Fusion genes in solid tumors: an emerging target for cancer diagnosis and treatment

Brittany C. Parker¹,² and Wei Zhang¹,²

Abstract
Studies over the past decades have uncovered fusion genes, a class of oncogenes that provide immense diagnostic and therapeutic advantages because of their tumor-specific expression. Originally associated with hematologic cancers, fusion genes have recently been discovered in a wide array of solid tumors, including sarcomas, carcinomas, and tumors of the central nervous system. Fusion genes are attractive as both therapeutic targets and diagnostic tools due to their inherent expression in tumor tissue alone. Therefore, the discovery and elucidation of fusion genes in various cancer types may provide more effective therapies in the future for cancer patients.

Key words: Cancer genomics, fusion genes, tumorigenesis, therapy, chromosomal instability

History of DNA Sequencing and the Discovery of Fusion Genes

Fusion genes were originally discovered in hematologic malignancies but have been recently found in several solid tumors through the use of modern, advanced sequencing technologies (Figure 1; Table 1). The first stretch of sequence published was the lac operon, in 1972[1]. A few years later, Sanger sequencing technology was developed and is still highly used in laboratories across the world today[2]. In 1983, the American biochemist Kary Mullis developed polymerase chain reaction (PCR), which revolutionized biochemistry and molecular biology[3]. More advances followed shortly, with the development of the first automated DNA sequencer by Applied Biosystems in 1987, and the development of next-generation sequencing in 2005.

Next-generation sequencing was created out of the demand for high-throughput, low-cost sequencing. This technology was able to revolutionize sequencing by producing thousands to millions of read sequences concurrently[4]. Detection of fusion genes became much easier compared with original methods, which utilized cytogenetic analysis (i.e. Giemsa staining of chromosomes during metaphase to observe abnormal gains or losses in chromosome structures) (Table 1). The ability to target these fusion genes has led to the development of many successful anti-cancer drugs and will translate to more targeted therapy opportunities in the future.

The beginning: fusion genes in hematologic malignancies

The first fusion gene, known as the Philadelphia chromosome, was discovered in 1973 in chronic myelogenous leukemia and
Fusion Genes in Solid Tumors

With the development of more sophisticated sequencing technologies came the discovery of fusion genes in solid tumors, including sarcoma, carcinoma, and tumors of the central nervous system. Each tumor type has both fusions that are tumorspecific and others that are common to several cancers, such as the fibroblast growth factor receptor 3 (FGFR3)–transforming acidic coiled-coil containing protein 3 (TACC3) fusion, which is found in brain, lung, and bladder cancers.

Fusion genes in sarcoma

Sarcomas account for approximately 2% of human cancers and are a heterogeneous group of cancers that arise from cells of mesenchymal origin, such as the bone, cartilage, muscle, and fat. Compared with carcinomas, which arise from epithelial cells (as in breast, colon, and lung cancers), sarcomas are quite rare, with only 15,000 new cases per year in the United States. Sarcomas are classified by the tissue from which they arise. For example, sarcomas arising from the bone, cartilage, and fat are called osteosarcoma, chondrosarcoma, and liposarcoma, respectively. The current standard of care to treat most sarcomas is surgery followed by radiation and chemotherapy.

Ewing sarcoma

Ewing sarcoma is a highly metastatic class of sarcoma and is the second most frequent bone tumor in children. Ewing sarcoma is...
characterized by undifferentiated, small, round cell tumors occurring in soft tissues and bone; 25% of patients with Ewing sarcoma have metastatic disease at the time of diagnosis. The first detected fusion genes in sarcoma were found in a patient with Ewing sarcoma in 1983. This fusion, which is prevalent in 90% of these patients, exhibits specific gene signatures consisting of genes that are up-regulated, such as insulin-like growth factor 1 receptor (IGF1R), and genes that are down-regulated, such as insulin-like growth factor binding protein 3 (IGFBP3). IGF-1R is a transmembrane receptor that promotes cellular transformation as well as cell survival, and is highly overexpressed in malignant tissues. Epidemiologic studies have illustrated that several cancers show a survival correlation with high IGF-1 (the ligand for IGF-1R) and low IGFBP-3 (a binding protein of IGF-1R). Efforts to produce a targeted therapy for EWSR1-FLI1–positive patients led to the development of molecules that suppress IGF-1R levels. IGF-1R blockade with these molecules showed promising results in vitro and in vivo, decreasing cell proliferation, tumorigenesis, and metastasis, and sensitizing cancer cells to radiation and chemotherapy. Although preclinical studies showed promising results, a less dramatic result was observed in phase II clinical trials, where it appeared that only some patients with EWSR1-FLI1–positive patients led to the development of molecules that suppress IGF-1R levels. IGF-1R inhibition and on developing more potent therapeutics for EWSR1-FLI1–positive patients. Recent studies have identified another small subset of Ewing sarcoma patients who have fusions between the nuclear factor of activated T-cell transcription factor family and the EWSR1 gene with the 3′ sequences of Friend leukemia virus integration 1 (FLI1), which encodes an ETS family motif, which allows for the activation of specific downstream genes that are up-regulated.
Small round cell tumors of the bone (EWSR1-ETS–negative)

Ewing sarcoma and osteosarcoma are the most predominant bone sarcomas. As mentioned previously, Ewing sarcoma is characterized by exhibiting fusions between EWSR1 and the ETS family of transcription factors[28]. Recently, other fusions have been observed in patient samples that histologically resemble Ewing sarcoma but lack the canonical fusion. Specifically, fusions between the BCL-6 corepressor (BCOR) gene and cyclin B3 (CCNB3) gene were identified in 4% (24/594) of EWSR1-ETS–negative patients[29]. The authors concluded that they discovered a new subset of “Ewing-like” tumors that are characterized by this BCOR-CCNB3 fusion but lack other known Ewing sarcoma fusions[29].

Synovial sarcoma

Synovial sarcoma is a type of soft tissue sarcoma that most commonly forms near the joints of the arm or leg but has been documented in various places in the body, including the heart, prostate, and brain. It is extremely aggressive and occurs equally documented in various places in the body, including the heart, prostate, and brain. It is extremely aggressive and occurs equally commonly in children and adults[30]. The term “synovial sarcoma” was coined from the appearance of the cancer as having a microscopic similarity to tumors of the synovium in the joints. A fusion that resulted from a reciprocal translocation was discovered in 1995 between the X chromosome and chromosome 18, fusing one of the three synovial sarcoma X (SSX) genes (SSX1, SSX2, and SSX4), which are cancer-testis antigens, with the transcriptional coactivator SS18 on chromosome 18[40-43]. This fusion occurs in almost all patients diagnosed with synovial sarcoma and joins the transcriptional activation domain of SS18 to the transcriptional repression domains of the SSX genes. In vitro and in vivo studies have shown that the presence of this fusion is required to support tumorigenesis[44]. The primary function of the SS18-SSX1 and SS18-SSX2 fusions is to serve as a bridge between activating transcription factor 2 (ATF-2) and the transducing-like enhancer of split 1 to repress ATF-2 target genes, leading to tumorigenesis. Treatment with histone deacetylase inhibitors abolished this effect[45], in agreement with preclinical models illustrating the sensitivity of synovial sarcomas to these inhibitors[47,48].

Other sarcomas

Clear-cell sarcoma is a highly aggressive but rare sarcoma that is most commonly diagnosed in elderly adults and often occurs in tendons within the extremities[49]. These sarcomas commonly harbor a translocation fusing EWSR1 on chromosome 22 to ATF1 on chromosome 12. This translocation was discovered in 1990 and occurs in approximately 90% of patients with this type of tumor[30,51].

Mixoid liposarcoma is a cancer that arises from the fat. A fusion between chromosomes 12 and 16 occurs in nearly 90% of these tumors and fuses the fused in sarcoma (FUS) gene to DNA damage-inducible transcript 3 (DDIT3), which has been found to exert oncogenicity by altering transcription activity and thereby manipulating the oncogenic NF-kB pathway[52].
Fusion genes in carcinoma

A carcinoma is a tumor arising from cells of epithelial origin, specifically those from the endodermal or ectodermal germ layer during embryogenesis. A carcinoma, then, retains properties of epithelial cells and most commonly occurs in the prostate, breast, lung, bladder, colon, and pancreas.

Prostate cancer

Prostate cancer arises from cells in the prostate and most commonly occurs in males over the age of 50. It is the sixth leading cause of cancer-related death in men worldwide. Three fusion genes have been characterized in prostate cancer, occurring in 50% to 70% of patients. These fusions join the androgen-regulated genes have been characterized in prostate cancer, occurring in 50% to 70% of patients. These fusions join the androgen-regulated genes with genes encoding the ETS transcription factors v-ets avian erythroleukemia virus E26 oncogene homolog (ERG), ETS variant gene (ETV1), and ETV4, which leads to the overexpression of these oncogenic transcription factors in an androgen-regulated manner. Fusions containing another androgen-regulated promoter for the solute carrier family 45, member 3 (SLC45A3) gene have also been reported to be fused to the same three ETS family members and behave in a similar fashion to TMPRSS2, although this fusion occurs less commonly. A more recent finding in prostate cancer is a fusion of SLC45A3 to the fibroblast growth factor receptor 2 (FGFR2) gene, which encodes a receptor tyrosine kinase implicated in various cancers, including breast, gastric, ovarian, lung, and endometrial cancers.

The current standard of care for prostate cancer patients can include anti-androgen therapy, which aims to limit the amount of androgens in the body that are capable of reaching the prostate. Research on prostate cancer should include studies of the effect of anti-androgen drugs on TMPRSS2 fusion-positive or SLC45A3 fusion-positive patients and/or cell lines.

Breast carcinomas

Secretory breast carcinoma is a rare (less than 1% of cases) type of breast carcinoma that occurs most commonly in young women (median age of 25 years). Patients diagnosed with secretory breast carcinoma usually have a favorable prognosis. This type of cancer is called “secretory” because an abundant secretion of mucin occurs within the tumor. In 2002, the ETV6–neurotrophic tyrosine receptor kinase, type 3 (NTRK3) fusion was discovered, which fused ETV6, an ETS family transcription factor located on chromosome 12, with NTRK3, which is located on chromosome 15. This fusion, originally characterized in congenital fibrosarcoma, was found to promote oncogenesis via activation of the Ras-MAPK and PI3K-AKT pathways.

Other fusions have been reported in metastatic breast cancers that fuse FGFR family members to various proteins, including FGFR3-AF4/FMR2 Family, member 3 (AFF3), FGFR2-caspase 7 (CASP7), FGFR2–coiled-coil domain containing 6 (CCDC6), and FGFR1–endoplasmic reticulum lipid raft-associated 2 (ERLIN2). However, these fusions are not recurrent.

Bladder cancer

Bladder cancer arises from the epithelial lining within the urinary bladder. More than half of the cases in men and one-third of the cases in women are associated with smoking. Bladder cancer is the fourth most common type of cancer in men and ninth most common in women in the United States. Bladder cancer is historically associated with activating mutations in the FGFR3 gene but has recently been shown to harbor FGFR3-TACC3 fusion in about 10% of patients. This fusion contains part of the TACC3 gene, which encodes a microtubule-associated protein known to be involved in mitosis. This fusion was found to promote MAPK signaling in bladder cancer cell lines, as well as increased cell proliferation and transformation. Around the same time, the FGFR3-BAI1–associated protein 2-like 1 (BAIAP2L1) gene fusion was discovered in 4 patients, and contained the FGFR3 gene fused to the BAIAP2L1 gene. This fusion links signals at the plasma membrane to actin reorganization within the cell and is expressed in the bladder, liver, testes, heart, and lung. This fusion protein is phosphorylated by Src, an event that promotes cell migration.

Colorectal cancer

Colorectal cancer is characterized by uncontrolled cell growth in either the large intestine or the appendix, and is the fourth most prevalent cancer worldwide. Colorectal cancer is the third most diagnosed cancer in the world and kills over 608,000 people annually, although 75% to 95% of colon cancer patients have no genetic predisposition for the disease. The first fusion discovered in colorectal cancer contains R-spondin family members, and is found in approximately 10% of colon tumors. R-spondin family proteins (RSPO) are involved in cellular proliferation, differentiation, and maintenance of stem cells by modulating the Wnt/β-catenin pathway. The protein tyrosine phosphatase receptor type K (PTPRK)-RSPO3 fusion joins RSPO3 to PTPRK, a putative tumor suppressor gene in melanoma, lymphoma, lung cancer, and prostate cancer. The other RSPO fusion connects the eukaryotic translation initiation factor 3, subunit E gene (EIF3E) to RSPO2, which is the largest translation initiation factor in mammals. Studies found that both RSPO family fusions, PTPRK-RSPO3 and EIF3E-RSPO2, activated the Wnt signaling pathway in vitro, and found that fusion-positive tumors carried alterations in the Wnt pathway. Thus, therapeutic strategies targeting Wnt pathway signaling may be proven to be an effective treatment for fusion-positive colorectal cancer.

Ovarian cancer

Ovarian cancer accounts for 3% of all cancers among women and is estimated to result in 140,000 deaths in women every year. Women are at the highest risk for developing ovarian cancer if they have a family history of breast, ovarian, endometrial, prostate, or colon cancers, and more so if their mother or sister had ovarian cancer. Ovarian cancers can further be classified into subtypes based on molecular features of the tumor.

Serous ovarian cancer is the most common subtype of ovarian cancer, and is especially lethal because it normally goes undetected until it has already progressed and spread to other tissues. The
estrogen receptor–related alpha (ESRRA)–C11orf20 fusion gene was discovered in 2011 and was found to occur in 15% of samples tested\[^{[96]}\]. The fusion connects the ESRRA gene to the C11orf20 gene, an uncharacterized but conserved gene in the mammalian genome. ESRRA is a nuclear receptor that resembles the estrogen receptor and regulates transcription. Interestingly, ESRRA expression correlates with poor prognosis in both breast and ovarian cancers\[^{[77,78]}\]. However, the functional role of this fusion has yet to be established.

**Lung cancers**

Non–small cell lung cancer (NSCLC) accounts for nearly 80% of lung cancer cases and exhibits a median survival of less than one year following diagnosis\[^{[99]}\]. NSCLC can be divided into 3 main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Adenocarcinoma accounts for approximately 40% of all lung cancers and starts in mucus-secreting cells. Although commonly found in smokers, this type of lung cancer is also the most prevalent lung cancer observed in non-smokers. The first fusion to be discovered in adenocarcinoma joined the echinoderm microtubule-associated protein-like 4 (EML4) gene on chromosome 2 to the anaplastic lymphoma receptor tyrosine kinase (ALK) on chromosome 2 via inversion. This highly transforming oncogene, EML4-ALK, is found in approximately 4% of NSCLC patients\[^{[100]}\]. The oncogenic function of the fusion is believed to be caused by overexpression of the ALK tyrosine kinase, which leads to constitutive activation of downstream signaling cascades, including Akt, MAPK, and signal transducer and activator of transcription 3 (STAT3)\[^{[101]}\]. The ALK inhibitor PF02341066, known as crizotinib, is currently undergoing clinical trials and has demonstrated significant clinical efficacy thus far in patients with EML4-ALK–positive NSCLC\[^{[102]}\]. Other fusions have also been reported in lung adenocarcinomas, including the kinesin family member 5B-rat proto-oncogene (KIF5B-RET)\[^{[103,104]}\], CCDC6-c-cors oncogene 1 (ROS1), and FGFR2-citron (CIT)\[^{[105]}\].

Lung squamous cell carcinoma accounts for 30% of NSCLCs. It arises from the tissue that lines the air passages in the lungs and is strongly linked to smoking. Three different fusions have been reported in lung squamous cell carcinoma, all of which contain members of the FGFR family. The FGFR3-TACC3 fusion, initially reported in glioblastoma multiforme (GBM)\[^{[106,107]}\] and bladder cancers\[^{[108]}\], has also been found in patients with lung squamous cell carcinoma (n = 4), whereas two other fusions, FGFR3-KIAA1967 (n = 1) and FGFR1-BCL2–associated anathogene (BAG4) (n = 1), were not recurrent\[^{[109]}\].

**Adenoid cystic carcinoma**

The adenoid cystic carcinoma subtype is a rare form of adenocarcinoma. Occurring most often in the salivary glands of the head and neck but sometimes in the uterus, this subtype spreads along the nerves or throughout the bloodstream. Adenoid cystic carcinoma is the most common malignant salivary gland tumor, and although tumors are typically slowly growing, they are still aggressive, yielding poor patient prognosis\[^{[110]}\].

In 2009, a group discovered the MYB–nuclear factor 1 B-type (NFIB) fusion, which formed as a result of translocation between chromosomes 6 and 9, with on occurrence rate of 90%. The MYB gene encodes the MYB proto-oncogene, which is a member of the myeloblastosis family of activating transcription factors. NFIB is a transcription factor that contains a DNA-binding and dimerization domain\[^{[111]}\]. In fact, pleomorphic salivary gland adenomas have also been shown to harbor fusions of NFIB with high mobility group ATHook 2 (HMGA2)\[^{[112]}\]. The formation of the MYB-NFIB fusion resulted in the deletion of the 3’ untranslated region of MYB. This allowed the fusion mRNA to go undetected by specific microRNA that usually would target, and therefore degrade, any mRNA transcribed from the MYB gene. A similar mechanism facilitating oncogene overexpression has recently been described in GBM (please see “GBM” section)\[^{[113]}\].

Overexpression of MYB then changed the expression landscape in these tumors and as a result increased the expression of MYB-activating genes, including survival genes B-cell lymphoma 2 (BCL2) and set nuclear oncogene (SET), as well as genes associated with cell proliferation and angiogenesis such as vascular endothelial growth factor a (VEGFA), and fibroblast growth factor 2 (FGF2). The authors of this study concluded that this fusion may serve as a highly beneficial therapeutic target for adenoid cystic carcinoma\[^{[114]}\].

**Mucoepidermoid carcinoma**

Mucoepidermoid carcinomas are common salivary gland neoplasms, account for 35% of all salivary cancers, and are most common in adults between the ages of 20 to 40 years. The mucoepidermoid carcinoma translocated 1 (MECT1)–Notch coactivator mastermind-like protein 2 (MAML2) fusion occurs in approximately 60% of patients with mucoepidermoid carcinoma\[^{[115]}\] and contains the MECT1 gene, also known as CREB-regulated transcription coactivator 1, fused to MAML2\[^{[116]}\]. The fusion was found to induce Notch signaling and cause cellular transformation of RK3E epithelial cells\[^{[117]}\]. Recent studies have shown that the presence of MAML2 rearrangements as measured by fluorescence in situ hybridization can be used as a mean to distinguish mucoepidermoid carcinoma from other oncocytic lesions\[^{[118]}\].

**Follicular thyroid carcinoma**

Thyroid cancer is the most common type of endocrine cancer and is classified according to histopathologic characteristics. The main type of thyroid cancer is papillary thyroid carcinoma (75% to 85% of cases), which often occurs in young females and most commonly metastasizes to cervical lymph nodes\[^{[119]}\]. The next most common type is follicular thyroid cancer (10% to 20% of cases) and is most common in women over the age of 50 years\[^{[120]}\]. Unlike papillary thyroid carcinoma, follicular thyroid carcinoma normally metastasizes via the bloodstream to the lung and bone.

In 2000, the paired box gene 8 (PAX8)–peroxisome proliferator-activated receptor gamma (PPARG) fusion was identified in 60% of follicular thyroid cancer cases\[^{[121]}\]. The fusion contains the transcription factor PAX8, a gene that encodes a nuclear protein involved in follicular cell development in the thyroid. PPARG is a regulator of fatty acid storage and glucose metabolism, where mice that do not have Pparg fail to generate adipose tissues\[^{[122]}\]. The fusion contains the
promoter and 5’ coding sequence for PAX8 and most of the coding sequence for PPARG. The PAX8 promoter being active in thyroid cells causes high expression of the fusion[94] and therefore induces tumorigenesis by increasing cell cycle progression, cell survival, and loss of anchorage-dependent cell growth[95].

Clear cell renal cell carcinoma (RCC)
RCC is cancer of the kidney that originates in the epithelial cells that line the proximal convoluted tubule. RCC makes up 80% of kidney cancer cases[39]. Clear cell RCCs are histologically characterized by cells with a clear cytoplasm surrounded by distinct cell membranes. Clear cell RCC cases make up 60% to 70% of RCC cases. The recurrent fusion SFPQ-TFE3, a fusion that was previously linked to non-clear cell translocation–associated RCC[94], was recently identified in small series of clear cell RCC patient samples (5 of 416 samples, 1.2%)[95]. Another fusion was also identified, connecting the trk-fused gene (TFG) gene to G protein-coupled receptor 128 (GPR128), in about 1% of patients analyzed[99].

Fusion genes in tumors of the central nervous system
Central nervous system tumors can be classified based on the cell type from which they arose in the brain or spinal cord. Tumors arising from glial cells, the meninges, pituitary glands, and nerve sheaths are termed glioma, meningioma, pituitary adenomas, and nerve sheath tumors, respectively. Glioma comprise 50.4% of all primary brain tumors[100]. Gliomas are further classified according to the type of glial cells from which they originate. More specifically, tumors arising from astrocytes are called astrocytoma, ependymal cells are ependymomas, and tumors arising in oligodendrocytes are called oligodendroglioma. According to the World Health Organization, each type of glioma is then further classified according to grade, or severity, of the tumor. Astrocytomas are graded on a scale from I to IV. Grade IV tumors, GBM, yield the worst prognosis for patients and are also the most common and aggressive type of primary brain tumor in humans.

GBM
The FGFR3-TACC3 fusion gene, which has been reported in bladder[22] and lung cancers[23], has recently been identified in a subset of glioblastoma patients, yielding a recurrence rate between 0% and 5%[20,21]. This fusion has been found to induce ERK and STAT3 signaling and also to promote tumorigenesis both in vitro and in vivo[20,21]. Similar to the MYB-NFIB fusion found in adenoid cystic carcinoma, the FGFR3-TACC3 fusion was found to be overexpressed via lack of microRNA regulation. Specifically, the 3’-untranslated region of FGFR3 is lost in the fusion, allowing it to go undetected by miR-99a, a microRNA that is highly prevalent in both GBM and normal brain[20]. Because of high miR-99a levels in the brain, expression of endogenous wild-type FGFR3 is exceedingly low. Therefore, treatment of FGFR3-TACC3–positive patients with an FGFR3 inhibitor may be proven to be a valuable therapy, as it would target tumor-positive (i.e., FGFR3-TACC3–positive) tissues while sparing normal, healthy tissues that do not express FGFR3[20]. Another fusion (FGFR1-TACC1) was also discovered in GBM but was only found in one patient[20].

Pilocytic astrocytoma
Pilocytic astrocytoma is a type of benign brain tumor that commonly arises in the cerebellum in the base of the brain and most frequently occurs in young adults. The most common fusion observed in pilocytic astrocytoma links the KIAA1549 gene to BRAF and occurs in 70% of pilocytic astrocytoma cases[101]. The BRAF gene encodes the proto-oncogene B-Raf, which is frequently mutated in a wide variety of cancer types[102].

Conclusions
Genomic instability is a hallmark of cancer and can be described as gene mutation, amplification, translocation, deletion, and inversion events. The discovery of fusion genes in hematologic malignancies in the 1970s led to the development of potent therapeutics. Fusion genes also showed their value by serving as a diagnostic tool to monitor treatment progress by measuring the disappearance of the fusion and, thus, the disappearance of the tumor tissue. The development of more sophisticated sequencing technologies in the early 21st century led to the discovery of more fusion genes in solid tumors. There are currently several clinical trials aimed at treating fusion-positive patients with a range of targeted therapies, which will hopefully lead to better treatment options for patients in the future.

Acknowledgments
This research was supported in part by the grant from the National Institutes of Health through MD Anderson Cancer Center (No. CA016672).

Received: 2013-10-08; accepted: 2013-10-10.

References
[1] Gilbert W, Maxam A. The nucleotide sequence of the lac operator. Proc Natl Acad Sci U S A, 1973,70:3561–3564.
[2] Sanger F, Nicklen S, Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A, 1977,74:5463–5467.
[3] Saiki RK, Scharf S, Faloona F, et al. Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. Science, 1985,230:1350–1354.
[4] Schuster SC. Next-generation sequencing transforms today’s biology. Nat Methods, 2008,5:16–18.
[5] Rowley JD. Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine.
fluorescence and Giemsa staining. Nature, 1973,243:290–293.

[6] Lifshitz B, Fainstein E, Marcelle C, et al. bcr genes and transcripts. Oncogene, 1988,2:113–117.

[7] Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia. Science, 1960,132:1497.

[8] Dreazen O, Klisak I, Jones G, et al. Multiple molecular abnormalities in Ph1 chromosome positive acute lymphoblastic-leukemia. Brit J Haematol, 1987,67:319–374.

[9] Shitivelman E, Lifshitz B, Gale RP, et al. Fused transcript of abl and bcr genes in chronic myelogenous leukemia. Nature, 1985,315:550–554.

[10] Manolov G, Manolova Y. Marker band in one chromosome-14 from Burkitt lymphomas. Nature, 1972,237:33–34.

[11] Zech L, Haglund U, Nilsson K, et al. Characteristic chromosomal abnormalities in biopsies and lymphoid-cell lines from patients with Burkitt and non-Burkitt lymphomas. Int J Cancer, 1976,17:47–56.

[12] Dalla-Favera R, Bregni M, Erikson J, et al. Human c-myc onc gene is located on the region of chromosome 8 that is translocated in Burkitt lymphoma cells. Proc Natl Acad Sci U S A, 1982,79:7824–7827.

[13] Larson RA, Kondo K, Vardiman JW, et al. Evidence for a 15;17 translocation in every patient with acute promyelocytic leukemia. Am J Med, 1984,76:827–841.

[14] Borrow J, Goddard AD, Sheer D, et al. Molecular analysis of acute promyelocytic leukemia breakpoint cluster region on chromosome 17. Science, 1990,249:1577–1580.

[15] Stefaniak C, Stratigos A, Katsambas A. Topical retinoids in the treatment of photoaging. J Cosmet Dermatol, 2005,4:130–134.

[16] Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood, 1988,72:567–572.

[17] Castaigne S, Chomienne C, Daniel MT, et al. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. Blood, 1990,76:1704–1709.

[18] Warrell RP Jr, Frankel SR, Miller WH Jr, et al. Differentiation therapy of acute promyelocytic leukemia with retinoin (all-trans-retinoic acid). N Engl J Med, 1991,324:1385–1393.

[19] Parker BC, Annala MJ, Cogdell DE, et al. The tumorigenic FGFR3-TACC3 gene fusion escapes miR-99a regulation in glioblastoma. J Clin Invest, 2013,123:855–865.

[20] Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. Science, 2012,337:1231–1235.

[21] Williams SV, Hurst CD, Knowles MA. Oncogenic FGFR3 gene fusions in bladder cancer. Hum Mol Genet, 2013,22:795–803.

[22] Wu YM, Su FY, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. Cancer Discov, 2013,3:636–647.

[23] Borden EC, Baker LH, Bell RS, et al. Soft tissue sarcomas of adults: State of the translational science. Clin Cancer Res, 2003,9:1941–1956.

[24] Wu YM, Su FY, Kalyana-Sundaram S, et al. Identification of targetable FGFR gene fusions in diverse cancers. Cancer Discov, 2013,3:636–647.

[25] Balamuth NJ, Womer RB. Ewing’s sarcoma. Lancet Oncol, 2010,11:184–192.

[26] Aurias A, Rimbaud C, Buffe D, et al. Chromosomal translocations in Ewing’s sarcoma. New Engl J Med, 1983,309:496–497.

[27] Turc-Carel C, Philip I, Berger MP, et al. Chromosomal translocation (11; 22) in cell lines of Ewing’s sarcoma. C R Seances Acad Sci III, 1983,296:1101–1103. [in French]

[28] Delattre O, Zucman J, Piougeast B, et al. Gene fusion with an ETS DNA–binding domain caused by chromosome-translocation in human tumors. Nature, 1992,359:162–165.

[29] Scotlandi K, Benini S, Sarti M, et al. Insulin-like growth factor I receptor-mediated circuit in Ewing’s sarcoma/peripheral neuroectodermal tumor: a possible therapeutic target. Cancer Res, 1996,56:4570–4574.

[30] Prieur A, Tirole C, Cohen P, et al. EWS/FLI-1 silencing and gene profiling of Ewing cells reveal downstream oncogenic pathways and a crucial role for repression of insulin-like growth factor binding protein 3. Mol Cell Biol, 2004,24:7275–7283.

[31] Hancock JD, Lessnick SL. A transcriptional profiling meta-analysis reveals a core EWS-FLI gene expression signature. Cell Cycle, 2008,7:250–256.

[32] Shelton JG, Steelman LS, White ER, et al. Synergy between PI3K/AKT and Raf/MEK/ERK pathways in IGF-1R mediated cell cycle progression and prevention of apoptosis in hematopoietic cells. Cell Cycle, 2004,3:372–379.

[33] LeRoith D, Roberts CT Jr. The insulin-like growth factor system and cancer. Cancer Lett, 2003,195:127–137.

[34] Forstenberger G, Senn HJ. Insulin-like growth factors and cancer. Lancet Oncol, 2002,3:298–302.

[35] Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. J Natl Cancer Inst, 2000,92:1472–1489.

[36] Iwasa T, Okamoto I, Suzuki M, et al. Inhibition of insulin-like growth factor receptor 1 by CP-751,871 radiosensitizes non–small cell lung cancer cells. Clin Cancer Res, 2009,15:5117–5125.

[37] Olmos D, Martins AS, Jones RL, et al. Targeting the insulin-like growth factor receptor in Ewing’s sarcoma: reality and expectations. Sarcoma, 2011,2011:402508.

[38] Szuhai K, Ijszenga M, de Jong D, et al. The NFATc2 gene is involved in a novel cloned translocation in a Ewing sarcoma variant that couples its function in immunology to oncology. Clin Cancer Res, 2009,15:2259–2268.

[39] Haldar M, Randall RL, Cåpecchi MR. Synovial sarcoma: from genetics to genetic-based animal modeling. Clin Orthop Relat Res, 2008,466:2156–2167.

[40] Turc-Carel C, Dal Cin P, Limon J, et al. Involvement of chromosome X in primary cytogenetic change in human neoplasia: nonrandom translocation in synovial sarcoma. Proc Natl Acad Sci U S A, 1987,84:1981–1985.

[41] Clark J, Rocques FJ, Crew AJ, et al. Identification of novel genes, SYT and SSX, involved in the t(X;18)(p11.2;q11.2) translocation found in human synovial sarcoma. Nat Genet, 1994,7:502–508.

[42] Crew AJ, Clark J, Fisher C, et al. Fusion of SYT to two genes, SSX1 and SSX2, encoding proteins with homology to the Kruppel-associated box in human synovial sarcoma. EMBO J.
Fusion genes in solid tumors

1995, 14: 2333–2340.

[43] Skytting B, Nilsson G, Brodin B, et al. A novel fusion gene, SYT-SSX4, in synovial sarcoma. J Natl Cancer Inst, 1999, 91: 974–975.

[44] Nagai M, Tanaka S, Tsuda M, et al. Analysis of transforming activity of human synovial sarcoma-associated chimeric protein SYT-SSX1 bound to chromatin remodeling factor hBRM/hSNF2 alpha. Proc Natl Acad Sci U S A, 2001, 98: 3843–3848.

[45] Lim FL, Soulez M, Koczan D, et al. A KRAB-related domain and a novel transcription repression domain in proteins encoded by SSX genes that are disrupted in human sarcomas. Oncogene, 1998, 17: 2013–2018.

[46] Su L, Sampaio AV, Jones KB, et al. Deconstruction of the SS18-SSX fusion oncprotein complex: insights into disease etiology and therapeutics. Cancer Cell, 2012, 21: 333–347.

[47] Ito T, Ouchida M, Morimoto Y, et al. Significant growth suppression of synovial sarcomas by the histone deacetylase inhibitor FK228 in vitro and in vivo. Cancer Lett, 2005, 224: 311–319.

[48] Liu S, Cheng H, Kwan W, et al. Histone deacetylase inhibitors induce growth arrest, apoptosis, and differentiation in clear cell sarcoma models. Mol Cancer Ther, 2008, 7: 1751–1761.

[49] Meis-Kindblom JM. Clear cell sarcoma of tendons and aponeuroses: a historical perspective and tribute to the man behind the entity. Adv Anat Pathol, 2006, 13: 286–292.

[50] Bridge JA, Borek DA, Neff JR, et al. Chromosomal abnormalities in clear cell–sarcoma. Implications for histogenesis. Am J Clin Pathol, 1990, 93: 26–31.

[51] Zucman J, Delattre O, Desmaze C, et al. EWS and ATF-1 gene fusion induced by t(12–22) translocation in malignant melanoma of soft parts. Nat Genet, 1993, 4: 341–345.

[52] Goransson M, Andersson MK, Forni C, et al. The myxoid liposarcoma FUS-DDIT3 fusion oncprotein deregulates NF-kappaB target genes by interaction with NFKB1. Oncogene, 2009, 28: 270–278.

[53] Berman JJ. Tumor taxonomy for the developmental lineage classification of neoplasms. BMC cancer, 2004, 4: 88.

[54] Baade PD, Youlden DR, Kinjaci L.J. International epidemiology of prostate cancer: geographical distribution and secular trends. Mol Nutr Food Res, 2009, 53: 171–184.

[55] Tomlins SA, Rhodes DR, Perner S, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science, 2005, 310: 644–648.

[56] Tomlins SA, Mehra R, Rhodes DR, et al. TMPRSS2-ETV4 gene fusions define a third molecular subtype of prostate cancer. Cancer Res, 2006, 66: 3396–3406.

[57] Yu JD, Yu JJ, Mani RS, et al. An integrated network of androgen receptor, polycomb, and TMPRSS2-ERG gene fusions in prostate cancer progression. Cancer Cell, 2010, 17: 443–454.

[58] Esquena-P, Perner S, Lafortgue CJ, et al. Prevalence of TMPRSS2-ERG and SLC45A3-ERG gene fusions in a large prostatectomy cohort. Modern Pathol, 2010, 23: 539–546.

[59] Katoh M. Cancer genomics and genetics of FGFR2 (Review). Int J Oncol, 2008, 33: 233–237.

[60] Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell, 2002, 2: 367–376.

[61] Knezevich SR, McFadden DE, Tao W, et al. A novel ETV6-NTRK3 gene fusion in congenital fibrosarcoma. Nat Genet, 1998, 18: 184–187.

[62] Wai DH, Knezevich SR, Lucas T, et al. The ETV6-NTRK3 gene fusion encodes a chimeric protein tyrosine kinase that transforms NIH3T3 cells. Oncogene, 2000, 19: 906–915.

[63] Tognon C, Garnett M, Kenward E, et al. The chimeric protein tyrosine kinase ETV6-NTRK3 requires both Ras-Erk1/2 and PI3-kinase-Akt signaling for fibroblast transformation. Cancer Res, 2001, 61: 8909–8916.

[64] Zeegers MPA, Tan FES, Dorant E, et al. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. Cancer, 2000, 89: 630–639.

[65] Chen G, Li T, Zhang L, et al. Src-stimulated IRTKS phosphorylation enhances cell migration. FEBS lett, 2011, 585: 2972–2978.

[66] Siegel R, Ward E, Brawley O, et al. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin, 2011, 61: 212–236.

[67] Watson AJ, Collins PD. Colon cancer: a civilization disorder. Dig Dis, 2011, 29: 222–228.

[68] Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. Lancet, 2010, 375: 1030–1047.

[69] Seshagiri S, Stawiski EW, Durinck S, et al. Recurrent R-spondin fusions in colon cancer. Nature, 2012, 488: 660–666.

[70] Kazanskaya O, Glinka A, Barrantes ID, et al. R-Spondin2 is a secreted activator of Wnt/beta-catenin signaling and is required for Xenopus myogenesis. Dev Cell, 2004, 7: 525–534.

[71] Mc Ardle L, Rafferty M, Maelandsmo GM, et al. Protein tyrosine phosphatases downregulated in melanoma. J Invest Dermatol, 2001, 117: 1255–1260.

[72] Nakamura M, Kishi M, Sakaki T, et al. Novel tumor suppressor loci on 6q22–23 in primary central nervous system lymphomas. Cancer Res, 2003, 63: 737–741.

[73] Scrima M, De Marco C, De Vita F, et al. The non-receptor-type tyrosine phosphatase PTPN13 is a tumor suppressor gene in non– small cell lung cancer. Am J Pathol, 2012, 180: 1202–1214.

[74] Mo W, Zhang J, Li X, et al. Identification of novel AR-targeted microRNAs mediating androgen signaling through critical pathways to regulate cell viability in prostate cancer. PloS one, 2013, 8: e56592.

[75] Browning KS, Gallie DR, Hershey JWB, et al. Unified nomenclature for the subunits of eukaryotic initiation factor 3. Trends Biochem Sci, 2001, 26: 284–284.

[76] Salzman J, Marinelli RJ, Wang PL, et al. ESRR-A-C11orf20 is a recurrent gene fusion in serous ovarian carcinoma. PLoS Biol, 2011, 9: e1001156.

[77] Ariazi EA, Clark GM, Mertz JE. Estrogen-related receptor alpha and estrogen-related receptor gamma associate with unfavorable and favorable biomarkers, respectively, in human breast cancer. Cancer Res, 2002, 62: 6510–6518.

[78] Sun PM, Sehouli J, Denkert C, et al. Expression of estrogen receptor-related receptors, a subfamily of orphan nuclear receptors, as new tumor biomarkers in ovarian cancer cells. J Mol
Fusion genes in solid tumors

Brittany C. Parker et al.

[79] Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med, 2002;346:92–98.

[80] Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non–small-cell lung cancer. Nature, 2007;448:561–566.

[81] Takezawa K, Okamoto I, Nishio K, et al. Role of ERK-BIM and STAT3-survivin signaling pathways in ALK inhibitor-induced apoptosis in EML4-ALK–positive lung cancer. Clin Cancer Res, 2011;17:2140–2148.

[82] Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer. N Engl J Med, 2010;363:1693–1703.

[83] Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med, 2012;18:375–377.

[84] Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med, 2012;18:378–381.

[85] Seo JS, Ju YS, Lee WC, et al. The transcriptional landscape and mutational profile of lung adenocarcinoma. Genome research, 2012;22:2109–2119.

[86] Fordice J, Kershaw C, El-Naggar A, et al. Adenoid cystic carcinoma of the head and neck—predictors of morbidity and mortality. Arch Otolaryngol Head Neck Surg, 1999;125:149–152.

[87] Qian F, Kruse U, Lichter P, et al. Chromosomal localization of the 4 genes (NFIA, B, C, and X) for the human transcription factor nuclear factor-I by FISH. Genomics, 1995;28:66–73.

[88] Geurts JMW, Schoenmakers EFPM, Roijer E, et al. Identification of NFIB as recurrent translocation partner gene of HMGIC in pleomorphic adenomas. Oncogene, 1998;16:865–872.

[89] Persson M, Andre Y, Mark J, et al. Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck. Proc Natl Acad Sci U S A, 2009;106:18740–18744.

[90] Tonon G, Modi S, Wu LZ, et al. t(11;19)(q21;p13) translocation in mucopidermoid carcinoma creates a novel fusion product that disrupts a Notch signaling pathway. Nat Genet, 2003;33:208–213.

[91] Artavanis-Tsakonas S, Matsuno K, Fortini ME. Notch signaling. Science, 1995;268:225–232.

[92] Garcia JJ, Hunt JL, Weinreb I, et al. Fluorescence in situ hybridization for detection of MAML2 rearrangements in oncocytic mucopidermoid carcinomas: Utility as a diagnostic test. Hum Pathol, 2011;42:2001–2009.

[93] Mitchel RS, Kumar V, Abbas AK et al. Robbins basic pathology. 8th edition. Philadelphia: W B Saunders Co, 2007.

[94] Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med, 2012;18:375-377.

[95] Jones JR, Barrick C, Kim KA, et al. Deletion of PPARgamma in adipose tissues of mice protects against high fat diet-induced obesity and insulin resistance. Proc Natl Acad Sci U S A, 2005, 102:6207–6212.

[96] Powell JG, Wang XY, Allard BL, et al. The PAX8-PPARgamma fusion oncogene in human thyroid carcinoma [corrected]. Science, 2000;289:1357–1360.

[97] Jones JR, Barrick C, Kim KA, et al. Deletion of PPARgamma in adipose tissues of mice protects against high fat diet-induced obesity and insulin resistance. Proc Natl Acad Sci U S A, 2005, 102:6207–6212.

[98] Powell JG, Wang XY, Allard BL, et al. The PAX8-PPARgamma fusion oncogene in human thyroid carcinoma [corrected]. Science, 2000;289:1357–1360.

[99] Jones DT, Kocialkowski S, Liu L, et al. Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res, 2006;66:8673–8677.

[100] Park BJ, Kim HK, Sade B, et al. Epidemiology. Lee JH (ed). Me- ningiomas: diagnosis, treatment, and outcome. London: Springer, 2008.

[101] Lipton J, Lu YJ, Sidhar SK, et al. Fusion of splicing factor genes PSF and NonO (p54nr) to the TFE3 gene in papillary renal cell carcinoma. Oncogene, 1997;15:2233–2239.

[102] Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature, 2002;417:949–954.