

Appendix 1: Molecular tumor markers and therapy-related genes

AFP	<p>Levels of alpha-Feto-Protein (AFP) are increased in Hepatoma and Teratoma (liver, pancreas, prostate). AFP has structural and functional similarities to albumin and is normally decreased in adults.</p> <p><i>Gibbs et al. Structure, polymorphism and novel repeated DNA elements revealed by a complete sequence of the human alpha-fetoprotein gene. Biochemistry 26: 1332–1343, 1987</i></p>
Albumin	<p>Specific product of hepatocytes. Detection of gene expression is specific for the diagnosis of hepatocellular carcinoma.</p>
APC	<p>The adenomatosis poliposis coli (APC) gene is a tumor suppressor. Germ line mutations in APC cause an inherited form of colorectal cancer (adenomatosis poliposis coli). Defects in the APC gene (mutations, LOH, methylation) are also frequently found in spontaneous colorectal carcinomas and other tumor types.</p> <p><i>Polakis P.: The adenomatous polyposis coli (APC) tumor suppressor. Biochimica Biophysica Acta 1332, F127-48, (1997)</i></p>
Aromatase	<p>Aromatase is catalyzing the formation of C18 estrogens from C19 androgens. Inhibitory anti-cancer drugs of aromatase prevent the production of estrogens and consequently the growth of estrogen dependent tumors. Expression of aromatase in tumors is may be considered as a prerequisite for a rational therapy with aromatase inhibitors.</p> <p><i>Johnston SR, Dowsett M Aromatase inhibitors for breast cancer: lessons from the laboratory. Nat Rev Cancer. 2003 Nov;3(11):821-31.</i></p>
BAX	<p>BAX is a pro-apoptotic mitochondrial membrane protein. It inhibits Bcl2 and accelerates the programmed cell death (apoptosis). Reduced expression of BAX in relation to Bcl2 correlates with non-response to 5-fluorouracil, epirubicin and cyclophosphamide.</p> <p><i>Le Blanc H. et al. Tumor-cell resistance to death-receptor induced apoptosis through mutational inactivation of the proapoptotic Bcl 2 homolog BAX. Nat Med, 2002. 8(3):p. 274-81</i></p> <p><i>Krajewski S. et al. Prognostic significance of apoptosis regulators in breast cancer. Endocr Relat Cancer, 1999. 6(1):p.29-40</i></p>
Bcl 2	<p>Bcl2 is coding for an anti-apoptotic mitochondrial membrane protein. Bcl 2 is overexpressed in many tumors and consequently causes resistance to apoptosis-inducing drugs (e.g. intercalating agents, alkylating agents, platinum compounds).</p> <p><i>Ikeguchi M.S. et al. Quantitative analysis of expression levels of BAX, Bcl 2 and survivin in cancer cells during cisplatin treatment. Oncol Rep, 2002. 9(5):p. 1121-6</i></p>
CEA	<p>Carcinoembryonic antigen (CEA) is found in gastrointestinal and colorectal tumors. Measurement of expression in blood is used for diagnosis of circulating cancer cells, since expression of CEA is usually absent in blood cells.</p> <p><i>Tremblay F.: Breast cancer masquerading as a primary gastric carcinoma. J Gastrointest Surg 2002 Jul – Aug; 6(4):614-6</i></p>
c-KIT	<p>c-kit (= CD117) is the receptor of the stem cell growth factor. The receptor type is a tyrosine kinase. In some special small-cell lung cancers and gastrointestinal tumors, c-kit is overexpressed. Overexpression is indicative for considering therapy with the tyrosine kinase-inhibitor Gleevec (STI571).</p> <p><i>Potti A et al. CD117 (c-KIT) overexpression in patients with extensive-stage small-cell lung carcinoma. Ann Oncol. 2003 Jun;14(6):894-7.</i></p> <p><i>Allander SV et al.: Gastrointestinal stromal tumors with KIT mutations exhibit a remarkably homogeneous gene expression profile. Cancer Res. 2001 Dec 15;61(24):8624-8.</i></p>
Cytokeratin CK19 CK20 CK7	<p>Cytokeratins (CK) are expressed in epithelial cells and usually not in mononuclear blood cells. Therefore, they are suitable for the detection of circulating tumor cells of epithelial origin.</p> <p>Which cytokeratins are used as detection markers depend on the tumor type:</p> <p>CK19: tumors of breast, lung and prostate CK20: gastrointestinal tumors CK7: tumors of ovaries, uterus, breast and stomach</p> <p><i>Burchill et al.: Detection of epithelial cancer cells in peripheral blood by reverse transcriptase PCR. British Journal of Cancer 71:278-281, 1995</i></p>
c-myc	<p>The gene for the transcription factor c-myc is amplified (DNA) or overexpressed (RNA) in advanced, aggressive tumors.</p> <p><i>Zajac-Kaye M.: Myc oncogene: a key component in cell cycle regulation and its implication for lung cancer. Lung Cancer 2001 Dec;34 Suppl 2:S43-6</i></p>
Cox 2	<p>Cyclooxygenase 2 (Cox2) is overexpressed in colorectal adenomas and tumors. These tumors can be treated with specific Cox-2 inhibitors, since high expression levels confer susceptibility to these drugs.</p> <p><i>Adlard et al.: Prediction of the response of colorectal cancer to systemic therapy. Lancet Oncology 3, 75-82 (2002)</i></p>
DCC	<p>DCC (Deleted in Colorectal Carcinoma) is a tumor suppressor, which is frequently altered by deletion or LOH in colorectal but also other tumors.</p>

DCK	<p>Desoxycytidine kinase (DCK) is activating drugs belonging to nucleoside analogues like gemcitabine or cytarabine. The activated drugs inhibit cell proliferation by blocking the DNA-polymerase. Tumor cells develop resistance to these drugs by a lowered DCK-expression which results in reduced DCK activity.</p> <p><i>Gregoire V. et al. Role of deoxycytidine kinase (DCK) activity in gemcitabine 's radioenhancement in mice and human cell lines in vitro. Radiother Oncol 2002 Jun; 63(3):329-338.</i></p> <p><i>Holland, Frei: Cancer Medicine 5, Section 1: Cancer Biology / Section 14: Chemotherapeutic agents – Pyrimidine and purine antimetabolites.</i></p>
DPD	<p>Dihydropyrimidine dehydrogenase (DPD) has a detoxifying enzymatic function. It catalyzes the degradation of 5-fluorouracil to an inactive metabolite. Overexpression of DPD correlates with resistance to 5-fluorouracil due to an accelerated degradation.</p> <p><i>Ichikawa et al.: Combination of dihydropyrimidine dehydrogenase and thymidylate synthase gene expressions in primary tumors as predictive parameters for the efficacy of fluoropyrimidine-based chemotherapy for metastatic colorectal cancer. Clin Cancer Res. 2003 Feb;9(2):786-91.</i></p> <p><i>Salonga D et al.: Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. Clin Cancer Res. 2000 Apr;6(4):1322-7.</i></p>
DHFR	<p>Dihydrofolate reductase (DHFR) provides reduced methyl-moieties for DNA-synthesis. DHFR is blocked by methotrexate. Tumor cells develop resistance to methotrexate by overexpression of DHFR.</p> <p><i>Banerjee D. et al. : Novel aspects of resistance to drugs targeted to dihydrofolate reductase and thymidylate synthase. Biochim Biophys Acta 2002 Jul 18; 1587(2-3):164 – 73</i></p>
ERCC1	<p>Excision repair cross complementation 1 (ERCC1) is capable to remove DNA-damages, e.g. induced by platinum compound drugs. Overexpression of ERCC1 induces resistance to drugs like oxaliplatin, cisplatin, carboplatin.</p> <p><i>Shirota et al. ERCC1 and Thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. Journal of clinical oncology 19, 4298-304 2001</i></p> <p><i>Rosell et al.: Molecular Predictors of Response to Chemotherapy in Lung Cancer. Seminars in Oncology 31, 20-7 (2004)</i></p>
EGFR	<p>EGFR is the receptor for the epidermal growth factor (EGF) and other members of the EGF family. Tumors overexpressing EGFR probably respond to treatment with EGFR-inhibitors like EGFR-antibodies (cetuximab, panitumumab).</p> <p><i>Moroni M et al.: Gene copy number for epidermal growth factor receptor (EGFR) and clinical response to antiEGFR treatment in colorectal cancer: a cohort study. Lancet Oncol. 2005 May;6(5):279-86.</i></p> <p><i>Janmaat ML, Giaccone G. The epidermal growth factor receptor pathway and its inhibition as anticancer therapy. Drugs Today (Barc). 2003;39 Suppl C:61-80.</i></p>
ER	<p>Estrogen receptor (ER) is the molecular target for tamoxifen. Treatment with tamoxifen is only recommended if the ER is expressed in the tumor. Loss of ER expression has been observed in 15% of patients with acquired resistance to tamoxifen.</p> <p><i>Osborne K.: Tamoxifen in the treatment of breast cancer. New England Journal of Medicine 339, 1609 (1998)</i></p>
ERBB2	<p>ErbB2 (also HER2/neu) is a tyrosine kinase involved in cell proliferation and differentiation. Tumors overexpressing ErbB2 can be treated with Herceptin (an ErbB2-antibody). Moreover, ER-positive tumors generally do not respond to tamoxifen if ErbB2 is overexpressed.</p> <p><i>Stebbing J. et al. Herceptin (trastuzumab) in advanced breast cancer. Cancer Treatment Reviews 26, 287-90 (2000)</i></p>
FGF2 (bFGF)	<p>Overexpression of the basic fibroblast growth factor (FGF2) occurs in many tumors. The drug suramin inhibits the binding of growth factors on its receptors and is therefore used in combination treatment of tumors especially overexpressing FGF2.</p> <p><i>Zhang Yet al.: Nontoxic doses of suramin enhance activity of doxorubicin in prostate tumors. J Pharmacol Exp Ther. 2001 Nov;299(2):426-33.</i></p>
FNTB	<p>Farnesyltransferase is catalyzing farnesylation of proteins like Ras. A logic requirement for a therapy with farnesyltransferase-inhibitors like Arglabin is expression of farnesyltransferase in the tumor cells.</p> <p><i>Sebati S et al.: Farnesyltransferase Inhibitors. Seminars in Oncology 31, 28-39 (2004)</i></p> <p><i>Shaikenov TE, et al.: Arglabin-DMA, a plant derived sesquiterpene, inhibits farnesyltransferase. Oncol Rep. 2001 Jan-Feb;8(1):173-9.</i></p>
GCS	<p>Glutamate cystein synthetase (GCS) is involved in the synthesis of glutathion. Anticancer drugs like nitrogen mustards or nitrosoureas are detoxified by conjugation with glutathion. Resistance to these drugs is observed in tumors with high levels of GCS expression.</p> <p><i>Holland, Frei: Cancer Medicine 5, Section 1: Cancer Biology / Section 14: Chemotherapeutic agents – Alkylating Agents</i></p>

G250	<p>G250 is a renal cell carcinoma-associated antigen is suitable for the detection of renal carcinomas. In contrast to normal renal tissues, it is expressed in about 80% of primary and metastatic renal carcinomas.</p> <p><i>Bismar T. et al.: Quantification of G250 mRNA expression in renal epithelial neoplasms by real-time reverse transcription PCR of dissected tissue from paraffin section Pathology, 35(6) :513-7, Dec. 2003</i></p>
GST-pi	<p>For detoxification purposes, glutathion-S-transferase pi (GST-pi) transmits glutathion moieties onto anticancer drugs like alkylating agents or platinum compounds. Resistance of tumors to these compounds is associated with increased expression of GST-pi.</p> <p><i>Holland, Frei: Cancer Medicine 5, Section 1: Cancer Biology / Section 14: Chemotherapeutic agents – Alkylating Agents)</i></p>
HCG-b	<p>beta-human chorionic gonadotropin (HCG-b) is used as a marker for the detection of germ cell tumors, malignant melanomas and chorion carcinomas.</p> <p><i>F.DoI et al. Detection of beta-human chorionic gonadotropin mRNA as a marker for cutaneous malignant melanoma. Int J Cancer 65 (1996) 454-459</i></p>
IFN-R	<p>Interferon receptor is analyzed in the context of immunotherapy of tumors. This receptor binds interferon, which has anti-proliferative properties. Interferon therapy is impaired by reduced expression of the IFN-R or by diminished receptor binding.</p> <p><i>Dinney CP. et al. Inhibition of basic fibroblast growth factor expression, angiogenesis and growth of human bladder carcinoma in mice by systemic interferon-alpha administration. Cancer Res 1998 Feb 15;58(4):808-14</i></p>
K-ras	<p>K-ras is often mutated in numerous tumor types (e.g. 40% of colorectal adenocarcinomas; 75% of pancreas carcinomas). Detection of K-ras mutations in stool samples can be used for early diagnosis of colorectal cancer.</p> <p><i>Frattini et al.: Tumor location and detection of K-ras mutations in stool from colorectal cancer patients. Journal of the National Cancer Institute 95, 72-73. (2003)</i></p>
MDR1	<p>Multidrug resistance 1 (MDR 1) is a glycoprotein capable to transport anticancer drugs out of the cells. Tumor cells overexpressing MDR1 are resistant to multiple drug types like <i>vinca</i>-alkaloides, anthracyclines, taxanes or mitomycin C.</p> <p><i>Borst et al.: A family of drug transporters: the multidrug resistance-associated proteins. Journal of the National Cancer Institute 92, 1295-1302 (2000)</i></p> <p><i>Litman et al.: From MDR to MXR: new understanding of multidrug resistance systems, their properties and clinical significance. CMLS 58, 931 – 59 (2001)</i></p>
MGMT	<p>o-6-methylguanin-DNA methyltransferase (MGMT) is a repair enzyme removing DNA-damages induced by toxic and alkylating agents. If overexpressed in tumors, resistance to nitrosoureas and hydrazines (dacarbazine) is observed.</p> <p><i>Ma S. et al Analysis of O6-methylguanine-DNA methyltransferase in melanoma tumours in patients treated with dacarbazine-based chemotherapy. Melanoma Res 2002 Aug; 12(4):335-42</i></p> <p><i>Nozoe T. et al. Smoking-related increase of O(6)-methylguanine-DNA methyltransferase expression in squamous cell carcinoma or the esophagus.. Cancer Lett 2002 Oct 8;184(1):49-55</i></p>
MRP2	<p>Multidrug resistance-associated protein 2 (MRP2) is a membrane associated glycoprotein which can transport glutathion-conjugated drugs out of the cell. Tumor cells overexpressing MRP2 are resistant to multiple anticancer-drugs like <i>vinca</i>-alkaloides, anthracyclines and methotrexate. In contrast to the related protein MRP1, also platinum compounds (cis- and carboplatin) are transported.</p> <p><i>Borst et al.: A family of drug transporters: the multidrug resistance-associated proteins. Journal of the National Cancer Institute 92, 1295-1302 (2000)</i></p>
MnSOD	<p>Manganese superoxide dismutase (MnSOD) is detoxifying reactive superoxide radicals. Many tumors are overexpressing MnSOD, possibly protecting them against some chemotherapeutics.</p> <p><i>Izutani R, wet al.: Expression of manganese superoxide dismutase in esophageal and gastric cancers. J Gastroenterol 1998 Dec;33(6):816-22</i></p>
PDGFR alpha	<p>Platelet derived growth factor receptor alpha (PDGF-R alpha) binds the PDGF-alpha, a growth and angiogenesis factor. PDGF-R alpha is frequently overexpressed in tumors and is inhibited by the drug Gleevec.</p> <p><i>Buchdunger E et al.: Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther. 2000 Oct;295(1):139-45.</i></p>
PDGFR beta	<p>Platelet derived growth factor receptor beta is mediating growth signals upon binding of its ligand, PDGF-beta. This receptor is also blocked by the drug Gleevec. Expression of PDGFR-beta is therefore a logic requirement of a therapy with Gleevec.</p> <p><i>Buchdunger E et al.: Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. J Pharmacol Exp Ther. 2000 Oct;295(1):139-45.</i></p>
PSA	<p>PSA is the prostate specific antigen, a protease synthesized in the prostate. Disseminated prostate carcinoma cells can be detected by measuring the gene expression of PSA in blood.</p> <p><i>Ghossein et al.: Molecular detection of micrometastases and circulating tumor cells in solid tumors. Clinical Cancer Research 5, 1950-60 (1999).</i></p>
p53	<p>p53 is a tumor suppressor gene and regulates the cell cycle. Mutations in p53 are the most frequent genetic alterations in human malignancies. Genetic alterations in p53 (mutations, LOH, expression) are therefore used as molecular tumor markers.</p> <p><i>Levine A.J. et al. The P53 tumorsuppressor gene. Nature 351, 453, 1991</i></p>

TS	<p>Thymidylate synthetase (TS) is the molecular target of 5-fluorouracil. Inhibition of TS by agents like 5-fluorouracil causes starvation of deoxynucleotides which results in inhibited DNA-synthesis and growth arrest. Poor response to therapy with 5-fluorouracil correlates with elevated TS expression</p> <p><i>Salonga D et al.: Colorectal tumors responding to 5-fluorouracil have low gene expression levels of dihydropyrimidine dehydrogenase, thymidylate synthase, and thymidine phosphorylase. Clin Cancer Res. 2000 Apr;6(4):1322-7.</i></p> <p><i>Ichikawa et al.: Combination of dihydropyrimidine dehydrogenase and thymidylate synthase gene expressions in primary tumors as predictive parameters for the efficacy of fluoropyrimidine-based chemotherapy for metastatic colorectal cancer. Clin Cancer Res. 2003 Feb;9(2):786-91.</i></p>
Telomerase (reverse transcription subunit)	<p>Telomerase compensates the shortening of the chromosomes during each cycle of DNA-replication. In differentiated normal tissues, telomerase is usually not active. However, reactivation of telomerase occurs in tumors and measuring telomerase gene expression can therefore be used as a tumor marker.</p> <p><i>McKenzie et al.: Applications of telomerase research in the fight against cancer.. Mol Med Today 1999 Mar;5(3):114-22</i></p>
Topo IIa	<p>Topoisomerase II alpha is catalyzing controlled cuts and reconnection of DNA-double strands during DNA-replication. Inhibitors of Topoisomerase II (anthracyclines, mitoxantron, etoposid) are provoking faulty action of Topo II, leaving behind DNA-damages.</p> <p>If Topo II is underexpressed in tumor cells, lesser DNA-damages occur and the therapy may fail. On the other hand, overexpression of Topo II sensitizes the cells to Topo II inhibitors.</p> <p><i>Tanner, M., P. Jarvinen, and J. Isola, Amplification of HER-2/neu and topoisomerase IIalpha in primary and metastatic breast cancer. Cancer Res, 2001. 61(14): p. 5345-8</i></p>
Topo I	<p>Topoisomerase I is catalyzing controlled cuts and reconnection of DNA-single strands during DNA-replication. Chemotherapeutics like irinotecan and topotecan disturb Topo I function, inducing breaks in DNA during DNA replication. Underexpression of Topo I renders the tumor cells more resistant to these drugs.</p> <p><i>Holland, Frei: Cancer Medicine 5, Section 1: Cancer Biology / Section 14: Chemotherapeutic agents – Topoisomerases</i></p>
TP	<p>Thymidine phosphorylase (TP) is involved in the metabolism of 5-fluorouracil. High expression levels correlate with resistance to therapy with 5-fluorouracil.</p> <p><i>Metzger R.: High basal level gene expression of thymidine phosphorylase (platelet-derived endothelial cell growth factor) in colorectal tumors is associated with nonresponse to 5-fluorouracil. Clin Cancer Res. 1998 Oct;4(10):2371-6</i></p> <p><i>Yoshinare K et al.: Gene expression in colorectal cancer and in vitro chemosensitivity to 5-fluorouracil: a study of 88 surgical specimens. Cancer Sci. 2003 Jul;94(7):633-8.</i></p>
TXNRD1	<p>Thioredoxin reductase (TXNRD1) is reducing thioredoxin, which protects proteins from oxidative damage. Thioredoxin reductase is often overexpressed in tumors. Elevated levels of thioredoxin possibly cause increased cell proliferation and resistance to apoptosis.</p> <p><i>Berggren, M., et al., Thioredoxin and thioredoxin reductase gene expression in human tumors and cell lines, and the effects of serum stimulation and hypoxia. Anticancer Res, 1996. 16(6B): p. 3459-66.</i></p>
UP	<p>The Uridine phosphorylase (UP) level is frequently elevated in tumor tissues compared to normal tissues. UP is catalyzing the formation of the active metabolite 5-fluorouracil-monophosphate from the inactive 5-fluorouracil. In tumor cells resistant to 5-fluorouracil down-regulation of UP has been observed.</p> <p><i>Chung, Y.M., et al., Establishment and characterization of 5-fluorouracil-resistant gastric cancer cells. Cancer Lett, 2000. 159(1): p. 95-101.</i></p> <p><i>Kanzaki, A., et al., Expression of uridine and thymidine phosphorylase genes in human breast carcinoma. Int J Cancer, 2002. 97(5): p. 631-5.</i></p>
VEGF	<p>Vascular endothelial growth factor (VEGF) is up-regulated in many tumors and is inducing angiogenesis by paracrine stimulation of endothelial cells. High expression levels of VEGF in tumor cells are associated with poor response to hormone therapy with tamoxifen and combination chemotherapy with FAC or CMF. New anticancer agents like bevacizumab (Avastin) are targeted specifically against VEGF.</p> <p><i>Sledge, G.W., Jr., Vascular endothelial growth factor in breast cancer: biologic and therapeutic aspects. Semin Oncol, 2002. 29(3 Suppl 11): p. 104-10.</i></p> <p><i>Bachelder, R.E., et al., Vascular endothelial growth factor is an autocrine survival factor for neuropilin-expressing breast carcinoma cells. Cancer Res, 2001. 61(15): p. 5736-40</i></p>