

Relevance of Fusion Genes in Pediatric Cancers: Toward Precision Medicine

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Pediatric cancers differ from adult tumors, especially by their very low mutational rate. Therefore, their etiology could be explained in part by other oncogenic mechanisms such as chromosomal rearrangements, supporting the possible implication of fusion genes in the development of pediatric cancers. Fusion genes result from chromosomal rearrangements leading to the juxtaposition of two genes. Consequently, an abnormal activation of one or both genes is observed. The detection of fusion genes has generated great interest in basic cancer research and in the clinical setting, since these genes can lead to better comprehension of the biological mechanisms of tumorigenesis and they can also be used as therapeutic targets and diagnostic or prognostic biomarkers. In this review, we discuss the molecular mechanisms of fusion genes and their particularities in pediatric cancers, as well as their relevance in murine models and in the clinical setting. We also point out the difficulties encountered in the discovery of fusion genes. Finally, we discuss future perspectives and priorities for finding new innovative therapies in childhood cancer.

Pediatric cancers represent 1% of all cancers¹ and comprise cancer cases diagnosed in children younger than 14 years² and adolescents and young adults aged 15–19 years.³ Pediatric cancers include more than 60 different types of cancer derived from different tissues. More than 250,000 cases are diagnosed worldwide each year among children and adolescents younger than 20 years (<http://www.childhoodcancerinternational.org>). Although 80% of pediatric patients reach long-term remission after treatment, 20% die from recurrence of the malignancy; therefore, more therapeutic targets are needed to improve survival rates.¹ Moreover, current treatments are based on multimodal aggressive chemotherapies, and it is well known that antineoplastic treatments have long-term side effects that could impact patients' quality of life.⁴

Pediatric cancers differ from adult cancers. In fact, most pediatric cancers arise from embryonal rather than epithelial cells;⁵ consequently, the etiology of pediatric cancers is different. Zhang et al.⁶ previously reported that 8%–10% of pediatric cancers are associated with germline alterations leading to a cancer predisposition (Table 1). The involvement of environmental factors in childhood cancer etiology is still discussed, but there is clearly a lower implication of exogenous toxic effects in children than in adults (e.g., smoking, alcohol consumption, sun exposure, and overweight and sedentary lifestyle). Very few environmental factors have been related to pediatric cancers

to date: ionizing radiation and electromagnetic fields are some of the effects that remain a source of controversy, whereas some chemicals such as dioxin, trichloroethane, pesticides, solvents, metals, petroleum products, boron, and pollution have been associated with specific cancer types.^{7,8} Other factors such as epigenetics and immune system deregulation have also been identified as being responsible for tumorigenesis.^{9,10}

Vogelstein et al.¹¹ highlighted that pediatric cancers usually harbor fewer genetic mutations than adult cancers. They explained that the lower mutation rate found in pediatric cancers may be due to the embryonal origin of these cancers, which did not have enough time to renew. As a consequence, the tumors harbor very few mutations at the basal state.¹¹ These differences in mutation patterns could also be explained in part by the difference in cancer initiation, such as the implication of exogenous toxic effects.

A possible hypothesis of their etiology could be the presence of chromosome rearrangements, which is one of the first mechanisms described to be responsible for carcinogenesis.¹² These rearrangements can lead, in some cases, to fusion genes, which are the juxtaposition of two previously separate genes localized on the same (intra-chromosomal) or two different (inter-chromosomal) chromosomes. This event can activate proto-oncogenes or inactivate tumor suppressor genes. It has also been shown in adult cancers that some tumors with driving fusions have a much lower mutational burden compared to tumors without fusions.¹³ Thus, pediatric cancers appear to be the consequence of chromosomal rearrangements rather than mutation events.

We should keep in mind that a recurrence of alterations (mutations and copy-number alterations) of genes involved in embryogenesis¹⁴ and epigenetic regulation are also described in pediatric cancers⁹ but will not be discussed here.

In this review, we describe recent molecular knowledge on fusion genes in pediatric cancers. We then outline the potential therapeutic utility of fusion genes, their relevance in murine models, and we

Received 2 November 2016; accepted 24 January 2017;
<http://dx.doi.org/10.1016/j.omtn.2017.01.005>.

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Table 1. Syndromes of Genetic Predisposition Found among Children with Cancer and the Corresponding Affected Genes

Genetic Predisposition	Affected Gene ^a
Li-Fraumeni syndrome	TP53/CHK2/SNF5
Familial Wilms tumor	FTW1/2
Familial retinoblastoma	RB1
Fanconi anemia	FANCA
IgA deficiency	IGAD1
Blood syndrome	BLM
Wiskott-Aldrich syndrome	WAS
Ataxia telangiectasia	ATM
Familial adenomatous polyposis	APC
Hereditary non-polyposis colon cancer	MSH2/MLH1/PMS2
Tuberous sclerosis	TSC1/2
Beckwith-Wiedemann syndrome	Complex
Xeroderma pigmentosum	ERCC2

^aChildren's Health and the Environment, WHO Training Package for the Health Sector (World Health Organization, <http://www.who.int/ceh>).

describe recent findings in the clinical setting as well as challenges associated with their discovery.

History of Fusion Genes

Fusion genes were primarily discovered in leukemia and other hematological diseases. In 1962, Nowell¹⁵ described the first specific chromosomal rearrangement in chronic myeloid leukemia (CML). In 1973, Rowley¹⁶ highlighted the existence of a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9q; 22q), named the "Philadelphia chromosome." Twenty years later in the early 1980s, molecular studies of the translocation revealed a fusion between the 3' part of the *ABL1* gene in chromosome 9 and the 5' part of the *BCR1* gene in chromosome 22.¹⁷ This translocation resulting in BCR-ABL was one of the first specific alterations found in human neoplasm. Ten years later, a tyrosine kinase inhibitor (TKI) targeting BCR-ABL, imatinib mesylate (Glivec; Novartis), was discovered and approved by the Food and Drug Administration (FDA) in 2001 as a cancer treatment for CML.¹⁸ This TKI was one of the first targeted therapies used for cancer treatment and led to a major improvement of CML prognosis, with a remission in 80% of cases. After this time, it became clear that fusions can drive cancer development and are potential therapeutic targets in anti-cancer treatment in a very specific manner. Consequently to imatinib mesylate's history, fusion genes in hematological neoplasia and sarcoma were discovered¹⁹ and, more recently, high-resolution sequencing technologies enabled exploration of more fusion genes in other tumors.^{20,21} It should be noted that most of the studies and discoveries to date were made among adult patients; nevertheless, some pediatric cancers have been described to also harbor fusion genes that are involved in patients' diagnosis and/or targeted treatments (Table 2). However, more explorations are needed to not only identify new targets

but also to understand the function of fusion genes and their correlation to tumor initiation and progression.²² Indeed, of all of the multiple fusions identified by next-generation sequencing in each pediatric pathology (Table 2), only a few of them received attention for extensive functional studies, thus precluding the investigation and discovery of new druggable targets.¹⁹

Molecular Mechanisms Underlying Fusion Genes

Four different structural chromosomal rearrangements are observed in gene fusion: translocation, insertion, inversion, and deletion.²³ According to the coding or regulatory sequences affected, the physiological consequences are different.

Abnormal mRNA Expression

One of the consequences of fusion genes is the abnormal expression of one of the genes involved in the fusion (usually the 3' part of a gene). More precisely, the 5' part of a gene (gene 1), including the regulatory sequences and the 5' UTR part, is fused to the 3' part of a second gene (gene 2), which often only includes the coding sequence and the 3' UTR. The consequence of such fusion is that if gene 1 is constitutionally expressed or highly expressed and gene 2 is a proto-oncogene, then gene 2 will be upregulated by the promoter and regulatory sequences of gene 1. In this case, the result is a strong transcriptional activation of proto-oncogene 2, whose own regulatory elements are lost and is put under the complete control of the first gene.²² Fusion genes leading to abnormal protein expression were first described in adult tumors. Among the best-known examples are the fusions involving immunoglobulin genes and the *MYC* proto-oncogene, found in various hematological malignancies. Several translocations were found to be responsible for the fusion of *MYC* with other genes: t(8;14) led to IGH-*MYC* fusion, t(2;8) gave IGH-*MYC*, and t(8;22) resulted in IGL-*MYC*. *MYC* is an important transcription factor that binds to DNA in a non-specific manner to activate genes involved in cell cycle progression and inhibition of apoptosis. In these cases, the *MYC* gene is upregulated due to its 5' fusion with immunoglobulin regulatory sequences (promoter and enhancers).^{22,24} Indeed, the fusion results in constitutive activation of the *MYC* oncogene, increasing cell proliferation and tumorigenicity.

Another often-mentioned example is the fusion *TMPRSS2-ERG* found in 50% of prostate cancers, affecting chromosome 21.²⁰ This rearrangement puts *ERG* under the complete dependence of *TMPRSS2* regulatory sequences, upregulated by androgens present in the tissue. This leads to an overexpression of *ERG*.²⁰

Chimeric Oncoproteins

Chromosome rearrangements can also generate chimeric oncoproteins. In this case, both coding sequences of respective functional domains are conserved in the fusion. Its translation results in a protein with functional domains derived from both of the fused genes. Most of the chimeric oncoproteins characterized act as aberrant transcription factors, with a strong activation of unspecific target genes resulting in cell transformation.²⁵

**Table 2. Main Fusions Identified in Pediatric Cancers**

Pathology (Total No. of Recurrent Fusions)	Fusion Transcript (Most Frequent and Recurrent) ^a	Chromosome Abnormality	Diagnosis	Reference	Prognosis
Leukemia (113)					
	NUP98-NSD1	t(5;11)	acute monoblastic, myeloblastic, and myelomonocytic leukemia	90	poor
	SET-NUP214	del(9)	acute monoblastic, myeloblastic, and myelomonocytic leukemia; T-ALL	91	poor
	IgH-MYC/CEBPD/BCL2/CRLF2/ID4	t(8;14), t(8;14), t(14;18), t(X;14), t(6;14)	ALL	92-96	poor
	MYC rearranged	t(8;14), t(2;8), t(8;22)	various hematologic malignancies	97-99	poor
	TCRA/B/D rearranged		ALL	100-102	no prognostic value
	KMT2A-AFF1	t(1;11)	ALL, biphenotypic leukemia, AML	103	poor
	E2A-PBX1	t(1;19)	B-ALL	104,105	poor
	MLL-AF4	t(4;11)	B-ALL	106	poor
	PAX5-ETV6	t(9;12)	B-ALL	107	good
	ETV6-RUNX1	t(12;21)	B-ALL, AML, acute myeloblastic leukemia	108	good
	CALM-AF10	t(10;11)	T-ALL	109	poor
	TEL-AML1/RUNX1	t(8;12), t(12;21)	T-ALL, B-ALL	108,110	good
	AML1-ETO	t(8;21)	AML	111	good
	RPN1-PRDM16/MECOM	t(1;3), inv(3)	AML	112,113	poor
	NPM-MLF1	t(3;5)	AML, acute erythroleukemia	114	poor
	DEK-CAN	t(6;9)	AML, acute myeloblastic leukemia	115	poor
	ETV6-MDS-1/CHIC2	t(3;12), t(4;12)	AML, acute myeloblastic leukemia	116,117	poor
	RUNX1-CBFA2T3	t(16;21)	AML, acute myeloblastic leukemia, acute myelomonocytic leukemia	118	good
	CBFB-MYH11	inv(16)	AML, acute monoblastic leukemia, acute myelocytic leukemia, CML	119	good
	PML-RARA	t(15;17)	AML, biphenotypic leukemia, acute promyelocytic leukemia, CML	120,121	good
	USP16-RUNX1	del(21)	CML	122	poor
	BCR-ABL	t(9;22)	CML; pediatric ALL; undifferentiated and biphenotypic leukemia	123,124	good
	IgH-MYC	t(8;14)	various hematologic malignancies	125	good
	KMT2A-ELL/MLLT1	t(11;19)	various hematologic malignancies	126	poor
	MLL rearranged		ALL, biphenotypic leukemia, AML	127	poor
	ZMYM2-FGFR1	t(8;13)	various hematologic malignancies	128	poor
Lymphomas (41)					
	IGH-BCL10/BCL11A/FOXP1	t(1;14), t(2;14), t(3;14)	extranodal marginal zone B cell lymphoma, CLL, diffuse large B cell lymphoma, MALT lymphoma	129-131	poor for t(1;14); no information available for t(2;14) and t(3;14)
	IGK-BCL2/KDSR/CDK6	t(2;18), t(2;7)	follicular lymphoma, splenic marginal zone B cell lymphoma	132,133	no information available
	NPM1-ALK	t(2;5)	mature B cell neoplasms, mature T cell neoplasms	52	good
	IGL-BCL2	t(18;22)	mature B cell neoplasms, CLL	134	poor
	IGH/IGK-MYC	t(2;8), t(8;14)	various B cell neoplasms	135	poor
	IGH/HSP90AA1/IGL-BCL6	t(3;14), t(3;22)	various lymphoma types	136,137	good
	IGH-CCND1/BCL2/CEBPA	t(11;14), t(14;18), t(14;19)	various lymphoma types	138	no prognostic value

(Continued on next page)



Table 2. Continued

Pathology (Total No. of Recurrent Fusions)	Fusion Transcript (Most Frequent and Recurrent) ^a	Chromosome Abnormality	Diagnosis	Reference	Prognosis
	PAX5-IGH	t(9;14)	various lymphoma types	139	no prognostic value
	IGK/IGH-BCL6/CCND1	t(2;11), t(2;3)	various lymphoma types	136,140	no prognostic value
	IGH-TRA	inv(14)	various T cell neoplasms	141	no information available
Brain Tumors (4)					
	GOPC-ROS1	del(6)	astrocytoma grade III-IV	142	no prognostic value
	FGFR1/3-TACC1/3	del(4)	glioblastoma	58	no prognostic value
	IER3IP1-HDHD2	del(18)	meningioma	143	no prognostic value
	SLC44A1-PRKCA	t(9;17)	neuroglial neoplasm	144	no prognostic value
	KIAA1549-BRAF	dup(7)	pilocytic astrocytoma, astrocytoma grade II, pediatric oligodendroglioma	50	good
Kidney Tumors (4)					
	MALAT1-TFEB	t(6;11)	adenocarcinoma	145	good
	SFPQ/CLTC/ASPSCR1-TFE3	t(X;1), t(X;17)	adenocarcinoma, renal cell carcinoma	146-148	poor
Bone and Soft-Tissue Tumors (37)					
	PAX3/7-FKHR	t(2;13), t(1;13)	alveolar rhabdomyosarcoma	28	poor
	ASPSCR1-TFE3	t(X;17)	alveolar soft-part sarcoma	46	poor
	THRAP3-USP6	t(1;17)	aneurysmal bone cyst	149	no prognostic value
	EWSR1-ATF1	t(12;22)	CCS	150	poor (unconfirmed data)
	EWSR1-WT1	t(11;22)	desmoplastic round cell tumor	151	poor
	EWS-WT1/CHN	t(11;22), t(12;22), t(9;22)	DSCRT; CCS of tendons and aponeuroses; chondrosarcoma	152	poor
	WWTR1-CAMTA1	t(1;3)	epithelioid hemangioendothelioma	153	no bad prognosis
	EWSR1-FLI1/ERG	t(11;22)	Ewing's sarcoma	154,155	no prognostic value
	FUS-ERG	t(16;21)	Ewing's sarcoma	156	poor
	ETV6-NTRK3	t(12;15)	infantile fibrosarcoma	157	good
	FUS-DDIT3	t(12;16)	liposarcoma	158	poor
	VGLL2 rearranged		scRMS; SRMS	159	no prognostic value
	AHRR-NCOA2	t(5;8)	soft-tissue tumor, special type	160	no prognostic value
	MLL4-GPS2	t(17;19)	spindle cell sarcoma	161	poor
	SS18-SSX1	t(X;18)	synovial sarcoma	162	poor
	CIC-DUX4	t(4;19)	undifferentiated round cell sarcoma	163	poor
Liver Tumors (1)					
	DNAJB1-PRKACA	t(19;19)	fibrolamellar hepatocellular carcinoma	143	poor

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CCS, clear cell sarcoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DSCRT, desmoplastic small round cell tumor; MALT, mucosa-associated lymphoid tissue; scRMS, sclerosing rhabdomyosarcoma; SRMS, spindle cell rhabdomyosarcoma; T-ALL, T-lineage acute lymphoblastic leukemia.

^aMost of the fusions are listed in the Mitelman database (<http://cgap.nci.nih.gov/Chromosomes/RecurrentAberrations>).

To date, several chimeric oncoproteins have been identified in blood malignancies but very few are described in carcinomas. One well-known example is the fusion RET-PTC found in papillary thyroid carcinomas, where RET (a gene involved in the regulation of cell survival, growth, differentiation, and migration) is constitutionally activated.²⁶ Concerning pediatric cancers, EWS-FLI1 fusion is found in 85% of Ewing's sarcoma, which results in a chimeric oncoprotein

between the amino terminus of EWS and the carboxy terminus of FLI, giving aberrant transcriptional activity.²⁷ In rhabdomyosarcomas, PAX3/7-FKHR fusions are found in 80%–85% of alveolar rhabdomyosarcomas and contain the PAX3/PAX7 DNA binding domain and the FKHR transcriptional activation domain. Therefore, PAX target genes are highly transcriptionally activated.²⁸ Occasionally, cryptic fusion partners occur in these fusion-driven tumors.



Gene Function Truncation

More recently, studies have shown a third impact of fusion genes resulting in the entire cutout of gene domains. The truncated gene is generally a tumor suppressor gene and is therefore inactivated by the truncation, leading to cell transformation. Inactivation of the tumor suppressor gene can occur through different mechanisms: the fusion can either act as the second hit (e.g., *CDKN2A* or *NF1* genes) or lead to a dominant effect on the wild-type protein (e.g., *PAX5* fusions) or even provoke haploinsufficiency of the disrupted protein (e.g., *RUNX1* fusions).^{29–32}

Another category that does not involve chromosomal rearrangements is the occurrence of read-through transcripts. This type of modification results in transcription-induced gene fusions (TIGFs) that are not induced by a modification in the DNA sequence but are a consequence of alternative splicing. Thus, the genes stay located far apart in the same chromosome or on different chromosomes, but mRNA fusion transcripts are formed as a consequence of *cis*-TIGFs or *trans*-TIGFs.³³ Most TIGFs probably represent random *in vivo* events with no impact on the cell's functions and some are also artifacts of deep sequencing. Nevertheless, some *cis*-TIGFs have been associated with specific organ localization, such as *SLC45A3-ELK4* and *MSMB-NCOA4* detected in normal and neoplastic prostate tissue^{33,34} and *SCNN1A-TNFRSF1A* and *CTSD-IFITM10* identified in normal and neoplastic breast tissue.³⁵

Relevance of Fusion Genes in Pediatric Cancers

Leukemia is the most common type of pediatric cancer (around 30% of total cases) and most of the recurrent identified fusions were found in this pathology, as detailed in Table 2.

Concerning pediatric solid tumors, several fusions have been described and can be grouped into two categories. The first category concerns fusions that were considered until now only as diagnostic markers, and the second category includes fusions providing new therapeutic targets.

In the first category, the most described example is Ewing's sarcoma. Ewing's sarcoma is characterized by a reciprocal translocation t(11;22) (q24;q12) leading to the fusion between *EWS* and *FLII* genes.³⁶ The corresponding chimeric protein acts as an aberrant transcription factor. Different translocations have been found in patients suffering from Ewing's sarcoma involving TET/ETS partners and the list is still growing.³⁷ Another example of fusions belonging to the first category are *PAX3/7-FKHR* fusions found in alveolar rhabdomyosarcomas due to the translocation t(2;13)(q35;q14) or, less commonly, t(1;13)(p36;p14), leading to *PAX3-FOXO1* (55%–70%) or *PAX7-FOXO1* (10%–22%) fusion genes, respectively.³⁸ The resulting fusion proteins harbor high transcriptional activity due to the juxtaposition of the PAX protein DNA binding domain and the FKHR activation domain.²⁸ In another example, Honeyman et al.³⁹ identified the *DNAJB1-PRKCA* fusion in 100% of patients with fibrolamellar hepatocellular carcinoma (FLHCC), a rare subset of pediatric hepatocarcinoma. Although its function is not yet elucidated, this fusion provides

a new and unique diagnostic biomarker for patients with FLHCC. Another fusion in this category is *C11orf95-RELA*, which was identified recently in ~70% of supratentorial ependymomas.⁴⁰ *RELA* is a gene encoding for the RelA p65 subunit of the nuclear factor κ B (NF- κ B) complex. When fused, *RELA* loses its upstream regulator sequences (5' UTR) but the coding sequence is conserved. The function of *C11orf95* is still unknown. *C11orf95* has been found fused with different partners, suggesting a possible role of its zinc-finger domains.⁴¹ The *C11orf95-RELA* fusion seems to arise through chromothripsis and leads to a constitutive activation of NF- κ B signaling.⁴⁰ Ependymomas are classified according to their location in the supratentorial, infratentorial region of the brain or the spinal cord.⁴² It is important to highlight that *C11orf95-RELA* is detected only in supratentorial ependymomas,⁴⁰ thus providing a new molecular diagnostic biomarker and possible new therapeutic target. Finally, the reciprocal translocation t(X;18; p11,q11), which is found in all cases of synovial sarcoma, leads to fusions involving the *SYT* gene (also named *SSX18*; namely, *SYT-SSX1* or *SYT-SSX2* fusions).^{43,44} The resulting chimeric oncoproteins contain the activation domain of *SYT* and the regulatory domain of *SSX1/2* genes. The newly protein appears to be a transcriptional co-regulator via protein-protein interactions and it has been described to be able to regulate SWI-SNF chromatin remodeling complexes.⁴⁵ This fusion is not found in any other tumor types which makes *SYT-SSX* an important diagnostic biomarker, and also relevant for prognostic purposes.⁴⁴

The second category includes fusions with therapeutic outcomes, such as *ASPSCR1-TFE3*,⁴⁶ *FGFR1-TACC1* and *FGFR3-TACC3*,^{47–49} *KIAA1549-BRAF*,^{50,51} *NPM-ALK*,^{52,53} and *NTRK* fusions (R. Nagasubramanian et al., 2016, J. Clin. Oncol., abstract).⁵⁴

ASPSCR1-TFE3 [t(X;17)(p11.2;q25)] and, more generally, *TFE3* fusions are found in more than 95% of patients with alveolar soft-part sarcoma and in a subset of patients with renal cell carcinoma.^{46,55} This oncoprotein acts also as an aberrant transactivator, stronger than the native *TFE3* protein, and has a nuclear localization. *MET* is among the genes strongly transactivated by *ASPSCR1-TFE3* protein.⁵⁶ This may lead to sensitivity to *MET* inhibitors *in vitro*,⁵⁷ which is currently being explored in a clinical trial with crizotinib (NCT01524926).

The *FGFR1-TACC1* and *FGFR3-TACC3* fusions were first identified in glioblastoma multiforme (GBM; also known as grade IV astrocytoma). They have since been found in various cancer types, such as bladder cancer, lung adenocarcinoma, head and neck cancer, nasopharyngeal carcinoma, and esophageal squamous cell carcinoma.^{47–49} The rearrangement that fuses the tyrosine kinase domains of fibroblast growth factor receptor (FGFR) to the transforming acidic coiled-coil (TACC) harbors a constitutive kinase activity. Interestingly, the inhibition of FGFR kinase by pharmacological agents counteracts the oncogenicity of the fusion *in vitro* and *in vivo* in glioblastoma.⁵⁸ Therefore, the discovery of *FGFR-TACC* fusions is of great interest and the role of FGFR inhibitors is currently being explored in clinical trials with multiple FGFR kinase inhibitors, such as BGJ398 and AZD4547 (NCT01975701 and NCT02824133).



KIAA1549-BRAF also belongs to the second category of fusions and is found in 65%–75% of sporadic pilocytic astrocytomas^{50,51} but is also detected in other pediatric brain tumors.^{59,60} Importantly, KIAA1549-BRAF leads to an over-activation of mitogen-activated protein kinase (MAPK) signaling,⁵⁰ resulting in an oncogenic addiction to this pathway.⁶⁰ The first experiments showing its therapeutic potential involved targeting cells transfected with the KIAA1549-BRAF fusion using the BRAF inhibitor vemurafenib (PLX4032), a selective BRAF^{V600E} inhibitor,⁶¹ as *BRAF* mutations also result in MAPK signaling activation. Although the anti-tumor effects of vemurafenib in *BRAF* (V600E)-mutated cells are well demonstrated, the treatment of cell lines expressing KIAA1549-BRAF with PLX4032 resulted in activation of the MAPK pathway, leading to increased cell proliferation in vitro and tumor growth in vivo.^{62,63} The mechanism underlying this paradoxical activation was explained by Poulikos et al.,⁶⁴ who described that PLX4032 is able to bind on RAF isoforms and induce interaction with RAS-GTP, which leads to the pathway activation. In *BRAF* (V600E)-mutated tumors, the level of RAS may not be sufficient to transactivate wild-type BRAF. This RAS activation is notably discussed as a mechanism responsible for the development of squamous cell carcinoma in normal skin tissue after BRAF^{V600E}-inhibiting treatment.⁶⁵

Second-generation BRAF inhibitors such as PLX PB-3 are currently being developed, which lead to inhibition of KIAA15-49-BRAF with decreased proliferation and tumorigenicity and may not induce the paradoxical MAPK activation. As a result, they could be more efficient for patients carrying KIAA1549-BRAF fusions (S.-S. Lang et al., 2012, *Neurosurgery*, abstract).

Because MEK is a downstream effector of RAF in the MAPK signaling pathway, KIAA1549-BRAF-positive cells may consequently be sensitive to MEK inhibitors (e.g., selumetinib and trametinib) that are able to block the pathway downstream of RAF and thus independently from the RAF alteration underlying the pathway activation. In a pre-clinical study, selumetinib (AZD6244) showed evidence of anti-tumor activity in a juvenile pilocytic astrocytoma xenograft model.⁶⁶ This is being currently explored in patients carrying KIAA1549-BRAF fusions (NCT01089101 and NCT02124772). Taken together, these findings demonstrate the importance of testing the suitability of a drug in a relevant setting. Their effectiveness is dependent on the cellular and the molecular context of the targeted tumors, and the “general” use of kinase inhibitors may be considered with caution.

Another example is the fusion NPM-ALK, caused by the translocation t(2;5)(p23;q35),⁵² which fuses the dimerization domain of NPM with the tyrosine kinase domain of ALK. ALK is a tyrosine kinase receptor; therefore, the fusion gives a chimeric oncoprotein with a constitutively activated kinase.⁵² The translocation is found in 30%–50% of advanced-stage anaplastic large cell lymphoma cases in adults;⁶⁷ 90% of anaplastic large cell lymphoma cases among children are ALK positive.⁶⁸ This fusion can be targeted via ALK inhibitors such as crizotinib or ceritinib, which have been registered for patients carrying non-small cell lung cancer (NSCLC) with ALK translocations

and gave promising results with high rates of response.⁶⁹ Promising results have also been reported in pediatric patients with anaplastic large cell lymphoma⁵³ (NCT00939770 and NCT01742286) (B. Georger et al., 2015, *J. Clin. Oncol.*, abstract).

Finally, and more recently, NTRK fusions involving either NTRK1, 2, or 3 located on chromosome 1 q21-q22 have raised great interest in the clinical setting, as they are found in different neoplasms in adults and children. A total of 22 different 5' partners were found to be fused with *NTRK* genes.⁵⁴ *NTRK* codes for the family of tropomyosin receptors, which, once fused, harbor a constitutively activated kinase function. This leads to cancer progression by activating different oncogenic pathways such as the MAPK or AKT pathways.⁷⁰ Among childhood neoplasms harboring NTRK fusions are found soft-tissue sarcoma, congenital infantile fibrosarcoma, glioblastoma, low-grade glioma, pilocytic astrocytoma, congenital mesoblastic nephroma, acute myeloid leukemia, and various other tumor types. Therefore, for these patients, targeting NTRK is of great clinical interest and a novel inhibitor (LOXO-101) is currently being evaluated in the clinical setting (NCT02637687) (R. Nagasubramanian et al., 2016, *J. Clin. Oncol.*, abstract).

Taken together, all of these studies emphasize the notion that fusions can be of great clinical interest not only as new therapeutic targets but also as biomarkers. Indeed, fusions specific to a cancerous disease are ideal for diagnostic purposes and for subgroup classifications; therefore, they can also be used as prognostic biomarkers. Some fusions, such as BCR-ABL in CML⁷¹ or NPM-ALK in ALCL,⁷² are even used to monitor the tumor load and treatment response (as minimal residual disease markers). Hence, even individual or non-recurrent fusions could have clinical value in an individual patient.⁷³ It should be kept in mind that current treatments are at their limits of toxicity and efficacy. Accordingly, specific treatments are needed to treat non-responsive patients and also to improve the quality of life of cured patients.

Issues Facing Discovery of Fusion Genes in Childhood Cancers

Analyses of fusions have a strong interest in the field of childhood cancers. The discovery step is still in its infancy for these malignancies, probably because studies addressing the discovery of fusion genes encounter important difficulties. The first difficulty comes from the biopsy and the way in which the DNA or RNA was extracted. The purity and quantity of the extracted material will impact the quality of further analysis. Most of the studies involved in fusion discovery use next-generation sequencing (NGS) techniques and new bioinformatics analysis methods. It is necessary to combine the strengths of both sequencing technologies and computational strategies, together with the discrimination of events tightly correlated with cancer development.⁷⁴ One difficulty encountered in gene fusion detection is the ability of discrimination between existent new discoveries and computer analysis artifacts. However, too stringent selection parameters applied to avoid false positives can preclude the detection of effective oncogenic fusions. Being able to cut out the artifacts from the analysis is one of the biggest challenges, since current techniques



of deep sequencing are more sensitive than before and allow the detection of rare events; however, the risk of false positives is still present.⁷⁵ It is also important to note that each bioinformatics tool used for fusion detection and its subsequent algorithms differ in terms of sensitivity and specificity, depending on the different filters and criteria applied. Therefore, combining several tools and even different types of analysis could be highly relevant.^{19,76}

Moreover, cancer and carcinomas especially often have highly rearranged genomes, and many of the gene fusions that are detected can represent “passenger” events that are caused by chromosomal instability.^{13,77} These passenger rearrangements are secondary events present in the tumor, which are different from the primary oncogenic event responsible for the development of the disease. They are particularly frequent in relapsing patients, where treatments by radiotherapy and ionization can lead to “passenger fusions” not involved in oncogenic processes.^{74,78} Among these patients, it is more difficult to distinguish the fusion gene capable of an oncogenic effect from the passenger fusions that can be constitutively present in normal and cancerous cells.

Regarding pediatric cancers, the emergence of NGS and new informatics tools to detect fusions have aimed to detect recurrent fusions with expected targetable domains, such as fusions with tyrosine kinase activities. However, considering the rarity of these types of neoplasia, the probability of finding rearranged genes is much lower than for adult cohorts.⁷⁸ In addition, the major difficulty is linked to the intratumoral heterogeneity, where subclonal fusion events can be weakly detectable, making their identification more complex.^{19,74}

Pertinence of Fusion-Based Murine Models in Childhood Cancers

Most *in vivo* studies have assessed the tumorigenic potential of a fusion gene in xenografted tumors on immunocompromised animals. Despite the validity of this experimental approach, some questions (e.g., the role of a fusion gene in early stages of the development of a pediatric cancer) remain difficult to answer using xenografted tumors. Therefore, several mouse models were developed in order to better understand pediatric tumors' oncogenesis. These models helped to demonstrate the importance of (1) the cell of origin, (2) the differentiation stage, and (3) a second hit in complement to the first one (fusion oncogene) necessary for disease development. With the first desire to provide new models to study pediatric cancers, four striking examples of Ewing's sarcoma, myxoid liposarcoma, alveolar rhabdomyosarcoma, and synovial sarcoma models have provided major information on the tumorigenesis mechanisms of fusion-harboring pediatric cancers.

Lin et al.⁷⁹ explored the role of EWS/FLI1 in Ewing's sarcoma and showed that its specific expression in mesenchymal cells of the embryonic limb buds impaired the development of mouse limbs but did not induce tumors. This suggested that the cell of origin may not be a mesenchymal stem cell. Interestingly, when *TP53* was simulta-

neously deleted, EWS-FLI1 promoted tumor formation.⁷⁸ Therefore, the presence of additional mutations notably in *TP53* seems to be required for the transformation process by EWS-FLI1 in Ewing's sarcoma.

In myxoid liposarcoma, previous studies demonstrated that the introduction of the *FUS-CHOP* transgene into the mouse genome led to the development of liposarcomas,^{80,81} but its specific expression in differentiated aP2-expressing adipocytes did not result in tumor formation,⁸² suggesting the importance of the “stage of differentiation” in driving the tumors.

In alveolar rhabdomyosarcoma, the expression of PAX3-FKHR fusion in mouse primary mesenchymal stem cells did not lead to tumor formation,⁸³ while its expression in differentiated muscle cells at a late stage of embryogenesis induced tumors but at a low frequency. The addition of *TP53* or *INK4A/ARF* disruption increased the frequency of alveolar rhabdomyosarcoma (RMS), emphasizing the fact that additional mutations to PAX3-FKHR fusion might be necessary to generate alveolar RMS.⁸⁴

Finally, in synovial sarcoma, tumors were observed in mice models only when the fusion gene *SYT-SSX2* was expressed in immature myoblasts.⁸⁵ This observation again highlights the importance of both the cell of origin and the differentiation stage factors in fusion-driven tumorigenesis.

What Is Next?

Despite all of the emerging challenges related to fusion detection, identifying new fusions remains one of the most important priorities of research in pediatric cancers where new therapeutic targets are needed. The difficulty in discovering new fusion genes is minimal compared to the vast clinical consequences in terms of prognosis, diagnosis, and new therapeutic opportunities and to the importance of understanding the molecular mechanisms underlying a fusion gene.

Characterization of genomic alterations found in pediatric cancers would clarify their relevance, help to classify patients into subgroups, and aid in the discovery of new therapeutic, prognostic, diagnostic, or predictive biomarkers. Moreover, functional studies are strongly needed to better understand the relevance of the biological pathways involving fusion genes in the development of pediatric malignancies. Indeed, well-characterized fusion genes could reveal new targets in pediatric cancers for which there are currently no specific therapies available.⁸⁶

It is well known that only a small number of relevant molecular subsets have been characterized (e.g., the four subtypes of medulloblastoma); therefore, particular attention should be given to the rare histological subgroups.⁸⁷ These subsets could be of strong interest for diagnosis determination, understanding new mechanisms of tumor progression or resistance, and could help to bring forward new unexpected therapeutic targets.



With small histological subgroups, high priority should be given to the future study of genomic alterations at relapse. In fact, several studies have reported the importance of analyzing tissues at relapse,^{88,89} and clinical trials such as MAPPYACTS (molecular profiling for pediatric and young adult cancer treatment stratification) conducted in our institute will contribute to this investigation (NCT02613962). The study of patients' genomic patterns at relapse could lead to better knowledge of cancer-driving and resistance mechanisms but could also allow better classification of patients.

Moreover, knowing that pediatric cancers are rare diseases that differ from one patient to another, an isolated fusion found only in a single patient should not be discarded and "case-by-case" studies as well as genome-based clinical trials are required. To counteract the hurdles due to the rarity of pediatric cancers, data sharing of high-throughput sequencing analysis would offer a personalized-medicine approach based on targeting junction oncogenes.⁸⁶ More specifically, new therapeutic technologies are emerging regarding the targeting of junction oncogenes, such as the use of small interfering RNA (siRNA). siRNAs allow inhibition of gene expression at the mRNA level, avoiding their translation. This type of strategy offers promising opportunities for targeted therapy, since it specifically targets fusion transcripts only expressed in tumor cells, without affecting other genes. Our laboratory showed previously that the inhibition of fusion oncogenes responsible for tumor progression of thyroid cancer (RET/PTC) or prostate cancer (TMPRSS2-ERG) by the injection of vectorized siRNAs led to a decrease in tumor growth.⁷³⁻⁷⁷

An increased number of new fusion genes are expected to be discovered, owing to worldwide projects (The Cancer Genome Atlas [TCGA], <https://tcga-data.nci.nih.gov/docs/publications/tcga/>) and to data-sharing platforms (e.g., the International Cancer Genome Consortium [ICGC] platform, <https://icgc.org/>; and the European Genome-phenome Archive [EGA], <https://ega.crg.eu/>).¹⁹ This will provide new opportunities of treatments, such as therapies based on siRNA technology for children carrying neoplasia.

ACKNOWLEDGMENTS

This study is supported by funding from "the Fondation ARC pour la recherche sur le cancer" within the Joint Translational Call 2014 "Translational research on human tumour heterogeneity to understand and overcome recurrence and resistance to therapy" TRANSCAN-2 JTC2014, ERA-NET ("Targeting Of Resistance in PEDIatric Oncology" [TORPEDO]).

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