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Continuing Medical Education (CME) Accreditation Statement: This journal-based CME activity ("ASIP 2011 AJP CME Program in Pathogenesis") has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Federation of American Societies for Experimental Biology (FASEB) and the American Society for Investigative Pathology (ASIP). FASEB is accredited by the ACCME to provide continuing medical education for physicians.

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The ASIP 2011 AJP CME Program in Pathogenesis is an annual journal-based CME program consisting of a series of 50 questions based on selected articles in the 2011 issues (Volumes 178 and 179) of The American Journal of Pathology (AJP). Monthly exams, consisting of up to 6 questions that are based on selected articles appearing in each monthly issue of the Journal, will be available online on the Journal website for registered participants. To receive CME credit for this journal-based CME activity, participants must achieve a score of at least 75% on a monthly exam and complete a Post-Test Evaluation. All exams must be completed by December 31, 2011 to receive CME credit. Participants will earn 6 AMA PRA Category 1 Credit(s)™ for successful completion of the January 2011 exam (a minimum of 5 questions answered correctly) and will earn 4 AMA PRA Category 1 Credit(s)™ for successful completion of each of the February – December 2011 exams (a minimum of 3 questions answered correctly for each monthly exam).

SAM Credit: The ASIP 2011 AJP CME Program in Pathogenesis is approved by the American Board of Pathology for up to 50 SAM credits. Physicians should only claim credit commensurate with the extent of their participation in the activity. After successfully completing the monthly CME exams as described above, participants may separately apply for SAM credit by completing SAM applications online on the ASIP website (www.asip.org). All SAM applications must be completed by December 31, 2011 for participants to receive SAM credit.

Objective/Target Audience: The objective of the ASIP 2011 AJP CME Program in Pathogenesis is to increase basic and applied pathology knowledge, focusing on the pathogenesis, diagnosis, prognosis, and the treatment of disease. The ASIP 2011 AJP CME Program in Pathogenesis is designed to meet the participants’ education needs in the physician competency area of Medical Knowledge, as defined by the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Medical Specialties (ABMS), and to support participants’ lifelong learning towards a goal of promoting patient safety and improving patient care. This journal-based CME program is specifically targeted to trainees, clinicians and researchers investigating mechanisms of disease who wish to advance their knowledge of the cellular and molecular biology of disease.

Educational Objectives: At the completion of the ASIP 2011 AJP CME Program in Pathogenesis, participants should be able to:

1. discuss the research underway and/or current molecular approaches to decipher the pathogenesis of disease;
2. demonstrate a gained level of knowledge of the methods and techniques being used by researchers and practitioners;
3. understand the link between pathogenesis and the development of new diagnostic, prognostic, and therapeutic approaches to infectious diseases (including bacterial, fungal, viral, and parasitic pathogens), to inherited diseases and syndromes, and to acquired diseases and syndromes spanning systems biology (including cardiovascular, pulmonary, renal, gastrointestinal, immunopathology, matrix biology, metabolic and endocrine pathobiology, musculoskeletal, neurologic, and vascular biology).

Disclosure Policy: The Federation requires that participants in FASEB-sponsored educational programs be informed of the organizers’ and the presenters’ (speaker, faculty, author, or contributor) academic and professional affiliation, and the existence of any relevant financial relationship an organizer or a presenter has with any proprietary entity producing health care goods or services consumed by, or used on patients, with the exemption of non-profit or government organizations and non-health care related companies. The intent of this disclosure is not to prevent a presenter from providing educational content but allows the participant to be fully knowledgeable in evaluating the information being presented.

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None of the organizers of this educational activity disclosed a relevant financial relationship. Relevant financial relationships of the authors of selected articles in this journal CME program will be disclosed in a footnote to the article and in each examination.

This Answer Booklet includes answer sheets for each of the twelve monthly exams. For each question, the correct answer is highlighted in red and an explanation of the correct answer is included as a “Rationale.”
1. Targeted cancer therapies aim to decrease the toxic burden of systemically administered treatments. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:12-18; DOI: 10.1016/j.ajpath.2010.08.004; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. To be effective, systemically delivered pharmacological compounds must reach high concentrations in the tumor and are therefore frequently toxic to the normal tissue or have limited success in curing the disease.
   b. One strategy of targeted therapy is selective delivery of highly toxic compounds coupled to high affinity ligands directed toward systemically accessible cancer proteins.
   c. Cancer-specific antigens must be expressed in a hypoxic environment to be effectively targeted.  
   d. Proteins with high potential as therapeutic targets are often expressed on the outer side of the plasma membrane or are deposited in the extracellular matrix (ECM).

Rationale: Cancer-specific antigens must be accessible from the circulatory system to be specifically targeted in systemic therapy. This is crucial for the effectiveness of drug uptake by the cancer lesion.

2. Ideally, tumor biomarkers of high therapeutic value should be expressed solely by the malignant tumor and be inaccessible in normal tissues. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:12-18; DOI: 10.1016/j.ajpath.2010.08.004; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. The ability of an antibody or other targeted therapeutic agent to reach a newly discovered biomarker should be validated in vivo to confirm that the agent can reach the biomarker under physiological circumstances.
   b. Only antibodies targeting biomarkers that show adequate tumor uptake should be pursued as targeted therapeutic agents.
   c. Successful biomarker-targeting reagents can also be coupled with imaging reagents, offering the possibility to directly monitor the biodistribution and therapeutic success of the cytotoxic counterpart.
   d. L19, a monoclonal antibody directed towards the extra domain (ED) A of laminin, was demonstrated to be effective in selective, targeted treatment of Hodgkin lymphoma patients.

Rationale: L19 is a monoclonal antibody directed toward the EDB domain of fibronectin. The EDA domain of fibronectin has also served as a target for antibodies carrying toxic payloads. These results demonstrate the value of ECM proteins to serve as accessible tumor targets.

3. The successful discovery of accessible tumor biomarkers is dependent upon the development and application of innovative proteome fractionation, isolation, and identification strategies. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:12-18; DOI: 10.1016/j.ajpath.2010.08.004; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Mass spectrophotometry delivers qualitative and quantitative information regarding the proteins in question.
   b. Intact proteins in a complex mixture are not suitable for identification by mass spectrophotometry.
   c. Proteins are identified via mass spectrophotometry by comparing the obtained amino acid sequence fingerprint with a suitable database.
   d. A major difficulty confronting the analysis of tumor tissue for targetable biomarker discovery is the large dynamic range of protein concentrations in the sample. Limitations in the dynamic range of mass spectrophotometry allow for only a certain concentration window (approximately four orders of magnitude) to be analyzed at a given time.
Rationale: Intact proteins as well as fragments obtained through enzymatic digestion can be sequenced using either matrix-assisted laser desorption/ionization–time-of-flight (MALDI-TOF) or surface-enhanced laser desorption/ionization–time-of-flight (SELDI-TOF) mass spectrophotometry technologies.

4. Melanoma is a malignant tumor that originates in melanin-producing cells. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:26-31; DOI: 10.1016/j.ajpath.2010.11.004; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Melanocytes can be found in different body tissues, such as heart, lung, and muscle.
   b. Cutaneous melanoma is the most frequent type of melanoma, representing approximately 5% to 7% of all skin malignancies.
   c. Environmental and individual risk factors as well as genetic pedigree may contribute to the risk of melanoma development.
   d. Multiple differences between melanoma cell genomes and those of normal melanocytes have been identified in genome-wide analysis studies. Point mutations, deletions, gene amplifications and translocations, and/or epigenetic modifications (such as promoter hypermethylation) appear to provide a significant growth advantage to melanoma cells as compared with normal skin cells.

Rationale: Melanocytes can be found in different body tissues, such as skin, uvea, leptomeninges, and mucous membranes.

5. The insulin-like growth factor (IGF) system mediates growth, differentiation, and developmental processes and is involved in a variety of metabolic activities. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:26-31; DOI: 10.1016/j.ajpath.2010.11.004; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Deregulation of the IGF system is linked to several pathologies, ranging from growth deficits to cancer development.
   b. At the organ level, IGFs display paracrine and autocrine pathways, often interacting with vitamin D, inflammatory molecules, or locally produced factors such as suppressors of cytokine signaling (SOCS), transforming growth factor (TGF)-β, and steroid hormones.
   c. Growing evidence suggests that IGF-1 is involved in the pathogenesis of various types of human neoplasias, including breast, prostate, colon, and lung cancers.
   d. The promoter region of IGF binding protein (BP)-3 is hypomethylated in human melanoma samples compared with normal nevi.

Rationale: The IGFBP-3 promoter region is highly methylated in human melanoma samples compared with normal nevi. Silencing of the EGFBP-3 promoter by methylation in melanoma cells may inhibit its overexpression, resulting in suppression of apoptosis and stimulation of cell survival and growth. IGF-1 binds to IGFBP-3 in a 1:1 molar ratio. IGFBP-3 regulates IGF-1 by protecting it from accelerated degradation in circulation and by facilitating its transport to target organs. IGFBP-3 is also believed to have an IGF-independent inhibitory effect on cell growth that is mediated through a specific cell membrane receptor. Higher IGFBP-3 serum levels were related to reduced cancer risk, suggesting a possible influence of IGFBP-3 in reducing IGF-1 bioactivity.

6. During tumorigenesis, the stroma accelerates carcinoma growth and progression. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:325-335; DOI: 10.1016/j.ajpath.2010.11.039; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Normal stromal fibroblasts and the ECM proteins they secrete are believed to exert an inhibitory constraint on tumor growth and progression.
   b. Via its chondroitin sulfate chains, syndecan-1 (Sdc1) expressed by stromal fibroblasts in breast carcinomas is causally involved in altered matrix production of tumor stroma.
   c. Major alterations occur in the stromal fibroblasts and the ECM during neoplastic transformation, giving rise to a permissive and supportive microenvironment for carcinomas.
   d. Sdc-2 and Sdc-4 have been implicated in fibronectin matrix assembly.

Rationale: Syndecans (Sdcs) constitute a family of transmembrane heparin sulfate proteoglycans with four known members (Sdc1-4). Sdcs interact with a wide variety of proteins, including growth factors and ECM constituents via their heparin sulfate-glycosaminoglycan chains. Sdc1 is aberrantly expressed by stromal fibroblasts in breast carcinomas and participates in a reciprocal carcinoma growth-promoting feedback loop that requires proteolytic shedding of its ectodomain. Sdc1 regulates ECM assembly and determines ECM fiber architecture. The data suggest that Sdc1 expression by stromal fibroblasts may be causally involved in altered matrix production of tumor stroma, facilitating the directional migration and invasion of breast carcinoma cells. Sdc-2 appears to be required to assemble laminin and fibronectin into a fibrillar matrix. Sdc-4 may participate in fibronectin matrix assembly.
1. Activation-induced cytidine deaminase (AID) is critical for the production of high-affinity, pathogen-specific antibodies. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:462-471; DOI: 10.1016/j.ajpath.2010.09.044; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. A naïve B cell may recognize a pathogen with only a weak affinity and must undergo further diversification to improve this interaction to the degree necessary for immunity.
   b. Secondary antibody diversification to produce high affinity antibodies primarily occurs in the bone marrow.
   c. AID creates point mutations in antibody sequences by deaminating cytidines to uridines specifically at the immunoglobulin locus.
   d. AID is critical for somatic hypermutation, which alters antibody affinity through point mutation, as well as for class switch recombination, which spurs recombinogenic events that substitute immunoglobulin isotypes.

Rationale: Unlike primary diversification, which occurs in the bone marrow, secondary diversification occurs primarily in the germinal centers, which are areas of the peripheral lymph nodes where mature B cells proliferate, differentiate, and mutate through somatic hypermutation and class switch recombination.

2. Aberrant AID expression or even its normal physiological function may lead to disease. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:462-471; DOI: 10.1016/j.ajpath.2010.09.044; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. The vast majority of B cell lymphomas occur in either the germinal center (GC) or post-GC B cell compartments, with AID being linked to many of the etiological events.
   b. Abnormal secondary diversification is associated with the onset of severe autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), myasthenia gravis, and Sjögren’s syndrome.
   c. The GC forms in peripheral lymphoid tissue two weeks after exposure to antigen.
   d. Sites of autoantibody production strongly express AID and exhibit hallmarks of somatic hypermutation.

Rationale: The GC is the source of both plasma and memory cells. It provides a microenvironment that forms in peripheral lymphoid tissue 5 to 7 days after exposure to antigen and is the site of secondary diversification.

3. The glomerulus is the primary target of most chronic renal diseases. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:609-620; DOI: 10.1016/j.ajpath.2010.10.031 and related Commentary Am J Pathol 2011, 178:485-489; 10.1016/j.ajpath.2010.10.038; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. When the glomerulus is severely injured, it undergoes glomerulosclerosis, characterized by excessive extracellular matrix deposition and glomerular cell death.
   b. Initiating events targeting any of the four major components of the glomerulus can result in glomerulosclerosis.
   c. Integrin-dependent functions are required for glomerular development and maintenance of glomerular homeostasis in both health and disease.
   d. The only integrin known to regulate glomerular development by mediating an interaction with the extracellular matrix is integrin α8β1.
Rationale: Mice lacking α8β1 have hypercellular glomeruli with an increased number of mesangial cells, increased mesangial matrix deposition, and minor abnormalities within the glomerular capillary networks. Integrin α8β1 is not the only integrin known to regulate glomerular development by mediating an interaction with the extracellular matrix. Selective deletion of the integrin α3 subunit in the podocyte results in massive proteinuria and nephrotic syndrome, and the glomeruli have a disorganized glomerular basement membrane, podocyte foot process effacement, and finally glomerulosclerosis. A similar, although more profound, glomerular phenotype occurs when the integrin β1 subunit (which can bind 12 different α subunits including the α3) is selectively deleted in podocytes.

4. Paracrine signaling between mesangial and endothelial cells is important for the maintenance of normal glomerular integrity. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:609-620; DOI: 10.1016/j.ajpath.2010.10.031, and related Commentary Am J Pathol 2011, 178:485-489; 10.1016/j.ajpath.2010.10.038; the authors of the referenced articles did not disclose any relevant financial relationships.]

a. TGF-β is expressed by both podocytes and mesangial cells and has been implicated in decreasing matrix production by mesangial cells.
b. TGF-β has multiple functions, including being a pro-fibrotic cytokine; it affects both mesangial and podocyte cell survival and proliferation.
c. Integrin αvβ8 can regulate cell functions in both TGF-β-independent and -dependent manners.
d. Mesangial cell sequestration of latent TGF-β by integrin αvβ8 modulates glomerular endothelial cell function.

Rationale: TGF-β is expressed by both podocytes and mesangial cells; it has been implicated in increasing matrix production by mesangial cells, leading to mesangial expansion and ultimately glomerular fibrosis.
1. Poly(ADP-ribosyl)ation (PARylation) is an essential post-translational protein modification. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:946-955; DOI: 10.1016/j.ajpath.2010.12.004; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. During PARylation, poly(ADPribose) (PAR) molecules are formed from donor nicotinamide adenine dinucleotide (NAD⁺) molecules and are covalently attached to target proteins via an ester linkage to glutamic acid (or, less commonly, to aspartic acid or lysine).
   b. PAR-binding consensus motifs frequently overlap with a functional domain, such as a protein- or DNA-binding domain, which results in altered functional properties of PARylation targets.
   c. PARylation is catalyzed by the PAR polymerase (PARP) family of enzymes.
   d. Only three PARP family members, PARP-1, PARP-8, and PARP-9, are DNA damage related.

   **Rationale:** There are 18 members of the PARP family of enzymes. Only two PARP family members, PARP-1 and PARP-2, are DNA damage related. PARP-1, the best understood member, is an abundant nuclear enzyme that accounts for at least 85% of cellular PARP activity.

2. PARP-1 has been linked to inflammatory responses in various disease models. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:946-955; DOI: 10.1016/j.ajpath.2010.12.004; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. In a model of sepsis, PARP-1 expression colocalizes with DNA breaks and correlates with sepsis-induced inflammation.
   b. In pulmonary inflammation models, PARP-1 induction results in a reduction of inflammatory cell recruitment to mouse airways.
   c. In a model of enterocolitis, the absence of PARP-1 is associated with delayed gut inflammation.
   d. PARP-1 induces inflammatory cytokines in cardiomyocytes infected with *Trypanosoma cruzi*.

   **Rationale:** In pulmonary inflammation models induced by intra-tracheal administration of lipopolysaccharide, PARP-1 suppression by genetic deletion or pharmacological inhibitors is beneficial in reducing inflammatory cell recruitment to mouse airways.

3. PARP-1 has been implicated in cytotoxic agent-induced inflammation, as well as other forms of noninfectious inflammation. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:946-955; DOI: 10.1016/j.ajpath.2010.12.004; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. Asbestos suppresses human mesothelial cell PARP-1 associated with H₂O₂ secretion.
   b. PARP-1 inhibition reduces the extent of inflammation by modulating oxidative stress in a model of contact hypersensitivity.
   c. PARP-1 is involved in murine colitis and ischemia-reperfusion models.
   d. PARP-1 activation accompanies depression of left ventricular function in chronic heart failure models.

   **Rationale:** Asbestos activates human mesothelial cell PARP-1 associated with H₂O₂ secretion, ATP depletion, and translocation of high mobility group box 1 protein (HMGB1) from the nucleus to the cytoplasm and into the extracellular space. Injecting mice and hamsters with asbestos validates the release of HMGB1 in the extracellular space of mesothelial cells and inflammatory cells around asbestos deposits.
4. The tumor stroma can be used as a prognostic signature for survival in human breast cancer. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1221-1232; DOI: 10.1016/j.ajpath.2010.11.076, and related Commentary Am J Pathol 2011, 178:966-968; DOI: 10.1016/j.ajpath.2010.12.013; Patricia J. Keely (DOI: 10.1016/j.ajpath.2010.11.076) receives consulting fees for the development of migration assays from Platypus, Inc.; the other authors of the referenced articles did not disclose any relevant financial relationships.]

   a. Increased mammographic density, which is due largely to an elevated collagen concentration, is one of the greatest risk factors for the development of breast cancer.
   b. Unstained collagen fibers in a tumor can be imaged by second harmonic generation, which can differentiate periodic structures that are not centrosymmetric, such as collagen, because they emit exactly half the excitation frequency.
   c. The tumor-associated collagen signature (TACS), as determined by second harmonic generation, corresponds to the way that the tumor-associated fibroblasts are organized with respect to the tumor cells.
   d. TACS-3 is a potential marker of a highly invasive tumor.

Rationale: The TACS corresponds to the way that the extracellular matrix is organized with respect to the tumor cells. TACS-1 is found in early tumors, with increased numbers of curved, apparently relaxed, collagen fibers around the tumor. TACS-2 develops as the tumor grows larger. The surrounding fibers become straight and parallel to the surface of the tumor, probably reflecting stretching of the fibers due to the expansion of the tumor. TACS-3 reflects a significant reorganization of the matrix, so that straight matrix fibers now lead directly into the tumor cell mass. In TACS-3, the fibers can act as pathways along which cells can crawl, as has been seen in multiphoton imaging of metastatic tumors.
1. Many different cell types may function as phagocytes in the brain. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1416-1428; DOI: 10.1016/j.ajpath.2010.12.051; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Macrophages and microglia are considered the professional phagocytes of the brain.
   b. Microglia are derived from the hematopoietic lineage and perform typical immune functions.
   c. Astrocytes are derived from neural stem cells but express many components of evolutionarily conserved phagocytic pathways.
   d. Neurons are not capable of phagocyte-like engulfment.

Rationale: Even neurons are capable of engulfment, although it may be better characterized as endocytosis or pinocytosis.

2. Glial cell activation results in phagocytosis as well as other downstream effects. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1416-1428; DOI: 10.1016/j.ajpath.2010.12.051; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Glial cell activation can lead to both cytokine secretion and production of reactive oxygen species.
   b. The use of one cell surface marker is insufficient to fully characterize the activation phenotype of glial cells.
   c. Classical activation, known as M1, is characterized by anti-inflammatory cytokines and free radicals.
   d. The immunomodulatory milieu in the central nervous system (CNS) differs from that in the periphery.

Rationale: Classical activation is known as M1 and is characterized by the secretion of proinflammatory cytokines and free radicals. Alternate activation, or M2, is a less well defined anti-inflammatory phenotype.

3. Phagocytosis is regulated by both cell-cell and cell-microenvironment interactions. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1416-1428; DOI: 10.1016/j.ajpath.2010.12.051; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Astrocytes can regulate microglial activation, perhaps through CD40-CD40 ligand interactions.
   b. Due to their prevalence in the CNS parenchyma, T cells likely regulate microglial activation via direct contact.
   c. Neuronal signals likely influence the activation of glia, as neuronal activity can dampen inflammatory cytokine production in vitro.
   d. Dead cells and cell debris activate microglial phagocytosis.

Rationale: T cells likely regulate microglial activation through the secretion of cytokines because they have relatively limited access to the CNS parenchyma.
4. A small population of cancer cells can regenerate a heterogenous tumor. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1805-1813; DOI: 10.1016/j.ajpath.2011.01.004; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Stem-like cancer cells (cancer stem cells) have a lower tumorigenic potential than other cells within a tumor.
   b. Colon cancer stem-like cells were successfully isolated using Hoechst 33342 staining.
   c. Cancer stem cells can be resistant to different forms of therapy, including chemotherapy and radiotherapy.
   d. The authors targeted colon cancer stem cells with cytotoxic T lymphocyte (CTL)-based immunotherapy and suggest that these cells may be good candidates for cancer vaccine targets.

Rationale: Cancer stem cells have a higher tumorigenic potential than other cells within a tumor. They can reinitiate tumors that resemble the parent tumor when transplanted into immunodeficient mice.
1. The US Food and Drug Administration (FDA) has approved targeted therapies for treating non-small cell lung cancer (NSCLC), which comprises 85% of lung cancer cases. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1940-1948; DOI: 10.1016/j.ajpath.2010.12.057; the author received support from Boehringer Ingelheim Pharmaceuticals, Inc. for editorial assistance; the author did not disclose any other relevant financial relationships.]

   a. The vascular endothelial growth factor (VEGF)-specific monoclonal antibody bevacizumab is FDA approved for treating advanced NSCLC.
   b. Erlotinib and gefitinib are reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors that are FDA approved in chemotherapy-pretreated patients.
   c. Erlotinib is FDA approved for treating either advanced NSCLC failing one chemotherapy regimen or advanced NSCLC that is maintained with first-line, platinum-based chemotherapy.
   d. According to data from recent clinical trials, gefitinib should be used preferentially over erlotinib in the treatment of NSCLC.

Rationale: Erlotinib improved both overall survival and progression-free survival versus placebo in a 2010 trial. No overall survival was seen in gefitinib trials.

2. The molecular features of NSCLC tumors have become important considerations for predicting response to selected therapies. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1940-1948; DOI: 10.1016/j.ajpath.2010.12.057; the author received support from Boehringer Ingelheim Pharmaceuticals, Inc. for editorial assistance; the author did not disclose any other relevant financial relationships.]

   a. In-frame deletions in exon 19 were the predominant form of all EGFR mutations, with an incidence of 44%.
   b. The second most common EGFR mutation was the single nucleotide substitution G719X in exon 18, accounting for 41% of all mutations.
   c. The incidence of EGFR mutations appears to vary greatly according to tumor histology, smoker status, sex, and ethnic descent.
   d. The activity of gefitinib or erlotinib seen in a subset of patients was largely attributable to somatic mutations in the catalytic tyrosine kinase domain of EGFR.

Rationale: The second most common EGFR mutation was the single nucleotide substitution L858R in exon 21, accounting for 41% of all mutations. Less frequent mutations included i) the single nucleotide substitution G719X in exon 18, ii) in-frame duplication/insertions in exon 20, and iii) rare missense mutations in exons 18–21, accounting for 4%, 5%, and 6% of remaining EGFR mutations, respectively.
3. Mutations in genes other than EGFR are associated with response to EGFR tyrosine kinase inhibitors. Based on the referenced Mini-Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:1940-1948; DOI: 10.1016/j.ajpath.2010.12.057; the author received support from Boehringer Ingelheim Pharmaceuticals, Inc. for editorial assistance; the author did not disclose any other relevant financial relationships.]

- Mutations in Kirsten rat sarcoma viral oncogene homolog (KRAS) result in constitutive activation of the protein and may lead to signaling independent of EGFR activation.
- A 13% incidence of echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusions was reported in a study of primarily non-Asian patients with metastatic NSCLC.
- KRAS mutations have predictive value in patients undergoing traditional chemotherapy.
- EML4-ALK-positive patients do not respond to erlotinib but have a 25% partial response rate to platinum-based chemotherapy.

Rationale: A recent meta-analysis concluded that KRAS mutations have no predictive value in patients undergoing traditional chemotherapy (whether for NSCLC, colorectal cancer, or other solid tumors). However, some evidence supports the utility of determining KRAS mutation status specifically in the context of EGFR tyrosine kinase inhibitor therapy.

4. Age-related macular degeneration (AMD) is the leading cause of vision loss among the elderly. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:2032-2043; DOI: 10.1016/j.ajpath.2011.01.036; the authors did not disclose any relevant financial relationships.]

- Bacterial infection is implicated in the pathogenesis of AMD since it causes photoreceptor degeneration, resulting in vision loss.
- Deposits of lipids with esterified and unesterified cholesterol are found in Bruch’s membrane early in the course of AMD.
- Advanced nonexudate, or dry, AMD is characterized by death of retinal pigment epithelial (RPE) cells.
- In wet AMD, new blood vessels develop underneath the retina and lead to exudation of fluid and hemorrhage.

Rationale: Photoreceptor degeneration as a consequence of oxidative stress-induced RPE cell degeneration results in vision loss and is implicated in the pathogenesis of AMD. Photoreceptors rely on the underlying RPE cells for nutritional and metabolic support and undergo secondary degeneration when RPE cells are targeted.
1. Ataxia-telangiectasia (A-T) is a multifaceted disease with complex pathology. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:2741-2752; DOI: 10.1016/j.ajpath.2011.02.022; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. A-T is caused by mutations in the gene encoding the PI3-kinase-like protein kinase ataxia-telangiectasia mutated (ATM).
   b. A-T patients commonly acquire hematological malignancies and recurrent bronchial malignancies that together are partly responsible for most of the mortality of the disease.
   c. Treatment of mice with rapamycin, inhibitor of the mammalian target of rapamycin complex 1 (mTORC1), significantly decreases the life span of ATM<sup>−/−</sup> mice.
   d. Cerebellar degeneration underlies the hallmark ataxia symptoms of A-T patients.

   **Rationale:** Treatment of mice with rapamycin significantly increases the life span of ATM<sup>−/−</sup> mice by delaying development of thymic lymphoma.

2. The CD8<sup>+</sup> T cell response is a crucial arm of the adaptive immune system. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:2741-2752; DOI: 10.1016/j.ajpath.2011.02.022; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. Immunodeficiency associated with decreased production of immunoglobulins A, E, and G and with thymic hyperplasia has been documented in A-T patients.
   b. Defects in the V(D)J recombination process, which results in a block in differentiation at the CD4<sup>+</sup>/CD8<sup>+</sup> double-positive stage in the thymus, cause lower thymic output of mature CD4<sup>+</sup> and CD8<sup>+</sup> cells.
   c. The immune function of mature T cells in A-T patients has been reported to be essentially normal.
   d. Viral T-cell responses and memory T-cell development were aberrant in the ATM<sup>−/−</sup> mice, even though their primary immune response was effective and the mutant mice could clear virus with similar efficiency as wild-type mice.

   **Rationale:** Immunodeficiency associated with decreased production of immunoglobulins A, E, and G and with thymic hypoplasia has been documented in A-T patients. Thymic hypoplasia involves decreased peripheral CD4<sup>+</sup> and CD8<sup>+</sup> lymphocyte pools resulting from developmental defects in the thymic microenvironment.

3. Head and neck squamous cell carcinoma (HNSCC) is a common type of cancer responsible for 250,000 deaths worldwide each year. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:2858-2866; DOI: 10.1016/j.ajpath.2011.02.030; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. HNSCC originates from mucosal tissues of the upper aerodigestive tract and spans the oral cavity to the larynx.
   b. Treatment methods include single and multimodality therapies using surgery, chemotherapy, and radiotherapy; however, the 5-year survival rate remains below 25%.
   c. Morphological examination of HNSCC has revealed that the pattern of tumor invasion, presence of perineural invasion, and presence of inflammatory cells correlate with clinical outcome.
   d. The World Health Organization estimates that there are over 500,000 new cases of HNSCC per year worldwide.

   **Rationale:** The 5-year survival rate remains just above 50%. A key constraint that limits the success of surgical treatment of HNSCC is its location. Adequate margins to guarantee removal of all tumor cells are difficult to achieve in many cases without compromising quality of life or survival.
4. Interactions between tumor cells and surrounding host stromal elements in the primary tumor-host microenvironment contribute to tumor cell invasion. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 178:2858-2866; DOI: 10.1016/j.ajpath.2011.02.030; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. The epidermal growth factor receptor (EGFR) is often overexpressed in HNSCC and correlates with poor prognosis.
   b. EGFR ligands are chemoattractants, directly stimulating cell motility and HNSCC invasion in vitro.
   c. Macrophages invaded together with tumor cells in vivo in response to EGF and chemokine (CXCL12) gradients and were required for HNSCC invasion.
   d. EGFR-mediated invasion of HNSCC can be activated either directly by EGF and/or by transactivation through CXCL12/CXCR4.

Rationale: Utilizing floor of mouth models of HNSCC, tumor cells and macrophages invaded together in response to applied gradients of EGF and CXCL12. However, macrophage contributions were not required for HNSCC invasion.
1. Cancer stem cells (CSCs) are tumor cells that possess the capacity for self-renewal and generation of heterogeneous lineages of cancer cells that comprise tumors. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2-11; DOI: 10.1016/j.ajpath.2011.03.005; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. CSCs in breast tumors were initially characterized in 2003 by the presence of cell-surface markers CD44+/CD24–/low/ESA and high expression of CD2, CD2, CD3, CD10, CD16, CD18, CD31, CD64, and CD140(b).
   b. Cancer cell lines enriched in CD44+/CD24–/low cells are not more tumorigenic than cell lines that contain only 5% of cells with that phenotype, indicating that only a subgroup of CD44+/CD24–/low cells are self-renewing.
   c. Breast tumor cells positive for activity of aldehyde dehydrogenase (ALDH) can generate tumors in NOD/SCID mice with phenotypic characteristics resembling the parental tumor, suggesting that the ALDH+ pool of cells contains the CSC population and that ALDH is a breast cancer stem cell marker.
   d. Breast cancer cells with the CD44+/CD24+/ALDH+ phenotype are more tumorigenic than CD44+/CD24– cells or ALDH+ cells.

Rationale: CSCs were initially characterized by the presence of cell-surface markers CD44+/CD24–/low/ESA and lack of expression of CD2, CD2, CD3, CD10, CD16, CD18, CD31, CD64, and CD140(b), which is referred to as lineage–.

2. CSCs require a highly specific and discrete microenvironment (the niche). Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2-11; DOI: 10.1016/j.ajpath.2011.03.005; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Up to 0.5% of the cancer cells that reach the circulation develop macrometastases.
   b. A permissive niche is fundamental for the establishment of metastatic lesions at distant sites, just as for the primary tumor site.
   c. Under the influence of a hyaluronic acid-enriched environment, either CD44-expressing tumor cells are reprogrammed to acquire certain stem cell properties or circulating CSCs find an appropriate environment for their expansion.
   d. The expression of the α6 integrin subunit correlates with reduced survival in breast cancer patients and increased metastatic potential and survival of breast carcinoma cells.

Rationale: Only 0.02% to 0.1% of the cancer cells that reach the circulation develop macrometastases.

3. Autism is a neurodevelopmental disorder characterized by problems in communication and social skills as well as repetitive behavior. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:66-74; DOI: 10.1016/j.ajpath.2011.03.034; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. The reelin protein encoded by the RELN gene plays a pivotal role in neuronal cell migration and prenatal development of neural connections.
   b. Linkage between RELN and autism is a replicated genetic finding in autism research.
   c. Reelin acts through α6β4 integrins and exerts proteolytic activity on the extracellular matrix (ECM).
   d. Reelin is coexpressed with HAR1F, which is a novel RNA gene expressed specifically in Cajal-Retzius neurons in the developing human neocortex from gestational week 7 to 19.

Rationale: Only 0.02% to 0.1% of the cancer cells that reach the circulation develop macrometastases.
Rationale: Reelin can act through α3β1 integrins, exerting proteolytic activity on extracellular matrix proteins, which are crucial for neuronal migration.

4. Recent studies suggest that reduced cell migration plays a role in the pathogenesis of autism. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:66-74; DOI: 10.1016/j.ajpath.2011.03.034; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Focal adhesions are sites of cell attachment to the ECM, where transmembrane integrins link the ECM to the cytoskeleton.
   b. Paxillin, vinculin, talin, focal adhesion kinase (FAK), Src family kinases, and p21-activated kinase (PAK) are among the proteins localized to focal adhesions.
   c. The phosphorylation of serine residues is critical to the activation of FAK.
   d. The authors compared B lymphoblasts from autistic subjects with age-matched controls to test the hypothesis that ECM proteins FAK-Src and their downstream signaling pathways are abnormally regulated in autism, leading to defects in cell adhesion, migration, proliferation, and cell function.

Rationale: The phosphorylation of tyrosine residues is involved in the activation of FAK. FAK is activated by signaling from the upstream integrins and undergoes autophosphorylation at Y397, which creates a binding site for Src via the SH2 domain and activates Src. The activated Src further phosphorylates FAK at Y576/577 and Y925, resulting in the full activation of FAK. The activated FAK/Src complex then initiates a cascade of phosphorylation events and new protein-protein interactions to trigger multiple intracellular signaling pathways.
1. *Cryptococcus neoformans* is a fungal pathogen that is acquired by inhalation of spores and/or desiccated yeasts. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:733-744; DOI: 10.1016/j.ajpath.2011.04.025; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Reactivation of latent pulmonary *C. neoformans* infection in immunocompromised HIV-1-infected patients leads to the development of cryptococcal meningitis.
   
   b. The annual death rate (>500,000) of HIV-1-infected patients in sub-Saharan Africa from cryptococcal meningitis exceeds that of tuberculosis-associated HIV cases.
   
   c. IL-12-dependent Th1 responses to *C. neoformans* have a detrimental role in pulmonary cryptococcosis.
   
   d. Allergic Th2-driven inflammation represents the immunopathological pathway of fatal meningoencephalitis by allowing cryptococci to grow inside the lung and disseminate to the brain.

   Rationale: IL-12-dependent Th1 responses are protective, with an additional contribution by IL-23-dependent Th17 responses. Th2 cells producing IL-4, IL-5, and IL-13 are detrimental. In the case of bronchopulmonary infection, dissemination to the brain seems to rely more on Th2 cytokines.

2. Pulmonary cryptococcosis and asthma share some pathophysiological features. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:733-744; DOI: 10.1016/j.ajpath.2011.04.025; the authors of the referenced article did not disclose any relevant financial relationships.]

   a. Similar to pulmonary cryptococcosis, eosinophil-deficient ΔdblGATA mice show decreased levels of pulmonary Th2-related cytokines and mononuclear cell recruitment.
   
   b. IL-13-dependent mucus production by goblet cells, IL-4-dependent IgE production, IL-5-dependent eosinophilia, and functional pulmonary impairment can be found in both pulmonary cryptococcosis and asthma.
   
   c. Airway epithelial cells and eosinophils are candidates for cross talk between resident tissue cells and leukocytes in pulmonary cryptococcosis.
   
   d. The data definitively demonstrate that basophils are involved in fatal Th2 initiation in pulmonary cryptococcosis.

   Rationale: Basophils were shown recently in models of parasitic disease and a protease allergen model to play an essential role in Th2 differentiation; however, the contribution of innate immune cells, such as basophils, in pulmonary cryptococcosis remains to be tested.
3. Eosinophils contribute to IL-4 production during pulmonary *C. neoformans* infection in mice. Based on the referenced article, select the ONE statement that is NOT TRUE: Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:733-744; DOI: 10.1016/j.ajpath.2011.04.025; the authors of the referenced article did not disclose any relevant financial relationships.]

- a. Even in the presence of IFN-γ, IL-4 production is detrimental in pulmonary cryptococcosis.
- b. IL-4 production by both eosinophils and antigen-specific Th2 cells is an early event in pulmonary cryptococcosis, starting within 2 weeks of infection.
- c. In cryptococcosis, eosinophils promote Th2 responses but are not essential for Th2 differentiation.
- d. Dissemination of cryptococci to the brain is only abrogated when IL-4, IL-13, or IL-4/IL-13 signaling is completely abolished.

Rationale: IL-4 production by both eosinophils and Th2 cells is a relatively late event in pulmonary cryptococcosis, starting 6 weeks after infection. The late onset of IL-4 production dominates the production of otherwise protective cytokines such as IL-17 and IFN-γ. This suggests a cytokine hierarchy underlying the role of IL-4 cryptococcosis, with IL-4 on top of IFN-γ/IL-17.

4. The incidence of esophageal squamous cell carcinoma (ESCC) continues to increase and its outcome remains poor despite recent advances in the detection of premalignant lesions and the development of combination therapies. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:992-1003; DOI: 10.1016/j.ajpath.2011.04.004; the authors of the referenced article did not disclose any relevant financial relationships.]

- b. Pea3 group transcription factors promote metastatic development and cancer progression through transcriptional activation of metastasis-related genes, eg matrix metalloproteinases (MMPs) and cyclooxygenase (COX)-2.
- c. Expression levels of Pea3, Erm, and Er81 are significantly higher in ESCC compared with nontumor esophageal epithelium.
- d. The authors did not succeed in developing stable cancer cell lines after lentiviral infection of Pea3 scramble short hairpin (shScr) RNAs and instead used transiently infected cells in the *in vitro* experiments.

Rationale: Expression levels of Pea3 and Erm are significantly higher in ESCC compared with nontumor esophageal epithelium. Er81 is not overexpressed in ESCC. The expression level of Pea3 in the primary tumors shows a significant positive correlation with the T stage, but not with the other clinicopathological parameters. A high level of Pea3 expression is associated with a shorter survival in the entire cohort and in patients with N1 stage disease. No association with survival is observed for Erm and Er81. Furthermore, Pea3 is highly expressed in seven ESCC cell lines but is not detectable in NE1 and NE3 (immortalized esophageal epithelial) cell lines.
1. Endothelial-to-mesenchymal transition (EndoMT) has recently emerged as a type of cellular transdifferentiation that may play a pathophysiological role in fibrotic disorders. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:1074-1080; DOI: 10.1016/j.ajpath.2011.06.001; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. Tumor growth factor (TGF)-β may induce EndoMT, during which cells lose their endothelial cell markers while acquiring those of mesenchymal cells.
   b. Originally, EndoMT was thought to occur rarely and only in embryonic cells and tissues.
   c. EndoMT is thought to be the most important contributor to cardiac fibrosis.
   d. TGF-β2 treatment of mouse endothelial cells induces their expression of the mesenchymal cell marker claudin 5.

Rationale: Claudin 5 is an endothelial cell marker. TGF-β2 treatment of murine endothelial cells induces their expression of mesenchymal cell markers, including α-SMA, transgrelin, and calponin, and reduces the expression of claudin 5.

2. Research into EndoMT-mediated pathological fibrosis of various organs and tissues has revealed possible routes for targeting and abrogating EndoMT. Based on the referenced Review, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:1074-1080; DOI: 10.1016/j.ajpath.2011.06.001; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. Inhibition of glycogen synthase kinase 3β (GSK-3β) phosphorylation by specific inhibition of protein kinase Cδ (PKC-δ) with rottlerin abolishes the acquisition of the myofibroblastic phenotype.
   b. In response to TGF-β1 treatment to promote EndoMT, the expression of the transcriptional repressors Snail1 and Snail2, which are involved in epithelial-to-mesenchymal transition (EMT), is greatly increased.
   c. EndoMT is blunted in transgenic mice heterozygous for Smad3, a transcription factor that is active downstream of TGF-β receptor, suggesting that a gene dosage effect occurs whereby sufficient Smad3 is needed to start and maintain EndoMT.
   d. A non-Smad pathway exists whereby TGF-β signaling can produce EndoMT by a different intracellular signaling route.

Rationale: The mRNA and protein expression of the transcription repressor Snail1 is greatly increased In EndoMT, whereas that of Snail2 is not affected.

3. Inflammatory bowel disease (IBD) is a term that encompasses both ulcerative colitis and Crohn’s disease, affecting more than one million patients in the US. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:1230-1242; DOI: 10.1016/j.ajpath.2011.05.013; the authors of the referenced article did not disclose any relevant financial relationships.]
   a. Most of the therapies developed to combat IBD are designed to ameliorate mucosal inflammation.
   b. Multiple drugs are used for therapy (eg, mesalazine, budesonide, methotrexate, prednisolone, and azathioprine), but prolonged use can result in side effects such as hepatotoxicity, osteoporosis, susceptibility to infection, and bone marrow suppression.
   c. Nearly 40% of patients with Crohn’s disease have surgery related to the disease at least once.
   d. The annual total cost to IBD patients in the US approaches $2 billion.

Rationale: Patients with Crohn’s disease face an even greater likelihood (approximately 70%) for surgery.
4. Numerous scenarios have been posited regarding the possible pathways by which the tripeptide KdPT reduces intestinal inflammation. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:1230-1242; DOI: 10.1016/j.ajpath.2011.05.013; the authors of the referenced article did not disclose any relevant financial relationships.]

a. KdPT has structural similarity to the C-terminus of α-melanocyte-stimulating hormone (KPV), has sequence homology with residues 193-195 (KPT) of IL-1β, and is thought to compete with the cytokine for binding to the IL-1 receptor.

b. In IL-10–deficient mice treated with the nonsteroidal anti-inflammatory drug piroxicam to induce colitis, subsequent administration of KdPT results in more numerous crypt abscesses and intestinal inflammation, suggesting that KdPT exacerbates the already weakened ability of these mice to ameliorate colitis.

c. Although KdPT does not bind the melanocortin-1 receptor in vitro, dextran sulfate sodium–induced colitis is aggravated in MC-1R–deficient mice treated with KdPT, possibly by reducing the capacity of KdPT to control intestinal inflammation.

d. KdPT, which may be taken up into cells via the H⁺-coupled transporter PepT1, stabilizes tight junction proteins in the intestinal epithelium, preventing the breakdown of the intestinal barrier.

Rationale: Piroxicam-treated IL-10–deficient mice develop colitis, which is ameliorated with subsequent administration of KdPT. Crypt abscesses were fewer, and weight loss was curtailed significantly compared to that observed in IL-10–deficient mice not treated with KdPT.
1. Several lines of evidence insinuate the existence of a retroviral etiology of human breast cancer. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2083-2090; DOI: 10.1016/j.ajpath.2011.06.046 and related Commentary Am J Pathol 2011, 179:1588-1590; 10.1016/j.ajpath.2011.08.003; the authors of the referenced articles did not disclose any relevant financial relationships.]

a. Mouse mammary tumor virus (MMTV) particles have been identified in milk and tumor tissues of breast cancer patients.

b. Reverse transcriptase has been found in milk.

c. In the referenced article, segments of exogenous MMTV sequences (MMTVels) were found in more than 70% of human infiltrating ductal carcinoma samples.

d. MMTV antigens have been detected in serum and in tumors.

Rationale: MMTVels were found in 35% of human infiltrating ductal carcinomas (IDC), in 27% of atypical ductal hyperplasias, in 80% of infiltrating ductal carcinomas in situ (DCIS), and in 19% of normal epithelial cells collateral to DCIS or IDC. Control samples did not contain any detectable MMTVels.

2. The contention that an MMTV env-like exogenous sequence is causatively linked to human sporadic breast carcinoma is controversial. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE regarding experiments/studies that still need to be conducted to determine if MMTV causes sporadic breast cancer: [See Am J Pathol 2011, 179:2083-2090; DOI: 10.1016/j.ajpath.2011.06.046 and related Commentary Am J Pathol 2011, 179:1588-1590; 10.1016/j.ajpath.2011.08.003; the authors of the referenced articles did not disclose any relevant financial relationships.]

a. Identification of the MMTV integration sites in the human genome whereby changes in signal transduction occur, triggering tumorigenesis.

b. Demonstration that MMTV can infect human cells in vitro.

c. Isolation of infectious viral particles from breast epithelium.

d. A vaccination program of unexposed individuals or prepubescent females that reduces breast cancer incidence.

Rationale: The ability of MMTV to successfully infect human cells has already been demonstrated (Cancer Res 2005, 65:6651-6659).
3. Colony-stimulating factor-1 (CSF1) blockade may prove to be a useful therapeutic intervention in various cancers. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE:


   a. Several cancers that depend on angiogenesis are refractory to vascular endothelial growth factor (VEGF) blockade.
   b. Tumor-associated macrophages (TAMs) produce a variety of pro-angiogenic factors in addition to VEGF (eg, basic fibroblast growth factor and tumor necrosis factor α) that may contribute to poor responsiveness to VEGF blockade.
   c. In addition to its many known actions, CSF1 is directly required for new blood vessel branching and anastomosis.
   d. TAMs that promote tumor growth require CSF1 as a survival factor.

Rationale: There is no evidence that CSF1 directly contributes to the growth of blood vessels. Rather CSF1’s effects are likely indirect, through the promotion of TAM actions that promote the release of angiogenic factors.

4. Leiomyosarcomas (LMS) are tumors of smooth muscle that occur in the female genital tract (gynecologic LMS) or in the deep soft tissues (nongynecologic LMS). Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE:


   a. TAMs were detected in primary LMS tumors but not in metastases.
   b. The majority of nongynecologic LMS with high microvessel density (MVD) were CSF1 positive.
   c. There was no significant correlation between MVD and VEGF-A expression.
   d. High MVD is predictive of poor prognosis in nongynecologic LMS but is not predictive in gynecologic LMS.

Rationale: TAMs were detected immunohistochemically at the site of both primary tumors and metastases. TAMs appear to play a role in the continued growth and propagation of nongynecologic LMS tumors.
1. The fibroblast growth factor binding proteins (FGFBPs) possess several functions relevant to the enhancement of FGF receptor signaling. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2220-2232; DOI: 10.1016/j.ajpath.2011.07.043 and related Commentary Am J Pathol 2011, 179:2144-2147; DOI: 10.1016/j.ajpath.2011.09.001; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. FGFBPs proteolytically cleave FGF family proteins.
   b. FGFBPs enhance the binding affinity of FGFs to their receptors
   c. FGFBPs increase the bioavailability of FGFs that are expressed in extremely low concentrations.
   d. FGFBPs protect FGFs from proteolytic degradation such that FGFs arrive at their receptors intact.

Rationale: FGFBPs do not proteolytically cleave FGFs. FGFBPs are chaperone proteins that shuttle FGFs from their storage site to their receptors.

2. The expression of FGFBP1 promotes wound repair and angiogenesis. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2220-2232; DOI: 10.1016/j.ajpath.2011.07.043 and related Commentary Am J Pathol 2011, 179:2144-2147; DOI:10.1016/j.ajpath.2011.09.001; the authors of the referenced articles did not disclose any relevant financial relationships.]

   b. Induction of FGFBP1 expression increased mouse fibroblast motility in vitro.
   c. FGF2 seems to be particularly important for wound reepithelialization.
   d. FGFBP1 binds to multiple FGFs.

Rationale: Different FGFs fulfill different functions. FGF2 seems to be particularly important for wound angiogenesis, whereas FGF7, FGF10, and FGF22 are important regulators of wound reepithelialization.

3. Alzheimer’s disease is characterized by two well-studied cellular pathologies. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2533-2550; DOI: 10.1016/j.ajpath.2011.07.044 and related Commentary Am J Pathol 2011, 179:2148-2151; DOI:10.1016/j.ajpath.2011.08.020; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. Amyloid β (Aβ) plaques consist of a proteolytically cleaved fragment, termed Aβ42, which is derived from amyloid precursor protein.
   b. Neurofibrillary tangle (NFT) formation originates in the neocortex, progressing to the transentorhinal complex and hippocampus.
   c. Hyperphosphorylated tau protein is the major constituent of NFT.
   d. NFT formation correlates positively with severity of dementia.

Rationale: Progression of tau pathology in Alzheimer’s disease originates in the transentorhinal cortex, progressing to the hippocampus and then to the neocortex.
4. Posttranslational events are thought to contribute to tau conformational changes that affect the formation of NFTs. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE:

```
a. Under normal conditions, tau is degraded by the proteasome or can be cleaved at D421 by caspase 3 and cleared by autophagy.
b. Aβ plaques activate mitogen-activated protein kinase (MAPK) kinase 4, which phosphorylates tau at S422, thus preventing cleavage of tau by caspase 3.
c. Accumulated pS422 tau cannot be cleared by autophagy and overwhelms the proteasome.
d. MAPK kinase 4 is the only known member of the MAPK superfamily that can directly phosphorylate tau.
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Rationale: MAPK kinase 4 activates other MAPKs, which can directly phosphorylate tau at distant sites.
ASIP 2011 Journal CME Program
AJP 2011 CME Program in Pathogenesis
American Society for Investigative Pathology
The American Journal of Pathology
Volume 179, Number 6 (December 2011)

www.asip.org/CME/journalCME.htm
Mark E. Sobel, MD, PhD, Director of Journal CME Programs

ANSWERS for CME Questions December # 1-4
1b, 2c, 3a, 4d

1. Asthma is a syndrome of chronic respiratory disease. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2730-2739; DOI: 10.1016/j.ajpath.2011.08.008 and related Commentary Am J Pathol 2011, 179: 2678-2682; DOI: 10.1016/j.ajpath.2011.08.031; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. Asthma is characterized by reversible airway obstruction, airway inflammation, and airway hyperresponsiveness.
   b. Asthma affects an estimated 250 million people worldwide.
   c. Increased ambient air pollutants, including particulate matter, are correlated with dramatic increases in the risk of respiratory and cardiovascular diseases.
   d. Epidemiological research demonstrated an association between the degree of traffic exposure and the lung function of asthmatic patients.

Rationale: Asthma affects an estimated 300 million people worldwide, with an expected increase to 400 million people by 2025. In the US, the prevalence of asthma among children increased from 3.6% in 1980 to 9.6% in 2009.

2. Children appear to be at increased risk of lung toxicity from traffic-related pollution. Based on the referenced article and related Commentary, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:2730-2739; DOI: 10.1016/j.ajpath.2011.08.008 and related Commentary Am J Pathol 2011, 179: 2678-2682; DOI: 10.1016/j.ajpath.2011.08.031; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. Environmental influences weigh heavily on early lung growth, particularly traffic-related pollution including diesel exhaust particulates (DEPs).
   b. DEP is a complex mixture of solid and liquid particulate matter, including elemental carbon, polycyclic aromatic hydrocarbons, acid aerosols, volatile organic compounds, carbon dioxide, and nitrogen dioxide.
   c. Alveolar number increases nearly threefold in the first 4 years of life, from approximately 30 million to 85 million.
   d. Children have imperfect airway epithelial barriers and immature immune systems, suggesting that particulate matter penetrates the airway epithelium in children to a greater degree than in adults, thus interacting with dendritic cells and altering immune system development.

Rationale: Alveolar number increases at least tenfold in the first 4 years of life, from approximately 20 million to 260 million. Increased exposure to polluted air at a young age could adversely affect alveolar budding, lung growth, and airway epithelial development.

3. Wilms tumor (WT) is an embryonal tumor of the kidney. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:3045-3055; DOI: 10.1016/j.ajpath.2011.08.006; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. WT is the most common childhood malignancy overall.
   b. Although modern multimodal management can cure 95% of WT patients with the most favorable risk profile, there remains a persistent cohort of children who ultimately fail therapy.
   c. WTs are thought to arise from nephrogenic mesenchyme during renal development.
   d. Mutations in known tumor-associated genes (WT1, WTX, and CATNB) occur in a third of WTs.

Rationale: WT is the most common childhood renal cancer. Among all childhood malignancies, it ranks as the fourth most common malignancy.

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The American Journal of Pathology, Volume 179, Number 6, December 2011
4. Many WTs show evidence of activated β-catenin-dependent Wnt signaling, but the molecular mechanism by which this occurs is unknown. Based on the referenced article, select the ONE statement that is NOT TRUE: [See Am J Pathol 2011, 179:3045-3055; DOI: 10.1016/j.ajpath.2011.08.006; the authors of the referenced articles did not disclose any relevant financial relationships.]

   a. There is evidence of activation of the canonical Wnt/β-catenin pathway in up to 75% of WTs with WT1 mutations.
   b. β-Catenin exists in the cytosol as either cadherin-associated or free form.
   c. A complex containing the adenomatosis polyposis coli (APC) protein, axin, WTX, and glycogen synthase kinase-3β phosphorylates serine/threonine residues on the N-terminus of excess free cytosolic β-catenin, leading to its degradation by the proteasomal machinery of the cell.
   d. WT1 and WTX have been shown to positively regulate canonical Wnt/β-catenin signaling.

Rationale: WT1 and WTX negatively regulate canonical Wnt/β-catenin signaling; therefore, inactivating mutations of WT1 and WTX would be expected to activate the Wnt/β-catenin signaling pathway.