macrophages. **This statement is TRUE.** F4/80 expression is down-regulated with some forms of macrophage activation.

d. Ly6G is a surface molecule expressed almost exclusively on human neutrophils and their precursors. **This statement is NOT TRUE.** Ly6G is a surface molecule expressed almost exclusively on murine neutrophils and their precursors. Like Ly6C, Ly6G is specific to the mouse. Therefore, the role of Gr-1^+ myeloid cells cannot be assessed in human tumors.

e. Anti-Gr-1 antibodies bind not only neutrophils and their BM precursors, but also inflammatory monocytes, DCs, and T cell subsets. **This statement is TRUE.** On the other hand, tumor-infiltrating TEMs and their circulating precursors are reported to be Gr-1 negative.

18. Signaling through the chemokine receptor CXCR3 is involved in wound healing and scar formation. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:1588-1591; DOI: 10.2353/ajpath.2010.100064 and Am J Pathol 2010, 176:1743-1755; DOI: 10.2353/ajpath.2010.090564; the authors of the referenced articles did not disclose any relevant financial relationships.]

a. CXCR3 is a G-protein-coupled receptor that recognizes the interferon-γ-inducible proteins IP-1 and IP-2. **This statement is NOT TRUE.** CXCR3 is a G-protein coupled receptor that recognizes IP-9 and IP-10 as well as CXCL9 and CXCL4.

b. Hypertrophic scar formation is caused by increased wound cellularity and excessive matrix deposition. **This statement is TRUE.** A scar results from an imbalance in the cellular responses to promotive and inhibitory signals that function in a paracrine fashion between the dermis and epidermis.

c. In the global CXCR3 knockout mouse, wound healing is markedly impaired and delayed. **This statement is TRUE.** These mice have notable defects in the organization of the epidermis and its basement membrane up to 90 days after injury.

d. The healing process is seemingly reversed in global CXCR3-knockout mice after 180 days. **This statement is TRUE.** The authors observed epidermal thickening, poor organization of the dermal extracellular matrix, and concomitant defects in mechanical properties, which represent properties similar to human hypertrophic scars.

e. CXCR3 is expressed on T cells, NK cells, monocytes, dendritic cells, endothelial cells, fibroblasts, and keratinocytes. **This statement is TRUE.** CXCR3 ligands act as potent leukocyte chemoattracants, and they are likely to modulate the abundance of NK and other T-cell populations at sites of acute and chronic injury. The delayed reappearance of a chronic wound phenotype in the present report may well reflect a contribution of the CXCR3 signal pathway in the immune system rather than resident epithelial and mesenchymal cells.
19. Neurodegenerative diseases are common and essentially untreatable. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2058-2066; DOI: 10.2353/ajpath.2010.091077; the author of the referenced article did not disclose any relevant financial relationships.]

a. Alzheimer’s disease affects about 35% of people over the age of 70.  **This statement is NOT TRUE.** Alzheimer’s disease, the most prevalent neurodegenerative disorder, affects about 10% of people over the age of 70.

b. Parkinson’s disease is the second most frequent neurodegenerative disease.  **This statement is TRUE.** Parkinson’s disease affects approximately 2% of individuals over the age of 70.

c. Advancing age is the most important risk factor for Alzheimer’s disease, Parkinson’s disease, and related neurodegenerative disorders.  **This statement is TRUE.** Because the population of the United States is aging, neurodegenerative diseases will represent an increasing burden on individuals, families, and the health care system in the coming years.

d. Huntington’s disease is a rare neurological disorder.  **This statement is TRUE.** Huntington’s disease is only one example of a group of disorders caused by expansion of a CAG repeat that encodes a polyglutamine stretch within the host protein.

e. Less common neurodegenerative diseases include progressive supranuclear palsy, Pick’s disease, and corticobasal degeneration.  **This statement is TRUE.** These diseases are characterized by significant tau pathology, and are often termed “tauopathies.”

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20. Molecular genetics has facilitated important insights into the pathogenesis of Huntington’s disease. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2058-2066; DOI: 10.2353/ajpath.2010.091077; the author of the referenced article did not disclose any relevant financial relationships.]

a. The gene for Huntington’s disease is located on the short arm of chromosome 4.  **This statement is TRUE.** This work was done using anonymous DNA markers, an early landmark application of molecular genetic technology to the study of neurodegenerative disease.

b. Huntingtin is a very large (>350kDa) protein.  **This statement is TRUE.** Molecular cloning of this locus revealed this novel protein of unknown function.

c. Cloning of the Huntington disease gene provided significant insight into the pathogenesis of Huntington’s disease.  **This statement is TRUE.** CAG trinucleotide expansion occurs within the gene.  When an allele has expanded sufficiently (>34 units), neurodegeneration occurs.

d. When the mouse homolog of the Huntington disease gene is inactivated, mice die in early embryogenesis.  **This statement is TRUE.** Simply reducing gene function is not a good model for this disorder.

e. Mice that overexpress mutant, polyglutamine expanded forms of huntingtin die shortly after birth.  **This statement is NOT TRUE.** Mice that overexpress mutant, polyglutamine expanded (the nucleotide forms of huntingtin have progressive neurological phenotypes, and in some models, neuronal cell loss and early death.)
21. Most cases of Parkinson’s disease do not have an obvious genetic basis. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2058-2066; DOI: 10.2353/ajpath.2010.091077; the author of the referenced article did not disclose any relevant financial relationships.]

a. Parkinson’s disease is characterized by the presence of abnormal protein aggregates in affected brain tissues. This statement is TRUE. Lewy bodies and Lewy neuritis are observed in Parkinson’s disease.
b. Genetic cloning of the first Parkinson’s disease gene was reported in 1997. This statement is TRUE. The autosomal dominant PARK1 locus encodes α-synuclein, an abundant neuronal protein of unknown function.
c. Missense mutations in α-synuclein are a common cause of Parkinson’s disease. This statement is NOT TRUE. Missense mutations in α-synuclein are a very rare cause of Parkinson’s disease. However, the presence of α-synuclein in Lewy bodies and Lewy neuritis suggests that this protein plays a role in both genetic and spontaneous Parkinson’s disease.
d. Models over-expressing α-synuclein replicate key biochemical and cell biological features of Parkinson’s disease. This statement is TRUE. These models include expression of human α-synuclein in yeast, C. elegans, mice, rats, and monkeys.
e. Although mutant forms of α-synuclein were somewhat more toxic that wild-type α-synuclein in a Drosophila model of Parkinson’s disease, there were very similar pathologies when either wild-type or mutant versions of the protein were expressed. This statement is TRUE. The recent description of duplications and triplications of the α-synuclein locus in familial Parkinson’s disease lends strong support to the hypothesis that wild-type α-synuclein can cause neuronal death and dysfunction in patients when levels of the protein are elevated.

22. Posttranslational modifications are important in determining neurotoxicity of aggregation-prone proteins in experimental models of Alzheimer’s disease and related tauopathies. Based on the referenced Award Lecture, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2058-2066; DOI: 10.2353/ajpath.2010.091077; the author of the referenced article did not disclose any relevant financial relationships.]

a. Neurofibrillary tangles are one of the major pathological hallmarks of Alzheimer’s disease. This statement is TRUE. Neurofibrillary tangles are comprised of abnormally hyperphosphorylated and aggregated tau protein.
b. Pathological protein aggregates in Alzheimer’s disease include extracellular amyloid plaques, which are composed of large, hypophosphorylated and hypomethylated amyloid precursor protein. This statement is NOT TRUE. Pathological protein aggregates in Alzheimer’s disease include extracellular amyloid plaques, which are composed of short Aβ peptides derived from the larger amyloid precursor protein.
c. Hirano bodies are eosinophilic, rod-shaped inclusions that are rich in actin, contain coflin, and bind phalloidin. This statement is TRUE. Hirano bodies are a lesser known, although frequent, pathological aspect of Alzheimer’s disease and related neurodegenerative disorders.
d. Hyperphosphorylated tau is present in neurofibrillary tangles. This statement is TRUE. Genetic findings strongly supported a causal role for tau in mediating neurodegeneration.
e. Increasing kinase activity enhances tau toxicity, whereas increasing phosphatase activity ameliorates the deleterious effects of tau expression. This statement is TRUE. These genetic findings supported a role for tau phosphorylation in mediating neurotoxicity.

23. Cancer cells are frequently characterized by abnormal receptor signaling. Based on the referenced Commentary and related article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2088-2091; DOI: 10.2353/ajpath.2010.091284 and Am J Pathol 2010, 176:2435-2446; DOI: 10.2353/ajpath.2010.081059; none of the authors disclosed any relevant financial relationships.]

a. Abnormal receptor signaling can involve cell-surface receptor tyrosine kinases, several types of extracellular matrix receptors, and different kinds of G protein-coupled cell surface receptors. This statement is TRUE. This aberrant signaling can drive tumor cell proliferation, angiogenesis, motility, migration, and invasion, as well as metastasis.
b. CXCR3, a chemokine receptor belonging to the G protein-coupled cell surface receptor family, exists as three alternatively-spliced forms: CXCR3-A, CXCR3-B, and CXCR3-alt. This statement is TRUE. CXCR3 can bind with high affinity to the interferon-γ-induced chemokines CXCL9, CXCL10, and CXCL11.
c. CXCR3 is expressed in several types of tumors, including melanoma, breast cancer, and colon cancer. This statement is TRUE. CXCR3 is also linked to basal cell carcinoma.
d. Expression of both CXCR3 and its ligands was increased significantly in non-lesional skin tissue relative to basal cell carcinoma lesions. This statement is NOT TRUE. Expression of both CXCR3 and its ligands was increased significantly in basal cell carcinoma lesions relative to non-lesional skin tissue.
e. The study by Lo et al implicates CXCR3 and CXCL3-ligand up-regulation in basal cell carcinoma genesis through potentially opposing autocrine and/or paracrine mechanisms. This statement is TRUE. The dual activities of CXCR3 signaling pathways may contribute to the poorly aggressive and rarely metastatic nature of basal cell carcinoma by recruiting T cells and inhibiting endothelial cells carrying high levels of CXCR3-B, resulting in angiostatic activity.
24. Experimental autoimmune encephalomyelitis (EAE) serves as a mouse model of multiple sclerosis. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2764-2775; DOI: 10.2353/ajpath.2010.090855; none of the authors disclosed any relevant financial relationships.]

   a. EAE is thought to be mediated by regulatory B cells. **This statement is NOT TRUE. EAE is thought to be primarily mediated by pro-inflammatory T cells.**
   
   b. There is evidence that Th17 cells initiate the inflammatory process in EAE. **This statement is TRUE. These interleukin-17-secreting T cells are antigen-specific and CD4⁺.**
   
   c. Th1 cells propagate the inflammatory process in EAE. **This statement is TRUE. These T cells secrete high levels of interferon-γ and low levels of interleukin-4.**
   
   d. Cytokines secreted by Th1 cells may suppress the effects of Th17 cells in EAE. **This statement is TRUE. Interferon-γ suppresses the selection and activity of Th17 cells.**
   
   e. Targeting Th17 cells at early stages of disease may inhibit disease initiation. **This statement is TRUE. Rescuing Th17 regulatory cells at early stages of disease suppresses disease development.**

25. Regulatory T cells can restrain T cell function. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2764-2775; DOI: 10.2353/ajpath.2010.090855; none of the authors disclosed any relevant financial relationships.]

   a. CD25⁺Foxp3⁺ CD4⁺ T cells likely suppress effector cell functions nonspecifically. **This statement is TRUE. These cells are classically referred to as T regulatory cells.**
   
   b. Tr1 cells are regulatory T cells that produce interleukin (IL)-10. **This statement is TRUE. Tr1 cells are antigen-specific.**
   
   c. Th3 cells are cells with regulatory function that produce tumor necrosis factor (TNF)-α. **This statement is NOT TRUE. Th3 cells are cells with regulatory function that produce transforming growth factor (TGF)-β.**
   
   d. Cells that express high levels of interferon-γ serve as regulatory cells in EAE. **This statement is TRUE. The Th17/Th1 ratio is an important factor in the dynamics of disease.**
   
   e. Th17 regulatory cells are highly susceptible to Fas-mediated apoptosis. **This statement is TRUE. Targeting these cells via FasL-induced apoptosis results in disease development.**

26. Limb girdle muscular dystrophy (LGMD2B) is caused by mutations in the dysferlin gene. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:2891-2900; DOI: 10.2353/ajpath.2010.090058; none of the authors disclosed any relevant financial relationships.]

   a. Patients with LGMD2B are often healthy into their late teens. **This statement is TRUE. Onset can be quite sudden, and there is little evidence of muscle weakness prior to disease initiation.**
   
   b. Patients with LGMD2B often have muscle inflammation. **This statement is TRUE. Dysferlin-deficient monocytes show increased phagocytic activity compared with normal cells.**
c. An inflammatory cascade may initiate, exacerbate, and possibly perpetuate the underlying myofiber-specific dystrophic process. This statement is TRUE. Mild myofiber damage in dysferlin-deficient muscle may stimulate this inflammatory cascade, or inflammasome.
d. Dysferlin plays a role in vesicle trafficking and membrane repair. This statement is TRUE. Dysferlin-deficient muscle has increased levels of vesicle trafficking-related proteins such as synaptotagmin-like protein, Slp2, small GTPase, and Rab27A.
e. Dysferlin is a transcription factor that directly regulates production of inflammasome components. This statement is NOT TRUE. Inflammasome components are present in muscle independently of dysferlin. The endogenous danger signals generated as a result of dysferlin-deficiency may contribute to the activation of the muscle inflammasome, which in turn generates a proinflammatory environment in muscle that leads to increased muscle inflammation and damage.

27. Galectin family members bind β-galactosidase derivatives. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 176:3023-3031; DOI: 10.2353/ajpath/2010.090876; none of the authors disclosed any relevant financial relationships.]

a. Galectins are nonglycosylated soluble proteins that can be found both intra- and extra-cellularly depending on cell type. This statement is TRUE. Galectin localization also depends on cell cycle stage and differentiation state.
b. Galectins have been implicated in a wide range of cellular functions, including embryonic development and wound healing. This statement is TRUE. Galectins have also been implicated in apoptosis, intercellular adhesion, cell migration, the immune response, and cancer.
c. Galectin-7 may function as an apoptotic regulator. This statement is TRUE. Galectin-7 can render tumor cells more susceptible to apoptotic stimuli.
d. Galectin-7 expression is decreased in chemically-induced mammary carcinomas as compared with normal mammary tissue. This statement is NOT TRUE. Galectin-7 expression is increased in chemically-induced mammary carcinomas as compared with normal mammary tissue.
e. Galectin-7 is a critical determinant in spontaneous metastasis of lung and bone-homing breast tumor cells. This statement is TRUE. Galectin-7 is specifically expressed in aggressive breast carcinomas.
28. Vascular smooth muscle cells play a major role in atherosclerosis, the underlying cause of most myocardial infarctions and strokes. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:4-9; DOI: 10.2353/ajpath.2010.090615; the authors of the referenced article did not disclose any relevant financial relationships.]

- a. Atherosclerosis occurs in large and medium-sized arteries and develops over time. **This statement is TRUE.** Atherosclerosis development starts with fatty streaks, progresses to intermediate lesions, and eventually proceeds to advanced and complicated lesions at risk of rupture.
- b. Vascular smooth muscle cell numbers decrease in moderate to advanced atheromas. **This statement is NOT TRUE.** Vascular smooth muscle cell accumulation is a hallmark of moderate to advanced atheromas.
- c. Within the plaque, vascular smooth muscle cells act by modulating extracellular matrix deposition and contraction. **This statement is TRUE.** Vascular smooth muscle cells also modulate proliferation and inflammation.
- d. Early in plaque development, vascular smooth muscle cells secrete inflammatory mediators, such as monocyte chemoattractant protein-1 (MCP-1), interleukins, and tumor necrosis factor-α. **This statement is TRUE.** These factors, along with adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), promote macrophage infiltration and accumulation.
- e. Vascular smooth muscle cells within an atherosclerotic plaque undergo phenotypic switching, moving from a more contractile to a synthetic state. **This statement is TRUE.** Vascular smooth muscle cells and other local cells can modify the local atherosclerotic milieu and remodel the extracellular matrix, which is critical in determining the stability of the plaque.

29. Biomechanical stress plays a key role in atherosclerotic vasculature. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:4-9; DOI: 10.2353/ajpath.2010.090615; the authors of the referenced article did not disclose any relevant financial relationships.]

- a. Large arteries undergo both shear stress and cyclic strain. **This statement is TRUE.** Veins experience only low levels of shear stress and cyclic strain.
- b. Biomechanical forces promote atherogenesis, specifically at curves, branch points, and bifurcations of vessels. **This statement is TRUE.** Atheromas most often arise in the branching coronary and carotid arteries, in the abdominal aorta at the branches for the abdominal arteries, and around the iliac bifurcation.
- c. Atherosclerosis affects local biomechanics, with increased arterial distensibility at both the site of atherosclerosis and in proximal normal tissues. **This statement is NOT TRUE.** Atherosclerosis decreases arterial distensibility at both the site of atherosclerosis and in proximal normal tissues. Vascular smooth muscle cell proliferation and inflammatory infiltrates, extracellular matrix synthesis and remodeling, excess free cholesterol, and interior necrosis and calcifications can further decrease vessel compliance in atherosclerotic plaques.
d. Mechanosensors are differentially regulated in atherosclerotic compared with normal vasculature. This statement is TRUE. The angiotensin type I receptor, which has been shown to be a mechanosensor in vascular smooth muscle cells, is upregulated in atherosclerosis. Furthermore, spontaneously hypertensive rats were shown to have more sensitive stretch-activated ion channels. Additionally, expression of integrin α5β1 on vascular smooth muscle cells is limited to atheromas.

e. One manner in which atherosclerotic changes arise following biomechanical stress is through modulation of gene transcription. This statement is TRUE. A variety of genes are upregulated in vascular smooth muscle cells in response to cyclic strain, including α-actinin, extracellular matrix components, cytoskeletal elements, integrins, MCP-1, protease-activated receptor -1, syndecans 1, 2, and 4, and many other genes.

30. Non-alcoholic fatty liver disease (NAFLD) often leads to liver failure and the development of hepatocellular carcinoma. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:10-12; DOI: 10.2353/ajpath.2010.100410 and Am J Pathol 2010, 177:153-165; DOI.2353/ajpath.2010.090895; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. Patients with NAFLD or non-alcoholic steatohepatitis (NASH) often have metabolic abnormalities, such as insulin resistance and hyperglycemia. This statement is TRUE. NAFLD is also characterized by hyperlipidemia and visceral adiposity.
   
   b. NAFLD/NASH results in lipid accumulation within hepatocytes. This statement is TRUE. Other histological hallmarks of NAFLD/NASH include balloon degeneration and sinusoidal fibrosis.
   
   c. NAFLD/NASH results in progressive liver injury in association with continued insult. This statement is TRUE. Most of these approaches have resulted in a rodent model that lacks key features of NAFLD/NASH.
   
   d. Previous animal models of NAFLD have taken a genetic approach, a dietary approach, or both. This statement is TRUE. Most of these approaches have resulted in a rodent model that lacks key features of NAFLD/NASH.
   
   e. Ogawa et al have generated an animal model of NAFLD using rabbits fed a high-fat diet that mimics all clinical features of NAFLD/NASH. This statement is NOT TRUE. Their model results in the development of progressive liver fibrosis and hepatic cholesterol accumulation, but there is no concurrent insulin resistance.

31. Resveratrol, a compound that occurs naturally in grapes, has been shown to have protective effects in aging, Alzheimer’s disease, tumorigenesis, and obesity. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:481-492; DOI: 10.2353/ajpath.2010.090836; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. The protective effects of resveratrol in mammals are mediated by NF-κB. This statement is NOT TRUE. The protective effects of resveratrol in mammals are thought to be mediated by the sirtuin family member Sirt1. Resveratrol is a potent activator of mammalian Sirt1. Most of the described effects of resveratrol in higher life forms on the regulation of glucose and insulin production and sensitivity, cell survival, fat metabolism, and effects of caloric restriction are thought to be mediated by Sirt1.
   
   b. Resveratrol improves vascular endothelial and post-ischemic cardiac function in various experimental models, such as those for myocardial infarction and diabetes. This statement is TRUE. The precise effects of resveratrol on post-developmental angiogenesis remain unknown.
   
   c. Resveratrol has been shown to be pro-angiogenic in the ischemic myocardium. This statement is TRUE. However, resveratrol inhibits anti-angiogenic properties in cancer.
   
   d. Resveratrol inhibits pathogenic angiogenesis. This statement is TRUE. This inhibition is sirtuin independent.
   
   e. Inhibition of eukaryotic elongation factor 2 kinase completely reverses the effects of resveratrol on blood vessel growth. This statement is TRUE. Inactivation of eukaryotic elongation factor 2 kinase by resveratrol induces cell cycle arrest and inhibits the proliferation and migration of vascular endothelial cells, severely blunting neovascular response after injury.
32. Cripto-1 signaling constitutes a key pathway in embryonic stem cells. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:532-540; DOI: 10.2353/ajpath.2010.100102; none of the authors disclosed any relevant financial relationships.]

a. After fertilization, totipotent stem cells of the blastocyst give rise to all tissues. **This statement is TRUE.** With subsequent cell divisions, stem cells retain their self-renewal capacity, but they become more restricted in their differentiation potential, becoming progenitor cells (adult or somatic stem cells) that give rise to differentiated somatic cells in specific tissues.

b. During embryonic development, Cripto-1/Nodal signaling is involved in regulating the formation of the primitive streak, patterning of the Anterior/Posterior (A/P) axis, specification of mesoderm and endoderm during gastrulation, and establishment of Left/Right (L/R) asymmetry of developing organs. **This statement is TRUE.** Mouse embryos that lack the *Cripto-1* gene (*Cripto-1*−/− mice) die at day 7.5 of embryogenesis due to defects in mesoderm formation and axial organization.

c. *Cripto-1*−/− mice exhibit defects in myocardial development. **This statement is TRUE.** These mice do not express terminal myocardial differentiation genes.

d. *Cripto-1*−/− embryoid bodies spontaneously differentiate toward hematopoietic cells. **This statement is NOT TRUE.** *Cripto-1*−/− embryoid bodies spontaneously differentiate toward neurons.

e. Cripto-1 is a direct transcriptional target of Oct-4. **This statement is TRUE.** Cripto-1 is highly enriched in both mouse and human embryonic stem cells, suggesting that Cripto-1 is a critical component of core pathways used by both mouse and human ES cells.

33. There is crosstalk between Cripto-1 signaling and other embryonically important signaling pathways. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:532-540; DOI: 10.2353/ajpath.2010.100102; none of the authors disclosed any relevant financial relationships.]

a. Mouse and human Cripto-1 have been identified as primary target genes of the Wnt/β-catenin signaling pathway during embryonic development and in colon carcinoma cells. **This statement is TRUE.** Wnt signaling and Wnt proteins are important for the maintenance of stem cells in the hair follicle of the skin, the crypt of the colon, and the hematopoietic and the nervous systems.

b. TGF-β family members can directly regulate Cripto-1 expression in human embryonal carcinoma cells and in human colon cancer cells by binding to specific TGF-β binding elements (TBES) within the *Cripto-1* promoter. **This statement is TRUE.** The TGF-β signaling pathway performs important functions during embryonic development and organogenesis as well as during various stages of carcinoma formation in several different tissues.

c. Cripto-1, in addition to functioning as a co-receptor for Nodal, can also bind GDF-1 and GDF-3. **This statement is TRUE.** Besides performing a central role in the patterning of the early embryo during gastrulation, Nodal has been shown to maintain the pluripotency of human embryonic stem cells together with Activin and fibroblast growth factors (FGFs). In the embryo, GDF-1 and GDF-3 are co-expressed with Nodal, suggesting a cooperative action among these ligands during embryonic development.
d. Lefty synergizes with Nodal signaling by binding to Cripto-1, allowing Nodal to bind to its receptor complex. \textit{This statement is NOT TRUE.} Lefty antagonizes Nodal signaling by binding to Cripto-1, preventing Nodal from binding to its receptor complex.

e. Cripto-1 binding to Notch1 induces Notch1 localization in the lipid raft fraction of the endoplasmic reticulum and enhances cleavage of the Notch1 extracellular domain through a furin-like convertase, resulting in the sensitization to ligand-induced activation of Notch signaling. \textit{This statement is TRUE.} Involvement of Notch signaling has also been implicated in adult stem cells from the hematopoietic system, central nervous system, skin, and intestinal mucosa.

34. Cripto-1 signaling is involved in human cancer. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:532-540; DOI: 10.2353/ajpath.2010.100102; none of the authors disclosed any relevant financial relationships.]

a. Cripto-1 induces \textit{in vitro} transformation of normal epithelial cells, promotes epithelial to mesenchymal transition (EMT), and stimulates angiogenesis. \textit{This statement is TRUE.} Stimulation of cell proliferation, motility, survival, and EMT by Cripto-1 is independent of Nodal and relies on activation of the c-Src/mitogen activated protein kinase (MAPK)/AKT signaling pathways through binding of Cripto-1 to the heparan sulphate proteoglycan Glypican-1.

b. Cripto-1 deficiency in the mouse mammary gland results in mammary hyperplasias and adenocarcinomas. \textit{This statement is NOT TRUE.} Overexpression of a human Cripto-1 transgene in the mouse mammary gland results in mammary hyperplasias and adenocarcinomas.

c. Cripto-1 is expressed at high levels in different types of human tumors, including breast, colon, gastric, pancreatic, lung, cervical, endometrial, skin, testis, bladder, and ovarian carcinomas. \textit{This statement is TRUE.} \textit{Cripto-1 might represent an example of an embryonic gene that is re-expressed in adult tissues, possibly in stem cells, in an inappropriate fashion and thereby may contribute to the pathogenesis of cancer.}

d. Cripto-1 is highly expressed in a subpopulation of human embryonal carcinoma cells with cancer stem-like characteristics. \textit{This statement is TRUE.} Emerging evidence clearly suggests that cancers can grow and metastasize from cancer stem cells.

e. Cripto-1 has been identified in a small subset of stem-like cells in human malignant melanomas. \textit{This statement is TRUE.} Cripto-1 has also been identified in androgen-responsive and refractory human prostate tumor cell lines.

35. miRNA expression profiles have been used to successfully classify many tumor types. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:908-917; DOI: 10.2353/ajpath.2010.091150 and Am J Pathol 2010, 177:541-543; DOI: 10.2353/ajpath.2010.100479; none of the authors disclosed any relevant financial relationships.]

a. miRNA genes undergo sequential cleavage through type III ribonucleases, Drosha and Dicer, to generate mature 21-24 nucleotide miRNAs. \textit{This statement is TRUE.} Intergenic and intronic miRNAs located on the opposite strand of a host gene are transcribed through the same RNA polymerase II-dependent processes as those at protein-coding loci. However, sequential cleavage of the pre-miRNA s occurs through type III ribonucleases.

b. The guide strand of a mature miRNA undergoes partial complementary base pairing with target sequences located in processed messenger RNAs. \textit{This statement is TRUE.} This base pairing results in translational suppression or mRNA degradation.

c. miRNAs are important determinants of an embryonic stem cell’s ability to self-renew or differentiate. \textit{This statement is TRUE.} These two opposing processes are intricately tied to the development of neoplasia.

d. Families of miRNAs can act as either tumor suppressors or oncogenes. \textit{This statement is TRUE.} Expression profiles of both miRNA genes and protein-coding genes have thus resulted in sub-classifications of tumor types and, by extension, generation of new ideas about the origins and potential treatment of human neoplasias.

e. Danielson et al report novel miRNA profiles during the transition from bone marrow-derived mesenchymal stem cells (MSCs) to differentiated skeletal muscle cells, as well as in leiomyomas and leiomyosarcomas of human origin. This statement is NOT TRUE. Danielson et al report novel miRNA profiles during the transition from bone marrow-derived MSCs to differentiated smooth muscle cells as well as in leiomyomas and leiomyosarcomas of human origin, and they provide novel insight into how miRNA profiling may be exploited to assist clinicians in accurately diagnosing these tumor types.
36. Anoikis is cell death resulting from loss of cell-cell and cell-matrix interactions. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1044-1052; DOI: 10.2353/ajpath.2010.091270; none of the authors disclosed any relevant financial relationships.]

a. The primary effector mechanisms of anoikis appear to be autophagy and apoptosis. This statement is TRUE. Cells undergoing anoikis kill themselves, therefore not killing the organism with tumor spread and ectopic growth.

b. Anoikis is regulated by apoptosis-signaling mechanisms. This statement is TRUE. Under certain circumstances, however, suppression of apoptosis is insufficient to abrogate cell death via anoikis, and autophagy mediates cell death.

c. Autophagy is capable of either promoting or inhibiting apoptosis. This statement is TRUE. Apoptotic pathways can in turn modulate autophagy, pushing cells into surviving anoikis.

d. For cancer cells to overcome anoikis and metastasize, tumors must both arrest autophagy and use apoptosis in a way that promotes their survival. This statement is NOT TRUE. For cancer cells to overcome anoikis and metastasize, tumors must both arrest apoptosis and use autophagy in a way that promotes their survival.

e. Beclin 1 provides a key point of crosstalk between apoptosis and autophagy and is thus important in anoikis. This statement is TRUE. Beclin 1 is known as Atg6 in yeast cells and is an early component of the autophagic vesicle, which is destined to later become an autophagosome.

37. Apoptosis can be divided into two pathways: extrinsic and intrinsic. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1044-1052; DOI: 10.2353/ajpath.2010.091270; none of the authors disclosed any relevant financial relationships.]

a. The extrinsic apoptotic pathway is death receptor-dependent. This statement is TRUE. The extrinsic pathway is initiated when membrane-bound death receptors bind with soluble ligands.

b. The intrinsic apoptotic pathway is ribosome-dependent. This statement is NOT TRUE. The intrinsic apoptotic pathway is mitochondria-dependent.

c. Both the extrinsic and intrinsic apoptotic pathways activate caspases. This statement is TRUE. Caspases are cysteine proteases that enzymatically destroy the cell in a manner that, unlike necrosis, avoids inflammation.

d. Fas receptor, tumor necrosis factor receptor 1 (TNFR1), and TNF-related apoptosis-inducing ligand receptor-1 or -2 (TRAIL R1/R2) are death receptors involved in the extrinsic apoptotic pathway. This statement is TRUE. They bind with soluble ligands such as Fas ligand, TNF-α, or TRAIL, respectively.

e. The intrinsic apoptotic pathway is activated in response to cell stressors including oxidative stress, DNA damage, viral infection, and ultraviolet radiation. This statement is TRUE: This pathway is intracellularly mediated by the Bcl-2 family of proteins.
38. Cells undergoing autophagy break down and recycle vital internal components. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1044-1052; DOI: 10.2353/ajpath.2010.091270; none of the authors disclosed any relevant financial relationships.]

- a. Autophagy is triggered by nutrient deprivation, starvation, and other stress stimuli. This statement is TRUE: Autophagy processes long-standing macromolecules and whole organelles, most notably the mitochondrion.
- b. Autophagy occurs in a wide range of biological phenomena, including development, starvation, and immunity. This statement is TRUE: Autophagy also occurs during aging, neurodegeneration, and cancer.
- c. The first phase of autophagy, induction, occurs in response to environmental stressors like nutrient deprivation, oxidative stress, infection, or hypoxia. This statement is TRUE. In the second phase, structures targeted for degradation are enveloped by a membrane called an autophagophore. The resulting double-layered membrane is an autophagosome.
- d. In the third phase of autophagy, an autophagosome fuses with a lysosome containing hydrolytic enzymes, forming an autophagolysosome. This statement is TRUE. The fourth and final phase of autophagy consists of the actual enzymatic degradation and recycling of materials, upon which the cell breaks down and recycles vital internal components.
- e. Under pro-autophagic conditions like death receptor signaling, Beclin 1 (Atg6 in yeast cells), TNF, and TRAIL aggregate and promote induction. This statement is NOT TRUE: Under pro-autophagic conditions like amino acid deprivation, Beclin 1 (Atg6 in yeast cells), PI3K III, and Vps34 aggregate and promote induction.

39. Several neurodegenerative diseases in which there is accumulation of misfolded proteins are associated with malfunction of both mitochondria and synaptic compartments. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1411-1421; DOI: 10.2353/ajpath.2010.091037; none of the authors disclosed any relevant financial relationships.]

- a. Malfunctions of mitochondrial metabolism may contribute to both aging and neurodegenerative disease. This statement is TRUE. These malfunctions include reduced ATP production, impaired Ca²⁺ buffering, and generation of reactive oxygen species.
- b. Inner-membrane structural alterations have been consistently implicated in processes associated with apoptosis and as a response to oxidative stress in various neurodegenerative diseases. This statement is TRUE. Numerous dilated or swollen cristae in particular have been implicated in various neurodegenerative diseases.
- c. Neuronal mitochondria display considerable morphological diversity, particularly in terms of the folding of the energy-transducing inner membrane, which forms numerous invaginations or cristae. This statement is NOT TRUE. Neuronal mitochondria display considerable morphological uniformity particularly in terms of the folding of the energy-transducing inner membrane, which forms numerous invaginations or cristae.
- d. The interdependence of synaptic activity and mitochondrial distribution has been described both at the presynaptic and the postsynaptic elements of dendritic spines of living hippocampal neurons. This statement is TRUE. Within the neuron, the synaptic compartment is the site at which demands on mitochondrial functions, such as energy supply and buffering of intracellular Ca²⁺, are especially significant.
- e. Sisková et al suggest that mitochondrial function is impaired and could potentially contribute to or even initiate the synaptic pathology in prion disease. This statement is TRUE. Mitochondrial dysfunction in prion disease appears to occur due to inhibition or modification of the respiratory complex rather than deletions of mitochondrial DNA.
40. MicroRNAs (miRNA) are short (20-22nt) non-coding RNAs that regulate gene expression post-transcriptionally. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1592-1599; DOI: 10.2353/ajpath.2010.100024; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. The first miRNA was discovered in 1986 in the zebrafish, where it was found to regulate post-embryonic development. This statement is NOT TRUE. The first miRNA was discovered in 1993 in the nematode Caenorhabditis elegan, where it was found to regulate post-embryonic development.
   
   b. miRNAs have been identified in plants, viruses, animals and humans. This statement is TRUE. Many have been evolutionarily conserved between species.
   
   c. More than 700 human miRNAs have been discovered to date. This statement is TRUE. The number is increasing rapidly.
   
   d. miRNA expression levels differ between normal and tumor tissues and vary among tumor types. This statement is TRUE. These data suggest that miRNAs play an important role in oncogenesis, leading to the notion of miRNA as potential biomarkers in early diagnosis of cancer.
   
   e. Since miRNAs can bind with different degrees of complementarity, these molecules can recognize and bind a variety of mRNAs. This statement is TRUE. These molecules then potentially regulate translation and mRNA degradation, and ultimately the expression of corresponding proteins.

41. Diagnostic surveillance along with improved treatment strategies have contributed to earlier detection and improved survival from colorectal cancer (CRC). Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1592-1599; DOI: 10.2353/ajpath.2010.100024; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Almost 50% of patients diagnosed with CRC will die of the disease. This statement is TRUE. CRC patient deaths are largely due to metastasis development, most commonly in the liver and lungs.
   
   b. Treatment decisions for CRC are almost exclusively based on genomic profiling. This statement is NOT TRUE. Treatment decisions for CRC are almost exclusively based on tumor stage as determined by radiological and/or traditional anatomic pathological evaluation.
   
   c. There is a diagnostic limitation in identifying high- and low-risk patients. This statement is TRUE. Patients may receive either insufficient or unnecessary treatment, respectively.
   
   d. Some miRNAs have been found to be overexpressed in CRC tissues with high tumor to normal ratios. This statement is TRUE. These miRNAs were also associated with poor overall survival.
   
   e. The targets of many miRNA molecules are associated with pathways and processes relevant for CRC carcinogenesis and progression. This statement is TRUE. Clinical relevance has not been verified for many of these differentially expressed miRNAs.
42. Glucose production in the liver depends on autophagy. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1600-1602; DOI: 10.2353/ajpath.2010.100679 and Am J Pathol 2010, 177:1936-1945; DOI: 10.2353/ajpath.2010.100363; the authors of the referenced articles did not disclose any relevant financial relationships.]

a. Autophagy is a tightly regulated catabolic process that involves the degradation of a cell’s own components. This statement is TRUE. Cellular components are degraded via lysosomal machinery.

b. Autophagy is a major mechanism by which a starving cell reallocates nutrients from unnecessary processes. This statement is TRUE. The cell reallocates nutrients to processes that are essential for cell survival.

c. Autophagy provides the biochemical intermediates for glucose production. This statement is TRUE. Autophagy provides these intermediates through the hydrolysis of proteins, glycogen, and triglycerides.

d. Autophagy involves the formation of a membrane around a targeted region of the cell, separating the contents from the rest of the cytoplasm. This statement is TRUE. The resultant vesicle then fuses with a lysosome, which subsequently degrades the vesicular contents.

e. Since insulin activates autophagy, conditions in which there is a deficiency in insulin, such as fasting, starvation, and type I diabetes, decrease autophagy in the liver. This statement is NOT TRUE. Insulin inhibits autophagy. Conditions in which there is an insulin deficiency, such as fasting, starvation, and type I diabetes, increase autophagy in the liver.

43. Suppressor of glucose by autophagy (SOGA) can explain how adiponectin leads to inhibition of autophagy during the activation of adenosine monophosphate kinase (AMPK). Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:1600-1602; DOI: 10.2353/ajpath.2010.100679 and Am J Pathol 2010, 177:1936-1945; DOI: 10.2353/ajpath.2010.100363; the authors of the referenced articles did not disclose any relevant financial relationships.]

a. AMPK integrates nutritional and hormonal signals in peripheral tissues and the hypothalamus. This statement is TRUE. AMPK mediates the effects of adipokines, such as adiponectin, to regulate food intake, body weight, and glucose and lipid homeostasis.

b. In insulin resistance, hyperinsulinemia, in the context of a decline in circulating adiponectin, eventually leads to a loss of adequate hepatic insulin signaling and enhanced gluconeogenesis in the liver. This statement is TRUE. Autophagy is increased by insulin resistance, which contributes to enhanced gluconeogenesis.

c. The lowered expression of SOGA (i.e., in response to adiponectin) is able to lower liver glucose production through the inhibition of autophagy, which results in a decrease in plasma glucose concentrations. This statement is NOT TRUE. The elevation of SOGA (i.e., in response to adiponectin) is able to lower liver glucose production through the inhibition of autophagy, which results in a decrease in plasma glucose concentrations.

d. Increasing adiponectin concentrations using pioglitazone in ob/ob mice had profound effects on liver SOGA expression. This statement is TRUE. These results support the hypothesis that the elevation of SOGA levels by adiponectin increases insulin sensitivity.

e. The Atkins diet may function by improving insulin sensitivity via the direct inhibition of autophagy in the liver, thus decreasing gluconeogenesis. This statement is TRUE. The Atkins diet relies heavily on ketosis as a method of reducing body fat, which, in itself, can be considered a form of cellular autophagy.
44. Cicatricial alopecias are an uncommon set of disorders that result in permanent and irreversible hair loss. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:2152-2162; DOI: 10.2353/ajpath.2010.100454; the authors of the referenced article did not disclose any relevant financial relationships.]

a. Clinically, cicatricial alopecia is characterized by the disappearance of blood vessels within an area of hair loss. This statement is NOT TRUE. Clinically, cicatricial alopecia is characterized by the disappearance of visible follicular ostia within an area of hair loss.

b. Histologically, alopecia development corresponds to hair follicle (HF) destruction. This statement is TRUE. Alopecia is also characterized by the subsequent replacement of hair follicles with fibrous tissue.

c. In primary cicatricial alopecia (PCA), the follicle itself is the target of the disease process. This statement is TRUE. In secondary cicatricial alopecia, hair follicles are destroyed coincidentally as part of a more generalized tissue-damaging event.

d. Tissue-damaging events that may lead to cicatricial alopecias include deep skin infection and thermal burn. This statement is TRUE. Other damaging events may include trauma or ionizing radiation.

e. Cicatricial alopecia may result in major disfigurement. This statement is TRUE. It also may result in discomfort and psychological distress.

45. PCA results from the irreversible destruction of key epithelial stem cells in the hair follicle. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:2152-2162; DOI: 10.2353/ajpath.2010.100454; the authors of the referenced article did not disclose any relevant financial relationships.]

a. During the hair cycle, phases of active growth in the hair follicles alternate with massive apoptosis-driven hair follicle regression and periods of relative quiescence. This statement is TRUE. Active growth, regression, and quiescence are called anagen, catagen, and telogen, respectively.

b. The constant and lifelong remodeling activity of the hair follicle absolutely depends on the presence of functional hematopoietic stem cells (HSCs). This statement is NOT TRUE. The constant and lifelong remodeling activity of the hair follicle absolutely depends on the presence of functional epithelial hair follicle stem cells (eHFSCs). These cells reside at the insertion point of the arrector pili muscle (APM), in the outermost layer of the outer root sheath—the so-called “bulge” region.

c. PCA causes the hair follicle to lose the capacity to maintain and regenerate itself. This statement is TRUE. This results from an inflammatory attack on the hair follicle.

d. The current classification of PCAs heavily relies on the predominant inflammatory infiltrate seen. This statement is TRUE. Disorders are grouped as lymphocytic, neutrophilic, mixed, or nonspecific.

e. PCA offers a highly accessible model for studying how various inflammatory events and immunoregulatory mechanisms combine to attack epithelial stem cell populations. This statement is TRUE. PCA also provides a model system in which to identify the signals that incite the inflammatory attack.
46. The immune response in hair follicles is key to the pathology of PCA. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:2152-2162; DOI: 10.2353/ajpath.2010.100454; the authors of the referenced article did not disclose any relevant financial relationships.]

a. The distal hair follicle epithelium has high numbers of intraepithelial T cells and Langerhans cells. This statement is TRUE. It is also densely surrounded by the key cellular protagonists of innate immunity (i.e., peri-follicular mast cells and macrophages) and expresses a battery of antimicrobial peptides, such as human β2-defensin, psoriasin, cathelicidin, and RNase 7.

b. The hair follicle immune system has established a complex system of checks and balances. This statement is TRUE. These checks and balances control and suppress the excessive hair follicle inflammation that leads to PCA.

c. Large stretches of the hair follicle epithelium express potent endogenous immunosuppressants. This statement is TRUE. These immunosuppressants, which include transforming growth factor (TGF)-β1/2 and α-melanocyte-stimulating hormone, most likely inhibit PCA development.

d. Some compartments of the hair follicle epithelium, most prominently the anagen hair bulb, appear to have established an area of relative immune privilege. This statement is TRUE. These compartments are characterized by low or absent expression of major histocompatibility complex (MHC) class I and class II molecules and by the local production of immunosuppressants.

e. The establishment of immune privilege in the anagen hair bulb is thought to result in the development of PCA. This statement is NOT TRUE. The collapse of the area of immune privilege of the anagen hair bulb is thought to result in PCA.

47. The stromal cell derived factor-1 (SDF-1):CXCR4 axis plays a key role in the recruitment of stem cells to areas of tissue injury in multiple organ systems. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:2166-2168; DOI: 10.2353/ajpath.2010.100803; Marc S. Penn, MD, PhD is listed on patent applications filed by the Cleveland Clinic Foundation for the use of SDF-1 and CXCR4 for tissue repair; and Am J Pathol 2010, 177:2268-2277; DOI: 10.2353/ajpath.2010.100134; ajp10-0134; the authors of the referenced article did not disclose any relevant financial relationships.]

a. The expression of SDF-1 at the time of acute injury induces the recruitment of endogenous tissue-specific stem cells. This statement is TRUE. SDF-1 expression during acute injury also directs the preservation of end-organ cells such as cardiac myocytes.

b. Re-establishing SDF-1 expression late after tissue injury could serve as a strategy to induce tissue repair. This statement is TRUE. This hypothesis is now the focus of an on-going clinical trial in patients with chronic heart failure (http://ClinicalTrials.gov, NCT01082094).

c. Up-regulation of CXCR4 on end-organ cells often occurs at a time when SDF-1 expression is declining. This statement is TRUE. One hypothesis to explain this apparent discrepancy is that since SDF-1:CXCR4 expression is intimately involved in tumor metastases; evolution has favored mammals that, in adulthood, have SDF-1 expression temporally misaligned with organ CXCR4 expression.

d. The presence of vascular changes associated with increased SDF-1 expression in patients with retinal detachment suggests that SDF-1 expression is associated with recruitment of bone marrow-derived endothelial progenitor cells. This statement is NOT TRUE. There is a lack of vascular changes associated with increased SDF-1 expression in patients with retinal detachment. This suggests that SDF-1 expression is not associated with bone marrow-derived endothelial progenitor cell recruitment. Rather, the mechanism of SDF-1-mediated healing or tissue preservation in the eye seems to be more related to that seen in the skin, the healing of which is also not associated with vascular growth.

e. SDF-1 expression in the eye in the setting of retinal detachment is associated with preservation of photoreceptors in the outer nuclear layer. This statement is TRUE. The effects of SDF-1 are specific in response to injury. Inhibition of SDF-1 signaling in the normal eye had no effects on cells in the outer nuclear layer.
48. Current research strategies in neurotrauma are aimed at targeting specific pathways of inflammation. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:2685-2687; DOI: 10.2353/ajpath.2010.100408 and Am J Pathol 2010, 177:3061-3070; DOI:10.2353/ajpath.2010.100158; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. The post-traumatic neuroinflammatory response has been shown to contribute, at least in part, to the development of secondary neuronal cell death. **This statement is TRUE.** Research strategies to prevent these pathological sequelae after spinal cord injury have largely failed in translation from the “bench to bedside.”

   b. High-dose steroids are the current standard of care in the management of acute spinal cord injury. **This statement is NOT TRUE.** High-dose steroids were recently recognized to be harmful, rather than beneficial, in the management of acute spinal cord injury.

   c. Inflammatory targets for neurotrauma treatment include pharmacological inhibition of the complement cascade. **This statement is TRUE.** The complement cascade represents the major effector arm of the innate immune system.

   d. It has been reported that two-thirds of all patients with spinal cord injury have elevated complement levels. **This statement is TRUE.** The authors of a 1980 study postulated that complement activation may propagate a “self-feeding” immunological response responsible for the failure of regeneration of the injured spinal cord.

   e. Genetically engineered mice are currently being used to elucidate specific inflammatory pathways involved in the pathophysiology of neuroinflammation after spinal cord injury. **This statement is TRUE.** Tissue-targeted chimeric complement inhibitors are also being explored.

49. Complement activation is a key component of the inflammatory cascade after neurotrauma. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:2685-2687; DOI: 10.2353/ajpath.2010.100408 and Am J Pathol 2010, 177:3061-3070; DOI:10.2353/ajpath.2010.100158; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. Complement inhibition or complement deficiency worsens injury and slows functional recovery following traumatic injury. **This statement is NOT TRUE.** Complement inhibition or complement deficiency ameliorates injury and improves functional recovery following traumatic injury.

   b. Complement can be activated by any one of three pathways that share a common terminal pathway that culminates in formation of the cytolytic membrane attack complex (MAC). **This statement is TRUE.** Complement can be activated by either the classical, lectin, or alternative pathway.

   c. Classical pathway activation is usually antibody-dependent. **This statement is TRUE.** Classical pathway activation is initiated when C1q binds to an immune complex.

   d. The lectin pathway is activated when mannose binding lectin (MBL; also known as mannose-binding protein (MBP)) binds to conserved carbohydrate structures. **This statement is TRUE.** Ficolin binding to conserved carbohydrate structures may also activate the lectin pathway.

   e. The alternative pathway provides an amplification loop for the classical and lectin pathways. **This statement is TRUE.** The alternative pathway is activated by spontaneous hydrolysis of C3 to a cleavage product (C3b analog) that binds factor B, leading to formation of the alternative...
50. The cellular and molecular mechanisms of complement-mediated neuroinflammation after spinal cord injury are not fully understood. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2010, 177:2685-2687; DOI: 10.2353/ajpath.2010.100408 and Am J Pathol 2010, 177:3061-3070; DOI:10.2353/ajpath.2010.100158; the authors of the referenced articles did not disclose any relevant financial relationships.]

a. fB⁻/⁻ mice, which lack protein factor B of the alternative pathway of complement activation, showed significantly improved locomotor function compared with wild-type controls. **This statement is TRUE.** These mice had significantly improved locomotor function scores for up to 21 days after trauma.

b. Compared to wild-type littermates, fB⁻/⁻ mice had significantly reduced neutrophil infiltration and complement deposition. **This statement is TRUE.** They also had reduced tissue damage in the injured spinal cord.

c. A neutralizing antibody to factor B was able to replicate the neuroprotective effects observed in fB⁻/⁻ mice. **This statement is TRUE.** Factor B is a potent inhibitor of the alternative complement activation pathway.

d. One of the putative mechanisms of complement-mediated neuronal death after spinal cord injury is represented by posttraumatic activation of phosphatidylinositol-specific phospholipase C (PI-PLC). **This statement is TRUE.** PI-PLC renders neurons vulnerable to MAC-mediated lysis.

e. Deficiency of CD59a, which activates the MAC, exacerbated spinal cord injury after neurotrauma. **This statement is NOT TRUE.** CD59a is a complement regulatory molecule that does not activate the MAC.