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. Allergic sensitization in asthma may result from a breakdown in immune tolerance to environmental allergens. Based on the referenced Review, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:3-13; DOI:10.2353/ajpath.2009.071151; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Regulatory T cells and plasmacytoid dendritic cells protect the airway against allergic inflammation. This statement is TRUE. The normal outcome of exposure to numerous indoor and outdoor allergens in non-atopic individuals is immunologic tolerance.

   b. When immunologic tolerance is broken, allergen-specific T cell helper (Th2) cells and IgE are generated. This statement is TRUE. Asthma is defined as a type-I allergic airway disease mediated by Th2 cells and IgE and is characterized by bronchial inflammation that is eosinophilic in nature.

   c. Immune cells, but not structural cells, lead to asthmatic symptoms in atopic individuals. This statement is NOT TRUE. Both immune cells and structural cells contribute to inflamed airways. The involved cells include eosinophils, mast cells, Th2 lymphocytes, dendritic cells, and macrophages as well as airway smooth muscle, mucous glands, and lung epithelium.

   d. Myeloid dendritic cells can cause Th2-skewed sensitization against the inhaled allergen. This statement is TRUE. Co-existing danger-associated molecular patterns may also skew the immune response from tolerance to Th2-mediated immunity.

   e. The breakdown in immune tolerance in asthma may be caused by both genetic and environmental factors. This statement is TRUE. Genetic factors such as predisposition to the development of atopy and environmental factors such as viral infection, intensity and frequency of exposure, and overall “hygiene” seem to contribute to both initial allergic sensitization and severity of response.
2. Immune tolerance in asthma may be overcome by systemic administration of antigen in the presence of a Th₂-skewing adjuvant. Based on the referenced Review, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:3-13; DOI:10.2353/ajpath.2009.071151; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Alum, aluminum hydroxide salts, is the prototypic Th₂-skewing adjuvant even though it lacks conserved pathogen-associated molecular patterns (PAMPs). This statement is TRUE. Alum induces the production of uric acid, which is an endogenous danger-associated molecular pattern (DAMP). Uric acid causes the recruitment of monocytes into the peritoneal cavity followed by their conversion into mature inflammatory cells that drive Th₂ immune responses.

b. The Nalp3 inflammasome is a crucial mediator of the Th₂-skewing properties of alum. This statement is TRUE. Nalp3 is an intracellular protein component belonging to the Nod-like receptor (NLR) arm of the innate immune system that senses both non-self and endogenous DAMPs.

c. Some allergens do not require an adjuvant to induce allergy. This statement is TRUE. Pollens, house dust mites, ragweed, molds, and cockroach proteins do not require alum to induce allergy. These common allergens have intrinsic enzymatic activity, which triggers danger signaling.

d. Contamination of experimental antigens with lipopolysaccharide (LPS) prevents allergic responses in mouse models. This statement is NOT TRUE. LPS contamination induces allergic responses to antigens that normally tolerate in the absence of LPS. This sensitization requires the functional LPS receptor, Toll-like receptor 4 (TLR4).

e. Environmental pollutants can function as adjuvants, increasing the severity of the allergic response. This statement is TRUE. Mice inhaling allergen in the presence of cigarette smoke exhibit increased levels of allergen-specific allergic response compared with mice inhaling allergen alone.

3. Hypersensitivity pneumonitis (HP) is the Th₁ counterpart to asthma. Based on the referenced Review, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:3-13; DOI: 10.2353/ajpath.2009.071151; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. HP is characterized by eosinophilic inflammation. This statement is NOT TRUE. HP is characterized by neutrophil infiltration and a non-atopic neutrophilic inflammation of the respiratory bronchioles, alveoli, and interstitial tissue of the lungs.

b. In HP, airway inflammation in susceptible individuals is initiated by the formation of IgG-antigen immune complexes and T-cell reactivity. This statement is TRUE. IgG and Th₁ cells release inflammatory cytokines that attract macrophages, neutrophils, and Th₁ and cytotoxic T cells into the distal airway walls, alveoli, and interstitium.

c. Whereas dendritic cells are key components of the Th₂ response in asthma, alveolar macrophages may stimulate Th₁ cells and inflammation in HP. This statement is TRUE. Alveolar macrophages in HP have increased expression of the T cell co-stimulatory molecules CD80 and CD86.

d. In asthma, allergens are mainly nonmicrobial in nature; however, the triggers of HP are mostly proteins from bacteria, fungi, and other organisms. This statement is TRUE. The most frequent forms of HP are caused by exposure to microorganisms growing on stored hay or corn (farmer’s lung), by inhalation of proteins present on feather dust and in bird droppings (bird fancier’s lung), or by exposure to contaminated water from air conditioning systems (humidifier fever).

e. Noneosinophilic inflammation is present in the airway lumen of approximately half of asthmatic patients. This statement is TRUE. Some studies show that a proportion of asthmatics, mostly suffering from severe asthma, have increased neutrophil cell counts in the airway lumen. There is ongoing debate as to whether severe asthma might represent a different form of asthma rather than an increase in asthma symptoms.
4. The use of radiation therapy to treat cancer also damages normal tissues. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:44-53; DOI:10.2353/ajpath.2009.080505; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Acute (early) radiation damage is most often observed in rapidly proliferating cells. **This statement is TRUE.** Acute effects are observed either during the treatment course or within a few weeks following treatment. Acute radiation damage is prevalent in tissues with rapidly proliferating cells such as the epithelial surfaces of the skin and alimentary tract.

   b. Radiation does not damage tissues with more slowly dividing cells. **This statement is NOT TRUE.** Radiation causes damage to vital organs, resulting in cell death of slowly dividing cells after a few divisions.

   c. Radiation results in tissue damage through both direct and indirect interactions. **This statement is TRUE.** Radiation activates various cell signaling pathways that lead to expression of pro-inflammatory and profibrotic cytokines, induction of vascular injury, and activation of the coagulation cascade.

   d. Radiation reactions can occur months to years following radiation exposure. **This statement is TRUE.** Late radiation reactions principally result from depletion of tissue-specific stem and progenitor cells, leading to fibrosis, organ dysfunction, and necrosis.

   e. Autologous tissue grafts are often used to reduce the severity of radiation damage. **This statement is TRUE.** Autologous tissue grafts are also used to repair tissue defects or involutional disorders that result from tumor removal.

5. Both preadipocytes and whole subcutaneous pads have been transplanted into patients undergoing radiation therapy, but adipose tissue is highly sensitive to radiation damage. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:44-53; DOI:10.2353/ajpath.2009.080505; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Irradiation induces a rapid loss of the hematopoietic cells resident in adipose tissue. **This statement is TRUE.** Hematopoietic cells are also lost from peripheral blood and bone marrow following irradiation, suggesting that hematopoietic cells in adipose tissue behave similarly to those in other tissues.

   b. Oxidative stress contributes to radiation damage in adipose tissue. **This statement is TRUE.** Oxidative stress levels correlate with both the dose of radiation and the levels of cell death.

   c. Adipose tissue is highly sensitive to lethal, but not sublethal, irradiation. **This statement is NOT TRUE.** Damage to adipose tissue was observed following either sublethal or lethal irradiation.

   d. Radiation decreased the number of proliferating cells and increased the number of apoptotic cells in inguinal fat pads. **This statement is TRUE.** Adipocyte precursors from irradiated mice have a lower proliferative capacity in clonal conditions or in liquid media than precursors from non-irradiated mice.

   e. Irradiation induces morphological changes and alteration in the differentiation potential of precursor cells. **This statement is TRUE.** The decrease in the adipogenic differentiation potential of precursor cells from irradiated mice could be due to either a decrease in the number of preadipocytes or a functional defect in the adipogenic lineage.
6. Patients with pseudoxanthoma elasticum (PXE) experience calcification and mineralization in their soft connective tissues. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:534-540; DOI:10.2353/ajpath.2009.080865; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. PXE mineralization is primarily found in elastic structures within soft connective tissue. This statement is TRUE. The primary manifestations of PXE are in the skin, the eyes, and the arterial blood vessels.

b. In the skin of PXE patients, primary lesions are small, yellowish papules. This statement is TRUE. As PXE progresses, primary lesions combine to form large plaques that are inelastic, leathery, and loose, with a yellow hue.

c. Manifestations of PXE in the eye involve mineralization of the vitreous humor. This statement is NOT TRUE. In PXE patients, mineralization of the Bruch’s membrane, the elastin-containing retinal layer, causes fractures, neovascularization, and retinal bleeding.

d. Mineralization of the arterial blood vessels in PXE results in arteriosclerosis, which often leads to hypertension. This statement is TRUE. Cardiovascular complications of PXE also include intermittent claudication, internal bleeding from the gastric arterial blood vessels, and, rarely, myocardial infarction at a relatively early age.

e. The patients in this study had PXE-like skin symptoms as well as a Vitamin K-dependent coagulation deficiency. This statement is TRUE. Heterogeneous causative mutations of PXE result in a diversity of symptoms.
7. Pseudoxanthoma elasticum (PXE) is an autosomal recessive genetic disease. Based on the referenced article, **select the ONE statement that is NOT true**: [See Am J Pathol 2009 174:534-540; DOI:10.2353/ajpath.2009.080865; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Mutations in the \textit{ABCC6} gene cause classic PXE. \textit{This statement is TRUE.} \textit{ABCC6} encodes an efflux transporter protein, \textit{ABCC6}. \textit{ABCC6} is expressed predominantly on the basolateral surface of hepatocytes and in the proximal tubules of kidneys.

b. Mutated \textit{ABCC6} is hyperactive, resulting in increased elastin production. \textit{This statement is NOT TRUE.} PXE is thought to be a metabolic disease. Non-functional \textit{ABCC6} transporters result in loss of critical, yet-to-be-identified metabolite(s) from circulation, leading to mineralization of the peripheral tissues.

c. Vitamin K-dependent coagulation factor deficiency (VKCFD) results in symptoms similar to PXE. \textit{This statement is TRUE.} VKCFD is an autosomal recessive disorder caused by mutations in either the \textit{GGCX} or \textit{VKORC1} genes.

d. \textit{GGCX} mutations result in the loss of an inhibitor of ectopic mineralization. \textit{This statement is TRUE.} \textit{GGCX} encodes \(\gamma\)-glutamyl carboxylase, which is required for activation of matrix gla protein (MGP), an inhibitor of ectopic mineralization. This study confirms \textit{GGCX} as the second gene locus causing PXE.

e. \textit{GGCX} is required for activation of vitamin K-dependent coagulation factors. \textit{This statement is TRUE.} In patients with \textit{GGCX} deficiency, vitamin K supplements correct the coagulation defect but do not prevent the connective tissue mineralization.

8. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that results in loss of muscle control. Based on the referenced Article, **select the ONE statement that is NOT true**: [See Am J Pathol 2009 174:574-585; DOI:10.2353/ajpath.2009.080557; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. About 10% of ALS cases are familial ALS, whereas 90% are sporadic. \textit{This statement is TRUE.} Mutations in the Cu/Zn superoxide dismutase -1 (\textit{SOD1, ALS1}) gene occur in approximately 20% of familial ALS cases.

b. ALS is characterized by a progressive loss of motoneurons. \textit{This statement is TRUE.} Mice overexpressing human mutated \textit{SOD1} (G93A-SOD1) develop a fatal motoneuron disease that resembles human ALS.

c. Potential mechanisms of ALS pathogenesis include perturbations in axonal transport and protein integrity. \textit{This statement is TRUE.} Disruptions in mitochondria, antioxidant status, and inflammation have also been proposed.

d. Toxicity due to hyperexcitability likely contributes to pathogenesis in ALS. \textit{This statement is TRUE.} Motoneuron hyperexcitability has been observed in both electrophysiological studies of ALS patients and in spinal cord slices of G93A-SOD1 mice.

e. Glutamate may decrease motoneuron hyperexcitability. \textit{This statement is NOT TRUE.} Glutamate may contribute to motoneuron hyperexcitability, and thus excitotoxicity, in ALS.

9. Motoneuron hyperexcitability may be caused by either excessive synaptic excitation or insufficient synaptic inhibition. Based on the referenced Article, **select the ONE statement that is NOT true**: [See Am J Pathol 2009 174:574-585; DOI:10.2353/ajpath.2009.080557; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. The hyperexcitability theory of ALS pathogenesis focuses on the contribution of excessive synaptic excitation. \textit{This statement is TRUE.} The alternate possibility of insufficient synaptic inhibition has not been well explored.

b. A reduction in inhibitory glycinergic innervation of motoneurons could result in excitotoxic dysfunction in ALS. \textit{This statement is TRUE.} A reduction in glycinergic innervation precedes major structural pathology in a mouse model of ALS (G92A-SOD1).

c. Inhibitory cholinergic innervation is preserved at early but not later stages of disease. \textit{This statement is TRUE.} A significant difference in the density of cholinergic interneurons was observed at the end stages of disease.

d. GABAergic inhibition is decreased in a mouse model of ALS (G92A-SOD1). \textit{This statement is NOT TRUE.} There is no difference in GABAergic innervation in G92A-SOD1 mice.

e. Injured neurons attempt compensation at mid-stage of disease. \textit{This statement is TRUE.} There is some recovery of glycinergic innervation in G92A-SOD1 mice at 10 weeks of age.
10. Intestinal stem cells are required for renewal of the intestinal epithelium. Based on the referenced Mini-Review of mouse stem cells, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:715-721; DOI:10.2353/ajpath.2009.080758; the authors of the referenced article did not disclose any potential conflicts of interest.]

- a. The intestinal epithelium is regenerated throughout adult life. This statement is TRUE. Proliferation occurs primarily in the crypt compartments.
- b. In the 4+ position hypothesis, intestinal stem cells are located directly above the noncycling Paneth cells in the 4+ position from the bottom of the crypt. This statement is TRUE. Every crypt is assumed to contain around six stem cells.
- c. The stem cell zone hypothesis postulates that small cycling crypt base columnar cells located between the noncycling Paneth cells comprise intestinal stem cells. This statement is TRUE. This hypothesis is based on both morphological and clonal marking evidence.
- d. By definition intestinal stem cells must be quiescent and resist apoptosis. This statement is NOT TRUE. The minimal criteria for stem cell identification are self-renewal and multipotency, both in vitro and in vivo.
- e. The newly identified molecular marker Lgr5 labels intestinal stem cells. This statement is TRUE. Lgr5+ crypt base columnar cells have been shown by lineage tracing both to self-renew and to give rise to all intestinal epithelial lineages.

11. Epidermal stem cells are capable of regenerating any type of epidermal lineage. Based on the referenced Mini-Review, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:715-721; DOI:10.2353/ajpath.2009.080758; the authors of the referenced article did not disclose any potential conflicts of interest.]

- a. Skin epidermal cells require replacement during both normal turnover and wound repair in response to injury. This statement is TRUE. Epidermal stem cells ensure skin maintenance.
- b. Epidermal stem cells reside exclusively in two distinct niches. This statement is NOT TRUE. Epidermal stem cells reside in three distinct niches: the bulge region of the hair follicle, the base of the sebaceous gland, and the basal layer of the interfollicular epidermis.
- c. During new hair growth, epidermal stem cells located in the base of the bulge of the hair follicle exit the niche, proliferate, and generate all of the epithelial cells for the newly formed hair follicle. This statement is TRUE. The hair follicle cycles between active growth (anagen), regression (catagen), and rest (telogen).
- d. Stem cells in the interfollicular epidermis proliferate and differentiate to form stratified layers of terminally differentiated keratinocytes. This statement is TRUE. These keratinocytes are constantly replaced by younger cells moving outwards.
- e. Lgr5 is a marker for hair follicle stem cells. This statement is TRUE. Lineage tracing confirms that Lgr5+ hair follicle cells are a long-lived hair follicle stem cell population.
12. The Wnt signaling pathways play a key role in the maintenance and activation of stem cells. Based on the referenced Mini-Review of mouse stem cells, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:1017-1026; DOI:10.2353/ajpath.2009.080551; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. In the intestinal tract, progenitor cells express β-catenin, a hallmark of Wnt activation. This statement is TRUE. Inhibiting Wnt signaling results in a complete loss of intestinal crypt cell proliferation.
   
   b. Inhibition of the Wnt pathway results in the loss of hair follicles in adults. This statement is TRUE. Conversely, activation of the Wnt signaling molecule β-catenin results in de novo hair growth.
   
   c. Elevated Wnt signaling in the skin is critical for wound repair. This statement is TRUE. Elevated Wnt signaling has been reported in wounded skin.
   
   d. There are around 80 Wnt target genes in the intestine. This statement is TRUE. The majority of these genes are expressed throughout the crypt compartment and are not restricted to stem cells.
   
   e. The Wnt target Lgr5 is an adhesion molecule related to the selectins. This statement is NOT TRUE. Lgr5 is an orphan G protein-coupled receptor with unknown function.

13. High serum cholesterol levels associate with the development of prostate cancer. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:1017-1026; DOI:10.2353/ajpath.2009.080551; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Cholesterol is a lipid that contributes to the development of cardiovascular disease. This statement is TRUE. High serum cholesterol levels result from both dietary and genetic components.
   
   b. High fat/high cholesterol ‘Western’ diets have been linked to prostate cancer incidence. This statement is TRUE. The contribution of specific dietary components to disease induction/progression remains unclear. Diets with a higher contribution of red meat may have a higher prostate cancer incidence.
   
   c. Studies clearly demonstrate that the incidence of prostate cancer increases after statin use. This statement is NOT TRUE. Statins, which are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, lower serum cholesterol levels. There is a negative association between statin use and prostate cancer incidence in some studies, although meta-analyses of placebo-controlled studies have not supported a link between statins and prostate cancer incidence.
   
   d. Statins interfere with the cholesterol synthesis pathway at an early step, blocking the formation of isoprenoid intermediates. This statement is TRUE. Isoprenoid intermediates are necessary for lipidation of critical signaling proteins. Bypassing isoprenoid synthesis inhibition in vitro reverses statin-induced apoptosis.
   
   e. The effects of statins on isoprenoid synthesis have been hypothesized to mediate the anti-tumor effects of statins. This statement is TRUE. However, this hypothesis is controversial because standard statin doses may not accumulate in tissues in sufficient levels to block isoprenoid synthesis.

14. There is a direct role for circulating cholesterol in the promotion of tumor growth. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:1017-1026; DOI:10.2353/ajpath.2009.080551; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. A high fat/high cholesterol Paigen diet elevates circulating cholesterol levels and promotes the growth of human prostate cancer xenografts. This statement is TRUE. An isocaloric low fat/no cholesterol diet was used to eliminate possible effects of energy disparity on tumor growth.
   
   b. Elevated circulating cholesterol levels modified tumor angiogenesis. This statement is TRUE. Higher cholesterol levels increased microvessel density and other indicators of vascularity.
   
   c. Tumors in hypercholesterolemic mice had fewer fibroblasts than tumors from the other cohorts. This statement is NOT TRUE. Mice with hypercholesterolemia had a greater number of fibroblasts in their tumors than the other cohorts. Stromal fibroblasts have been implicated in tumor progression as well as in promoting angiogenesis through the secretion of stromal cell-derived factor 1 (SDF-1).
   
   d. The cholesterol uptake inhibitor ezetimibe significantly increased tumor cell apoptosis and decreased tumor cell proliferation. This statement is TRUE. Ezetimibe is a cholesterol-lowering drug that binds to and blocks NPC1L1, the gut transporter responsible for dietary and biliary cholesterol absorption.
   
   e. Ezetimibe decreased cholesterol levels and reduced the quantity of tumor-associated blood and blood vessels. This statement is TRUE. Reducing cholesterol levels also increased the levels of the angiogenesis inhibitor thrombospondin-1.
15. Although different immunoglobulins can differ structurally, they are built from the same basic components. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1139-1148; DOI:10.2353/ajpath.2009.080879; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Two light chains and two heavy chains combine to form an immunoglobulin molecule. **This statement is TRUE.** Non-covalent bonds and disulfide bridges join light chains and heavy chains of immunoglobulin molecules to form a structure with twofold symmetry.

b. There are five immunoglobulin isotypes: IgG, IgM, IgE, IgA, and IgD. **This statement is TRUE.** Each isotype can possess either a κ or λ light chain, but has a unique (γ, μ, ε, α, δ) heavy chain.

c. Unique sequences at the N-terminal region of light and heavy chains determine antigen specificity. **This statement is NOT TRUE.** Sequences at the C-terminal region of light and heavy chains determine antigen specificity.

d. IgM and IgA commonly form multimers through disulfide bridges between heavy chains. **This statement is TRUE.** IgA forms a functional dimer, and IgM most often forms a functional pentamer.

e. Immunoglobulins can be both membrane bound and secreted. **This statement is TRUE.** Membrane-bound immunoglobulin functions as the B cell receptor, whereas secreted immunoglobulins serve as serum antibodies.
16. Immunoglobulins can be expressed by cancer cells. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1139-1148; DOI:10.2353/ajpath.2009.080879; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Human epithelial cancers of the breast, colon, liver, and lung can produce IgG. This statement is TRUE. Both IgG heavy chain RNA and protein have been identified in human epithelial cancer cells.
   b. Immunoglobulin μ, δ, and ε are the primary immunoglobulin heavy chain isotypes expressed in cancer cells. This statement is NOT TRUE. Immunoglobulin heavy chains expressed in cancer cells consist mainly of γ, μ, and α isotypes.
   c. Cancer cells are more likely to express immunoglobulin κ chains than λ chains. This statement is TRUE. Immunoglobulin κ chains have been identified in breast, lung, liver, prostate, colorectal, and gastric cancers. Although immunoglobulin λ chains have been reported in gastric cancer, no evidence of λ chain expression has been found in other epithelial cancer cell lines.
   d. Tumor cell lines can produce monoclonal immunoglobulin. This statement is TRUE. Monoclonal V-D-J recombination has been found in a colon carcinoma cell line.
   e. A novel immunoglobulin gene has been discovered in cancer cells. This statement is TRUE. SNC73 is a novel immunoglobulin that was discovered by subtractive hybridization using cDNA of normal mucosal tissues and colorectal cancer mRNA.

17. Cancer cells can express proteins that regulate immunoglobulin expression. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1139-1148; DOI:10.2353/ajpath.2009.080879; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. RAG1 and RAG2 mediate V-D-J recombination in immunoglobulin positive cancer cell lines. This statement is TRUE. RAG1 and RAG2 are required for V-D-J recombination of immunoglobulin molecules. These molecules have been detected in cell lines derived from lung cancer, colon cancer, uterus cervical cancer, liver cancer, prostate cancer, gastric cancer, breast cancer, and nasopharyngeal carcinoma.
   b. A putative RNA editing enzyme, activation-induced cytidine deaminase (AID) is essential for both class switch recombination and somatic hypermutation of immunoglobulin molecules, and is reportedly expressed in six breast cancer cell lines. This statement is TRUE. AID has not been detected in other epithelial cell lines, however.
   c. The transcription factor Pax5 regulates immunoglobulin expression in a colon cancer cell line. This statement is TRUE. Pax5 induces large scale contraction of the immunoglobulin locus, promoting V-D-J recombination between distal regions.
   d. The transcription factor EBF has been found in five epithelial cancer cell lines. This statement is TRUE. EBF-deficient mice do not undergo V-D-J recombination.
   e. Latent membrane protein 1, which is required for affinity maturation, up-regulates immunoglobulin heavy chain expression in cancerous cells. This statement is NOT TRUE. Latent membrane protein 1 is not required for affinity maturation, but is an Epstein Barr Virus-expressed oncogene that upregulates immunoglobulin κ expression in a nasopharyngeal cancer cell line.
18. Galectin-3 is a β-galactosidase-binding protein that is related to the metastatic transition of many tumor types. Based on the referenced article, select the ONE statement that is NOT true: [See Am J Pathol 2009 174:1515-1523; DOI:10.2353.ajpath.2009.080816; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. In human prostate cancer, intact galectin-3 has been shown to be down-regulated with progressive tumor stages. This statement is TRUE. In other cancer types, including thyroid cancer, gastric carcinoma, and cancer of the head and neck, galectin-3 is up-regulated with an increase in malignancy.

b. Galectin-3 is a substrate for matrix metalloproteinases (MMPs) and is cleaved in human breast cancer. This statement is TRUE. In breast cancer, cleaved galactin-3 co-localized with MMP-2 and MMP-9.

c. Galectin-3 is cleaved during the progression of prostate cancer. This statement is TRUE. Previous identification of galectin-3 expression in prostate cancer was limited to intact galectin-3.

d. Over-expressing galectin-3 in prostate cancer cells resulted in a decreased metastatic phenotype. This statement is NOT TRUE. Decreasing galectin-3 levels with siRNA resulted in reduced metastatic phenotype including reduced cell migration, invasion, cell proliferation, anchorage-independent colony formation, and tumor growth in nude mice.

e. In a prostate cancer cell line, galectin-3 inhibition resulted in suppression of MMP-2 and MMP-9 expression. This statement is TRUE. Galectin-3 knockdown also contributed to reduced cell migration and cell invasion.
19. Epithelial-mesenchymal transition (EMT) describes a series of progressive changes in cell phenotype. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1588-1593; DOI:10.2353/ajpath.2009.080545; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. EMT was originally described as contributing to cellular remodeling in heart morphogenesis. This statement is TRUE. EMT has been proposed in a range of events, including mesoderm and neural crest formation.
   b. EMT refers to a single conserved process. This statement is NOT TRUE. EMT-related processes can vary in intensity from a transient loss of cell polarity to total cellular reprogramming.
   c. During EMT, epithelial cells down-regulate cell-cell adhesion structures. This statement is TRUE. These cells become isolated and motile.
   d. Cells undergoing EMT reorganize their cytoskeleton. This statement is TRUE. During EMT, epithelial cells alter their polarity and switch expression from keratin- to vimentin-type intermediate filaments.
   e. During EMT, epithelial cells become resistant to anoikis. This statement is TRUE. These cells no longer undergo apoptosis when they detach from the extracellular matrix.
20. An EMT/EMT-like phenotype is observed during the progression of some cancers. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1588-1593; DOI: 10.2353/ajpath.2009.080545; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. With regard to EMT in the cancer environment, the loss of cell-cell adhesion in any cancer is sufficient to cause an EMT. This statement is NOT TRUE. EMT applies to only epithelial-derived cancers, which account for approximately 90% of human tumors, including breast, colon, liver, and lung cancer. Although epithelial cells must down-regulate their cell-cell adhesion structures to intravasate and metastasize, the loss of cell-cell adhesion is not sufficient to make an EMT. 

   b. Genes active during the course of carcinoma progression and metastasis are active during EMT. This statement is TRUE. Cancer-activated genes are also active during early embryogenesis, tissue morphogenesis, and wound healing. 

   c. Carcinosarcomas, which display a mix of epithelial and stromal cells, are thought to be derived from common epithelial progenitor cells. This statement is TRUE. The epithelial progenitor cells undergo EMT to form the mesenchymal population. 

   d. The term EMT implies complete trans-differentiation and does not describe the incomplete differentiation or dedifferentiation often seen in tumors. This statement is TRUE. “EMT-like” may be used to describe an intermediate phenotype observed during tumor cell renewal and adaptation to specific microenvironments. An “EMT-like” phenotype in human carcinomas can be described based on the state of cell polarization, the state of cell cohesiveness, and intermediate filament protein expression. 

   e. Many genes involved in progenitor/stem cell maintenance are also expressed in EMT/EMT-like carcinoma cells. This statement is TRUE. Genes expressed in both progenitor/stem cells and EMT/EMT-like cells include CD24, CD44, CD49/α6, CD29/β1, and Slug (Snail2). 

21. Multiple cellular pathways lead to EMT and EMT-like phenotypes. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1588-1593; DOI: 10.2353/ajpath.2009.080545; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. The Wnt signaling pathway is one of five main pathways that have been found to trigger EMT-associated processes. This statement is TRUE. Tyrosine kinase receptor (EGF, FGF, HGF< PDFG, IFG), integrin, Wnt, NF-κB, and TGFβ signaling pathways have all been implicated in EMT-associated processes. 

   b. CXCR4 appears to contribute to EMT-like phenotypes and tumor progression in mouse models. This statement is TRUE. ILEI and RKIP have also been implicated in EMT-like processes in mouse models. 

   c. Downregulation of H-cadherin is implicated in cell-cell dissociation and invasion in mouse pancreas, prostate, and mammary gland cancer models. This statement is NOT TRUE. E-cadherin downregulation is implicated in these murine cancer models. Snail (Snail1), Slug (Snail2), Twist, SIP1/Zeb and E47 negatively regulate E-cadherin expression. 

   d. Snail family member over-expression in epithelial cell lines can induce an EMT. This statement is TRUE. Snail family members have been shown to be involved in cell motility, proliferation control, differentiation, and apoptotic regulation in vivo and in cell models. 

   e. Hypoxia genes contribute to EMT. This statement is TRUE. HIF-1, a key hypoxia effector, increases Snail and Twist expression levels.

- Ablating vascular endothelial growth factor (VEGF)-recruitable bone marrow-derived cells blocks angiogenesis and tumor growth. This statement is TRUE. These cells have been proposed to be endothelial progenitor cells (EPCs).
- CD31-positive bone marrow cells contribute to angiogenesis in myeloablated mice. This statement is TRUE. CD31 is an endothelial cell marker, which supports the hypothesis that these cells are EPCs.
- Parabiotic mice, which have surgically joined circulatory systems, demonstrate the contribution of bone marrow-derived cells to angiogenesis in a physiological, non-myeloablative setting. This statement is TRUE. Wild-type and green fluorescent protein (GFP)-labeled mice were surgically connected, which allowed for identification of circulating cells.
- Green fluorescent protein (GFP)-labeled bone marrow-derived cells are found in newly formed vessels in parabiotic mice and express the macrophage marker F4/80. This statement is TRUE. Circulating monocytes express both the monocyte marker CD14 and the endothelial cell marker VEGFRF2.
- Bone marrow-derived cells that contribute to angiogenesis in parabiotic mice express endothelial progenitor cell (EPC) markers. This statement is NOT TRUE. F4/80- and CD31-positive, GFP-labeled cells do not express EPC markers, and no GFP-positive cells in these mice would qualify as EPCs.
23. The stem cell origin of cancer hypothesis postulates that cancer may originate in cells closely related to the germ line. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1985-1992; DOI:10.2353/ajpath.2009.081143; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Primordial germ cells that migrate to adult tissues instead of the genital ridges during development may establish “classical” germ line tumors. This statement is TRUE. Classical germ line tumors include seminoma, ovarian tumor, yolk sac tumor, mediastinal- and brain-germ cell tumors, teratoma, and teratocarcinoma.

b. Cancer/testis antigens, which are normally expressed in only the germ line, are also expressed in various tumor cell types. This statement is TRUE. Tumors that express cancer/testis antigens include gastric, lung, liver, and bladder carcinomas, melanomas, medulloblastomas, pediatric sarcomas, and germinal tumors.

c. Several types of cancer secrete germ line-specific proteins. This statement is TRUE. Several types of cancer secrete either the β subunit of human chorionic gonadotropin or its fragments and/or carcinoembryonic antigen.

d. The Oct-4 promoter DNA in very small embryonic/epiblast-like stem cells (VSELs) is in a hypermethylated state. This statement is NOT TRUE. The Oct-4 promoter DNA in VSELs is in a hypomethylated state and transcriptionally active. Various tumor types express Oct-4 transcription factors, which are a marker of embryonic, epiblast, and germ line primordial stem cells. Gastric, lung, bladder, and oral mucosa carcinomas as well as germinal tumors all express Oct-4.

e. VSELs, which express germinal markers and differentiate into cells from all three lineages, may initiate cancer development. This statement is TRUE. The authors suggest that VSELs may initiate cancer by acquiring mutations, maintaining genomic imprinting, and fusing with other somatic cells as well as by contributing to tumor expansion by providing stroma and endothelial precursors.
24. Inflammatory bowel disease (IBD) is a group of inflammatory diseases of the large and small intestine. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1993-1995; DOI: 10.2353/ajpath.2009.081138; and Am J Pathol 2009 174:2254-2264; DOI:10.2353/ajpath.2009.080831; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. IBD affects approximately 1.4 million people in the United States. This statement is TRUE. The most prevalent types of IBD are Crohn’s disease and ulcerative colitis.
b. IBD is thought to be caused by abnormal activation of the mucosal immune system. This statement is TRUE. The native flora of the intestinal lumen are thought to inappropriately and continuously activate the mucosal immune system, resulting in IBD.
c. Prototypic Th2 cytokines, including interleukin-4, activate macrophages to produce various mediators that are instrumental in IBD pathogenesis. This statement is NOT TRUE. Prototypic Th1 cytokines, including interferon-γ, activate macrophages to produce various mediators that are instrumental in IBD pathogenesis in murine models.
d. The proinflammatory cytokine tumor necrosis factor (TNF)-α is produced by the innate immune system and may contribute to the pathogenesis of IBD. This statement is TRUE. TNF-α signaling induces the expression of numerous adhesion molecules and hyaluronan on the luminal surface of intestinal epithelial cells, allowing for monocyte adhesion. Anti-TNF-α therapy is used to therapeutically treat IBD.
e. Interleukin-1β and interferon-γ may also contribute to the pathogenesis of IBD. This statement is TRUE. Interleukin-1β and interferon-γ may contribute to the pathogenesis of IBD in part by modulating the synthesis of hyaluronan.


a. Platelets amplify the inflammatory response by releasing pro-inflammatory molecules. This statement is TRUE. Platelets are often found at sites of inflammation.
b. Interactions between platelets and leukocytes result in the production of inflammatory molecules and lipid mediators that could not be produced by either cell type independently. This statement is TRUE. Platelets upregulate adhesion molecules upon endothelial attachment; this allows direct binding of platelets to leukocytes. Increased leukocyte-platelet interactions have been reported in IBD.
c. Both abnormal platelet number and function have been reported in patients with IBD. This statement is TRUE.
d. Patients with IBD often have reactive thrombocytosis. This statement is TRUE. Patients with IBD have higher levels of activated platelets in peripheral circulation, spontaneous platelet aggregation, and increased susceptibility to aggregating agents.
e. Inflamed tissues in IBD decrease the coagulant activity of platelets. This statement is NOT TRUE. IBD patients have intravascular microthrombi due to an increase of pro-coagulant behavior in inflamed tissues.
26. Platelets and hyaluronan (HA) activate monocytes, cells known to contribute to numerous chronic inflammatory states. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 174:1993-1995; DOI: 10.2353/ajpath.2009.081138; and Am J Pathol 2009 174:2254-2264; DOI:10.2353/ajpath.2009.080831; the authors of the referenced articles did not disclose any potential conflicts of interest.]

   a. HA is essential for cell migration, tissue remodeling, and malignant tumor behaviors. This statement is TRUE. HA interacts with the extracellular matrix and cell surface receptors such as CD44, RHAMM (receptor for hyaluronic acid-mediated motility), and LYVE-1 (lymphatic vessel endothelial hyaluronan receptor-1).
   b. Platelets can bind to HA on microvessel surfaces. This statement is TRUE. Circulating platelets bind to activated microvessel endothelial cell surfaces.
   c. Platelets express hyaluronidase (HYAL) type 2, but not HYAL1. This statement is TRUE. Megakaryocytes also exclusively contain HYAL2, whereas HYAL1 is found in all other tissues.
   d. Platelet HYAL2 generates HA fragments with anti-inflammatory properties. This statement is NOT TRUE. HYAL2, in concert with CD44, generates HA fragments with pro-inflammatory properties. These fragments can activate the IκBα/NFκB (nuclear factor κB) pathway in macrophages, which then upregulate expression of interleukin-6 and interleukin-8.
   e. HYAL inhibitors that decrease the formation of HA fragments could have therapeutic value. This statement is TRUE. HYAL inhibitors could decrease the formation of inflammatory fragments without affecting the homeostatic, physiologic roles of HA.
ANSWERS for CME Questions # 27-30

27. Interstitial lung disease and many types of lung injury contribute to the development of lung fibrosis. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:3-16; DOI:10.2353/ajpath.2009.081170; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. In the United States, idiopathic pulmonary fibrosis (IPF) claims more lives annually than many types of cancer. This statement is TRUE. Effective therapy for IPF is lacking.
   b. The distal airspace and parenchyma of the lung are remodeled during pulmonary fibrogenesis. This statement is TRUE. Pulmonary fibrogenesis is also characterized by excessive accumulation of the extracellular matrix and apoptosis-resistant myofibroblasts.
   c. Pulmonary fibrosis was long believed to be initiated and propagated by persistent lung inflammation. This statement is TRUE. However, IPF lungs lack classic inflammatory biomarkers, and fibrosis proceeds in animal models in the absence of inflammation.
   d. Corticosteroid and other anti-inflammatory therapies have been helpful in treating IPF. This statement is NOT TRUE. Corticosteroids and other anti-inflammatory therapies have not been helpful in treating IPF.
   e. The epithelium in many cases initiates and perpetuates fibrogenic signaling. This statement is TRUE. Epithelial cell stress may signal to the innate macrophage population in an effort to restore alveolar integrity.

28. Emerging concepts suggest that lung fibrosis can be considered as “disordered redevelopment” of the lung. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:3-16; DOI:10.2353/ajpath.2009.081170; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. Epithelial and mesenchymal interactions are critical for lung fibrogenesis. This statement is TRUE. These interactions are also prominent in developmental morphogenesis of the lung.
   b. Recent microarray data from experimental models suggest that expression patterns and signaling pathways of fibrosis are similar to those that occur in lung development. This statement is TRUE. There is a growing recognition of the roles of epigenetic reprogramming and context-dependent signaling in profibrotic phenotype alterations.
   c. The epithelium plays a critical role in the initiation and continuation of fibrosis. This statement is TRUE. Signaling by impaired epithelial cells may alter the function of both fibroblasts and macrophages.
   d. In fibrogenesis, fibroblasts may have alternate origins and phenotypic plasticity. This statement is TRUE. Local structural fibroblasts may arise through transdifferentiation of other cells as well as recruitment of bone marrow-derived cells.
   e. Alternatively activated macrophages express decreased arginase 1 (Arg1) activity compared with classically activated macrophages. This statement is NOT TRUE. Arg1 activity is increased in alternatively activated macrophages, limiting nitric oxide production and enhancing production of collagen precursors used in wound healing. Alternately-activated macrophages are important in tissue remodeling. Macrophage activation related to tissue repair rather than microbial protection may skew macrophage responses to lead to tissue remodeling.
29. Transforming growth factor (TGF)-β1 induces fibrosis in the absence of inflammation. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:3-16; DOI:10.2353/ajpath.2009.081170; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Replication-deficient adenoviral vectors containing cDNAs of specific genes mimic non-inflammatory pulmonary fibrosis when transferred to the lung epithelium of rodents. This statement is TRUE. In these models, the degree of fibrosis directly correlated with TGF-β1 expression levels.
b. Over-expression of active TGF-β1 in rat lung resulted in prolonged and severe interstitial and pleural fibrosis. This statement is TRUE. TGFβ1-induced fibrosis developed and progressed without extensive inflammation.
c. Interleukin (IL)-13-induced fibrosis was significantly ameliorated by treatment with a TGF-β agonist. This statement is NOT TRUE. IL-13-induced fibrosis was significantly ameliorated by treatment with a TGF-β antagonist.
d. Gremlin, a bone morphogenic protein (BMP) antagonist that is upregulated by TGF-β1 in a mitogen-activated protein kinase (MAPK)-dependent manner, disrupts the balance between TGF-β1 and BMPs in IPF and in mouse models of non-inflammatory fibrosis. This statement is TRUE. Restoration of BMP-7 signaling inhibits asbestos-induced fibrosis in mice.
e. Responses elicited by TGF-β are classically mediated by intracellular signaling via Smad proteins. This statement is TRUE. The role of Smad signaling in TGF-β-driven fibrosis has been demonstrated in vivo using Smad3-null mice, which are resistant to TGF-β1-mediated pulmonary fibrosis.

30. The risk of developing gastric adenocarcinoma is strongly associated with Helicobacter pylori infection. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175: 365-375; DOI:10.2353/ajpath.2009.081165; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. H. pylori infection causes persistent chronic gastritis. This statement is TRUE. In susceptible individuals, chronic gastritis may progress to atrophy, intestinal metaplasia, dysplasia, and eventually intestinal-type gastric cancer.
b. H. pylori infection results in a severe (8-10-fold) increase in the levels of gastrin early in the course of the infection. This statement is NOT TRUE. H. pylori infection results in a mild (1.5-2-fold) increase in the levels of gastrin early in the course of the infection.
c. Gastrin is a mucosal growth factor. This statement is TRUE. There is a possible association between hypergastrinemia, H. pylori infection, and gastric cancer.
d. Mice that over-express gastrin develop invasive gastric cancer in the absence of H. pylori infection. This statement is TRUE. Insulin-gastrin transgenic mice develop invasive gastric cancer at 20 months of age.
e. Gastrin has distinct effects on carcinogenesis of the gastric corpus and of the gastric antrum. This statement is TRUE. Gastrin is an essential cofactor for gastric corpus carcinogenesis. On the contrary, gastrin deficiency can predispose animals to antral carcinogenesis.
ANSWERS for CME Questions # 31-34
31a, 32e, 33d, 34b

31. Through alternative splicing, multiple mRNA transcripts can be produced from a single RNA precursor. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:461-472; DOI:10.2353/ajpath.2009.081135; the authors of the referenced article did not disclose any potential conflicts of interest.]

   a. RNA splicing occurs when specific nucleotide sequences at intron-exon boundaries within the pre-mRNA are recognized by DNA polymerase β. This statement is NOT TRUE. The spliceosomal splicing machinery consists of a complex of small nuclear ribonucleoproteins (snRNPs) and proteins that assemble in a temporally- and spatially-specific manner to catalyze intron excision and ligation of exon ends.

   b. Splice site selection by the spliceosome is flexible, allowing the generation of differentially spliced mRNA isoforms of the same gene. This statement is TRUE. Alternative splicing may occur in response to less-than-optimal splice site sequences or variations in activity of protein kinases or phosphatases, in the stoichiometry of splicing regulatory factors, or even key core components of the spliceosome. These differences can result in the excision of an exon that is normally included in coding, the inclusion of an intron, the inclusion of an exonic cassette that is not normally recognized, or the use of alternative 5' or 3' splice sites.

   c. Alternative splicing contributes to the diversity of the human proteome. This statement is TRUE. Alternative splicing allows for multiple protein products to be produced from a single gene, enhancing the diversity of a limited genome.

   d. Alternative splicing occurs during normal development. This statement is TRUE. Alternative splicing has also been associated with diseases such as cystic fibrosis and retinitis pigmentosa, among others.

   e. Cancer cells may express alternatively spliced mRNAs that are distinct from those that occur physiologically. This statement is TRUE. Some of these mRNAs may have oncogenic function.
32. Cancer-related peptide hormone receptor splice variants may exhibit distinct pharmacological or functional properties from wild-type receptors. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:461-472; DOI:10.2353/ajpath.2009.081135; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. A peptide receptor splice variant may result in constitutive activity. This statement is TRUE. Some cancer-associated spliceoforms arise from genes with an established role in carcinogenesis or tumor progression, such as tumor suppressor genes, proto-oncogenes, and genes involved in cell motility. Constituent activity of certain receptors may contribute to neoplastic growth.

b. Cancer-associated receptor spliceoforms may show altered affinity for ligands of wild-type receptors. This statement is TRUE. Many splice variants of genes involved in cell death have decreased ligand-binding affinity, antagonizing the pro-apoptotic effect of their wild-type counterparts in a dominant-negative fashion, thus stimulating tumor growth.

c. Cancer-related splice variants may be expressed at different levels or in different patterns than in non-malignant tissue. This statement is TRUE. Often, splice variants are expressed at higher levels in cancerous tissues. Overexpression of a splice variant of the proto-oncogene MDM2 leads to malignant transformation of transfected cells in vitro and spontaneous tumor formation in vivo.

d. Some splice variants appear to arise de novo in cancer. This statement is TRUE. These splice variants are not found under normal conditions.

e. The CD44 splice variant CD44v5 was found to decrease tumor cell invasiveness. This statement is NOT TRUE. Splice variants of genes involved in cell migration can stimulate invasion of cancer. For example, the CD44 splice variant CD44v5 was found to increase tumor cell invasiveness.

33. Splice variants may be used clinically for diagnostic and therapeutic purposes. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:461-472; DOI:10.2353/ajpath.2009.081135; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Detection of specific splice variants can identify tumor cells in clinical specimens. This statement is TRUE. The mRNA ratio of two CD44 splice variants, CD44v8-10, which is expressed predominantly in epithelial cancers, and CD44v10, which occurs in normal leukocytes, can distinguish malignant conditions from reactive ones.

b. Determining the ratio of cancer-related splice variants may be used in cancer prognosis. This statement is TRUE. The ratio of CD44v8-10 versus standard CD44 mRNA levels in urine samples correlates with bladder cancer stage, metastasis, and survival.

c. Splice variants may serve as serum markers for cancer. This statement is TRUE. If the protein product of a spliceoform is soluble and secreted from tumor cells, it may be detectable in the serum with an antibody-based assay.

d. Radiolabeled splice variant-specific DNA probes may be used for targeted tumor scintigraphy. This statement is NOT TRUE. Radiolabeled splice variant-specific antibodies may be used for targeted tumor scintigraphy. Fibronectin-extracellular domain B (EBD)-expressing lung cancers and liver metastases as small as 4 to 6 mm could be imaged with an intravascularly injected [125I]-labeled antibody specifically recognizing the EDB domain.

e. Specific antibodies coupled to a radionucleotide or chemotherapeutic reagent may be targeted to tumor-specific spliceoforms. This statement is TRUE. Phase I trials were performed with various toxic anti-CD44v6 antibodies in patients with head and neck or breast cancer; however, tumor response rates were small.
34. Epidemiological studies have shown that a diet high in omega-3 polyunsaturated fatty acids can slow disease progression in patients with advanced age-related macular degeneration (AMD). Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:799-807; DOI:10.2353/ajpath.2009.090089; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. AMD is the most common cause of legal blindness in elderly people throughout the world. This statement is TRUE. AMD involves the destruction and deterioration of the photoreceptor and retinal pigment epithelium (RPE) specific to the macula.

b. AMD can be treated with topical steroids. This statement is NOT TRUE. To date, except for the suppression of choroidal neovascularization in patients with the “wet” form of AMD, there is no definitive treatment for AMD. Care for earlier stage AMD is limited to risk factor management.

c. Mammalian cells lack the enzyme required to synthesize the precursors of omega-3 fatty acids. This statement is TRUE. Omega-3 fatty acids must therefore be consumed in the diet.

d. Vital retinal functions require the presence of omega-3 fatty acids. This statement is TRUE. Docosahexaenoic acid (DHA) and eicosapentanoic acid (EPA, the precursor to DHA) are the two major omega-3 fatty acids that are concentrated in the retina and retinal vascular endothelium. Photoreceptors are also abundantly enriched in omega-3 fatty acids.

e. Epidemiologic retrospective studies suggest that omega-3 fatty acids or fish intake protect against advanced AMD. This statement is TRUE. The results from this study demonstrated an obvious benefit of long chain omega-3 fatty acid intake in a mouse strain that exhibits certain pathological features of human AMD-like lesions.
35. Adipocyte differentiation stimulates mitochondrial biogenesis. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:927-939; DOI:10.2353/ajpath2009.081155; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. During adipogenesis, undifferentiated adipoblasts undergo sequential changes in the activity of several transcription factors that are involved in mitochondrial biogenesis. This statement is TRUE. CREB (cAMP response element binding protein), C/EBP (CCAAT/Enhance binding protein), and PPARγ (peroxisome proliferator-activated receptor γ) control the expression of genes encoding proteins involved in both adipocyte differentiation and mitochondrial biogenesis. These effects often rely on PGC-1 (PPARγ co-activator 1) and other co-activators.

b. Adipocyte differentiation results in an increase in the abundance of mitochondrial proteins. This statement is TRUE. This increase is detectable in vitro in differentiating adipocytes 4 days after induction of the differentiation program, and the enhanced mitochondrial biogenesis is sustained up to 10 days post-differentiation.

c. Adipocyte differentiation requires a large amount of ATP. This statement is TRUE. Mitochondrial biogenesis is required to produce the excess ATP required for adipogenesis.

d. The decreased rate of oxygen consumption in adipocytes supports increased mitochondrial biogenesis. This statement is NOT TRUE. Adipocytes have an increased rate of oxygen consumption, which supports increased mitochondrial biogenesis.

e. De novo mitochondrial biogenesis due to adipogenesis leads to qualitative changes in mitochondria. This statement is TRUE. Adipocyte mitochondria express pyruvate carboxylase, aconitase, and enzymes involved in fatty acid metabolism, such as acylCoA synthetase and various forms of acyl-CoA hydrogenase.
36. Mitochondrial dysfunction in adipocytes contributes to multiple pathologies. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:927-939; DOI:10.2353/ajpath2009.081155; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Mitochondrial diseases may result from mutations in either the mitochondrial or nuclear genomes. **This statement is TRUE.** Mitochondrial proteins are encoded by both mitochondrial and nuclear DNA.

b. Increased mitochondrial density and oxidative metabolism are early events in obesity-associated complications. **This statement is NOT TRUE.** Reduced mitochondrial density and oxidative metabolism are early events in the complications associated with obesity.

c. Patients with non-alcoholic steatohepatitis, who suffer from mitochondrial injury, experience obesity accompanied by diabetes and hypertriglyceridemia with insulin resistance. **This statement is TRUE.** Non-alcoholic steatohepatitis is characterized by increased lipid peroxidation, alterations in the mitochondrial ultrastructure, depletion in mtDNA, and low oxidative phosphorylation activity.

d. Impaired mitochondrial activity in human immunodeficiency virus (HIV)-positive patients treated with highly active antiretroviral therapy (HAART) leads to lipodystrophy (ectopic fat storage). **This statement is TRUE.** Lipodystrophy syndrome is associated with peripheral lipatrophy and an increase in the amount of visceral white adipose tissue, as well as glucose homeostasis abnormalities and insulin resistance.

e. In whole transcriptome studies on white adipocytes from \textit{ob/ob} mice, the abundance of numerous transcripts encoding mitochondrial proteins is decreased with the onset of obesity. **This statement is TRUE.** After treatment with the PPAR\textsubscript{γ} agonist rosiglitazone, half of the obesity-down-regulated genes were found to be up-regulated. Rosiglitazone treatment in \textit{ob/ob} mice triggers mitochondrial biogenesis in white adipocytes, a process accompanied with remodeling of mitochondria shape and size.

37. Mitochondria provide potential therapeutic drug targets for treating obesity and diabetes. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:927-939; DOI:10.2353/ajpath2009.081155; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Mild mitochondrial uncoupling, induced by the protonophore carbonyl cyanide p-trifluoromethoxy phenylhydrazine (FCCP), is able to reduce the intracellular triglyceride content of lipid droplets in differentiated adipocytes. **This statement is TRUE.** FCCP down-regulates several energy and carbon flux requiring processes.

b. Mitochondrial uncoupling proteins such as UCP-1 may serve as functional targets for obesity. **This statement is TRUE.** These proteins are involved in adaptive thermogenesis, fatty acid oxidation, aging, prevention of reactive oxygen species formation, and body weight regulation.

c. Overexpression of the uncoupling protein UCP-3 results in increased adiposity and cholesterolemia compared with wild-type counterparts. **This statement is NOT TRUE.** UCP-3 transgenic mice have decreased adiposity, reduced cholesterolemia, higher insulin sensitivity, and lower blood glucose levels accompanied by a higher metabolic rate, despite higher food intake than their wild-type counterparts.

d. Bioactive food components such as poly-unsaturated fatty acids may prevent or reverse the reduced mitochondrial density and diminished oxidative capacity found in obesity. **This statement is TRUE.** Partial replacement of the plant omega-3 poly-unsaturated fatty acid linoleic acid with the long chain marine omega-3 poly-unsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) leads to increased mitochondrial density, reduced white adipose tissue mass, and increased fatty acid oxidation.

e. Polyphenols may increase mitochondrial biogenesis and oxidative capacity. **This statement is TRUE.** Dietary resveratrol, a polyphenol, was shown to deacetylate PGC-1\textalpha, reduce white adipose tissue mass, increase mitochondrial density, and improve mitochondrial oxidative capacity.
Drug abuse exacerbates HIV-associated neurocognitive disorders (HAND). Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009 175:1148-1159; DOI:10.2353/ajpath2009.081067; the authors of the referenced article did not disclose any potential conflicts of interest.]

- HIV infection in the central nervous system (CNS) results in ongoing inflammation and neurological damage that leads to the development of HAND. This statement is TRUE. HIV enters the central nervous system soon after initial infection. HAND occur in as many as 50% of infected individuals.
- The incidence and severity of HAND are exacerbated by drug abuse. This statement is TRUE. Increased extracellular dopamine in the brain mediates the addictive effects of many abused drugs, including the psychostimulants cocaine and methamphetamine.
- Dopamine increases HIV replication in human macrophages. This statement is TRUE. Within the CNS, macrophages are the primary source of HIV.
- Macrophages express dopamine receptors 1 and 2 (D1R and D2R, respectively). This statement is TRUE. Activation of D2R increases levels of HIV replication.
- Quinpirole is a widely used specific dopamine receptor 5 (D5R) agonist. This statement is NOT TRUE. Quinpirole is widely used as a specific D2R agonist, but studies have shown it to have activity against other D2-like dopamine receptors. Other agonists often lack a high degree of specificity for distinguishing between DR of the same subtype; however they do distinguish very well between the D1-like and D2-like classes. There are no agonists that distinguish well between D1R and D5R.
39. The field of epigenetics examines alterations in phenotype or gene expression for which there are no underlying changes in gene sequence. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:1353-1361; DOI:10.2353/ajpath.2009.081142; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Methylation of CpG-containing DNA sequences results in decreased transcription of associated genes. **This statement is TRUE.** Rare CpG-containing sequences in the DNA are cytosine methylated by a family of DNA methyltransferases.

b. Histone modifications including acetylation and methylation alter gene expression. **This statement is TRUE.** Histones also undergo a variety of other modifications including phosphorylation, sumoylation, and ubiquitination.

c. Chromosome remodeling through the SWI/SNF complex can either increase or decrease the level of transcription, depending on chromatin context. **This statement is TRUE.** The contextual differences that regulate these effects could include promoting chromatin accessibility to both coactivators and repressors through nucleosome displacement or through DNA displacement from nucleosomes.

d. Patterns of histone methylation are important for establishing patterns of DNA methylation. **This statement is TRUE.** Patterns of repressive histone methylation, specifically histone H3 lysine 27 methylation established in stem cells, correlate with genes that are commonly hypermethylated in cancer.

e. Chromatin remodeling is independent of changes in DNA methylation and histone modification. **This statement is NOT TRUE.** Chromatin remodeling is programmed in part by changes in DNA methylation and histone modification.
40. Deregulation of DNA methylation is a common alteration leading to cancer development. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:1353-1361; DOI:10.2353/ajpath.2009.081142; the authors of the referenced article did not disclose any potential conflicts of interest.]

- Patterns of DNA methylation in tumor cells differ considerably from normal cells. This statement is TRUE. Early studies revealed global hypomethylation of DNA sequences from tumor cells compared with those from normal cellular counterparts; these studies have been confirmed by high-throughput techniques.
- Many high-throughput techniques have been developed to profile CpG methylation. This statement is TRUE. These techniques include restriction landmark genomic screening (RLGS), bisulfite sequencing, differential methylation hybridization (DMH), DNA immunoprecipitation using antibodies directed against 5-methylcytosine (MeDIP), and array or sequence-based detection methods.
- Hypomethylation may play several roles in oncogenesis, including increasing genomic instability as well as contributing to the overexpression of various genes. This statement is TRUE. \textit{MAGE}, \textit{CAGE}, \textit{CYCLIND2}, \textit{S100A4}, and \textit{CD30} may be overexpressed due to hypomethylation. Hypomethylation may also contribute to loss of genetic imprinting for genes such as \textit{IGF2}.
- The first hypomethylated gene identified was \textit{calcitonin}, which is hypomethylated in a subset of small cell lung carcinoma cases. This statement is NOT TRUE. \textit{Calcitonin} was the first hypermethylated gene, occurring in a subset of small cell lung carcinoma cases. Local hypermethylation of specific genes appears to play an important role in cancer, perhaps because hypermethylation of some genes can promote genomic instability.
- Changes in DNA methylation have been associated with chemotherapy resistance. This statement is TRUE. For example, methylation of the \textit{MLH1} gene is associated with increased resistance to cisplatinum and alkylating agents.

41. Histone modification may contribute to cancer development. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:1353-1361; DOI:10.2353/ajpath.2009.081142; the authors of the referenced article did not disclose any potential conflicts of interest.]

- Histone tail acetylation at lysine residues on histones H3 and H4 causes transcriptional repression of genes that lead to cancer development. This statement is NOT TRUE. Histone tail acetylation at lysine residues on histones H3 and H4 causes transcriptional activation of genes that lead to cancer development. Acetylation neutralizes the negative charge of DNA and generally renders DNA more accessible to transcription factors.
- Heterochromatin protein 1 (HP1), a histone reader, is down-regulated in metastatic breast cancer, papillary thyroid carcinoma, and medulloblastoma. This statement is TRUE. Overexpression of HP1 in metastatic breast cancer cells decreased invasiveness, whereas knockdown of HP1 in non-metastatic cells increased invasiveness, suggesting HP1 functions as a metastasis suppressor.
- The inhibitor of growth (ING) proteins are histone code readers that function as tumor suppressors. This statement is TRUE. ING proteins interact with p53 to induce apoptosis, cellular senescence, and growth arrest.
- Rearrangement of the \textit{mixed lineage leukemia} (\textit{MLL}) gene in human lymphoid and myeloid acute leukemias contributes to transformation. This statement is TRUE. MLL has histone methyltransferase activity. MLL fusion proteins potently up-regulate target genes including \textit{HOXAT}, \textit{HOX9} and the HOX co-factor \textit{MEIS1}, which are essential for MLL fusion protein-mediated transformation.
- Enhancer of Zeste (\textit{EZH2}) is a histone code writer that is disrupted in cancer. This statement is TRUE. Up-regulation of \textit{EZH2} is seen in a number of tumor types including lymphomas, prostate cancer, and breast cancer, in which the expression level appears to correlate with disease progression. \textit{EZH2} may contribute to cancer progression by maintaining a stem cell-like phenotype.
42. Cancer may be caused by changes in chromatin remodeling. Based on the referenced Biological Perspectives article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:1353-1361; DOI:10.2353/ajpath.2009.081142; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Chromatin remodeling is detected using DNase hypersensitivity and Southern blot analysis to assess nucleosomal position (phasing) in tumor tissues. This statement is TRUE. These methods are difficult and insensitive and have prevented more detailed studies in chromatin remodeling in cancer.

b. INI1 (SNF5/SMARCB1/BAF47), a core component of the SWI/SNF complex, is overexpressed in malignant rhabdoid tumors as well as other primitive undifferentiated pediatric sarcomas. This statement is NOT TRUE. Expression of INI1 (SNF5/SMARCB1/BAF47), a core component of the SWI/SNF complex, is decreased in malignant rhabdoid tumors as well as other primitive undifferentiated pediatric sarcomas.

c. Mutations have been identified in the BRG1 ATPase of the SWI/SNF complex in a variety of solid tumors including lung, prostate, pancreas, colorectal, and breast carcinoma, among others. This statement is TRUE. BRG1 interacts with RB, so it has been postulated that BRG1 mutations disrupt the ability of RB to act as a tumor suppressor.

d. The SWI/SNF ATP-dependent chromatin remodeling complex promotes chromatin accessibility, resulting in altered gene expression that may lead to cancer. This statement is TRUE. The SWI/SNF ATP-dependent chromatin remodeling complex destabilizes the interaction between DNA and nucleosomes, allowing transcription factor binding as well as transcriptional elongation.

e. Acquired mutations of ATRX are associated with the alpha thalassemia myelodysplastic syndrome (ATMDS). This statement is TRUE. ATRX belongs to the SWI/SNF family of chromatin remodeling proteins.
43. Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels that are highly expressed in the non-neuronal tissues of the lung. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:1799-1801; DOI:10.2353/ajpath.2009.090689 and Am J Pathol 2009, 175:1868-1882; DOI:10.2353/ajpath.090212; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. nAChRs function as ion channels that mediate the flux of sodium. This statement is NOT TRUE. nAChRs function as ion channels that mediate the flux of calcium.
b. There are over a dozen different nAChR subunit proteins. This statement is TRUE. These proteins are divided into α and β subfamilies. The pentameric ion channels consist of either a single type of α subunit (homopentamers) or a combination of α and β subunits (heteropentamers). The airway epithelium expresses the α3, α4, α5, α7, α9, β2, and β4 nicotinic receptor subunits.
c. nAChRs bind to both the endogenous ligand acetylcholine and exogenous ligands such as nicotine. This statement is TRUE. nAChRs undergo complex allosteric changes in response to ligand binding.
d. nAChR activation often leads to a positive feedback loop that induces receptor expression. This statement is TRUE. However, chronic stimulation of nAChRs can lead to channel desensitization and decreased activity.
e. Non-neuronal nAChRs in the lung have been linked to regulatory proteins such as src and phosphatidylinositol 3-kinase, which can control cell proliferation. This statement is TRUE. Neuronal nAChRs are classically linked to the plasma membrane depolarization required for neurotransmission, whereas non-neural nAChRs act most frequently as calcium channels.

44. Proliferating cells in the developing lung express high levels of α7 nAChR, suggesting a physiological role for α7 nAChR in normal lung function. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:1799-1801; DOI:10.2353/ajpath.2009.090689 and Am J Pathol 2009, 175:1868-1882; DOI:10.2353/ajpath.090212; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. α7 nAChR expression coincides with epithelial differentiation during the regeneration of the human airway epithelium in vitro. This statement is TRUE. α7 nAChR expression also coincides with epithelial differentiation in vivo during fetal development.
b. Inactivating α7 nAChR function in vitro increases cell proliferation during the initial steps of epithelial regeneration. This statement is TRUE. α7 nAChR inactivation leads to epithelial alterations such as basal cell hyperplasia and squamous metaplasia, remodeling that is observed in many bronchopulmonary diseases.
c. Basal cells express high levels of α7 nAChR. This statement is TRUE. Basal cells play a critical role in epithelial regeneration and maintaining tissue homeostasis.
d. The regeneration of the airway epithelium after injury in α7 nAChR–deficient mice is delayed and characterized by a transient hyperplasia of basal cells. This statement is TRUE. Moreover, one-year-old α7 nAChR-deficient mice more frequently have basal cell hyperplasia.
e. α7 nAChRs stimulate basal cell proliferation. This statement is NOT TRUE. α7 nAChRs limit basal cell proliferation. The injury response in airways of α7 nAChR-deficient mice was characterized by significant basal cell hyperplasia when compared with wild-type mice.
45. Infants are born with an immature immune system that must mature during childhood, but the mechanisms that regulate human thymic instruction of immune maturation after birth remain poorly understood. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:2043-2052; DOI:10.2353/ajpath.2009.090015; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. Fetal immune responses are dominated by production of T-helper cell (Th) 1 cytokines including interferon (IFN)γ. **This statement is NOT TRUE.** Fetal immune responses are dominated by Th2 cytokine production with characteristically negligible IFNγ production. There is an absence of appropriate environmentally-driven Th1 immunity in infants.

b. Although the immunological importance of the thymus may partially diminish with age, its function persists even in later life. **This statement is TRUE.** The thymus is a primary lymphoid organ that is critical for the development of normal adaptive immunity. A critical aspect of the education of the immune system in the thymus is the acquisition of tolerance to self-antigens without preventing carefully-controlled adaptive responses against foreign antigens.

c. Allergic asthma can be defined as a complex set of chronic inflammatory airway syndromes characterized by eosinophilic infiltration and airway hyperactivity. **This statement is TRUE.** Eosinophils synthesize, store, and release a wide range of potent pro-inflammatory cytokines, chemokines, and growth factors.

d. Eosinophils home naturally to the thymus in neonates in the absence of any detectable danger signal. **This statement is TRUE.** Thymic eosinophils, along with thymic dendritic cells, may be involved in the education of thymocytes.

e. Eosinophils contribute to both localized innate and acquired immunity associated with Th1 and Th2 immune profiles and systemic adaptive responses. **This statement is TRUE.** Eosinophils have been shown to act as antigen-presenting cells.

46. Recent evidence suggests that eosinophils may have a wide range of biological, pathophysiological, structural, and immunological functions spanning the immune and inflammatory spectrum. Based on the reference article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:2043-2052; DOI:10.2353/ajpath.2009.090015; the authors of the referenced article did not disclose any potential conflicts of interest.]

a. The number of eosinophils in the human thymus decreases with age. **This statement is TRUE.** In children, Luna-positive eosinophils were primarily located in the medullary region of the thymus, but many were also found in the trabeculi and within the structure of Hassall’s corpuscles.

b. Eosinophils within Hassal's corpuscles of the thymus were frequently observed in children up to 12 years of age. **This statement is NOT TRUE.** Eosinophils within the corpuscles were frequently observed in thymi from very young children (2 to 4 weeks of age) but were rarely seen in older children.

c. Eosinophils in the thymus express indoleamine 2,3-dioxygenase (IDO). **This statement is TRUE.** IDO is an intracellular enzyme that depletes tryptophan. IDO-mediated tryptophan catabolism generates a cascade of pharmacologically-active catabolites known as kynurenines, which have been shown to be involved in immune regulation.

d. Dendritic cells are an important source of IDO. **This statement is TRUE.** Dendritic cells express both constitutive and IFNγ-inducible forms of IDO.

e. In allergy and asthma, induction of IDO and oxidative catabolism of tryptophan may promote a Th2-biased setting through selective apoptosis of Th1 cells. **This statement is TRUE.** Conversely, IDO/tryptophan may foster a Th1 condition (e.g., autoimmune diseases including diabetes mellitus and rheumatoid arthritis) through suppression of adaptive T-cell-mediated immunity associated with inflammation and host immune defense.
47. CD4+ T cell subsets differ in cytokine production and function and thus play distinct roles in the immune response. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:2255-2256; DOI:10.2353/ajpath.2009.090891 and Am J Pathol 2009, 175:2489-2500; DOI:10.2353/ajpath.2009.090530; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. T-helper (Th) 1 cells are involved in delayed-type hypersensitivity reactions and cell-mediated immunity. This statement is TRUE. A Th1 immune response is associated with a pro-inflammatory response, low antibody titers, and inhibition of B-cell activation. Th1-associated cytokines include interleukin-2, interferon-γ, and lymphotoxin.

b. Th2 helper T cells are involved in B-cell antibody production and in the pathogenesis of allergic reactions. This statement is TRUE. Th2-associated cytokines include interleukin-4, -5, -6, -9, -10, and -13.

c. The Th2 response accentuates the activity of Th1 cytokines. This statement is NOT TRUE. The Th2 response can inhibit the activity of Th1 cytokines.

d. Both Th1 and Th2 reactions are important in a variety of immune-regulated conditions, including the pathogenesis of autoimmune diseases, tolerance in solid organ transplantation, and clearance of infectious pathogens. This statement is TRUE. Many immune responses involve a balance between the Th1 and Th2 subsets, as well as incorporating other defined and possibly not yet defined T-cell subsets.

e. Defects in the immune responses (T-cell, tumor necrosis factor-α, or interferon-γ deficiencies) and/or deviation to Th2 immunity promote alternative activation of macrophages over classical activation of macrophages. This statement is TRUE. Classically activated macrophages are activated by Th1 cytokines. This is particularly significant since alternatively activated macrophages have been demonstrated to harbor Cryptococcus neoformans.
48. Cryptococcus neoformans is a dimorphic, often encapsulated, fungus that can cause significant morbidity and mortality in infected hosts. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:2255-2256; DOI:10.2353/ajpath.2009.090891 and Am J Pathol 2009, 175:2489-2500; DOI:10.2353/ajpath.2009.090530; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. C. neoformans infection in HIV-positive individuals may cause fatal mycosis. This statement is TRUE. C. neoformans is also a problem in organ transplant recipients, patients with hematological malignancies, and those undergoing immunosuppressive therapies.

b. 50% of C. neoformans cases in the United States are reported in immunocompetent hosts. This statement is TRUE. C. neoformans has a high potential to adapt to extreme environmental conditions and a variety of hosts. New high-virulence strains of C. neoformans may therefore contribute to infection of immunocompetent individuals.

c. C. neoformans may develop mechanisms that result in evasion of the immune response, such as immune deviation. This statement is TRUE. Successful clearance of C. neoformans relies on development of a Th1 immune response and classical activation of macrophages. C. neoformans may skew the immune response to a Th2 immune response.

d. Localized pulmonary disease is the most commonly identified form of C. neoformans infection. This statement is TRUE. However, the pathogen can disseminate, resulting in meningoencephalitis.

e. Dissemination into the bloodstream and subsequent sepsis is the major cause of mortality in uncontrolled cryptococcosis. This statement is NOT TRUE. Dissemination into the central nervous system and the subsequent development of meningitis/encephalitis is the major cause of mortality in uncontrolled cryptococcosis.

49. Highly virulent C. neoformans strains are associated with non-protective immune responses with potentially lethal consequences. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:2255-2256; DOI:10.2353/ajpath.2009.090891 and Am J Pathol 2009, 175:2489-2500; DOI:10.2353/ajpath.2009.090530; the authors of the referenced articles did not disclose any potential conflicts of interest.]

a. The immune response to C. neoformans is often driven by a Th1 (and the more recently identified Th17) immune response, in addition to classical activation of macrophages. The statement is TRUE. This response is commonly associated with a marked inflammatory infiltrate that is at first neutrophilic, followed by fibrosis and a granulomatous response.

b. C. neoformans strain H99 can induce a classic Th2 response. This statement is TRUE. The H99 strain grows in the lungs in an uncontrolled fashion, readily disseminates to the central nervous system, and causes 100% mortality in a variety of immunocompetent mouse strains. It has been postulated that this Th2 response is responsible for H99's increased virulence.

c. C. neoformans strain H99 induces a Th1/Th17 immune response in a mouse model deficient in two Th2 cytokines, interleukin-4 and -13. This statement is TRUE. In the absence of interleukin-4 and -13, H99-infected mice switch from a robust immune response with the Th2 phenotype and alternative macrophage activation to that of a mixed Th1/Th17 phenotype and classical macrophage activation.

d. A Th1 response to H99 resulted in both reduced pulmonary infection and increased survival of infected mice. This statement is NOT TRUE. A Th1 response to H99 resulted in a reduction in pulmonary infection but not a significant increase in overall survival, as mice succumbed to fatal meningoencephalitis.

e. Mechanisms other than Th2 immune bias are largely responsible for the central nervous system (CNS) tropism and systemic dissemination of C. neoformans strain H99. This statement is TRUE. Th2 immune bias is a crucial mechanism for pulmonary virulence of H99, whereas other mechanisms are largely responsible for its CNS tropism and systemic dissemination.
50. Angiogenesis is necessary for solid tumor progression and metastasis. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2009, 175:2657-2667; DOI:10.2353/ajpath.2009.090202; the authors of the referenced article did not disclose any potential conflicts of interest.]

- Inhibiting the development of abnormal tumor blood vessels is a promising therapeutic strategy for treating cancer. This statement is TRUE. Bevacizumab, an anti-vascular endothelial growth factor (VEGF)-neutralizing antibody, prolongs the survival of patients with advanced cancer of the colon, breast, or kidney when used with conventional chemotherapeutic drugs.
- Tumor blood vessels have the same structural characteristics as normal blood vessels. This statement is NOT TRUE. Tumor blood vessels differ from their normal counterparts in many respects. Tumor blood vessels have fewer pericytes, exhibit leakiness, and display uneven thickness of the basement membrane.
- Tumor endothelial cells may possess molecular characteristics distinct from those of normal endothelial cells. This statement is TRUE. Endothelial cells derived from human renal cell carcinomas express biological features that are different from those of normal endothelial cells.
- Endothelial cells from hematopoietic tumors harbor chromosomal aberrations. This statement is TRUE. In these tumors, tumor endothelial cells may transdifferentiate from hematopoietic tumor cells.
- Chromosomal aberrations have been observed in human tumor endothelial cells (hTECs) isolated from human malignant epithelium. This statement is TRUE. In human renal cell carcinomas, 22% to 58% (median 33%) of uncultured hTECs were aneuploid, whereas normal endothelial cells were diploid. Aneuploidy has also been observed in murine tumor endothelial cells isolated from nonepithelial tumors, liposarcoma, and melanoma.