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TP53 in bone and soft tissue sarcomas

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Abstract

Genomic and functional study of existing and emerging sarcoma targets, such as fusion proteins, chromosomal aberrations, reduced tumor suppressor activity, and oncogenic drivers, is broadening our understanding of sarcomagenesis. Among these mechanisms, the tumor suppressor p53 (TP53) plays significant roles in the suppression of bone and soft tissue sarcoma progression. Although mutations in *TP53* were thought to be relatively low in sarcomas, modern techniques including whole-genome sequencing have recently illuminated unappreciated alterations in *TP53* in osteosarcoma. In addition, oncogenic gain-of-function activities of missense mutant p53 (mutp53) have been reported in sarcomas. Moreover, new targeting strategies for TP53 have been discovered: restoration of wild-type p53 (wtp53) activity through inhibition of TP53 negative regulators, reactivation of the wtp53 activity from mutp53, depletion of mutp53, and targeting of vulnerabilities in cells with TP53 deletions or mutations. These discoveries enable development of novel therapeutic strategies for therapy-resistant sarcomas. We have outlined nine bone and soft tissue sarcomas for which TP53 plays a crucial tumor suppressive role. These include osteosarcoma, Ewing sarcoma, chondrosarcoma, rhabdomyosarcoma (RMS), leiomyosarcoma (LMS), synovial sarcoma, liposarcoma (LPS), angiosarcoma, and undifferentiated pleomorphic sarcoma (UPS).

Keywords

TP53; mutation; MDM2; bone; sarcoma; targeted therapy

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Conflicts of interest statement

The authors declare no conflict of interest.

1. Introduction

Bone and soft tissue sarcomas are tumors of mesenchymal origin. Sarcomas are exceptionally rare tumors, comprising less than 1% of all human cancers. Most sarcomas arise from abnormal differentiation processes of mesenchymal stem cells (MSCs) and their derived cell lineages (Eid & Garcia, 2015, Lye, Nordin, Vidyadaran, & Thilakavathy, 2016). Sarcomas commonly occur in children and young adults (Ognjanovic, Olivier, Bergemann, & Hainaut, 2012). Sarcoma prognosis remains poor, especially in cases of distant metastasis (Meyer & Seetharam, 2019). Although advanced chemotherapy and surgery have improved patients' prognosis, treatment options for most sarcomas have remained stagnant for the past 30–40 years (Meyer & Seetharam, 2019, Scheidt, et al., 2019). Therefore, understanding the molecular mechanisms driving sarcoma malignancy would significantly accelerate development of novel therapeutic strategies.

Advances in molecular biology have enabled precise and detailed discovery in the genome and expression profiles of tumor tissues, as compared with those of non-tumor tissues. Several unappreciated mutations and chromosomal abnormalities are found in osteosarcoma, including genes associated with IGF signaling, alterations in the PI3K/mTOR pathway, and somatic structural variations in TP53 (Behjati, et al., 2017, X. Chen, et al., 2014, Perry, et al., 2014, Sayles, et al., 2019). Genome sequencing of Ewing sarcoma reveals mutations related to DNA repair machineries (Brohl, et al., 2017). Indeed, Anderson et al. (Anderson, et al., 2018) show that complex chromosome rearrangements at the early stage of Ewing sarcoma development may contribute to EWS-ETS gene fusions and other DNA rearrangements. Additionally, multi-platform molecular landscape analysis of 206 adult soft tissue sarcomas, including leiomyosarcoma (LMS), de-differentiated liposarcoma (LPS), undifferentiated pleomorphic sarcoma (UPS), and synovial sarcoma, has recently revealed previously unappreciated sarcoma-type-specific changes in copy number variation, methylation pattern, RNA expression profile, and protein expression, which could have an impact on sarcoma diagnosis and therapy (Cancer Genome Atlas Research Network. Electronic address & Cancer Genome Atlas Research, 2017). These findings have further confirmed the significance of mutations and genetic abnormalities in the *TP53* gene on bone and soft tissue sarcoma progression. Mutations in *TP53* are detected in about half of all tumors, remaining the most frequently mutated gene in human cancers (Hung & Anderson, 1997, Taubert, Meye, & Wurl, 1998, Zhou, Hao, & Lu, 2018). Previously, mutations in *TP53* were thought to occur at a relatively low frequency in sarcomas (Toguchida, et al., 1992). This is mainly because mutations in *TP53* were identified by sequencing only exonic regions in the DNA binding domain or by performing immunohistochemistry (IHC) to detect positive staining in p53-mutated tumors due to the long half-life of the mutant protein. However, recent whole-genome sequencing analyses have revealed more frequent alterations in TP53, including structural alterations in *TP53* intron 1. Thus, the significance of TP53 in sarcoma could have been underestimated, which drives us to revisit the roles of TP53 in sarcomagenesis. Since the variety of alterations to TP53 and TP53 upstream regulators are detected in sarcomas, we will also discuss several distinct TP53 targeting strategies in this review article (Table 1).

TP53 is a transcription factor that is stabilized following genotoxic stress and induces transcription of genes associated with cell cycle arrest, apoptosis, and metabolism, thereby functioning as a tumor suppressor (D. Lane & Levine, 2010, Ranjan & Iwakuma, 2016). Typically, tumor suppressors have loss-of-function (LOF) mutations or deletions in cancers; however, the majority of TP53 mutations are missense mutations in the DNA binding domain, such that mutant TP53 (mutp53) not only loses the tumor suppressive function but also gains oncogenic functions (GOF: gain of function) independent of wild-type TP53 (wtp53) (Parrales & Iwakuma, 2015). The most frequently mutated codons are R175, R248, and R273. There are roughly two types of TP53 mutations. The first is a DNA contact type in which mutations occur at amino acids that directly interact with DNA (e.g., K120, R248, R273, R280). The second is a conformational or misfolded type, in which mutations do not occur in DNA-contacting amino acids but instead alter the three-dimensional structure of TP53, thereby losing the DNA binding activity (Adhikari & Iwakuma, 2009, D. Lane & Levine, 2010). Increasing evidence suggests that not all TP53 mutants have identical GOF activity. However, overall, the majority of TP53 mutants lose tumor suppressive function, at least partially, and some mutants show distinct oncogenic activities to promote malignant progression (M. P. Kim & Lozano, 2018, Mantovani, Collavin, & Del Sal, 2019, Parrales & Iwakuma, 2015). These mutants' oncogenic properties are seen throughout a variety of cancers including bone and soft tissue sarcomas.

Mutp53's oncogenic properties are also demonstrated in Li-Fraumeni syndrome (LFS), an autosomal dominant familial cancer-prone syndrome. The link between germline mutations of *TP53* and LFS was confirmed by molecular testing in 1990 (Malkin, et al., 1990). Over 70% of patients with LFS inherently harbor a mutation in the *TP53* gene in their germlines and frequently develop various types of cancer at early ages, including osteosarcoma, rhabdomyosarcoma (RMS), brain tumors, breast cancer, leukemias, and adrenocortical carcinoma (Correa, 2016, Malkin, et al., 1990). Osteosarcoma is the most common sarcoma in patients with LFS, though rates are only slightly higher for osteosarcoma than brain tumors and RMS (Correa, 2016, Guha & Malkin, 2017). Even a low-penetrance *TP53* R337H mutation, found in a clustered population in southeast Brazil, is associated with an increased frequency of adrenocortical tumors, choroid plexus carcinoma, and osteosarcoma (Seidinger, et al., 2011). Additionally, Mirabello et al. (Mirabello, Yeager, et al., 2015) report that young-onset osteosarcoma has a higher frequency of LFS-associated *TP53* mutations. Moreover, they show that the presence of a rare *TP53* variant leading to an exonic splice site change, rs1800372 (p.R213R), is associated with metastasis at diagnosis of osteosarcoma (Mirabello, Yeager, et al., 2015).

In this review article, we revisit the significance of TP53 in bone and soft tissue sarcoma with updated literatures by focusing on osteosarcoma, Ewing sarcoma, chondrosarcoma, RMS, LMS, synovial sarcoma, LPS, angiosarcoma, and UPS. For each sarcoma we explore the roles of TP53 in tumor development, malignancy, and the prognosis of these sarcomas, as well as potential and optimal therapeutic strategies targeting TP53 for each sarcoma (Table 2).

2. Osteosarcoma

Osteosarcoma is the most common primary cancer of the bone and arises during the process of osteoblastic differentiation from MSCs (Mortus, Zhang, & Hughes, 2014, Tang, Song, Luo, Haydon, & He, 2008). Osteosarcoma is commonly detected near the epiphyseal plate of long bones, most commonly in children. A combination of surgery and chemotherapy, including high-dose methotrexate, cisplatin, and doxorubicin, is the main therapeutic strategy for osteosarcoma. Although this treatment has improved 5-year survival rate of patients to 70% in the past three decades, some patients develop resistance to chemotherapy, and the long-term survival of patients with relapse remains below 20% (Harrison, Geller, Gill, Lewis, & Gorlick, 2018, Y. Zhang, J. Yang, et al., 2018). To overcome this poor prognosis, it is crucial to learn about the genetics and molecular pathogenesis of this disease.

Osteosarcomas frequently show complex karyotypes and genomic instability including gene amplifications (*MYC, CCNE, Rad21, VEGFQ, AURKB, CDK4*), deletions (*TP53, RB1, PTEN*), somatic nucleotide variants (SNVs) or short indels (*TP53, ATRX, RBs, PRKDC*), and structural variants (SVs: *TP53, LRP1B, RB1, FHIT*) (Martin, Squire, & Zielenska, 2012, Sayles, et al., 2019). While many other sarcomas are often characterized by chromosomal translocations (including Ewing sarcoma, RMS, synovial sarcoma, and LPS), until now no such representative translocation has been identified in osteosarcoma (Martin, et al., 2012). Mutation of *TP53* is well-correlated with genomic and chromosomal instability in human high-grade osteosarcoma (Al-Romaih, et al., 2003, Zuffa, et al., 2008). One early immunohistochemistry (IHC) study shows that 27 out of 46 (58.7%) osteosarcoma specimens exhibit TP53 overexpression, a common indicator of TP53 missense mutations (W. Guo, Wang, & Feng, 1996), while other studies show fewer TP53 mutations in osteosarcoma (Mendoza, Konishi, Dernell, Withrow, & Miller, 1998, Miller, et al., 1996, Mirabello, Koster, et al., 2015). Intriguingly, Masuda et al. (Masuda, Miller, Koeffler, Battifora, & Cline, 1987) first reported intron 1 rearrangements in the *TP53* gene in 3 out of 6 human osteosarcoma samples in 1987. Indeed, a recent whole-genome sequencing of 34 osteosarcoma samples has discovered similar mutations in the *TP53* gene. Nine (26%) have *TP53* point mutations, and 19 (55%) have structural variations in the *TP53* gene, the majority of which are translocations with breakpoints in the first intron (X. Chen, et al., 2014). This finding is supported by the report by Ribi et al. (Ribi, et al., 2015), where 16% of sporadic osteosarcomas show intron 1 rearrangements, while no other tumors have such *TP53* rearrangements. The intron 1 rearrangements are also detected in a four-generation LFS family (Ribi, et al., 2015). The most recent study by Sayles et al. (Sayles, et al., 2019) demonstrates that *TP53* alterations including structural variation (SV) and somatic nucleotide variants (SNVs) are detected in 74% of human osteosarcoma. Since rearrangements in intron 1 cannot be detected by exon sequencing and IHC, alterations in *TP53* have likely been underestimated. Biologically, loss of TP53 activity is shown to promote osteogenic differentiation of bone marrow stromal cells, as well as osteosarcoma development from MSCs (He, et al., 2015, Velletri, et al., 2016). Thus, TP53 has strong impact on preventing the malignant transformation of MSCs.

Genetic deletion or mutations of *TP53* in mice with the C57BL/6 background often results in osteosarcoma development (Lang, et al., 2004). Also, mice expressing gain-of-function

(GOF) TP53R172H (R172H is equivalent to human R175H) spontaneously develop metastatic tumors, including osteosarcoma at a high frequency (~30% in the C57BL/6 background) (Lang, et al., 2004, Olive, et al., 2004). This metastatic GOF activity by mutp53 can be mediated by upregulation of the ONZIN-CXCL5-MAPK axis or by binding of mutp53 with TP63, TP73, and ETS2 (Do, et al., 2012, Lang, et al., 2004, Pourebrahim, et al., 2017, Xiong, et al., 2014, Y. Zhang, Q. Hu, et al., 2018). Moreover, combined deletion of *TP53* and *RB1* in mouse osteoblasts results in development of metastatic osteosarcoma at a high frequency (Walkley, et al., 2008). Thus, deletions and mutations in *TP53* significantly contribute to osteosarcoma progression in mouse models, supporting findings in humans.

TP53 has been implicated in chemotherapy sensitivity, mainly through induction of apoptosis and senescence as well as inhibition of autophagy (J. Fan & Bertino, 1999, Hu, et al., 2017, Z. Wang & Sun, 2010). Previous studies have shown that mutations in *TP53* are associated with chemoresistance or poor event-free survival in human osteosarcoma (Goto, et al., 1998, Tsuchiya, et al., 2000). Loss of heterozygosity (LOH) of *TP53* in osteosarcomas is associated with chemoresistance (Goto, et al., 1998). The work by Asada et al. (Asada, Tsuchiya, & Tomita, 1999) supports this, showing that deletion of *TP53* is found in an osteosarcoma cell line with acquired resistance to cisplatin. However, multiple meta-analyses suggest that while TP53 mutations could serve as an effective prognostic marker only for 2- or 3-year overall survival of patients with osteosarcoma, TP53 status does not appear to be correlated with development of metastases and chemotherapy response in patients with osteosarcoma (Z. Chen, Guo, Zhang, & Guo, 2016, Fu, et al., 2013, Gokgoz, et al., 2001, Pakos, Kyzas, & Ioannidis, 2004, Wunder, et al., 2005, Yao, et al., 2014). These clinical studies do not examine the structural alterations in *TP53* introns. Considering frequent observations of the *TP53* intron 1 rearrangement, it may be important to re-evaluate the clinical significance of TP53 alterations in malignancy, response to chemotherapy, and metastasis of human osteosarcoma and other types of cancer.

Alterations to regulators of TP53 can also contribute to development of osteosarcoma (Morrow & Khanna, 2015). One crucial regulator of TP53 stability and degradation is the protein MDM2 (murine double minute 2). MDM2, which acts as the major E3 ubiquitin ligase for TP53, is overexpressed in ~30% of human cancers. *MDM2* copy number is amplified more than 3-fold in 14.7% of high grade osteosarcoma (Overholtzer, et al., 2003). Ito et al. (Ito, et al., 2011) show that 35% of osteosarcoma cases have over 3-fold *MDM2* amplification. However, mutations in *TP53*, but not copy number of *MDM2*, are correlated with overall genomic instability in high-grade human osteosarcoma (Overholtzer, et al., 2003). Although a multivariate analysis shows that the *MDM2* polymorphism T309G which increases MDM2 expression levels via an extra SP1 binding site in the *MDM2* promoter is associated with an increased risk of developing high-grade osteosarcomas in female patients (Toffoli, et al., 2009), there is no conclusive literature showing correlation of MDM2 overexpression with survival and prognosis of human osteosarcoma.

Another major inhibitor of TP53 is MDM4 (Haupt, Hernandez, Vijayakumaran, Keam, & Haupt, 2019). Although it is a homolog of MDM2, MDM4 does not have ubiquitin ligase activity like MDM2. However, MDM4 still binds with TP53 and inhibits TP53 activity. Also, MDM4 hetero-dimerizes with MDM2 through the C-terminal RING finger domain to

induce TP53 degradation as a cofactor of MDM2 (Haupt, et al., 2019). Similar to MDM2, 35% of osteosarcoma cases show *MDM4* amplification over 3-fold (Duhamel, et al., 2012, Ito, et al., 2011). In addition, multiple studies have highlighted the expression of MDM4 splice variants in different tumor types (Bardot & Toledo, 2017). One MDM4 splice variant, *MDM4-S,* which skips exon 6 and prematurely terminates in exon 7, encodes a truncated MDM4 protein carrying only the N-terminal TP53-binding domain along with 13 novel amino acids (Bardot & Toledo, 2017, Pant, et al., 2017). Overexpression of MDM4-S has been linked to poor prognosis in osteosarcoma, soft tissue sarcoma, and other cancers (Dewaele, et al., 2016, Lenos, et al., 2012, Lenos & Jochemsen, 2011). Thus, MDM4-S overexpression can serve as an effective biomarker for TP53 pathway attenuation in cancers (Lenos, et al., 2012).

Pagetic osteosarcoma and TP53

Paget's disease of bone (PDB), which occurs in approximately 3% of adults over 50 years old, is a metabolic bone disease characterized by increased bone resorption and subsequent excessive disorganized bone formation (Ouslander & Beck, 1982). PDB occurs rarely in Asian and African regions, while individuals in Europe, North America, and Australia show a high prevalence rate of PDB (Gennari, Rendina, Falchetti, & Merlotti, 2019, Gruener & Camacho, 2014). One of the genes implicated in PDB is Sqstm1/p62, which plays roles in NF-κB activation as a scaffolding/adaptor protein and selective macroautophagy as an autophagosome cargo protein (Duran, et al., 2008, L. Fan, Yin, Zhang, & Hu, 2018, McManus & Roux, 2012). Patients with PDB have a high incidence of osteosarcoma, called Pagetic osteosarcoma. The prevalence of Pagetic osteosarcoma is estimated to be about 1%, which is several hundred- to thousand-fold higher than the prevalence of osteosarcoma in the general population depending on the age (Greditzer, McLeod, Unni, & Beabout, 1983, Hansen, Nellissery, & Bhatia, 1999, Mirabello, Troisi, & Savage, 2009). Pagetic osteosarcoma accounts for 50% of osteosarcoma cases in patients over 60 years of age (Gennari, et al., 2019, Yochum, 1984). Although *MYC* gene amplification and *TP53* mutations are detected in Pagetic osteosarcomas and loss of TP53 activity is reported to reduce Sqstm1/p62 levels, the direct role of TP53 in Pagetic osteosarcoma development remains unclear (Goiran, et al., 2018, Reddy, 2004, Ueda, Healey, Huvos, & Ladanyi, 1997).

TP53-targeted therapy in osteosarcoma

Because TP53 alterations have been underestimated in osteosarcoma, most early studies in osteosarcoma focus on restoring wtp53 activity by inhibiting a TP53 negative regulator, MDM2 (Table 1) (Hientz, Mohr, Bhakta-Guha, & Efferth, 2017). The first report for an MDM2 inhibitor is Nutlin-3a (Vassilev, et al., 2004). Nutlin-3a binds MDM2 in the TP53-binding pocket and activates TP53 without causing DNA damage in cancer cells, leading to cell cycle arrest, apoptosis, and growth inhibition in osteosarcoma xenograft mouse models (Tovar, et al., 2006, Vassilev, et al., 2004, B. Wang, Fang, Zhao, Xiang, & Wang, 2012). Nutlin-3a shows synergy with other chemotherapy drugs and CDK inhibitors, and oridonin, a diterpenoid extracted from medicinal herbs (Cheok, Dey, & Lane, 2007, X. H. Wang, Zhang, Bao, & Liu, 2017). Unfortunately, clinical trials for Nutlin-3a in various tumor types have yet to show much success due to significant side-effects including bone marrow suppression (Ray-Coquard, et al., 2012). Several other compounds that inhibit MDM2-TP53

binding have been identified, including RG7112 (Tovar, et al., 2013), SAR405838 (S. Wang, et al., 2014), APG-115 (Yi, et al., 2018), AMG 232 (D. Sun, et al., 2014), and MK-8242 (Wagner, et al., 2017). Some of these MDM2 inhibitors are currently in clinical trials (D. P. Lane, Brown, Verma, & Cheok, 2011, Morrow & Khanna, 2015, Tovar, et al., 2013, Wagner, et al., 2017, S. Wang, et al., 2014). Besides MDM2 inhibitors, investigators have discovered MDM4 inhibitors (e.g., CTX1, K-181, SJ-172550), as well as MDM2/MDM4 dual inhibitors (e.g., DIMP53–1, pDI analogs) (Bista, et al., 2012, Karan, et al., 2016, Philippe, et al., 2016, Soares, et al., 2017, Uesato, et al., 2016). The effects of these inhibitors on osteosarcoma need to be tested in the future.

When tumors carry missense mutp53, restoration of wtp53 activity from mutp53 can be an efficient strategy for anti-cancer therapy (Table 1) (Parrales & Iwakuma, 2015). PRIMA-1 is the first small molecule that is shown to restore sequence-specific DNA binding and transcriptional activities of TP53 with tumor suppressive effects in mutp53-expressing cells (V. J. Bykov, Issaeva, et al., 2005). Since then, many compounds have been identified, and details of these compounds are summarized elsewhere (Binayke, Mishra, Suman, Das, & Chander, 2019, V. J. N. Bykov, Eriksson, Bianchi, & Wiman, 2018, Parrales & Iwakuma, 2015). Of these, APR-246, a PRIMA-1 analog, shows synergy in inhibiting tumor cell growth with camptothecin, a quinoline alkaloid, in the Saos2 osteosarcoma cell line exogenously expressing TP53 R273H (Saos2-TP53R273H) (V. J. Bykov, Zache, et al., 2005). STIMA-1, a small molecule compound with structural similarities to CP-31398 that stabilizes the active conformation of TP53 (Wischhusen, Naumann, Ohgaki, Rastinejad, & Weller, 2003), is also shown to stimulate DNA binding of mutp53, induce expression of TP53 target genes, and trigger apoptosis in H1299-TP53R175H lung adenocarcinoma and Saos2-TP53R273H osteosarcoma cells (Zache, et al., 2008). Additionally, stictic acid, which was identified though computational methods for a transiently open binding pocket in the TP53 core domain, is shown to upregulate p21 and PUMA in Saos2 cells expressing TP53 R175H and G245S (Wassman, et al., 2013).

Other than these compounds to increase wtp53 activity, drugs that can deplete mutp53 can also be used to inhibit tumor growth of mutp53-expressing osteosarcoma. This is based on the observations that cancer cells are addicted to oncogenes, including mutp53, and that depletion of mutp53 may lead to reactivation of proteins or pathways suppressed by mutp53 (Iyer, et al., 2016, Parrales & Iwakuma, 2015). HSP90 inhibitors and cholesterol-lowering drugs (statins) are agents have been shown to induce degradation of mutp53 mediated by MDM2 and/or CHIP ubiquitin ligases and inhibit tumor progression including osteosarcoma (Alexandrova, et al., 2015, Parrales, et al., 2016).

Another way to target TP53 mutations is to treat cells with a compound that inhibits proteins or pathways unique and essential for survival and proliferation (vulnerabilities) in *TP53*-null or mutated cells with minimal impact on wtp53-expressing cells (Table 1) (Lu, et al., 2016, Tongyang, et al., 2015). Such a compound may inhibit function of proteins that show a synthetically lethal interaction with TP53 mutations, including CHK1, ATM/CHK2, Plk1, Wee1, and MK2 (Chung, et al., 2018, Gurpinar & Vousden, 2015, Harada, et al., 2011, Jiang, et al., 2009, Morandell, et al., 2013, Origanti, Cai, Munir, White, & Piwnica-Worms, 2013, Tongyang, et al., 2015, X. Wang & Simon, 2013, Weidle, Maisel, & Eick, 2011).

Since ~80% of osteosarcoma cases have TP53 alterations, targeting vulnerable pathways and proteins in cells lacking wtp53 activity would be a reasonable treatment strategy. Intriguingly, Yu et al. (Yu, et al., 2015) identify HDAC (histone deacetylase) inhibitors through a 54 FDA-approved agent screen as agents having anti-growth activity and synergistic effects with proteasome inhibitors in five TP53-inactive pediatric osteosarcoma cell lines, although the underlying mechanism remains unclear.

3. Ewing sarcoma

Ewing sarcoma accounts for approximately 1% of childhood cancers and is the second most common bone cancer in children, although it can also arise in soft tissues (Grunewald, et al., 2018). The femur is the most frequently affected bone. The origin of Ewing sarcoma remains controversial as both MSCs and neural crest stem cells (NCSCs) have been implicated as the cell of origin (Lin, Wang, & Lozano, 2011, Todorova, 2014). Microscopically, the tumor consists of small round cells with regular round nuclei and a narrow rim of clear or faintly eosinophilic cytoplasm (Burchill, 2003).

The current chemotherapy protocols for Ewing sarcoma include combinations of doxorubicin, cyclophosphamide, vincristine, actinomycin-D, ifosfamide, and etoposide (Ozaki, 2015). These treatments have improved the overall 5-year survival of localized Ewing sarcoma to 70%. However, overall survival of metastatic Ewing sarcoma remains stagnant at ~30% (Balamuth & Womer, 2010, Kridis, et al., 2017).

This malignancy is characterized by translocation between a gene of the RNA-binding TET family (e.g., EWSR1, FUS) and a gene of the ETS-transcription family (e.g., FLI1, ERG, ETV1, ETV4, and FEV). In the majority of cases (~85%), the EWS-FLI1 fusion resulting from a t(11;22) translocation is detected (Renzi, Anderson, Light, & Gupta, 2018). However, it remains unclear why this fusion occurs and how exactly the fusion protein contributes to Ewing sarcoma development. A recent study by Anderson et al. (Anderson, et al., 2018) using whole-genome sequence analyses of 124 Ewing sarcomas indicates that chromoplexy, a sudden burst of loop-like genomic rearrangements involving multiple chromosomes and genes, rather than reciprocal translocation, is the potential cause of the *EWSR1–ETS* fusion in 42% of cases. The loop-like genomic rearrangements and fusions are also detected in other sarcomas including chondromyxoid fibroma and synovial sarcoma (Anderson, et al., 2018).

Molecular and genetic profiles of Ewing sarcoma have been assessed in a genome-wide association study of 733 Ewing sarcoma cases and 1,346 unaffected individuals of European ancestry by Crompton et al. (Crompton, et al., 2014). They reveal new susceptibility loci at 6p25.1, 20p11.22, and 20p11.23, in addition to previously reported loci at 1p36.22, 10q21.3, and 15q15.1. They identify candidate genes at 6p25.1 (RREB1) and 20p11.23 (KIZ) (Crompton, et al., 2014). Brohl et al. (Brohl, et al., 2014) also show that Ewing sarcoma has frequent mutations in the cohesin complex subunit *STAG2* (21.5%), homozygous deletion of *CDKN2A* (13.8%) and mutations of *TP53* (6.2%), as well as an increased prevalence of the *BRCA2* K3326X polymorphism (7.3%). Other genome sequencing studies also identify mutations in cancer-related genes including *KDR, STK11, MLH1, KRAS,* and *PTPN11*, as

well as in DNA double-strand break repair, in Ewing sarcoma tissues (Brohl, et al., 2017, Zhang, et al., 2016).

With regard to *TP53* mutations, multiple articles have found that genetic alterations in the *TP53* gene are detected only in ~10% of Ewing sarcomas (Komuro, et al., 1993, Lerman, et al., 2015, Neilsen, Pishas, Callen, & Thomas, 2011, Radig, et al., 1998). The two most frequently detected *TP53* mutations in Ewing sarcoma are the C176F and R273X (Sand, Szuhai, & Hogendoorn, 2015). Although mutation frequency of *TP53* is low in Ewing sarcoma, TP53 still plays a crucial role in inhibiting Ewing sarcoma progression. Li et al (Y. Li, et al., 2010) report that EWS-FLI1 binds to and inhibits TP53's transcriptional activity, which may explain why TP53 mutations are detected only in ~10% of Ewing sarcoma. To support this finding, silencing of EWS-FLI1 reactivates NOTCH signaling and subsequently activates TP53 to induce cell cycle arrest in Ewing sarcoma cells (Ban, et al., 2008). Additionally, EWS-FLI1 significantly inhibits p300-mediated acetylation of TP53 at Lys-382 (Y. Li, et al., 2012). These results strongly suggest the inhibitory role of EWS-FLI1 in TP53 activity as well as the vital tumor inhibitory role of TP53 in Ewing sarcoma progression. However, a study by Lessenick et al. (Lessnick, Dacwag, & Golub, 2002) shows that EWS-FLI1 induces a TP53-dependent growth arrest in primary human fibroblasts, which is rescued by wtp53 inhibition. The observed discrepancy may be due to difference in the experimental settings including cancer cells vs non-transformed cells.

Several clinical studies also support the important role of TP53 in inhibiting Ewing sarcoma progression. An IHC study by de Alava et al. (de Alava, et al., 2000) shows that positive TP53 staining in Ewing's sarcoma is a poor prognostic factor. This finding is supported by studies by Huang et al. (H. Y. Huang, et al., 2005) and Abdu et al. (Abudu, et al., 1999), demonstrating significant correlation of TP53 mutations with poor overall survival and response to chemotherapy. On the other hand, a study by Lerman et al. (Lerman, et al., 2015) fails to observe an association between TP53 mutations and event-free survival of patients. The discrepancy among these studies may be caused by the methodology used to determine TP53 mutations. Whole-genome sequencing, rather than IHC and exome sequencing, would be necessary to clarify the significance of *TP53* mutations in Ewing sarcoma.

Similar to osteosarcoma, MDM2 overexpression is not high (~10%) (Kovar, et al., 1993). Ladanyi et al. (Ladanyi, et al., 1995) report that only three out of 30 Ewing sarcoma specimens have *MDM2* gene amplification, all of which have metastasis at diagnosis, while only one out of 15 specimens without *MDM2* amplification has metastasis, suggesting correlation between *MDM2* amplification and metastasis. Thus, the TP53 pathway may play a crucial role in the suppression of Ewing sarcoma progression.

Given the infrequent rate of mutations of TP53 in Ewing sarcoma, restoring TP53 activity by inhibiting upstream inhibitors of TP53 is a rational therapeutic strategy (Neilsen, et al., 2011, Stolte, et al., 2018). Through a genome-scale CRISPR-Cas9 screening, Stolte et al. (Stolte, et al., 2018) identify MDM2, MDM4, USP7, and PPM1D as druggable targets for Ewing sarcoma. They also demonstrate that ATSP-7041, a stapled peptide inhibitor of MDM2 and MDM4, shows anti-tumor efficacy *in vitro* and in mouse models. Additionally, P5091, a USP7 inhibitor, and GSK2830371, a Wip1/PPM1D inhibitor, decrease viability of

Ewing sarcoma cells, in a TP53-dependent manner (Stolte, et al., 2018). Pishas et al. (Pishas, et al., 2011) show that Nutlin-3a induces cell death, mainly apoptosis, in Ewing sarcoma cells expressing wtp53, and Nutlin-3a's effect is synergistic with the chemotherapeutic agents: vincristine, actinomycin D, doxorubicin, and etoposide. Similarly, Sonnemann et al. (Sonnemann, et al., 2011) observe that nutlin-3a induces apoptosis and senescence with increased TP53 level and mRNA expression of TP53 downstream target genes in wtp53-expressing Ewing sarcoma cells (Sonnemann, et al., 2011). Also, YK-4–279, a small molecule inhibitor of EWSR1–ETS's transcriptional activity through inhibition of its interaction with RNA helicase A, is shown to reduce Ewing sarcoma development regardless of TP53 status. The effects of YK-4–279 are additive with Nutlin-3a, *in vitro* and in a xenograft zebrafish model of human Ewing sarcoma cell lines (van der Ent, et al., 2014). Another way to restore wtp53 activity in Ewing sarcoma is to inhibit CD99. CD99 is expressed in most cases of Ewing sarcoma and is required to maintain malignancy (Pasello, Manara, & Scotlandi, 2018, Ventura, et al., 2016). Guerzoni et al. (Guerzoni, et al., 2015) find that dAbd C7, a novel human monospecific bivalent single-chain fragment variable diabody against CD99, induces cell death in Ewing sarcoma cells, through MDM2 degradation and TP53 reactivation; the anti-CD99 dAbd C7 shows additive effects with doxorubicin to suppress Ewing sarcoma malignancy.

When Ewing sarcoma expresses mutp53, APR-246 can be used to induce apoptosis by reactivating wtp53 activity in tumors. APR-246 is currently in early-phase clinical trials for Ewing sarcomas (Aryee, et al., 2013). Intriguingly, curcumin may radiosensitize TP53-mutated Ewing sarcoma cells by upregulating p21 and Bax and downregulating BCL-XL and MCL1, although the mechanism behind reactivation of wtp53 from mutp53 remains unclear (Veeraraghavan, Natarajan, Herman, & Aravindan, 2010). Another small molecule TP53 reactivator, RITA/NSC652287, is shown to induce apoptosis and effectively reduce tumor growth of Ewing sarcoma cell lines; however, this effect of RITA is independent of the TP53 status. As an additional mechanism of action of RITA in Ewing sarcoma cells, RITA induces degradation of IGF-1R, a regulator of anchorage-independent growth, in a manner dependent on MDM2 (Di Conza, et al., 2012). More studies are required for evaluating efficacy of targeting the TP53 pathway for Ewing sarcoma therapy.

4. Chondrosarcoma

Chondrosarcoma is a heterogeneous group of bone malignancies with cartilage-forming tumor cells, and it is the second most common form of primary malignant bone tumor (Chow, 2018, M. J. Kim, Cho, Ayala, & Ro, 2011). Chondrosarcoma generally grows slowly and rarely metastasizes, and the prognosis of surgically resected chondrosarcoma is good with a ~50% 5-year survival rate (M. J. Kim, et al., 2011). However, chondrosarcoma is generally chemo- and radiotherapy resistant, likely due to a low percentage of dividing cells and poor tumor vascularization. Because surgical resection is the primary treatment for chondrosarcoma, more efficient treatment options for metastatic and recurrent disease are required (Gelderblom, et al., 2008).

Genetically, chondrosarcoma can be subtyped to chromosomal translocation-positive and translocation-negative types. Extraskeletal myxoid chondrosarcoma, a slow-growing, low-

grade sarcoma with high frequency of metastases and local recurrence, has a t(9;22)(q22;q12) translocation, creating the *EWSR1-NR4A3*, *RBP56-NR4A3*, and *TCF12-NR4A3* fusion genes, while mesenchymal chondrosarcoma, a rare, fast-growing, high-grade sarcoma, has a *HEY1-NCOA2* fusion gene resulting from intrachromosomal rearrangement of 8q21.13 and 8q13.3 or a *IRF2BP2-CDX1* fusion gene resulting from t(1;5)(q42;q32) (Chow, 2018, Nazeri, Gouran Savadkoohi, Majidzadeh, & Esmaeili, 2018, Nyquist, et al., 2012, Panagopoulos, et al., 2002, Sandberg, 2004, Stenman, Andersson, Mandahl, Meis-Kindblom, & Kindblom, 1995, L. Wang, et al., 2012). On the other hand, de-differentiated chondrosarcoma, a high grade, non-chondroid sarcoma associated with low-grade cartilaginous lesions, have structural aberrations in chromosomes 1 and 9, as well as numerical aberrations (trisomy and tetrasomy) in chromosomes 7 and 19, without having distinct chromosomal translocations (Bridge, Bhatia, Anderson, & Neff, 1993, Dijkhuizen, et al., 1994, Hameed, et al., 2009, Olsson, Paulsson, Bovee, & Nord, 2011, Sakamoto, 2014). Also, clear cell chondrosarcoma, a rare, slow-growing low-grade sarcoma with low metastatic potential, does not have chromosomal translocations.

A whole-genome sequencing analysis by Tarpey et al. (Tarpey, et al., 2013) reveals that 37% of chondrosarcoma cases have *COL2A1*γ gene deletion and rearrangements, while mutations in *IDH½* are found in 59% of cases, similar to the previous findings by Amary et al. (Amary, et al., 2011) and Totoki et al. (Totoki, et al., 2014). Additionally, they detect mutations in *TP53* (20%), the RB pathway (33%), and Hedgehog signaling (18%) (Tarpey, et al., 2013). Mutations in *TP53* and *RB1* are the most common changes involved in the later stage of chondrosarcoma (Oshiro, et al., 1998, Samuel, Costa, & Lindskog, 2014). Also, deletion and silencing of *p16*, an upstream regulator of RB1, are implicated in de-differentiated chondrosarcoma (Asp, et al., 2000, Sakamoto, 2014). In conventional and de-differentiated chondrosarcoma, alterations in the *TP53* gene are observed in 20–50% of cases, while alterations in the RB pathway are detected in 30–96% of cases, depending on the methods of detection (exome sequencing or IHC) (Blasenbreu, et al., 1998, Schrage, et al., 2009, Tarpey, et al., 2013). A higher incidence of *TP53* mutation is found in atypical chondrosarcomas, de-differentiated types, and mesenchymal types, while overexpression (indicating missense mutations) or alteration in *TP53* is correlated with high histologic grade, presence of metastasis or local recurrence, and reduced overall survival (Dobashi, et al., 1993, Oshiro, et al., 1998, Simms, Ordonez, Johnston, Ayala, & Czerniak, 1995, Wadayama, Toguchida, Yamaguchi, Sasaki, & Yamamuro, 1993). Moreover, overexpression of MDM2 by IHC is found in 33% of high-grade chondrosarcoma, which is positively correlated with histological grades (Schrage, et al., 2009). Thus, the TP53 pathway is altered in over half of high-grade chondrosarcomas. Furthermore, a mouse model overexpressing Gli2, a protein that plays a role in regulating growth plate chondrocyte differentiation, in combination with *TP53* heterozygosity develops chondrosarcoma. This is due to additive effects of overexpression of Gli2 and *TP53* deficiency on inhibition of apoptosis mediated through IGFBP3 downregulation in chondrocytes (Ho, et al., 2009, M. J. Kim, et al., 2011).

Chemotherapy is generally not effective in chondrosarcoma with the exception of mesenchymal chondrosarcoma (Dai, Ma, He, & Jha, 2011). As mentioned above, signaling pathways of IGF, Hedgehog, RB, and TP53, as well as these interactions, are implicated in chondrosarcoma progression, and these pathways can be potential therapeutic targets

(Bovee, Hogendoorn, Wunder, & Alman, 2010, Jamil, Howie, & Salter, 2010). Intriguingly, van Oosterwijk et al. (van Oosterwijk, et al., 2013) identify that the Src pathway is involved in chondrosarcoma chemoresistance. To support their finding, dasatinib, a dual BCR/ABL and Src family tyrosine kinase inhibitor, is shown to be effective in a phase 2 clinical study for multiple sarcomas, including chondrosarcoma, and significantly sensitizes chondrosarcoma cell lines harboring *TP53* mutations to doxorubicin, (Schuetze, et al., 2017). Appropriate TP53-tageting agents may be chosen to enhance efficacy of current treatment regimens for chondrosarcoma, depending on TP53 status (Polychronidou, et al., 2017).

5. Rhabdomyosarcoma (RMS)

Rhabdomyosarcoma (RMS) is a malignant tumor most commonly found in the head & neck, trunk, genitourinary tract, or limbs, and accounts for about half of all childhood soft tissue sarcomas (Egas-Bejar & Huh, 2014). RMS is generally thought to derive from the myogenic progenitors of striated muscle or MSCs, with the specific cell of origin (e.g. satellite cells, myoblasts) determining RMS subtype and therapy (Abraham, et al., 2014, X. Sun, et al., 2015). The main varieties of RMS are alveolar RMS (ARMS), embryonal RMS (ERMS) which has two histopathologic variants: spindle cell and botryoid (Esiashvili, Prabhu, Kahn, & Paulino, 2013), and pleomorphic RMS (PRMS) (Ruiz-Mesa, Goldberg, Coronado Munoz, Dumont, & Trent, 2015). The ERMS and ARMS subtypes are most common in children and adolescents, while adults typically develop PRMS (Egas-Bejar & Huh, 2014, Ruiz-Mesa, et al., 2015). Remission rates for RMS with modern therapies are now >90% in children without metastasis (Mazzoleni, et al., 2005); however, the 5-year survival rate for metastatic RMS remains less than 30%, and adult RMS also shows poor prognosis (Egas-Bejar & Huh, 2014).

RMS can also be subtyped to chromosome translocation-positive (ARMS) and -negative (ERMS, PRMS) types. The majority of ARMS cases (~85%) express PAX-FKHR fusion proteins resulting from translocation of a PAX family member (i.e. *PAX3, PAX7*) located on chromosome 1 or 2 to the *FKHR* gene locus on chromosome 13 (Stegmaier, et al., 2011). The PAX-FKHR fusion protein in ARMS maintains myogenic lineage but inhibits terminal myogenic differentiation through induction of MyoD and inhibition of cell cycle arrest (Graf Finckenstein, Shahbazian, Davicioni, Ren, & Anderson, 2007). Normal myogenic cells also express the *PAX/FKHR* mRNA, as well as other chimeric fusion mRNAs, during normal myogenesis, suggesting that a portion of this population of cells may become transformed during this process, producing ARMS tumors (Xie, et al., 2016). ERMS tumors frequently display chromosomal abnormalities including aneuploidy and polyploidy, and are characterized by loss of heterozygosity on the short arm of chromosome 11 (Goldstein, Meller, Issakov, & Orr-Urtreger, 2006). Although the t(1 or 2;13) chromosome translocation is rare in ERMS, both PAX3 and PAX7 are frequently overexpressed in ERMS (Goldstein, et al., 2006). PRMS also do not normally have the PAX-FKHR fusion and can have a highly complex karyotype, sometimes with abnormalities in every chromosome (Goldstein, et al., 2006). Similar to ERMS, PRMS tumors overexpress both PAX3 and FOXO1 (FKHR) (Goldstein, et al., 2006).

Neither ARMS nor ERMS harbors many somatic mutations or genetic alterations (Shern, et al., 2014), but tumors lacking the PAX-FKHR fusion protein tend to have a higher burden of somatic mutations in the TP53 and RB1 pathways (S. J. Xia, Pressey, & Barr, 2002). Interestingly, ERMS is proposed to originate at an earlier stage of myogenic development than ARMS (Stewart, et al., 2018). Using whole-genome and transcriptomic sequencing, Seki et al. (Seki, et al., 2015), further subdivide RMS to into four ARMS/ERMS subtypes based on somatic mutations: A1, A2, E1, and E2. While A1 and A2 show expression of PAX-FKHR and cell cycle regulators, the E1 and E2 subtypes contain mutations in the FGFR4/RAS/AKT pathways, as well as *PTEN* mutations (Seki, et al., 2015). E1 and E2 also have greater chromosomal and epigenetic aberrations evidenced by changes in allelic imbalance and gene copy number (Seki, et al., 2015).

Mutations in *TP53* in RMS range from 0.02% to 15% (Ognjanovic, Martel, et al., 2012, Seki, et al., 2015, Taylor, et al., 2000), while amplification of *MDM2* is detected at less than 10% of RMS (Ognjanovic, Martel, et al., 2012, Seki, et al., 2015, Taylor, et al., 2000). Because ARMS rarely shows inactivation or mutations of TP53, other mechanisms may be responsible for reduced wtp53 activity. One such mechanism may be the overexpression of PAX proteins or the PAX-FHKR oncoprotein, since these proteins repress wtp53 transcriptional activity in RMS (Stuart, Haffner, Oren, & Gruss, 1995). PAX3 specifically downregulates TP53 protein levels, but not transcription (Pani, Horal, & Loeken, 2002). Interestingly, PAX5 can directly inhibit *TP53* mRNA expression by binding to the *TP53* promoter, a trait shared by PAX2 and PAX8 (Stuart, et al., 1995).

On the other hand, ERMS tissues and their derived cell lines have a relatively high frequency of mutations or aberrations in the TP53/MDM2 axis (Felix, et al., 1992). Specifically, Seki et al. (Seki, et al., 2015) reveal that the E2 subtype of ERMS has a high rate (>45%) of TP53 mutation or copy number loss of *TP53* (Seki, et al., 2015). Also, metastases of ERMS have high levels of TP53 expression (Leuschner, et al., 2003), and the presence of TP53 mutations significantly reduces survival of patients of the E1/E2 subtypes (Seki, et al., 2015). Intriguingly, in a $kRAS^{G12D}$-induced zebrafish ERMS model, deletion of *TP53* enhances invasion and metastasis (Ignatius, et al., 2018), while expression of a dominant-negative mutp53 in mouse MSCs expressing PAX-FKHR fusion protein is sufficient to induce ARMS tumors in mice (Ren, et al., 2008). Thus, although clinical relevance of TP53 appears not to be robust, TP53 and its upstream regulators may contribute to malignant progression of RMS, in specific subtypes or cellular contexts. Additionally, DNp73, the N-terminal deleted dominant-negative form of a TP53 family member, is frequently overexpressed in RMS (>80%) and is also shown to inhibit myogenic differentiation and contribute to transformation of mouse myoblast cells and RMS progression *in vivo* (Cam, et al., 2006).

As mentioned above, prognosis of recurrent or metastatic RMS remains poor, and new treatment strategies should be developed (Shern, et al., 2014). CP-31398, a small molecule drug which enhances wtp53 activity and restores wtp53 function from mutp53, is shown to induce ROS-dependent cell cycle arrest and apoptosis in wtp53-carrying A204 and mutp53-expressing ERMS cell lines to reduce their tumor growth in xenograft mouse models (Xu, et al., 2010). Given that ARMS and PRMS rarely have TP53 mutations, compounds that restore wtp53 activity would also be efficient. On the other hand, for ERMS which often

carries TP53 mutations, reactivating wtp53 activity from mutp53 may be an effective way to treat patients.

6. Leiomyosarcoma (LMS)

Leiomyosarcoma (LMS) is a soft tissue sarcoma arising from the smooth muscle cells lining small blood vessels (Danielson, et al., 2010, Rubio, et al., 2010). LMS most frequently occurs in the uterus (ULMS), but also arises in the abdomen, retroperitoneum, and large blood vessels (non-uterine LMS) (Beck, et al., 2010, Bleeker, Quevedo, & Folpe, 2012, X. Guo, et al., 2015). Although ULMS is considered distinct from non-uterine LMS, these two types are genetically more similar to one another than other sarcomas (Abeshouse, et al., 2017, Miettinen & Fetsch, 2006). Individuals with LFS or the condition called hereditary leiomyomatosis and renal cell carcinoma (HLRCC) have a higher risk of developing LMS (Farid & Ngeow, 2016). Another risk factor for ULMS is tamoxifen exposure for unrelated conditions, such as breast cancer (Bleeker, et al., 2012). The prognosis for ULMS is worse than for other LMS, with a recurrence rate between 53%−71%, and the five-year overall survival for these patients is 15%−25% (D'Angelo & Prat, 2010). On the other hand, 39% of non-uterine LMS patients experience recurrence either locally or distantly, with retroperitoneal LMS cases having a higher recurrence rate of 51% (Gladdy, et al., 2013). The five-year overall survival for non-uterine LMS is 64% (Mankin, et al., 2004). The first line chemotherapy for LMS is presently a combination of gemcitabine and docetaxel (Momtahen, Curtin, & Mittal, 2016, Seddon, et al., 2017); however, a recent study suggests that doxorubicin may have better outcomes in combination with gemcitabine than docetaxel (Seddon, et al., 2017).

Unlike other sarcomas, LMS does not have a key fusion protein driving its tumorigenesis, although a small group of ULMS (<2.5%) is found to express an ALK fusion protein (KANK2-ALK, ACTG2-ALK) (Davis, et al., 2019). Rather, the general molecular alterations in LMS affect activities of the tumor suppressors TP53, PTEN, and/or RB1 with deletion of *PTEN* and *RB1* and mutations of *TP53* (Chudasama, et al., 2018, Grossmann, Layfield, & Randall, 2012, Gunderson, et al., 2016, Yang, et al., 2009). Cytogenetic studies of LMS suggest that loss of tumor suppressors can be an initiating event in LMS, while oncogene activation may occur at a later stage of malignant progression, because low-grade tumors contain more DNA copy number losses, while high-grade tumors have more copy number gains (Grossmann, et al., 2012). Interestingly, loss of TP53, but not RB1, is sufficient to transform MSCs and induce LMS formation in mice (Rubio, et al., 2010). Besides these tumor suppressors, LMS often has mutations in *ATRX* (Alpha thalassemia/mental retardation syndrome X-linked) with a mutation rate of ~30% in ULMS (Gunderson, et al., 2016, Mäkinen, et al., 2016). ATRX is a SWI/SNF chromatin remodeling protein which acts as a tumor suppressor (Kadoch & Crabtree, 2015). ULMS also harbors mutations in *MED12* (mediator complex subunit 12), a coactivator involved in the interaction of transcription factors with RNA polymerase II, at a ~20% frequency, but this does not occur in non-uterine LMS (Mäkinen, et al., 2016, Mäkinen, Kämpjärvi, Frizzell, Bützow, & Vahteristo, 2017). *MED12* mutation is also common in the benign tumor leiomyoma (Ravegnini, et al., 2012), suggesting that ULMS harboring *MED12* mutations may represent the small population of tumors known to originate from leiomyoma (Mäkinen, et al., 2017).

Intriguingly, ULMS tumors frequently have one or more hallmarks of “BRCAness”, enabling the use of a PARP inhibitor for ULMS treatment (Chudasama, et al., 2018, Seligson, et al., 2018).

TP53 is mutated in ~50% of all LMS and ~35% of ULMS (Abeshouse, et al., 2017, Gao, Seebacher, Hornicek, Guo, & Duan, 2018, O’neill, McBride, Connolly, & McCluggage, 2007). LMS frequently shows gene amplifications near the gene locus of *MDM2*, 12q15 (Ragazzini, et al., 2004); however, *MDM2* amplification is rare in LMS (Miura, et al., 2012, Miyajima, et al., 2001, Yang, et al., 2009). Importantly, there is a correlation between abnormalities in *TP53* and an advanced clinicopathological stage or poor prognosis in LMS (Konomoto, Fukuda, Hayashi, Kumazawa, & Tsuneyoshi, 1998, Patterson, et al., 1994), suggesting potential value for TP53-tageting therapies. Indeed, a mutp53 reactivator, PRIMA-1, is shown to reduce viability of IB134 ULMS and IB138 soft tissue LMS cell lines harboring *TP53* mutations, while it is less effective in the wtp53-expressing IB139 LMS cell line (Grellety, et al., 2015). Also, Gendicine, a recombinant adenoviral vector expressing wtp53, is clinically used in China and shows a 66.7% remission rate and a 91.7% responsive rate in combination with chemotherapy in ULMS (Y. Xia, Du, Wang, & Li, 2018, W.-W. Zhang, et al., 2018). These results support the idea that restoring wtp53 activity in tumors may be beneficial for LMS patients.

7. Synovial Sarcoma

Synovial sarcoma comprises up to 10% of all soft tissue sarcomas and is the second most common soft tissue sarcoma in patients younger than 30 years old, although the majority (70%) of patients are older than 30 years old (Mark D. Murphey, et al., 2006, Stacchiotti & Van Tine, 2017). The prognosis of synovial sarcoma is worse with increased age (Jang, et al., 2007, Stacchiotti & Van Tine, 2017). Tumors frequently occur in the lower half of the body, particularly near the knee joint, but can occur in the head and neck areas of the upper body (Gopalakrishnan, et al., 2017, Mark D. Murphey, et al., 2006). MSCs are thought to be the cell of origin for synovial sarcoma (Garcia, et al., 2012, Norifumi Naka, et al., 2010). Tumors have the appearance of synovial tissue, but are unrelated to the synovium, and they are comprised of two main cell types: epithelial cells and mesenchymal spindle cells (El Beaino, Araujo, Lazar, & Lin, 2017, Mark D. Murphey, et al., 2006). The presence of one or both of these cell types as well as the degree of cellular differentiation defines the sarcoma’s subtype: monophasic (mesenchymal), biphasic (epithelial and mesenchymal), and small cell (poorly differentiated) (El Beaino, et al., 2017). Importantly, over half (50–70%) of synovial sarcomas metastasize, which makes overall survival for synovial sarcoma less than 40% (Krieg, et al., 2011).

A recent whole-genome sequencing analysis has revealed that 95% of synovial sarcomas express the fusion oncoprotein SS18 (synovial sarcoma translocation, chromosome 18)-SSX, making it a defining characteristic of synovial sarcoma (Vlenterie, et al., 2015). The t(X:18)(p11.2;q11.2) chromosomal translocation creates an in-frame fusion of *SS18* to *SSX1, SSX2,* or *SSX4*, leading to generation of a SS18-SSX protein (Clark, et al., 1994, de Leeuw, Balemans, Weghuis, & van Kessel, 1995, Skytting, et al., 1999). Although the SS18-SSX lacks a DNA binding domain, it interacts with other chromatin regulators, including

components of the SWI/SNF complex (e.g., hBRM, BRG1), to act as an oncoprotein that drives synovial sarcoma progression (Clark, et al., 1994, de Leeuw, et al., 1995, Skytting, et al., 1999). To support this, SS18-SSX proteins have been found to bind with a non-canonical polycomb repressive complex 1 (PRC1.1) and co-associate with SWI/SNF and KDM2B complexes to aberrantly regulate the expression of developmentally regulated transcription factors and mesenchymal differentiation genes (Banito, et al., 2018). Additionally, SS18-SSX plays roles in activation of the WNT/β-catenin and PI3K/AKT pathways and stabilization of MDM2, leading to inhibition of TP53 activity (Arcy, Maruwge, Ryan, & Brodin, 2008, Bozzi, et al., 2008).

Synovial sarcomas do not frequently display mutations in the *TP53* gene (D'Arcy, Ryan, & Brodin, 2009). Despite its low rate of mutations (~6%), TP53 alteration may be an effective prognostic indicator because tumors with missense mutations in the *TP53* gene show significantly reduced 5-year survival when compared to non-mutated tumors (Schhneider-stock, et al., 1999). Also, over 3-fold gene amplifications of *MDM2* and *MDM4* are observed in 33% and 44% of synovial sarcoma tissues, respectively, which has an inverse correlation with TP53 mutations (Ito, et al., 2011). This is supported by the finding of that SS18-SSX1 induces TP53 degradation by MDM2 (Arcy, et al., 2008). Thus, TP53 activity appears to be lowered in synovial sarcoma through MDM2/MDM4.

Presently, synovial sarcomas are mainly treated with doxorubicin, ifosfamide, and pazopanib, a multi-targeted tyrosine kinase inhibitor, in addition to surgical resection (In, Hu, & Tseng, 2017). These therapies are mainly effective to non-metastatic synovial sarcoma but are limited in effectiveness in tumors with metastases. Hence, the overall 10-year survival rates are 50–60% (Lewis, et al., 2000). Obviously, new therapeutic strategies must be developed for metastatic synovial sarcomas. Since TP53 mutation is uncommon in synovial sarcoma, restoration of wtp53 activity in tumors by MDM2/MDM4 inhibitors may be a rational strategy for this type of sarcoma. Indeed, Nutlin-3a and MI-219, two small molecule inhibitors of MDM2, are shown to inhibit the growth of synovial sarcoma cells *in vitro* (Banito, et al., 2018, D'Arcy, et al., 2009, Wade, Li, & Wahl, 2013).

8. Liposarcoma (LPS)

Liposarcoma (LPS) is the most common adult soft tissue sarcoma and represents ~25% of all soft tissue sarcomas. It is a tumor derived from the mesenchymal adipogenic lineage, and most commonly arises in the limbs, retroperitoneum, and the paratesticular areas of the body (Brill, et al., 2010, Bui, et al., 2011, Peng, et al., 2011). LPS is often confused for a benign tumor (L. G. Dodd, 2012), posing a threat for patient care. There are four key subtypes of LPS which have been identified based on cytogenetic features: myxoid/round cell LPS, pleomorphic LPS, well-differentiated LPS, and de-differentiated LPS (Bui, et al., 2011, Genadry, Pietrobono, Rota, & Linardic, 2018). The subtypes can be distinguished by the presence of the FUS-CHOP fusion oncoprotein (myxoid/round cell LPS), MDM2 overexpression (well-differentiated, and de-differentiated LPS), and chromosomal abnormalities (pleomorphic LPS) (L. G. Dodd, 2012). LPS has about a 20% rate of recurrence overall, with de-differentiated LPS showing a higher local recurrence rate of 37.6% (Vos, et al., 2018). Distant metastasis occurs in ~20% of all LPS, while in the

pleomorphic subtype metastasis occurs in ~45% of tumors (Vos, et al., 2018). Although LPS has a relatively good prognosis overall with a five-year overall survival rate of ~80%, de-differentiated and pleomorphic LPS show significantly worse prognosis with overall 5-year survival rates at ~40% (Ng, Scharschmidt, Mayerson, & Fisher, 2013, Vos, et al., 2018). Pleomorphic LPS also tends to have highly variable karyotypes (Mandahl, et al., 2017).

A chromosomal translocation t(12;16)(q13;p11) results in the creation of a fusion oncoprotein, FUS-CHOP (also referred to as TLS-CHOP), which is present in myxoid/round cell LPS but not in other types (Rodriguez, et al., 2011, Tornin, et al., 2018). In rare cases, t(12;22)(q13;q12) translocation creates the EWS-CHOP fusion protein (Rodriguez, et al., 2011). FUS is an RNA-binding protein involved in regulation of gene expression, genomic integrity, and mRNA/microRNA processing, while CHOP is an ER-stress response transcription factor (Nishitoh, 2011). Overexpression of FUS-CHOP in the mouse genome under the human *EF1α* promoter is shown to induce LPS in 100% of mice (Pérez-Losada, et al., 2000). LPS tumors developed in *FUS-CHOP* transgenic mice express high levels of the adipocyte regulatory protein PPARγ (Pérez-Losada, et al., 2000). FUS-CHOP–overexpressing primary mesenchymal progenitor cells (MPC) also form tumors resembling human myxoid LPS (Riggi, et al., 2006). Transcription profile analysis of these tumors and non-xenografted MPCs expressing FUS-CHOP reveals repression of CTGF, PERP, and TFPI, as well as induction of growth factors (PDGFA, HGF), cytokines (IL6), growth factor receptors (MET), cell cycle regulators (CDK4, MDM2), proteolytic enzymes (MMP-11, CTSD, PLAT), and adipocyte differentiation-associated factors, (ADFP, FASN, HMGCR, RGS2) (Riggi, et al., 2006). Moreover, the FUS-CHOP fusion protein enhances invasiveness of LPS cells by activating the SRC/FAK/RHO/ROCK pathway, and enhances metastatic potential of LPS cells by transcriptionally upregulating MMP2 proteases (Patil, et al., 2014, Tornin, et al., 2018).

Intriguingly, supernumerary ring chromosomes and giant rod marker chromosomes are observed in myxoid/round cell, well-differentiated, and de-differentiated LPS (Laroche-Clary, et al., 2017, Macchia, et al., 2018, Mandahl, et al., 2017, Pedeutour, et al., 1999). These supernumerary chromosomes frequently amplify the *CDK4, HMGA2*, and *MDM2* genes from chromosome 12q (Mandahl, et al., 2017, Pedeutour, et al., 1999, Szymanska, et al., 1996). Also, well-differentiated and de-differentiated LPSs carry neochromosomes due to amplifications and rearrangements of chromosome 12q encoding oncogenes (*MDM2, CDK4, YEATS2*) and adipocytic differentiation factors (*HMGA2, CPM*) (Beird, et al., 2018). A recent study with exome and RNA sequencing analyses using 17 patients with both well-differentiated and de-differentiated LPSs reveals that the two subtypes share only 8.3% of their somatic mutations between matched tumors, suggesting the possibility that these tumors arise from a common origin and diverge at an early stage of tumor development (Beird, et al., 2018). Moreover, de-differentiated tumors show greater genomic instability attributed to an early clonal divergence from well-differentiated LPS tumors (Beird, et al., 2018).

An earlier study by Barretina et al. (Barretina, et al., 2010) identify mutations in *TP53* and *NF1*, as well as *PIK3CA* mutations in myxoid/round-cell LPSs. To support their finding, SNP arrays, whole exome sequencing, and targeted exome sequencing by Kanojia et al.

(Kanojia, et al., 2015) identify c*arboxypeptidase M* (*CPM*), which cleaves C-terminal arginine or lysine residues from polypeptides, as an oncogene which is involved in the EGFR pathway and is recurrently amplified in well-differentiated and de-differentiated LPS. They also report *FGFR1* amplification at chromosome 8p11.23, classical *CDK4*, *HMGA2*, and *MDM2* amplification at the chromosome 12q13–15 region, and deletion of *TP53BP1* at chromosome 15q15 in de-differentiated LPS. Moreover, their functional analyses reveal the tumor suppressive role of neurofibromin 1 (NF1), which negatively regulates RAS through hydrolysis of RAS-GTP, in LPS, irrespective of subtype (Kanojia, et al., 2015).

Mutations in *TP53* are not usually high in LPS (10–20%), except for pleomorphic LPS in which ~60% of cases show *TP53* mutations. This is likely because the *MDM2* gene is amplified in the majority of well-differentiated and de-differentiated LPSs, leading to functional inactivation of TP53 without mutations (Abeshouse, et al., 2017, Barretina, et al., 2010, Ghadimi, et al., 2011, Kawai, et al., 1994, Nakayama, et al., 1995, Taubert, et al., 1998). However, mutations in *TP53* are associated with proliferation, tumor aggressiveness, reduced patient survival, and advanced disease in LPS (Antonescu, et al., 2001, Kawai, et al., 1994, Schneider-Stock, et al., 1999). Moreover, subcutaneous transplantation of mouse adipose-derived mesenchymal stem/stromal cells (ASCs) expressing FUS-CHOP results in formation of LPS-like tumors only when cells are null for *TP53*, although this is not observed in human ASCs (Rodriguez, et al., 2011). Since *TP53*-null mouse ASCs develop LMS, these data may indicate that FUS-CHOP predisposes *TP53*-null mouse ASCs to adipogenic differentiation (Rodriguez, et al., 2011). To support this finding, Charytonowicz et al. (Charytonowicz, et al., 2012) generate a mouse model expressing *FUS-CHOP* specifically in mesoderm tissues. Although the *FUS-CHOP* transgenic mice are not tumor-prone, mice show development of sarcoma resembling myxoid/round cell LPS upon deletion of the *TP53* allele(s). Clinically, *TP53* mutations are detected in 15–30% of cases of human myxoid/round cell LPS and are correlated with unfavorable outcomes (Antonescu, et al., 2001, Dei Tos, et al., 1997, Schneider-Stock, et al., 1999). Thus, FUS-CHOP and TP53 loss may have cooperative effects on myxoid round cell LPS progression.

Chemotherapeutic drugs for primary and metastatic LPS include doxorubicin and ifosfamide in the first-line setting, and other drugs including docetaxel and gemcitabine are also used (Kollár & Benson, 2014). However, due to high frequency of *MDM2* amplification and low frequency of *TP53* mutations in LPS, especially in well-differentiated and de-differentiated LPS, use of MDM2 antagonists to restore TP53 activity (e.g., Nutlin-3a, RG7112, SAR405838) can be a major therapeutic strategy (Ray-Coquard, et al., 2012). Nutlin-3a has been extensively studied in multiple cancers, including in *MDM2*-amplified LPS cells, to restore wtp53 activity and induce apoptosis (Muller, et al., 2007). A Nutlin-3a analog, RG7112, has been clinically tested for the treatment of patients with well-differentiated or de-differentiated LPS (Obrador-Hevia, et al., 2015, Ray-Coquard, et al., 2012). Although RG7112 stabilizes disease progression in many cases, it has significant adverse effects including neutropenia and thrombocytopenia, in as many as 40% of patients (Ray-Coquard, et al., 2012). SAR405838 is also shown to inhibit de-differentiated LPS progression in *in vitro* and *in vivo* mouse models; it induces stabilization of TP53, upregulation of TP53 targets, and induction of apoptosis in de-differentiated LPS, which has enabled this drug to enter early-phase clinical trials for multiple malignancies (Bill, et al., 2016). As stated

above, *TP53* mutation status is correlated with recurrence, metastasis, and advanced stage of LPS (Antonescu, et al., 2001, Kawai, et al., 1994, McGovern, Zhou, & Jones, 2017, Schneider-Stock, et al., 1999). Hence, mutp53-targeted therapies may be efficacious for these aggressive LPS, which should be tested clinically in the future.

9. Angiosarcoma

Angiosarcomas are malignant endothelial-cell tumors originating from vascular or lymphatic tissues (Young, Brown, Reed, Hughes, & Woll, 2010). Angiosarcomas can occur spontaneously or secondarily to ionizing radiation or chronic lymphedema; they are subdivided into cutaneous, lymphoedema-associated, radiation-induced, primary-breast, and soft-tissue types (Behjati, et al., 2014, Young, et al., 2010). Surgical resection followed by high-dose radiotherapy, is the standard of care. However, recurrence is frequent, and most patients ultimately develop metastases, leading to poor prognosis (Florou & Wilky, 2018). Tyrosine kinase inhibitors and vascular-targeted therapies can be efficacious, but some patients still develop drug resistance (Florou & Wilky, 2018, Spiker & Ramsey, 2018, Young, et al., 2010). Better understanding of the molecular mechanisms of angiosarcoma malignancy is essential for discovery of new treatments and improvement of current therapeutic regimens.

Analyses of whole-genome, exome, and targeted sequencing with primary and secondary angiosarcomas have provided useful information in determining the potential causes of tumorigenesis. Behjati et al. (Behjati, et al., 2014) identify recurrent mutations of angiogenesis-related genes, *PTPRB* (*receptor-type tyrosine-protein phosphatase β*) and *PLCG1* (*phospholipase C, γ1*) in angiosarcomas. The *PTPRB* gene has predominantly truncating mutations in 26% of tumors, with an activating R707Q missense mutation in 9% of cases (Behjati, et al., 2014). Also, Murali et al. (Murali, et al., 2015) report that more than 50% of angiosarcomas carry some genetic alterations impacting the MAPK pathway. These include mutations in *KRAS*, *HRAS*, *NRAS*, *BRAF*, *MAPK1*, and *NF1*, as well as amplifications in *MAPK1*/*CRKL*, *CRAF*, or *BRAF*. Moreover, the most frequently detected genetic aberrations are mutations in *TP53* (35%) and losses of *CDKN2A* (26%). *MYC* amplifications are detected in the majority (88%) of radiation-induced angiosarcomas, which is mutually exclusive of alterations in *TP53* and *CDKN2A*. Additionally, *FLT4* amplifications and mutations or rearrangements of *PTPRB, PLCG1, CIC*, *FLT4*, and *KDR* genes are detected in angiosarcomas (S. C. Huang, et al., 2016). Thus, whole-genome sequencing analyses further confirm the molecular heterogeneity of angiosarcomas.

The involvement of TP53 in angiosarcomas is also shown by Naka et al (N. Naka, et al., 1997), where frequency of *TP53* mutations is dependent on the site of tumors with an overall occurrence of ~50%. In addition to TP53 mutations, upregulation of MDM2 is reported in two-thirds of angiosarcoma cases (Zietz, et al., 1998). Intriguingly, increased VEGF levels are observed in ~80% of cases, which is correlated with increased protein levels of TP53 and MDM2 (Zietz, et al., 1998). The involvement of TP53 in angiosarcoma is also shown by mouse studies showing occurrence of angiosarcoma in *TP53* knockout mice (Landuzzi, et al., 2014, Lang, et al., 2004). Specifically, over 65% of alymphocytic *TP53* knockout mice (*Rag2*$^{-/-}$*;Il2rg*$^{-/-}$*;TP53*$^{-/-}$, referred to as *RGKO-TP53*$^{-/-}$) spontaneously develop

hemangiosarcoma (Landuzzi, et al., 2014). Furthermore, Li et al. (Q. Li, et al., 2014) observe that ~34% of mice carrying hypomorphic *TP53* alleles with overexpression of MDM2 (*MDM2*^{Tg} *TP53*$^{Neo/Neo}$) spontaneously develop angiosarcoma. Moreover, cre-mediated restoration of wtp53 expression in angiosarcoma developed in *MDM2*^{Tg} *TP53*$^{Neo/Neo}$ mice results in inhibition of tumor growth in a syngeneic transplant model, suggesting that TP53 restoration is a potential therapeutic strategy for angiosarcomas (Q. Li, et al., 2014). Considering the high frequency of TP53 mutations in angiosarcoma, TP53-targeted therapies may be an option for anti-angiosarcoma treatment. Meanwhile, continuous efforts to understand the genetic heterogeneity of angiosarcomas and the identification of molecular targets for each subtype of angiosarcoma are necessary to determine the best therapy for each subtype (Florou & Wilky, 2018). (Mehren & Joensuu, 2018)

10. Undifferentiated Pleomorphic Sarcoma (UPS)

Undifferentiated pleomorphic sarcoma (UPS) is an aggressive bone and soft tissue sarcoma, originally called malignant fibrous histiocytoma and later reclassified as UPS in 2002 by the World Health Organization (WHO) (Matushansky, et al., 2009, M. D. Murphey, 2007). UPS is categorized to four subtypes based on the histology: storiform-pleomorphic, myxoid, giant cell, and inflammatory types. The storiform-pleomorphic type is the most common (~70%), followed by the myxoid variant (~20%), while giant cell and inflammatory types are rare. Of these subtypes, the myxoid variant is the least aggressive and has the best prognosis. Most patients are between 50 and 70 years old, and the most common tumor location is the lower extremities (Dei Tos, 2006, M. D. Murphey, 2007).

Due to clinical and genetic heterogeneity, few studies have analyzed the molecular profiles of UPS (R. D. Dodd, 2016). Conventional comparative genomic hybridization (CGH) and gene expression profiling analyses reveal similarity between UPS and LMS including loss of 13q14–21 as the most common deletion and alterations of the RB and TP53 pathways (Carneiro, et al., 2009). Using *Ptch1*, *TP53* and/or *RB1* conditional knockout mouse models, Rubin et al. (Rubin, et al., 2011) show that ERMS and UPS are a continuum of myodifferentiation, with satellite cells giving rise to UPS. Also, loss of *RB1*, but not *TP53*, promotes undifferentiated phenotypes to mimic UPS (Rubin, et al., 2011). However, recent multi-platform molecular landscape analyses using human soft tissue sarcomas identify molecular similarity between UPS and myxofibrosarcoma and suggest the involvement of the Hippo pathway in UPS pathogenesis (Cancer Genome Atlas Research Network. Electronic address & Cancer Genome Atlas Research, 2017). Moreover, some previously diagnosed peripheral UPSs, which do not have characteristics of well-differentiated LPS but have *MDM2* gene amplifications, later turned out to be de-differentiated LPS (Le Guellec, et al., 2014). Overall, due to complex molecular heterogeneity and difficulty of diagnosis, the genetic and molecular profiling of UPS remains unclear. Nonetheless, Serrano et al. (Serrano, et al., 2016) recently show that the RAS/MAPK and PI3K/mTOR pathways are activated in the majority of cases of UPS, while activation of the RAS/MAPK pathway is correlated with an increased risk of disease recurrence and impaired overall survival (R. D. Dodd, 2016).

Regarding the involvement of TP53 in UPS, a study using a large series of 143 soft tissue sarcomas identifies genomic deletion of the *TP53* locus in 18.4% of tumors and *TP53* mutations in 32% (Perot, et al., 2010). Intriguingly, most UPS (87.2%) retain one wild-type *TP53* allele. Furthermore, most tumors which do not have *TP53* alterations show deletion or silencing of the *p14*ARF gene, a negative regulator of MDM2 (Perot, et al., 2010). These results suggest that the p14ARF-MDM2-p53 pathway plays crucial roles in UPS pathogenesis. Hence, restoring wtp53 activity may be one option for treating UPS.

11. Conclusions and future perspectives

In this review we have summarized the role of TP53 in bone and soft tissue sarcomas with emphasis on TP53 and mutations/deletions in *TP53* as therapeutic targets. Alterations to *TP53* or other genes in the TP53 pathway often occur in sarcomas. Notably, over 70% of osteosarcoma has structural variants or mutations in the *TP53* gene, Ewing sarcoma is rarely mutated for *TP53* due to EWS-FLI1's inhibitory effect on TP53, non-uterine LMS has a high rate (~50%) of *TP53* mutation, and well- and de-differentiated LPSs are defined by amplification of *MDM2*. Evolving new technologies, including next generation sequencing, would enable identification of novel therapeutic targets, some of which may directly or indirectly alter TP53 activity. While current TP53-targeted therapies have some drawbacks in a clinical setting, including bone marrow suppression and other side effects, improved TP53-targeted therapies to restore wtp53 activity, reactivate wtp53 activity from mutp53, deplete mutp53, and target vulnerabilities in *TP53*-mutated/deleted cells may prove effective in therapy-resistant bone and soft tissue sarcomas in the near future.

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Abbreviations

TP53	tumor protein p53
MDM2	mouse double minute 2
MDM4	mouse double minute 4
IHC	immunohistochemistry
RMS	rhabdomyosarcoma
ERMS	embryonic rhabdomyosarcoma
ARMS	alveolar rhabdomyosarcoma
PRMS	pleomorphic rhabdomyosarcoma
LPS	liposarcoma

LMS	leiomyosarcoma
ULMS	uterine leiomyosarcoma
ASCs	adipose-derived mesenchymal stem/stromal cells
LFS	Li-Fraumeni Syndrome
LOF	loss of function
GOF	gain of function
PDB	Paget's disease of bone
MSC	mesenchymal stem cell

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Table 1.

Strategy targeting TP53

TP53 status	Targeting Strategy
Wild-type TP53 (reduced activity)	Restoration of wild-type TP53 activity MDM2 antagonists (e.g., Nutlin-3a, RG7112, RG7388), MDM4 inhibitors, MDM2/4 dual inhibitors, RITA
TP53-null	Target vulnerabilities in cells lacking wild-type TP53 activity Inhibitors for wee1 kinase, Chk1, and polo-like kinase 1
Mutant TP53	Target vulnerabilities in cells lacking wild-type TP53 activity Inhibitors for wee1 kinase, Chk1, and polo-like kinase 1 Reactivation of wild-type TP53 activity from mutant TP53 e.g. PRIMA-1, PRIMA-1Met, CP-31398, STIMA-1, Stictic acid Mutant TP53 depletion Statins, HSP90 inhibitors

Table 2.

TP53 mutation rate in sarcomas and suitable targeting strategies

Sarcoma	Overall TP53 mutation rate	Notable TP53/MDM2 alterations	Suitable TP53 targeting strategies
Osteosarcoma	~80%	1) *TP53* intron 1 rearrangements, 2) *MDM2/MDM4* gene amplification	1) MDM2/MDM4 antagonists to restore wild-type TP53 activity, 2) Targeting vulnerability imposed by TP53 deletion/mutations
Ewing sarcoma	~10%	1) Inhibition of wild type TP53 by EWS-FLI fusion protein	1) Restoring wild-type TP53 activity
Chondrosarcoma	~20%	1) *MDM2* gene amplification, 2) Alterations in the TP53 pathway in >50% of cases	1) Restoring wild-type TP53 activity by MDM2 antagonists, 2) Targeting vulnerabilities imposed byTP53 deletion/mutations
Rhabdomyosarcoma	< 15%	1) Reduced wild-type TP53 activity and expression by PAX-FHKR and PAX proteins, 2) TP53 deletions/mutations in E2 subtype of ERMS	1) Restoring wild-type TP53 activity, 2) Targeting vulnerabilities imposed by TP53 deletion/mutations, reactivating wild-type TP53 deletions/mutations in activity from mutant TP53, or depleting mutant TP53 (ERMS)
Leiomyosarcoma	~50%	1) TP53 missense mutations	1) Targeting vulnerabilities imposed by TP53 mutations, reactivating wild-type TP53 activity from mutant TP53, or depleting mutant TP53
Synovial sarcoma	~5%	1) Inhibition of wild-type TP53 by SS18-SSX and *MDM2/MDM4* gene amplification	1) Restoring wild-type TP53 activity by MDM2/MDM4 antagonists
Liposarcoma	10–20%	1) *MDM2* gene amplification, 2) TP53 missense mutations in pleomorphic LPS	1) Restoring wild-type TP53 activity by MDM2 antagonists, 2) Targeting vulnerabilities imposed by TP53 deletion/mutations, reactivating wild-type TP53 activity from mutant TP53, or depleting mutant TP53 (Pleomorphic LPS)
Angiosarcoma	< 50%	1) TP53 missense mutations, 2) MDM2 upregulation	1) Targeting vulnerabilities imposed by TP53 deletion/mutations, reactivating wild-type TP53 activity from mutant TP53, or depleting mutant TP53, 2) Restoring wild-type TP53 activity by MDM2 antagonists
Undifferentiated pleomorphic sarcoma	~30%	1) Retaining one wild-type TP53 allele in > 85% or p14ARF deletion/silencing, 2) TP53 missense mutations	1) Restoring wild-type TP53 activity by MDM2 antagonists, 2) Targeting vulnerabilities imposed by TP53 deletion/mutations, reactivating wild-type TP53 activity from mutant TP53, or depleting mutant TP53