

ASIP Summer Academy – 2009

Molecular Mechanisms of Human Disease

Solid Tumors – Transcripts, Tyrosine Kinases, and Therapeutics

PathPack: Solid Tumors SAM Questions

1. The distinction between benign and malignant neoplasms is extremely important for the understanding of the biology of these tumors, as well as for determination of the proper clinical treatment for affected patients. Based on the Coleman lecture “Introduction to Cancer Pathobiology,” select the ONE most important characteristic that distinguishes a benign tumor from a malignant neoplasm.
 - a. Small size.
 - b. Absence of local invasiveness.
 - c. Slow growth rate.
 - d. Tissue site of neoplasm.
 - e. Histogenesis of the neoplasm.

2. Based on the Coleman lecture “Introduction to Cancer Pathobiology,” select the ONE statement concerning benign neoplasms that is NOT true.
 - a. Benign neoplasms do not cause significant adverse effects in patients.
 - b. The size of a benign neoplasm may cause adverse effects in patients.
 - c. The location of a neoplasm may cause adverse effects in patients.
 - d. Leiomyomas arise from smooth muscle cells.
 - e. Polyps are benign epithelial neoplasms that project above a mucosal surface to produce a macroscopically visible structure.

3. Based on the Coleman lecture “Introduction to Cancer Pathobiology,” select the ONE statement concerning neoplasms that is NOT true.
 - a. Chondrosarcomas are malignant neoplasms that arise from the mesenchymal tissue.
 - b. Leiomyosarcomas are malignant neoplasms that arise from smooth muscle cells.
 - c. Seminomas are benign neoplasms of the testicular epithelium.
 - d. Teratomas contain recognizable cells or tissues representative of more than one germ-cell layer and originate from totipotent cells such as those found in ovary and testis.
 - e. Teratomas may be benign or malignant.

4. Based on the Coleman lecture “Introduction to Cancer Pathobiology,” select the ONE statement that is NOT true.
 - a. Malignant epithelial neoplasms may spread through the lymphatic system.
 - b. Hematogenous spread of malignant epithelial neoplasms occurs principally through the venous system.
 - c. Malignant epithelial neoplasms may directly spread to adjacent tissues.
 - d. Malignant epithelial neoplasms may seed body cavities.
 - e. Hamartomas are malignant epithelial neoplasms characterized by disorganized tissue.

5. Based on the Coleman lecture “Introduction to Cancer Pathobiology,” select the ONE statement that is NOT true.
 - a. Anaplasia implies dedifferentiation or loss of the structural and functional differentiation of normal cells.
 - b. Pleomorphism refers to variation in size and shape.
 - c. Squamous cell carcinoma refers to a malignant neoplasm in which the neoplastic cells grow in a glandular pattern.
 - d. Metaplasia is reversible change in which one adult cell type (for example epithelial or mesenchymal) is replaced by another cell type.
 - e. Dysplasia is loss in the uniformity of individual cells and a loss in their architectural orientation.

6. Based on the Coleman lecture "Introduction to Cancer Pathobiology," select the ONE statement that is NOT true.

- a. Cachexia results from anorexia in a patient with increased metabolic rate.
- b. Cachexia affects patients with advanced disease.
- c. Cachexia refers to a progressive loss of body fat and lean body mass.
- d. Cachexia cannot be treated.
- e. The only effective treatment for cancer cachexia is removal or elimination of the malignant neoplasm.

7. The TNM system is the major convention for staging neoplasms. Based on the Coleman lecture "Introduction to Cancer Pathobiology," select the ONE best true statement corresponding to a T3N1M1 hepatocellular carcinoma.

- a. A solitary tumor (>2cm) without lymph node spread or distant metastasis.
- b. A solitary tumor (<2cm) with vascular invasion, without lymph node invasion or distant metastasis.
- c. Multiple tumors involving more than one lobe of the liver, with positive lymph nodes and distant metastasis.
- d. A solitary tumor (>2cm) with vascular invasion, positive lymph nodes and distant metastasis.
- e. Multiple tumors involving more than one lobe of the liver, without lymph node involvement or distant metastasis.

8. The term "carcinogenesis" refers to the pathogenic process or processes and mechanism or mechanisms of cancer induction. Based on the Coleman lecture "Molecular Carcinogenesis and Cancer Genes," select the ONE best true statement concerning carcinogens.

- a. Carcinogens are always chemicals.
- b. Carcinogens are never physical agents.
- c. A carcinogen is any agent that causes cancer.
- d. Infectious agents are not carcinogens.
- e. Carcinogens are always environmental agents from exogenous sources.

9. Based on the Coleman lecture "Molecular Carcinogenesis and Cancer Genes," select the ONE best true statement.

- a. Initiating agents are complete carcinogens.
- b. Promoting agents are complete carcinogens.
- c. Complete carcinogens are not sufficient for cancer induction.
- d. Complete carcinogens act as both initiating and promoting agents.
- e. Complete carcinogens drive cancer development after initiation.

10. Based on the Coleman lecture "Molecular Carcinogenesis and Cancer Genes," select the ONE best true statement.

- a. Mutagens cause changes in the base composition of the DNA (mutations), but do not cause cancer.
- b. Carcinogens cause cancer, but do not cause mutations in the DNA.
- c. All mutagens are carcinogenic.
- d. All carcinogens are mutagenic.
- e. Mutagens cause DNA mutations and carcinogens cause cancer.

11. Based on the Coleman lecture "Molecular Carcinogenesis and Cancer Genes," select the ONE best true statement.

- a. Cancer genes include proto-oncogenes, tumor suppressor genes, and other genes that control cell proliferation directly or indirectly.
- b. Proto-oncogenes typically encode proteins that function in DNA repair.
- c. Tumor suppressor genes encode proteins that function in DNA repair.

- d. Proto-oncogenes can be broadly classified as negative mediators of neoplastic transformation.
- e. All proto-oncogenes have an identified retroviral homolog.

12. Based on the Coleman lecture “Molecular Carcinogenesis and Cancer Genes,” select the ONE statement that is NOT true.

- a. Genes can be inactivated or activated by DNA rearrangement.
- b. The Philadelphia chromosome occurs in 95% of chronic myelogenous leukemias.
- c. The Philadelphia chromosome has a t(8;14) translocation that results in a *BCR-ABL* fusion gene.
- d. Burkitt’s lymphoma is characterized by a translocation that places the c-myc proto-oncogene in proximity to the immunoglobulin heavy chain (IgH) locus.
- e. Chronic myelogenous leukemia cells that express a BCR-ABL fusion protein have enhanced tyrosine kinase activity compared to cells with the normal ABL protein.

13. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE statement that is NOT true.

- a. Wilm’s tumor is an example of cancer predisposition affecting a particular organ.
- b. Families with Li-Fraumeni syndrome may display a high incidence of several types of cancer.
- c. Families with a high incidence of Xeroderma pigmentosum have a specific DNA repair deficiency.
- d. Hereditary cancer predisposition occurs when a person inherits two copies of a mutated gene, one from each parent.
- e. Hereditary cancers account for 5-10% of total cancer incidence.

14. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE statement that is NOT true.

- a. Breast cancer risk increases with age.
- b. Family history is a risk factor in breast cancer.
- c. History of child bearing is an important risk factor in breast cancer.
- d. Age at first menstruation is a risk factor in breast cancer.
- e. The average woman has a 20% chance of breast cancer development.

15. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE statement that is NOT true.

- a. The *BRCA1* gene is tumor suppressor gene on chromosome 17.
- b. *BRCA1* has 24 exons.
- c. The *BRCA2* gene is a tumor suppressor gene on chromosome 13.
- d. *BRCA2* has 27 exons.
- e. *BRCA2* has been implicated in ovarian cancer as well as breast cancer, while *BRCA1* is involved in only breast cancer.

16. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE true statement that is NOT true.

- a. Approximately 300 different *BRCA2* pathogenic mutations have been reported.
- b. The *BRCA2* 6174 delT mutation is 5% prevalent in the Ashkenazi Jewish community.
- c. The *BRCA1* 185delAG mutation is 1% prevalent in the Ashkenazi Jewish community.
- d. Compared to 185delAG, the *BRCA1* 1294del140 and 5382insC mutations are less prevalent in the Ashkenazi Jewish community.
- e. Approximately 600 different pathogenic *BRCA1* mutations have been reported.

17. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE statement regarding risk factors for colorectal cancer that is NOT true.

- a. Polyps are a risk factor for colorectal cancer.
- b. Inflammatory bowel disease is a risk factor for colorectal cancer.
- c. Obesity is a risk factor for colorectal cancer.
- d. A vegetarian diet that is low in saturated fats is a risk factor for colorectal cancer.
- e. Smoking is a risk factor for colorectal cancer.

18. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE statement regarding Lynch syndrome that is NOT true.

- a. Lynch syndrome, an alternate name for HNPCC, accounts for 5% to 10% of all colorectal cancer.
- b. The lifetime risk of colorectal cancer in Lynch syndrome families is over 70%.
- c. People with Lynch syndrome are diagnosed with colorectal cancer at an average age of 45.
- d. Mutations in *MSH2* and *MLH1* have a greater contribution to HNPCC than do mutations in the DNA mismatch repair genes such as *PMS1* and *PMS2*.
- e. HNPCC is inherited in an autosomal recessive manner.

19. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE statement concerning microsatellite instability that is not TRUE.

- a. Neoplasms with mismatch repair deficiency are best identified by immunohistochemistry.
- b. Although the *MSH3* gene on chromosome 5 is a DNA mismatch repair gene, mutations are not frequently found in HNPCC.
- c. The majority of HNPCC cases associated with *MLH1* are due to promoter hypermethylation.
- d. Microsatellite instability can be identified using PCR-based diagnostics that examine expansion and contraction of microsatellite sequences.
- e. An advantage of mononucleotide loci over dinucleotide loci is that they are monomorphic or quasimonomorphic, obviating the need for testing of matched normal tissue.

20. Based on the Tsongalis lecture “Molecular Genetics of Human Cancer,” select the ONE statement concerning hereditary colon cancer that is not TRUE.

- a. Orocuteaneous pigmented spots in Peutz-Jeghers syndrome increase in intensity in adulthood.
- b. The lifetime risk of cancer in Peutz-Jeghers syndrome is 93%.
- c. Familial adenomatous polyposis (FAP) accounts for 1% of colorectal cancer cases.
- d. Colorectal cancer usually occurs by age 40 in people with FAP.
- e. FAP is caused by mutations in the *APC* gene.

21. Based on the Monga lecture “Molecular Pathobiology of Liver Cancer,” select the ONE statement about hepatic adenomas that is NOT true.

- a. Hepatic adenomas occur in greater frequency in males than in females.
- b. Hepatic adenoma is the benign proliferation of hepatocytes in an otherwise normal liver.
- c. Hepatic adenoma presents grossly as a solitary, yellowish mass due to lipid accumulation.
- d. Hepatic adenomas are prone to hemorrhage because of hypervascularity and lack of a true capsule.
- e. Surgical resection of hepatic adenomas is often recommended because of the risk of hemorrhage and because there is a risk of neoplastic transformation.

22. Based on the Monga lecture “Molecular Pathobiology of Liver Cancer,” select the ONE statement about hepatocellular carcinoma (HCC) that is NOT true.

- a. The incidence of HCC is rising.
- b. Fibrolamellar (FL)-HCC is a common variant of HCC that arises in the background of cirrhosis and is usually seen in an older group of patients.
- c. HCC is the fifth most common cancer world-wide.

- d. HCC is the third most common cause of cancer-related death world-wide.
- e. The prognosis for HCC is typically very poor.

23. Based on the Monga lecture “Molecular Pathobiology of Liver Cancer,” select the ONE statement about causes of HCC that is NOT true.

- a. Germline mutations in HCC are frequently found in *EGFR* and *PTEN*.
- b. The most common mutations in HCC are somatic and affect *TP53*, *CTNNB1*, *PTEN*, *PIK3CA*, and *EGFR*.
- c. Aflatoxin B1 is produced by *Aspergillus flavus*, a mold that grows on improperly stored grain (such as wheat and corn).
- d. Aflatoxin B1 is a direct acting liver carcinogen that causes a high rate of p53 somatic mutation.
- e. The most frequent p53 mutation caused by aflatoxin B is a G to T transversion at codon 249.

24. Based on the Monga lecture “Molecular Pathobiology of Liver Cancer,” select the ONE statement about causes of HCC that is NOT true.

- a. Loss of p53 function can compromise maintenance and stability of the genome as a result of faulty regulation of DNA repair.
- b. Hepatitis B virus (HBV) infection synergizes with aflatoxin B1 exposure to efficiently cause neoplastic transformation of liver.
- c. Greater than 10% of hepatitis C virus (HCV) patients develop HCC within 10 years of infection.
- d. Most patients with HCV that develop HCC have cirrhosis.
- e. HCC core protein may directly induce reactive oxygen species (ROS) in the absence of inflammation.

25. Based on the Funkhouser lecture “Pathobiology of Lung Cancer,” select the ONE statement that is NOT true.

- a. Lung cancers are typically classified as small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).
- b. NSCLC includes several morphologic subtypes, including squamous cell carcinoma, adenocarcinoma, and large cell undifferentiated carcinoma.
- c. Primary neoplasms of the lung are more common than metastatic neoplasms to the lung.
- d. The presence of keratin pearls in the histological assessment of lung cancer is diagnostic for squamous cell carcinoma.
- e. Squamous cell carcinomas occur primarily among cigarette smokers.

26. Based on the Funkhouser lecture “Pathobiology of Lung Cancer,” select the ONE statement that is NOT true.

- a. In primary lung cancer, the *EGFR* gene is often mutated.
- b. The majority of *EGFR* mutations in smokers are point mutations throughout the sequence of the gene so screening for mutations requires sequencing of the entire gene and molecular diagnosis is not practical.
- c. Most activating *EGFR* mutations encode a receptor with constitutive activation of the tyrosine kinase domain.
- d. Patients with activating *EGFR* mutations respond better to tyrosine kinase inhibitors than do patients with wild-type *EGFR*.
- e. Patients with *KRAS* mutations do not respond as well to tyrosine kinase inhibitors.

27. Based on the Funkhouser lecture “Pathobiology of Lung Cancer,” select the ONE statement that is NOT true.

- a. More than 85% of lung carcinoma deaths occur in cigarette smokers.
- b. Anthracosis (tarring of the lung) is associated with smoking.
- c. Emphysema leads to pulmonary arterial hypotension.
- d. Of the 4,000 chemical compounds in tobacco, approximately 1% are considered carcinogenic.
- e. Chronic bronchitis and desquamative interstitial pneumonia are associated with smoking.

28. Based on the Papadopoulos lecture “The Molecular Pathobiology of Colorectal Cancer,” select the ONE statement that is NOT true.

- a. Mutations of *HRAS*, *KRAS*, and *NRAS* occur in approximately 50% of human colorectal cancers and larger adenomas.
- b. Most *KRAS* mutations are found in codon 12 or 13.
- c. Activation of Ras results in decreased transcription of growth-promoting genes.
- d. There is a high frequency of mutations in *PIK3CA* in human cancer, with hot spots in the helical domain and the C-terminus of the kinase domain.
- e. Most colorectal cancers with loss of heterozygosity of 17p had mutations of the remaining copy of p53.

29. Based on the Papadopoulos lecture “The Molecular Pathobiology of Colorectal Cancer,” select the ONE statement that is NOT true.

- a. The examination of the genomes of cancers such as colorectal cancer has given rise to a new graphical display of molecular information called the genomic landscape of cancer.
- b. Each spot on the genomic landscape map represents a single gene.
- c. Tall peaks on the genomic landscape reflect a single gene locus that is mutated frequently.
- d. Small peaks on the genomic landscape reflect a single gene locus that is mutated in some cancers, but not frequently.
- e. Green areas on the genomic landscape reflect single gene loci that are mutated most frequently.

30. Based on the Kleeer lecture “Molecular Pathobiology of Breast Cancer,” select the ONE statement about ductal carcinoma *in situ* (DCIS) that is NOT true.

- a. DCIS is a clonal lesion.
- b. Patients with DCIS that receive no treatment are at elevated risk for development of invasive ductal carcinoma.
- c. DCIS is considered to be a direct precursor of invasive ductal carcinoma.
- d. DCIS of all nuclear grades can progress to invasive ductal carcinoma.
- e. Amplification of 16q is a consistent genomic alteration in all grades of DCIS.

31. Based on the Kleeer lecture “Molecular Pathobiology of Breast Cancer,” select the ONE statement about breast cancer that is NOT true.

- a. Positivity for estrogen receptor (ER) and progesterone receptor (PR) predict response to targeted therapies.
- b. Increasing size of a breast neoplasm is not associated with increased likelihood of disease progression.
- c. The number of positive lymph nodes is associated with the likely extent of systemic spread.
- d. Five-year survival rates diminish from nearly 100% among patients at low stage of disease at diagnosis (localized disease) to <30% in patients with high stage disease at diagnosis (distant metastasis).
- e. The overall prognosis of lobular invasive breast carcinoma is the same as that of ductal invasive breast carcinoma.

32. Based on the Kleeer lecture “Molecular Pathobiology of Breast Cancer,” select the ONE statement about breast cancer that is NOT true.

- a. Approximately half of all breast cancers are of the luminal A subtype.
- b. While the molecular subtypes of breast cancer are based on gene expression signatures, classification of these cancers for the purposes of prognosis and therapeutic decisions can be accomplished based solely upon estrogen receptor status.
- c. Luminal B subtype cancers are triple positive for ER, PR, and HER2.
- d. HER2-positive breast cancers over-express the *HER2* gene as a consequence of *HER2* gene amplification.
- e. A positive test for HER2 is an excellent predictor of response to trastuzumab treatment.

33. Based on the Brahmer lecture “Current Applications of Targeted Cancer Therapies,” select the ONE statement about chemotherapy that is NOT true.

- a. Chemotherapeutic drugs are typically DNA damaging agents.
- b. Chemotherapy is most effective against rapidly dividing cells.
- c. Chemotherapy can be potentially be personalized based upon characteristics of cancer cells.
- d. Supplementation with folic acid and vitamin B12 resulted in less efficacy of pemetrexed and cisplatin treatment.
- e. Patients with ERCC1-positive tumors benefited from adjuvant cisplatin-based chemotherapy, but patients with ERCC1-negative tumors did not benefit.

34. Based on the Brahmer lecture “Current Applications of Targeted Cancer Therapies,” select the ONE best true statement about trastuzumab.

- a. Trastuzumab blocks the HER2 receptor, neutralizing its ability to signal.
- b. Trastuzumab binds to the intracellular ATP binding site of HER2.
- c. Trastuzumab inhibits the phosphorylation of the HER2 receptor.
- d. Trastuzumab inhibits HER2 receptor dimerization.
- e. Trastuzumab binds to HER1/EGFR and is approved for treatment of lung cancer.

35. Based on the Tsongalis lecture “Cancer Pharmacogenomics,” select the ONE statement that is NOT true about treatment of colorectal cancer.

- a. The active metabolite of irinotecan is SN-38.
- b. Uridine diphosphate glucuronosyl-transferase 1A1 (UGT1A1) glucuronidates SN-38 and inactivates the active metabolite of irinotecan.
- c. Enzyme expression of UGT1A1 is inversely related to the number of TA repeats in the promoter region of the *UGT1A1* gene.
- d. The *28/*28 genotype of *UGT1A1* has 7 TA repeats, resulting in decreased UGT1A1 activity, a longer half-life for SN38, and increased toxicity (such as severe diarrhea).
- e. Patients with Gilbert’s syndrome (hyperbilirubinemia) have increased expression of UGT1A1.

36. Based on the Tsongalis lecture “Cancer Pharmacogenomics,” select the ONE best statement that is true about treatment of chronic myelogenous leukemia (CML).

- a. Binding of imatinib mesylate to the BCR-ABL fusion protein results in a conformational change that destroys its kinase activity.
- b. Imatinib mesylate binds to the ATP binding site of the kinase domain of BCR-ABL, preventing phosphorylation of substrates.
- c. Imatinib mesylate binds to the substrate binding pocket of BCR-ABL.
- d. Persistence of BCR-ABL kinase activity in the presence of imatinib is mostly due to insertions in the fusion gene.
- e. Allogeneic stem cell transplantation is no longer used as a therapy for CML.

37. Based on the Miller lecture “Targeting Therapy to Glioblastoma: Genomics-driven drug-biomarker co-development for gliomas,” select the ONE statement that is NOT true.

- a. Gliomas account for 40% of all primary brain tumors and 78% of malignant primary brain tumors.
- b. Glioblastoma multiforme (GBM) accounts for approximately 30% of primary brain tumors.
- c. GBM, also known as grade 4 astrocytoma (A4), is characterized by microvascular proliferation and small areas of necrotizing tissue that is surrounded by anaplastic cells (pseudopallisading necrosis).
- d. Patients with GBM have poorer survival compared to those with A2 astrocytomas.
- e. Because they are diffuse, gliomas are not easily resectable or amenable to successful local irradiation; systemic chemotherapy is usually part of the therapeutic approach.

38. Based on the Papadopoulos lecture "Discovery of Biomarkers and Targets for Cancer Therapy," select the ONE statement that is NOT true.

- a. Among a panel of pancreatic cancers evaluated, all had at least 20 non-silent point mutations.
- b. Breast and colorectal tumors had a greater number of non-silent point mutations per tumor than do brain tumors.
- c. The percentage of C:G to T:A transversions in breast cancers was greater than the percentage in pancreatic, brain and colorectal tumors.
- d. The percentage of T:A to C:G transversions in breast cancers was similar to the percentage in pancreatic, brain and colorectal tumors.
- e. There were fewer T:A to A:T transitions in each of the cancers studied (breast, pancreatic, colorectal, brain) than T:A to C:G transversions.

39. Based on the Papadopoulos lecture "Discovery of Biomarkers and Targets for Cancer Therapy," select the ONE statement that is NOT true.

- a. In the panel of pancreatic cancers studied, not all pancreatic cancers displayed detectable chromosomal amplification.
- b. The median number of genetic alterations in pancreatic cancer was estimated to be >60.
- c. The majority of pancreatic cancers had at least 40 genetic alterations.
- d. In pancreatic cancer, chromosomal deletions typically outnumbered non-silent point mutations.
- e. The excess number of genetic alterations in pancreatic cancer cells reflects genomic instability inherited to the cancer phenotype.

40. Based on the Papadopoulos lecture "Discovery of Biomarkers and Targets for Cancer Therapy," select the ONE statement that is NOT true.

- a. A good molecular target is a (loss of function) tumor suppressor gene.
- b. Driver mutations reflect genetic changes that are essential or necessary for development of a cancer.
- c. Passenger mutations reflect genetic changes that are not necessary for tumorigenesis but may contribute to the cancer phenotype.
- d. Driver and passenger mutations can be distinguished based upon frequency of mutation among cancers of a specific type.
- e. Identification of driver mutations identifies pathways that are necessary for neoplastic transformation and tumorigenesis.