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Molecular drug targets in myeloproliferative neoplasms: mutant ABL1, JAK2, MPL, KIT, PDGFRA, PDGFRB and FGFR1

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Abstract

Therapeutically validated oncoproteins in myeloproliferative neoplasms (MPN) include BCR-ABL1 and rearranged PDGFR proteins. The latter are products of intra- (*e.g.* FIP1L1-PDGFRA) or inter-chromosomal (*e.g.* ETV6-PDGFRB) gene fusions. BCR-ABL1 is associated with chronic myelogenous leukaemia (CML) and mutant PDGFR with an MPN phenotype characterized by eosinophilia and in addition, in case of FIP1L1-PDGFRA, bone marrow mastocytosis. These genotype–phenotype associations have been effectively exploited in the development of highly accurate diagnostic assays and molecular targeted therapy. It is hoped that the same will happen in other MPN with specific genetic alterations: polycythemia vera (*JAK2* V617F and other *JAK2* mutations), essential thrombocythemia (*JAK2*V617F and *MPL*515 mutations), primary myelofibrosis (*JAK2* V617F and *MPL*515 mutations), systemic mastocytosis (*KIT*D816V and other *KIT* mutations) and stem cell leukaemia/lymphoma (*ZNF198-FGFR1* and other *FGFR1* fusion genes). The current review discusses the above-listed mutant molecules in the context of their value as drug targets.

Keywords: V617F • polycythemia • thrombocythemia • myelofibrosis • eosinophilia • mastocytosis

Introduction

Myeloid malignancies are stem cell-derived clonal disorders and include three broad clinicopathologic categories: acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN). Such classification is however operational and not precise; for example, some patients present with histologic features that are reminiscent of both MPN and MDS and are assigned the diagnosis of 'MDS/MPN' overlap [1]. The history of MPN dates back to 1951 when William Dameshek coined the term 'myeloproliferative disorders (MPD)' as a clinicopathologic category that included chronic myelogenous leukaemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) [2, 3]. These 'classic' MPD are

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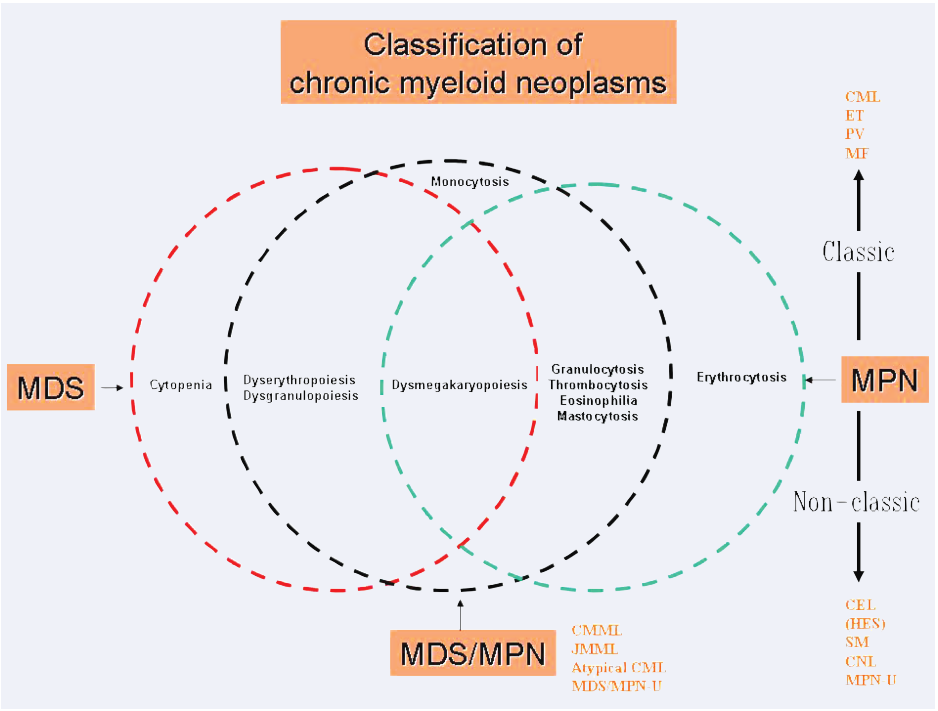

Fig. 1 Histological hallmarks that distinguish myelodysplastic syndrome (MDS) from myeloproliferative neoplasm (MPN) and MDS/MPN. CML, chronic myelogenous leukaemia; PV, polycythemia vera; ET, essential thrombocythemia; MF, primary myelofibrosis; CEL, chronic eosinophilic leukaemia; HES, hypereosinophilic syndrome; SM, systemic mastocytosis; CNL, chronic neutrophilic leukaemia; MPN-U, MPN, unclassifiable; CMML, chronic myelomonocytic leukaemia; JMML, juvenile myelomonocytic leukaemia; MDS/MPN-U, MDS/MPN, unclassifiable.

now included in an expanded category of 'MPN', according to the World Health Organization (WHO) classification system, which also includes systemic mastocytosis (SM) and chronic neutrophilic (CNL) and eosinophilic (CEL) leukaemias (Table 1) [4]. Current classification of chronic myeloid neoplasms is semi-molecular although primarily based on myeloid cell morphology and presence or absence of effective haematopoiesis; Fig. 1 illustrates the histological hallmarks that distinguish MDS, MPN and MDS/MPN.

Pathogenetic breakthroughs in MPN began in 1960 when the Philadelphia (Ph) chromosome was described in CML [5, 6]. This historic discovery later (1980–1990) led to the identification of *BCR-ABL1* as the disease-causing mutation in CML [7–9]. In 1993 and 1994, stem cell factor receptor (*KIT*) and platelet-derived growth factor receptor-β (*PDGFRB*) mutations were associated with SM (*KIT* D816V and *KIT* V560G) [10] and an MPN phenotype characterized by eosinophilia and monocytosis (*ETV6-PDGFRB*) [11]. In 1998, a fibroblast growth factor 1 (*FGFR1*) mutation was described in stem cell leukaemia/lymphoma (SCLL; *ZNF198-FGFR1)*. In 2003, *FIP1L1-PDGFRA*, a karyotypically occult platelet-derived growth factor receptor-α (*PDGFRA)* mutation, was described in association with an MPN phenotype characterized by eosinophilia and mastocytosis [12]. The molecular pathogenesis of *BCR-ABL1*-negative classic MPN remained elusive until early 2005 [13–16] when several groups reported a Janus kinase 2 (*JAK2)* gain-of-function (GOF) mutation (*JAK2*V617F) in PV, ET and PMF. In 2006, a GOF thrombopoietin receptor (*MPL)* mutation (*MPL*W515L) was reported in *JAK2*V617F-negative PMF [17]. In 2007, other *JAK2* mutations (exon 12 mutations) in *JAK2*V617F-negative patients with PV were described [18]. Additional *MPL* and *JAK2* exon 12 mutations have since been added to the list [19–21].

The above-listed revelations in putative disease-causing or disease-promoting genetic changes have ignited much interest in the development of molecular targeted therapy in MPN. Proof-of-principle in this regard has already been accomplished with the use of imatinib mesylate (IM) in CML [22] and *PDGFR*-rearranged MPN [12, 23]. On the other hand, therapeutic targeting of *KIT*D816V or mutant *FGFR1* has not been as successful whereas phase I/II clinical trials evaluating anti-JAK2 drugs are currently ongoing. In this review, I will provide a clinically relevant overview of mutant molecules of interest in adult MPN and discuss the current state of affairs in regards to targeted therapy.

BCR-ABL1

The stage for the discovery of *BCR-ABL1* in CML was set in 1960 when Peter Nowell and David Hungerford described the Ph chromosome [5]. In 1967, Philip Fialkow and colleagues applied polymorphisms in the X-linked glucose-6-phosphate dehydrogenase (G-6-PD) locus to establish CML as a stem cell-derived clonal disorder [24]. In 1972, Janet Rowley clarified the constitution of the Ph chromosome as a reciprocal translocation between chromosomes 9 and 22; t(9;22)(q34;q11) [25].

In 1982, the human homologue (*ABL1;* 225 kb total gene size) of v-*abl* was mapped to chromosome 9 [26] and shown to be involved in the Ph translocation [27]. In 1984, the chromosome

22 breakpoint was mapped to a 5.8 kb area and named the 'breakpoint cluster region (bcr)', which is part of the *BCR* gene (135 kb total gene size) [28, 29]. In 1990, retroviral infection of haematopoietic stem cells with *BCR-ABL* was shown to induce CML-like disease in mice [7–9].

ABL1

ABL1 is a cytoplasmic protein tyrosine kinase (PTK) that plays a role in non-erythroid myelopoiesis [30], cytoskeletal rearrangement and inhibition of cell migration [31]. Wild-type ABL1 exists in two isoforms that can localize to both the cytoplasm and nucleus, influencing cell proliferation/survival and apoptosis [32–34]. ABL1 contains both an SH2 and an SH3 (autoregulatory) domain in addition to the catalytic kinase domain and undergoes a treatment-relevant conformational change when activated by phosphorylation of the activation loop tyrosine residues [35].

BCR-ABL1

The chromosome 9 breakpoints in CML involve a large, ~200 kb region within the *ABL1* alternative first exons (1a and 1b), but invariably result in fusion genes that incorporate *ABL1* exon 2 [36]. In contrast, the breakpoints on chromosome 22 are clustered within three much smaller regions of the *BCR* gene [37]; the major breakpoint cluster region (M-bcr; a 5.8 kb region spanning exons 12–16 and resulting in a p210 fusion protein) [28], the minor breakpoint cluster region (m-bcr; upstream of M-bcr and involving the first intron and resulting in a p190 fusion protein) [38, 39] and μ-bcr involving intron 19 that is downstream of M-bcr and resulting in a p230 fusion protein [40]. By far the most frequent chromosome 22 breakpoint in CML is M-bcr and the other two, in the context of CML, are extremely rare. There are usually two junction variants of M-bcr; b2a2 and b3a2, without any documented clinical relevance [41].

BCR-ABL1 gets transcribed as a chimeric mRNA (8.5-kb) as opposed to the normal ABL1 mRNA (a 6- or 7-kb) [42] and subsequently translated to an activated BCR-ABL1 gene product (most commonly 210-kD) instead of the normal *ABL1* gene product (145-kD) [43]. BCR-ABL1 localizes to the cytoskeleton and displays an up-regulated tyrosine kinase activity [44] that leads to the recruitment of downstream effectors of cell proliferation and cell survival and consequently leukaemogenesis, as has been demonstrated in cell lines, primary cells and mouse transplant or transgenic models [7, 8, 45–47]. BCR-ABL1 signal transduction involves several adapter molecules (*e.g.* GRB2, GAB2, CRKL, etc.) and signalling pathways (*e.g.* Ras, PI3K, JAK-STAT, etc.) that are all thought to contribute to the pathogenesis of CML [35, 48, 49].

Anti-BCR-ABL1 targeted therapy in CML

In 1996, Brian Druker and his colleagues described the *in vitro*, anti-BCR-ABL1 activity of imatinib mesylate (IM) [22], a

Table 1 Classification of chronic myeloid neoplasms modified from the 2008 World Health Organization classification scheme [313]

1. Myelodysplastic syndromes (MDS)
1.1. Refractory cytopenia (RC) with uni-lineage dysplasia (RCUD)
1.1.1. Refractory anaemia (RA)
1.1.2. RA with ring sideroblasts (RARS)
1.1.3. Refractory neutropenia
1.1.4. Refractory thrombocytopenia
1.2. RC with multi-lineage dysplasia (RCMD)
1.3. RA with excess blasts (RAEB)
1.4. MDS with isolated del(5q)
1.5. MDS, unclassifiable
1.6. Childhood MDS
2. Myeloproliferative neoplasms (MPN)
2.1. Classic
2.1.1. Chronic myelogenous leukaemia, *BCR-ABL1* positive (CML)
2.1.2. Polycythemia vera (PV)
2.1.3. Essential thrombocythemia (ET)
2.1.4. Primary myelofibrosis (PMF)
2.2. Non-classic
2.2.1. Chronic neutrophilic leukaemia
2.2.2. Chronic eosinophilic leukaemia, not otherwise specified (CEL-NOS)
2.2.3. Mastocytosis
2.2.4. MPN, unclassifiable
3. MDS/MPN
3.1. Chronic myelomonocytic leukaemia (CMML)
3.2. Juvenile myelomonocytic leukaemia (JMML)
3.3. Atypical chronic myeloid leukaemia, *BCR-ABL1*-negative (aCML)
3.4. MDS/MPN, unclassifiable
3.4.1. Provisional entity: RARS and thrombocytosis (RARS-T)
4. Myeloid and/or lymphoid neoplasms with eosinophilia and abnormalities of,
4.1. *PDGFRA*
4.2. *PDGFRB*
4.3. *FGFR1 (8p11 myeloproliferative syndrome; a.k.a. stem cell leukaemia/lymphoma)*

2-phenylaminopyrimidine class kinase inhibitor that targets ABL1 [50], PDGFR [51], ARG [52] and KIT [53]; the mechanism of action involves competitive inhibition of the ATP binding site of the kinase [54]. Consequently, orally administered IM has been shown to be effective in the treatment of neoplastic diseases with mutations involving the aforementioned kinases: CML [55–61], Ph-positive acute lymphoblastic leukaemia (ALL) [56, 62], gastrointestinal stromal tumours (known to harbour *KIT* or *PDGFR* mutations) [63, 64] and PDGFR-rearranged MPN [12, 23, 65–69].

In newly diagnosed patients with chronic phase CML (CP-CML), IM is now recommended as the initial treatment of choice [70]. In the International Randomized Study of Interferon and STI571 (IRIS), interferon alpha/cytarabine combination was compared with IM in 1106 newly diagnosed CP-CML patients. The results of this trial were recently updated in 2006 [71]. IM was found to be superior to combination chemotherapy in terms of both response rates and progression-free survival; the 553 patients initially assigned to IM therapy had been followed for at least 5 years and the best observed rates for complete haematological and cytogenetic remissions were 97% and 82%, respectively. Five-year survival was 89%.

Imatinib resistance and second-generation anti-BCR-ABL1 kinase inhibitors

IM is not as effective in advanced phase CML as it is in CP-CML [56]. Furthermore, approximately 20% of CP-CML patients either fail treatment, for one reason or another, or transform into advanced phase disease. IM-resistance has operationally been classified into primary (not achieving complete cytogenetic remission) and secondary (loss of response). In each instance, several underlying mechanisms have been implicated and include altered BCR-ABL1/IM cellular concentration ratio due to increased *BCR-ABL1* expression or abnormal cellular drug transport, activation of alternative signal pathways, inherent IM-resistance by *BCR-ABL1* leukaemia stem cells and emergence of IM-resistant *BCR-ABL1* mutations. The latter is by far the most frequent and best understood mechanism of IM resistance.

The crystal structure of IM bound to the ABL1 indicates that the drug stabilizes the oncoprotein in an enzymatically inactive conformation [54]. *BCR-ABL1* mutations induce IM resistance by hindering drug-oncoprotein binding at critical contact points or prevent the formation of inactive structural conformation that is required for IM activity [72]. At present, more than 50 *BCR-ABL1* mutations have been described and most affect the ABL1 kinase domain; in general four categories of mutations are identified and seven mutations account for two-thirds of the cases (G250, Y253, E255, T315, M351, F359, H396): phosphate-binding loop (*e.g.* E255, Y253, Q252, G250; affecting ATP binding site); IM binding site (*e.g.* T315); catalytic domain (*e.g.* F359); and activation loop (*e.g.* H396; forcing an active conformation and thus making IM unable to bind) [73]. Not all these mutations are IM-insensitive and some (*e.g.* T315, E255, Y253) are more resistant than others (*e.g.* M244, G250, Q252, F317, E355, F359, V379, H396) [74].

The development of second generation kinase inhibitors and better understanding of mutant ABL1 conformation dynamics have had some success in addressing the aforementioned challenges of IM resistance [75–80]. New drugs include more potent ABL1 inhibitors such as nilotinib, dual ABL1/Src inhibitors such as dasatinib and bosutinib, dual ABL1/Lyn inhibitors such as INNO-406, ABL1-substrate binding inhibitors (*i.e.* non-ATP competitive) such as ONO12380. Most but not all (*e.g.* T315) *ABL1* mutations are sensitive to one or more of the above listed new drugs whose value as salvage therapy for IM-refractory disease is being validated [75–80]. Finally, there is more and more discussion about IM-resistant *BCR-ABL1*-positive leukaemia stem cells and their dependence on both altered *BCR-ABL1* expression and other signalling pathways [81]. Whether or not going after such quiescent leukaemia stem cells is therapeutically essential, in patients achieving complete molecular remissions with currently available drugs, remains to be seen.

Other ABL1 mutations

In the context of myeloid malignancies, *ETV6* is the only currently known non-*BCR* fusion partner for ABL1 although other ABL1 fusion proteins have been described in acute lymphoblastic leukaemia (ALL) [82]. *ETV6-ABL1,* which corresponds to t(9;12)(q34;p13), has been associated with ALL [83–86], AML (with transient response to IM) [87–89] and atypical CML (with minor response to imatinib) [85, 90–92]. Like *BCR-ABL1*, *ETV6-ABL1* encodes for an activated and transforming ABL1 [87, 93]. The PNT oligomerization motif of ETV6 is thought to activate the ABL1 kinase by a similar mechanism to the BCR coiled coil oligomerization domain in the context of the BCR-ABL1.

JAK2 and *MPL* mutations

Like ABL1, JAK2 is a cytoplasmic PTK and mutant *JAK2*, like mutant *ABL1*, has now been associated with classic MPN. JAK2 is a member of the Janus family of kinases that were incidentally discovered around 1989 and set aside as 'just another kinase' [94]. Their name was later modified to Janus kinases (JAKs) [95] after the Roman god with two faces because they contain two symmetrical kinase-like domains; the C-terminal JAK homology 1 (JH1) domain possesses tyrosine kinase function while the immediately adjacent JH2 domain is enzymatically inert but is believed to regulate the activity of JH1. The possible role of *JAK2* mutations in haematological malignancy was first suspected after the observation that a dominant mutation in *HOP*, a *JAK* homologue in *Drosophila*, induced leukaemia-like defects [96].

Janus kinases

There are four JAKs (JAK1, JAK2, JAK3 and tyrosine kinase 2) and they all contain seven JH domains organized into four regions; kinase (JH1), pseudo-kinase (JH2), FERM (the N-terminal JH7,

JH6, JH5, and part of JH4) and SH2-like (JH3 and part of JH4) [97]. In human beings, *JAK1* is located on chromosome 1p31.3, *JAK2* on 9p24, *JAK3* on 19p13.1 and *TYK2* on 19p13.2. At present, human cancer-relevant *JAK* mutations have been described for *JAK1* (T-ALL, AML, breast cancer, lung cancer) [98–101], *JAK3* (AMKL cell lines and primary cells, breast cancer, gastric cancer) [98, 102] and *JAK2* (MPN primarily and other myeloid malignancies infrequently, trisomy 21 associated ALL) [13–16, 103–105]. However, other than *JAK2* mutations in MPN and *JAK1* mutations in T-ALL, the other associations are rare.

JAK2 fusion mutations

GOF *JAK2* fusion mutations have been associated with T or pre-B ALL, T-cell lymphoma, AML and MPN-U; these include *ETV6-JAK2*, t(9;12)(p24;p13), *PCM1-JAK2*, t(8;9)(p22;p24), *BCR-JAK2*, t(9;22)(p24;q11.2) and *SSBP2-JAK2*, t(5;9)(q14.1;p24.1) (Table 2) [106–114]. PCM1 displays multiple coiled-coil motifs and it is believed that these are preserved and function as a dimerization domain in *PCM1-JAK2*. In *ETV-6-JAK2*, the chimeric protein includes the Helix-Loop-Helix oligomerization domain of ETV6 fused to the kinase domain of JAK2 and the fusion oncogene induces both T and B cell lymphoid neoplasms in transgenic mice [106, 107, 115, 116]. In a more recent study, expression of *ETV-6-JAK2* in human cord blood cells resulted in Epo-independent erythroid differentiation *in vitro* and induction of myelofibrosis in an *in vivo* xenotransplantation model [117]. In *BCR-JAK2*, the fusion protein includes the coiled-coil dimerization domain of BCR and the JAK2 kinase domain [112]. The patient in this particular instance had MPN-U and did not respond to imatinib. Another patient with *BCR-JAK2* had AML [114]. The *BCR-JAK2* fusion in this instance had a different *BCR* breakpoint, although it was similar to that of *BCR-ABL1*. The most recently described *JAK2* fusion partner, *SSBP2,* is located at 5q14.1 and the associated phenotype was pre-B ALL [118]. The NH_2 terminus of the SSBP2 protein contains a LisH motif that is believed to function as the dimerization domain.

JAK2V617F

JAK2 V617F is an exon 14 G to T somatic mutation. The nucleotide change at position 1849 results in the substitution of valine to phenylalanine at codon 617. *JAK2* V617F was first described in 2005 in patients with PV, ET and PMF [13–16]. Subsequently, the mutation has also described in other myeloid neoplasms [103, 119]. As of the time of this writing, JAK2V617F has not been reported in lymphoid disorders [120–123], solid tumour [124–126] or secondary myeloproliferation [127, 128]. In general, mutational frequency is estimated at over 95% in PV, 50% in ET or PMF, 20% in certain other MPNs including refractory anaemia with ringed sideroblasts and thrombocytosis (RARS-T) and less than 5% in AML or MDS [104, 129–131].

JAK2 V617F induces a PV-like phenotype in murine transplant models: erythrocytosis but not thrombocytosis, low serum Epo level, splenomegaly, extramedullary haematopoiesis, granulocytosis, megakaryocytic hyperplasia and ultimately bone marrow fibrosis and anaemia [14, 132, 133]. However, in a recent study of *JAK2* V617F transgenic mice, manipulation of mutant gene expression resulted in either an ET (lower expression compared to wild-type allele) or PV phenotype with (equal expression) or without (higher expression) thrombocytosis [134]. Such mutant allele burden-dependent phenotypic variation in transgenic mice was also demonstrated by another study [135].

Current information regarding mutant allele burden in human beings with MPN partially recapitulates what was seen in the above-mentioned experiments with transgenic mice. In other words, mutant allele burden in patients with ET is significantly lower than that seen in patients with either PV or PMF [136–140]. At least in PV, a higher allele burden is the result of *JAK2*V617F homozygosity, which is accomplished by mitotic recombination [13, 16, 141]. Some have suggested that such homologous recombination and genomic instability in general is facilitated by *JAK2* V617F [142]. However, the interaction between *JAK2* V617F homozygosity and mutant allele burden, in terms of phenotypic determination, is currently not clear [143, 144].

In human beings, *JAK2* V617F occurs at a primitive stem cell level and is chronologically an early event [145–147]. Some but not all [148] studies have suggested *JAK2*V617F clonal involvement of NK [149], T [150] and B [150] lymphocytes. Regardless, there is evidence to suggest that *JAK2*V617F may not be the initial clonogenic event in either PV or other MPNs and that its presence might not be mandatory for endogenous colony formation [151–153]. The demonstration of *JAK2*V617F-negative leukaemia clones arising in *JAK2*V617F-positive MPN patients lends further support in this regard [154, 155]. In the latter instance, both mutation positive and negative cells were shown to share the same cytogenetic abnormality and thus probably arose from a common ancestral clone [154]. On the other hand, *JAK2*V617F or other *JAK2* mutations might be a necessary component of the PV phenotype, because they are detected in all patients with the disease [20]. Furthermore, recent studies suggest that germline genetic variation [156] and/or the occurrence of other concomitant mutations [19] might explain why the same mutation is present in apparently different disease phenotypes.

Other reported *JAK2* exon 14 mutations include D620E (PV, MPN, unclassifiable), E627E (MPN, unclassifiable), K607N (AML), L611S (B-ALL), JAK2DeltaIREED (DS-associated B-ALL), C616Y (PV), V617F from c.1848_1849delinsCT (post-ET MF) and V617F/C618R from c.1849–1852GTCT > TTTC (PV) [125, 157–163]. In addition, an activating *JAK2*T875N was described in an AMKL cell line [164]. There is no doubt that the list of such mutations will grow with time and, interestingly, some of the new mutations identified in PV co-existed with *JAK2*V617F.

JAK2 exon 12 mutations

In 2007, a set of *JAK2* exon 12 mutations were described in *JAK2*V617F-negative patients with PV in whom erythrocytosis was the predominant feature [165]. Because of the latter feature, some of the cases were assigned the diagnosis of 'idiopathic' erythrocytosis although their serum Epo level was almost always below the

reference range and EECs were demonstrated in every instance when tested. The majority of the cases (10 of 11) in the original report [165] were found to harbour one of four exon 12 *JAK2* mutant alleles: N542-E543del (4 cases), F537-K539delinsL (3 cases), K539L (2 cases), H538QK539L (1 case). All four exon 12 mutant alleles induced cytokine-independent/hypersensitive proliferation in erythropoietin receptor-expressing cell lines and constitutive activation of JAK-STAT signalling [165]. In addition, *JAK2*K539L induced a PV phenotype in a mouse transplant model. Also, in this first report, the four newly described *JAK2* exon 12 mutations, which include both in-frame deletions and tandem point mutations, appeared to be specific to either PV or 'idiopathic' erythrocytosis. Unlike the case with PV-associated *JAK2*V617F, exon 12 *JAK2* mutations were heterozygous but associated with stronger abnormal JAK2 activation.

Many other studies have now confirmed the observations from the above-mentioned study [20, 166–170] and in the process, most [20, 166, 167] but not all [168, 170] of the studies suggested that exon 12 mutations occurred in virtually all *JAK2*V617F-negative PV cases (*i.e.* approximately 3% of all PV cases). Furthermore, several other exon 12 mutation variants were added to the list including R541-E543delinsK, I540–E543delinsMK, V536–I546dup11, F537–I546dup10+547L and E543–D544del [167–169]. Among all currently described exon 12 mutations, the most frequent was N542–E543del comprising 17 of 52 cases reported at the time of the latest report [168]. In general, many *JAK2* exon 12 mutation-positive patients present with apparently 'isolated' erythrocytosis but because of their association with subnormal serum Epo level and the presence of EECs, they fulfil the 2008 WHO diagnostic criteria for PV [171]. Finally, information presented at the 2007 American Society of Hematology (ASH) meeting suggested that *JAK2* exon 12 mutations, as is the case with *JAK2*V617F, might clonally involve both B and NK lymphocytes [172] and also occur in ET and 'idiopathic' abdominal vein thrombosis [173, 174]. Obviously, more studies are needed to fully appreciate the phenotypic spectrum of these mutations.

JAK2 mutations associated with trisomy 21 associated acute lymphoblastic leukaemia

A recent report in *Lancet* described somatically acquired GOF *JAK2* mutations (*JAK2*R683G/S/K; exon 16 and mostly heterozygous) in 16 of 88 (18%) patients with Down's syndrome-associated B-ALL but only 1 of 216 patients with sporadic ALL [105]. The latter patient had an isochromosome 21q. The mutations caused constitutive JAK-STAT activation and cytokine-independent growth of BaF3 cells that was inhibited by JAK inhibitor I. Overall prognosis did not appear to be affected.

MPL mutations

MPL (myeloproliferative leukaemia virus oncogene homologue) belongs to the haematopoietin receptor superfamily and enables its ligand, thrombopoietin (Tpo), to facilitate both global haematopoiesis (early expansion of differentiating clones) and megakaryocyte growth and differentiation [175–177]. The gene for MPL maps to chromosome 1p34 and contains 12 exons [178]. Germline *MPL* mutations have been associated with either familial thrombocytosis (GOF transmembrane domain mutation; S505N) [179] or congenital amegakaryocytic thrombocytopenia (LOF mutations) that often progresses to aplastic anaemia [180–182]. In addition, an *MPL* single nucleotide polymorphism (G1238T) that results in a K39N substitution is found in approximately 7% of African Americans [183]. Such patients display higher platelet counts and lower MPL expression, when compared to patients without the specific *MPL* polymorphism [183].

In 2006, a somatic GOF *MPL*W515L mutation (a G to T transition at nucleotide 1544 resulting in a tryptophan to leucine substitution at codon 515 of the transmembrane region) was described in *JAK2*V617F-negative PMF [17]. Subsequently, an additional *MPL* mutation involving the same 515 codon (*MPL*W515K) was incidentally discovered during screening for *MPL*W515L and the prevalence of both mutations was determined at approximately 5% in PMF and 1% in ET [184]. More recent studies have identified other somatic *MPL* mutations including *MPL*W515S and *MPL*S505N (mentioned above in association with familial thrombocytosis) and higher prevalence rates: approximately 4% in ET (9% in *JAK2*V617F-negative cases) and up to 11% in PMF [185–188]. Most recently, using SNP-array karyotyping, biallelic *MPL*W515L mutation and uniparental disomy 1p was demonstrated in some patients with RARS-T, thus providing a mechanism of homozygosity similar to that of JAK2V617F [189].

As is the case with *JAK2*V617F, *MPL*515 mutations are early, stem cell-derived events involving both myeloid and lymphoid progenitors [190–192] and *MPL*W515L has been shown to transform cell lines in terms of both cytokine-independent growth and Tpo hypersensitivity, activate JAK-STAT/ERK/Akt and induce PMF-like disease in mice that is characterized by a rapid fatal course, marked thrombocytosis, leukocytosis, hepatosplenomegaly and bone marrow fibrosis [17]. Interestingly, some patients display multiple *MPL* mutations and others a minor *JAK2*V617F cloner together with an *MPL* mutation [187, 193]. Again, these observations support the secondary nature of such mutations and underscore the complexity of pathogenetic mechanisms in MPNs. Finally, preliminary information suggests that *MPL* mutations favour megakaryocytic/myeloid as opposed to the erythroid skewed proliferation/differentiation seen with *JAK2* mutations [151, 191].

Clinical and prognostic correlates of JAK2 and MPL mutations

Virtually all patients with PV carry a *JAK2* mutation (97% with *JAK2*V617F and the rest with *JAK2* exon 12 mutations) [20]. In PV, *JAK2*V617F 'homozygous' as opposed to 'heterozygous' state has been associated with a higher haemoglobin level, higher leukocyte count, lower platelet count and presence of pruritus [139, 194]. A somewhat similar set of correlations were made for higher mutant allele burden in PV, measured by quantitative

assays [137, 140, 195]. The small number of patients with *JAK2* exon 12 mutations are more likely to present with isolated erythrocytosis but there is substantial phenotypic overlap with *JAK2* V617F-positive PV [18, 168].

In ET, the presence of *JAK2*V617F has been associated with advanced age, higher haemoglobin level, increased leukocyte count and decreased platelet count [136, 196–198]. In mutation-positive patients with ET, *JAK2*V617F allele burden has been directly correlated with leukocyte count, platelet count and the presence of palpable splenomegaly [136, 139, 140]. Similarly in PMF, the presence of *JAK2*V617F has been associated with an older age at diagnosis and higher leukocyte count [199]. In addition, *JAK2*V617F 'homozygous' PMF patients displayed an even higher incidence of leukocytosis, marked splenomegaly and pruritus [200]. Both PMF and ET patients with *MPL* mutations were found to be older and more anaemic than their *MPL* mutation-negative counterparts [186, 188].

JAK2 or *MPL* mutations in MPNs might not have prognostic relevance. In ET, overall or leukaemia-free survival was not affected by either the presence of *JAK2*V617F or its allele burden [136, 196]; the impact on the risk of thrombosis or fibrotic transformation is less clear [136, 139, 196, 201]. Equally unclear is the prognostic relevance of *JAK2*V617F allele burden in PV where a higher mutant allele burden is implicated by some but not by others as an adverse prognostic factor for fibrotic transformation, thrombosis and need for chemotherapy [137, 139, 194, 195]. In PMF, *JAK2*V617F presence was associated with inferior survival in one but not in another study [199, 202]. Similarly divergent results were reported in terms of leukaemic transformation rate and need for chemotherapy or splenectomy [200, 203]. The most recent study on the subject matter revealed shortened overall and leukaemia-free survival in PMF patients with lower as opposed to higher quartile *JAK2*V617F allele burden [203].

Anti-JAK2 small molecule therapy

A number of anti-JAK2 drugs have undergone preclinical testing and some have already been introduced into clinical trials [204]. Amongst them, some are *JAK2* selective ATP-mimetic small molecules: *e.g.* TG101209, TG101348, INCB018424, XL019, CEP701 and SB1518 [205–208]. TG101209, an orally available small molecule JAK2-selective kinase inhibitor, is one of the first compounds to undergo extensive preclinical testing [209]. The drug's anti-JAK2 kinase activity was estimated at an IC_{50} of 6 nM, compared to 169 nM for JAK3 [209]. In HEL cells (homozygous for *JAK2*V617F) and other *JAK2*V617F-transduced cell lines, TG101209 induced apoptosis and inhibited phosphorylation of *JAK2*V617F, STAT5 and STAT3 (IC_{50} of approximately 600 nM) [209]. At similar or lesser drug concentrations, the drug also inhibited colony growth of primary cells from *JAK2*V617F-positive PV patients and *MPL*W515L-positve PMF patients [209]. Furthermore, the growth inhibitory effect of TG101209 was relatively selective to mutated-colonies. TG101348, a drug that is very similar to TG101209, was also shown to display similar *in vitro* as well as *in vivo* anti-PV and anti-MPN activity in the context of exon 12, exon 14 *JAK2* and *MPL* mutations [205, 210–212]. In a murine model of polycythemia vera, oral TG101348 therapy resulted in significant reduction of haematocrit, leukocyte count, extramedullary haematopoiesis, myelofibrosis and *JAK2*V617F-expressing clones [211]. TG101348, but not TG101209, is currently undergoing phase I/II clinical trial in PMF and post-PV/ET MF.

Several other potent JAK2 inhibitors have also been reported to have *in vitro* or *in vivo* (*i.e.* mouse models) activity against *JAK2*V617F-driven cell proliferation and signal transduction. Among them, INCB018424, XL019, CEP-701 and SB1518 are currently undergoing clinical trials in patients with advanced stages of PMF or post-PV/ET MF (INCB018424, XL019, CEP701), PV (XL019, CEP701), *JAK2*V617F-positive ET (CEP701) and acute and chronic haematologic malignancies (SB1518) [206–208, 213, 214]. All of these drugs display potent JAK2 inhibitory activity but their *in vitro* JAK2 selectivity, in the context of the JAK family of kinases, is different. For example, JAK3 is spared by TG101348, XL019 and INCB018424 but not by CEP701. Similarly, JAK1 is spared by TG101348 and XL019 but not by INCB018424.

Preliminary results regarding INCB018424 in PMF and post-PV/ET MF are encouraging in terms of the drug's toxicity profile and its activity against splenomegaly and constitutional symptoms [213]. More follow-up is required to determine the drug's effect on anaemia, leukoerythroblastosis, myelofibrosis, cytogenetic abnormalities or *JAK2*V617F allele burden. Results regarding other JAK2 inhibitors are too early to comment on. Nevertheless, the expected anti-inflammatory cytokine effect of this class of drugs is expected to be a confounding variable in terms of both toxicity and efficacy assessment.

KIT mutations

In 1993, Furitsu and colleagues described a mutant *KIT* allele with two-point mutations as being responsible for the ligand-independent constitutive activation of KIT in a human mast cell leukaemia cell line (HMC-1); one mutation was located at the JM region at codon 560 and nucleotides 1699–1701 (V560G; GTT→GGT) and the other at the kinase domain at codon 816 and nucleotides 2467–2469 (D816V; GAC→GTC) [10]. One year later (1994), Tsujimura *et al.* reported a kinase domain point mutation at nucleotide 2468 (GC to TA) resulting in an amino acid substitution at codon 814 (*KIT*D814Y), in a murine mastocytoma cell line, P-815 [215]. In both instances, either the mutations themselves [215] or their corresponding murine constructs (V559G and D814V) [10] were shown to produce constitutive activation of KIT signalling in cell lines.

Nagata and colleagues were the first to describe one of the aforementioned mutations (*KIT*D816V) in blood mononuclear cells from patients with SM and an associated non-mast cell myeloid neoplasm but not in those with indolent or aggressive SM, solitary mastocytoma or chronic myelomonocytic leukaemia

[216]. However, subsequent studies have shown the presence of *KIT*D816V or other *KIT* mutations (*KIT*D820G, *KIT*V560G, *KIT*D816Y, *KIT*E839K, *KIT*D816F, *KIT*F522C, etc.) in other categories of mast cell disease (MCD) including indolent and aggressive SM [217–222]. It is currently touted that all patients with MCD carry a *KIT* mutation but its laboratory detection might be hampered by the use of non-informative cell source or inadequate assay sensitivity [223, 224]. JM *KIT* mutations have also been described in canine mastocytomas [225].

KIT

KIT is located at chromosome 4q12 and encodes KIT, a class III receptor tyrosine kinase [226, 227]. The type III class also includes PDGFR, CSF-1 and Flt3 and is characterized by an extracellular component of five immunoglobulin-like domains, a trans-membrane segment, a juxtamembrane (JM) domain and a cytoplasmic kinase domain with a 70–100 amino acid kinase insert near its centre [228]. Normally, KIT is activated when bound to its ligand, the stem cell factor (SCF), which is encoded by *SCF* on chromosome 12q22 [229–231]. KIT (CD117) is notably expressed by mast cells, haematopoietic stem cells, germ cells, melanocytes and Cajal cells of the gastrointestinal tract and is therefore functionally relevant for mast cell development, haematopoiesis, gametogenesis and melanogenesis [232]. KIT signalling and the corresponding cellular response depends on the specific cell type involved and the putative downstream effectors include PI3K-Akt, Src family of kinases, Ras-Erk, phospholipase Cγ, MAPK and JAK-STAT [233].

Mutant *KIT*

Activating *KIT* mutations have been described in a spectrum of haematologic (*e.g.* mastocytosis, acute leukaemia) and non-haematologic (*e.g.* gastrointestinal stromal cell tumour, germ cell tumour) malignancies [232]. Among these, SM is considered an MPN by virtue of its clonal derivation from the haematopoietic stem cell [234–236]. Observations from several laboratory studies support the oncogenic role of *KIT* mutations. For example, in murine experiments, D814Y has been shown to induce ligand-independent mast cell growth *in vitro*, tumourigenicity *in vivo*, and mast cell differentiation [237]. Similarly, retroviral infection of haematopoietic progenitors with mouse *KIT*D814Y and *KIT*V559G mutants induces autonomous myeloid and mast cell colony formation as well acute leukaemia in murine transplant models [238]. Furthermore, transgenic mice expressing *KIT*D816V restricted to their mast cells display an SM phenotype that closely resembles the clinically heterogeneous disease in man [239]. This is in contrast to another report [240] that suggested a differentiating but not transforming potential for the mutation, which nevertheless probably participates in enhancing mast cell chemotaxis [241] and clustering [236]. Mutant Kit signalling might involve both PI3K [242] and Src [243] participation although utilization of pathway molecules might be different between the wild-type and mutant protein [244].

Systemic mastocytosis

The 2008 World Health Organization (WHO) classification system for myeloid malignancies considers SM as a myeloproliferative neoplasm (MPN) [4]. WHO-defined SM should be distinguished from *PDGFR*-mutated (*FIP1L1-PDGFRA, PRKG2-PDGFRB)* myeloid malignancy associated with bone marrow mastocytosis and either eosinophilia or basophilia [69, 245]. The latter but not the former are effectively treated by IM. SM is sometimes associated with a clonally related second myeloid neoplasm, which is not surprising considering its origin as a stem cell disease with multilineage clonal involvement.

Targeted therapy in systemic mastocytosis

Although several drugs have shown *in vitro* anti-KIT activity [246–249], the immediately most relevant, in terms of clinical development, include the tyrosine kinase inhibitors IM, nilotinib, dasatinib and PKC412. During *in vitro* experiments involving both cell lines and primary cells from patients with SM, IM inhibited wild-type KIT and KIT mutants with trans-membrane (F522C) and juxta-membrane (V559G and V560G) but not kinase (D816V or D814V) domain mutations [222, 250, 251]. Similarly, not all juxta-membrane mutations are sensitive to IM (*e.g.* V559I) [252]. Consistent with these *in vitro* observation, IM therapy is ineffective in SM associated with *KIT*D816V [253] whereas others have shown activity in MCD associated with the trans-membrane *KIT*F522C mutation [222]. In contrast to the experience from my own institution, Droogendijk *et al.* treated 11 patients with D816V-positive SM with 400 mg/day of IM and found some 'clinical improvement' in some patients [254].

Nilotinib is more potent than IM in its *in vitro* anti-*BCR-ABL* activity but is similarly ineffective against *KIT*D816V [255]. Other studies have, however, shown a more promising activity of nilotinib against kinase domain *KIT* mutations [256]. In contrast, dasatinib has shown potent anti-KIT activity in mast cell and leukaemia cell lines with different *KIT* mutants including those with D816V [257, 258]. In the largest study of dasatinib therapy in SM [259], the drug was given at a starting dose of 70 mg PO bid to 33 SM patients: 18 indolent, 9 aggressive and 6 with associated non-mast cell myeloid neoplasm. Two (6%) patients, both of whom were D816V-negative, achieved complete remission. Nine (27%) patients experienced symptomatic improvement. The results of another case report series of four patients with SM treated with dasatinib were equally unimpressive [260].

PKC412 has shown *in vitro* activity against transformed and primary cells with kinase domain KIT mutants (D816Y and D816V) [261, 262]. In a preliminary report, transient improvement in liver function test abnormalities, peripheral blood mast cell percentage and plasma histamine levels were seen in a patient with SM

treated with PKC412 [263]. Similarly, oral PKC412 (100 mg bid) was administered to 15 SM patients (60% with detectable *KIT*D816V) with evidence of clinical activity in 11 (73%) patients including increase in haemoglobin ($n = 1$) and reduction of ascites ($n = 2$) or pleural effusion ($n = 2$). In four patients, the bone marrow mast cell burden was reported to have decreased from 50–60% to 10–15% range.

PDGFR mutations

Both platelet-derived growth factor receptors α (*PDGFRA* located on chromosome 4q12) and β (*PDGFRB* located on chromosome 5q31-q32) are involved in MPN-relevant activating mutations. Clinical phenotype in both instances includes prominent blood eosinophilia and excellent response to IM therapy.

PDGFRA mutations

In regards to *PDGFRA* mutations, the most intensively studied has been the *FIP1L1-PDGFRA*, a karyotypically occult del(4)(q12), that was described in 2003 as an imatinib-sensitive activating mutation [12]. Subsequent studies have demonstrated the stem cell origin of the particular mutation [264, 265] and functional studies have demonstrated transforming properties in cell lines and the induction of MPD in mice [266, 267]. Cloning of the *FIP1L1-PDGFRA* fusion gene identified a novel molecular mechanism for generating this constitutively active fusion tyrosine kinase, wherein a ~800 kb interstitial deletion within 4q12 fuses the 5' portion of *FIP1L1* to the 3' portion of *PDGFRA* [12]. Molecular studies have shown that the breakpoint in *FIP1L1* is relatively promiscuous, whereas the *PDGFRA* breakpoint is restricted to exon 12 that encodes part of the protein–protein interaction module with two fully conserved tryptophans (WW domain) containing the JM region with resultant disruption of its autoinhibitory activity [268]. Further biochemical analysis has shown that, in contrast with most tyrosine kinase fusions associated with human cancers, the *FIP1L1* encoded sequences are dispensable for transformation, and there is no requirement for a dimerization motif; disruption of the autoinhibitory juxtamembrane motif as an invariant consequence of disruption of exon 12 is the basis for constitutive activation of PDGFRA kinase activity [269].

FIP1L1-PDGFRA occurs in a very small subset of patients who present with the phenotypic features of either SM or HES but the presence of the mutation reliably predicts complete haematologic and molecular response to imatinib therapy [67, 69, 270]. *FIP1L1-PDGFRA* mutation (T674I) that is homologous to the resistance-inducing, 'gatekeeper' T315I mutation in *BCR-ABL* has been described [12, 271, 272] and *in vitro* salvage with other kinase inhibitors including PKC412 [266] and sorafenib [273] has been demonstrated whereas such activity has not been conclusively shown for nilotinib [274, 275].

PDGFRA activation associated with CEL has also been described with karyotypically apparent fusion mutations including *KIF5B-PDGFRA*, t(4:10)(q12;p11) [276], *BCR-PDGFRA*, t(4;22)(q12;q11) [277] and *CDK5RAP2-PDGFRA*, ins(9;4)(q33;q12q25) [278]. In the former instance, the breakpoints involved exon 3 of the kinesin family member 5B and exon 12 of *PDGFRA* resulting in an in-frame fusion. The patient achieved complete haematological and molecular remission with imatinib therapy [276]. *BCR-PDGFRA* represents an in-frame fusion with *BCR* breakpoints in intron 7/exon 12/exon 1/exon 17 and *PDGFRA* breakpoint in exon 12/exon 13 and is also sensitive to imatinib therapy [277, 279, 280]. *CDK5RAP2-PDGFRA* also represents an imatinib-sensitive in-frame fusion involving exon 13 of *CDK5RAP2* and intron 9/exon 12 of PDGFRA [278]. As is the case with *FIP1L1-PDGFRA*, currently known *PDGFRA* breakpoints are noted to be tightly clustered in the JM region, which once again highlights a key regulatory role for this domain.

PDGFRB mutations

The association between eosinophilic myeloid malignancies and *PDGFRB* rearrangement was first characterized and published in 1994 where fusion of the tyrosine kinase encoding region of *PDGFRB* to the *ets*- like gene, *ETV6* (*ETV6-PDGFRB*, t(5;12)(q33;p13) was demonstrated [11]. The fusion protein was transforming to cell lines and resulted in constitutive activation of PDGFRB signalling [281]. Since then, several other *PDGFRB* fusion transcripts with similar disease phenotypes have been described [282–290], cell line transformation [287–289] and MPD-induction in mice has been demonstrated [287], and imatinib therapy was effective when employed [23, 283, 284, 286, 290]. Additional evidence regarding the oncogenicity of activated PDGFRB comes from experiments with mice where either *ETV6-PDGFRB* or *H4-PDGFRB* induced lymphoblastic lymphoma [289, 291]. In most of these mutations, PDGFRB is fused to the N-terminal segment of a partner protein that encodes for one or more oligomerization domains.

FGFR1 mutations

There are at least four members of the FGFR protein family (FGFR1, FGFR2, FGFR3 and FGFR4) with additional variants resulting from alternative splicing. Structurally, FGFRs feature extracellular, trans-membrane, juxta-membrane and kinase domains. FGFRs are functionally important in embryonal development and tissue integrity and germline FGFR mutations result in various birth defects including achondroplasia/hypochondroplasia (FGFR3), Crouzon syndrome (FGFR2) and Kallmann syndrome (FGFR1). Somatic *FGFR3* mutations have been described in benign skin tumours, urothelial cancer and multiple myeloma and *FGFR2* mutations in endometrial carcinoma. In the context of myeloid malignancies, somatic *FGFR1* mutations have been

Table 2 Mutations of putative pathogenetic relevance in myeloproliferative neoplasms

JAK2	*MPL*	*PDGFRA*	*PDGFRB*	*FGFR1*
(phenotype)	*(phenotype)*	*(phenotype)*	*(phenotype)*	*(phenotype)*
***JAK2*V617F** (PV, ET, PMF)	***MPL*W515L**/K (PMF, ET)	***FIP1L1-PDGFRA*** del(14q12) (CEL with mastocytosis)	***ETV6-PDGFRB*** t(5;12)(q33;p13) (CMML with eosinophilia)	***ZNF 198-FGFR1*** t(8;13)(p11;q12) (SCLL)
***JAK2* Exon 12 mutations** *F537-K539delinsL H538QK539L K539L N542-E543del (PV)*		***BCR-PDGFRA*** t(4;22)(q12;q11) (CEL, MPN-U)	***RABAPTIN-5-PDGFRB*** t(5;17)(q33;p13) (CMML) ***HCMOGT-1-PDGFRB*** t(5;17)(q33;p11.2) (JMML with eosinophilia)	***FOP-FGFR1*** t(6;8)(q27;p11) (SCLL)
ETV6-JAK2 t(9;12)(p24;p13) (AML, MPN-U)		***KIF5B-PDGFRA*** t(4;10)(q12;p11) (CEL)	***CEV14-PDGFRB*** t(5;14)(q33;q32) (AML with eosinophilia) ***NIN-PDGFRB*** t(5;14)(q33;q24) (MPN with eosinophilia) ***KIAA1509-PDGFRB*** t(5;14)(q31;q32) (CMML with eosinophilia)	***FGFR1OP2-PDGFRA*** ins(12;8)(p11;p11p22) (SCLL)
BCR-JAK2 t(9;22)(p24;q11.2) (MPN-U, AML)		***CDK5RAP2-PDGFRA*** ins(9;4)(q33;q12q25) (CEL)	***TP53BP1-PDGFRB*** t(5;15)(q33;q22) (MPN-U with eosinophilia)	***TIF1-FGFR1*** t(7;8)(q34;p11) (SCLL)
PCM1-JAK2 t(8;9)(p22;p24) (AML, MPN-U)			***PDE4DIP-PDGFRB*** t(1;5)(q23;q33) (MPN-U with eosinophilia)	***MYO18A-FGFR1*** t(8;17)(p11;q23) (SCLL)
SSBP2-JAK2 t(5;9)(q14.1;p24.1) (pre-B ALL)			***HIP1-PDGFRB*** t(5;7)(q33;q11.2) (CMML with eosinophilia)	***HERV-K-FGFR1*** t(8;19)(p12;q13.3) (SCLL)
			H4-PDGFRB t(5;10)(q33;q22) (MPN-U)	***BCR-FGFR1*** t(8;22)(p11;q11) (CML-like MPN)
				CEP110-FGFR1 t(8;9)(p12;q33) (SCLL)
				CPSF6-FGFR1 t(8;12)(p11;q15) (SCLL)

PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; AML, acute myeloid leukaemia; MPN-U, unclassified MPN; CEL-SM, chronic eosinophilic leukaemia associated with systemic mastocytosis; CMML, chronic myelomonocytic leukaemia; JMML, juvenile myelomonocytic leukaemia; SCLL, stem cell leukaemia-lymphoma syndrome.

specifically associated with SCLL (also known as the 8p11 myeloproliferative syndrome).

SCLL is an extremely rare disease usually characterized by a mixed myeloid and lymphoid phenotype. The typical presentation is one of aggressive lymphoblastic lymphoma (usually T cell), eosinophilia, monocytosis and other blood and bone marrow evidence of clonal myeloproliferation. The disease rapidly progresses into acute leukaemia (usually myeloid). The hallmark of SCLL is a cytogenetic translocation between chromosome 8p11 and a spectrum of partner chromosomes as outlined in Table 2; these translocations result in fusion oncogenes that always involve exon 9 of *FGFR1*, located on 8p11 (Table 2) [292–307].

In SCLL, *FGFR1* mutation is present in both myeloid and lymphoid lineage cells and some of the associated fusion genes have

been shown transform cell lines [301, 308–310] and induce SCLL (*ZNF198-FGFR1)* [311] or CML (*BCR-FGFR1)* [310] like disease in mice. Consistent with this laboratory observation, some patients with *BCR-FGFR1* mutation manifest a more indolent, compared to SCLL, disease phenotype [301]. The mechanism of FGFR1 activation in SCLL is similar, in most cases, to that seen with PDGFRB-associated CEL; the tyrosine kinase domain of FGFR1 is juxtaposed to a dimerization domain from the partner gene, although oligomerization motifs are not always identified in the partner gene [307].

SCLL is refractory to usual chemotherapy and some (*e.g.* PKC412) but not other (*e.g.* imatinib) kinase inhibitors have been shown to inhibit *in vitro* kinase activity as well as cell proliferation induced by *ZNF198-FGFR1* [301, 312]. Haematopoietic stem cell expression of *ZNF198-FGFR1* in mice induces an MPN phenotype as well as activation of the downstream effector molecules PLC-γ, STAT5 and phosphatidylinositol 3-kinase/AKT [312]. PKC412 (*N*-benzoyl-staurosporine) is a small molecule tyrosine kinase inhibitor with activity against FLT3, protein kinase C, CDC2 and receptors for PDGF, FGF and VEGF. The drug has been shown to inhibit ZNF198-FGFR1 kinase and downstream effector activity, reduce proliferation of *ZNF198-FGFR1* transformed cell lines and favourably affect survival of mice with *ZNF198-FGFR1*-induced MPN [312]. Whether or not the drug will work in human beings with SCLL is not currently clear although one PKC412-treated patient experienced an improvement in leukocytosis, lymphadenopathy and splenomegaly over 6 months before receiving allogeneic stem cell transplant [312].

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