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Clinical Cancer Research

Molecular Pathways: Fibroblast Growth Factor Signaling: A New Therapeutic Opportunity in Cancer

A. Nigel Brooks, Elaine Kilgour, and Paul D. Smith

Abstract

The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling axis plays an important role in normal organ, vascular, and skeletal development. Deregulation of FGFR signaling through genetic modification or overexpression of the receptors (or their ligands) has been observed in numerous tumor settings, whereas the FGF/FGFR axis also plays a key role in driving tumor angiogenesis. A growing body of preclinical data shows that inhibition of FGFR signaling can result in antiproliferative and/or proapoptotic effects, both *in vitro* and *in vivo*, thus confirming the validity of the FGF/FGFR axis as a potential therapeutic target. In the past, development of therapeutic approaches to target this axis has been hampered by our inability to develop FGFR-selective agents. With the advent of a number of new modalities for selectively inhibiting FGF/FGFR signaling, we are now in a unique position to test and validate clinically the many hypotheses that have been generated preclinically. *Clin Cancer Res; 18(7); 1855–62. ©2012 AACR.*

Background

Fibroblast growth factors (FGF) and their receptors (FGFR) tightly regulate key cell behaviors, such as proliferation, differentiation, migration, and survival, and are fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults. Dysregulation of the FGF/FGFR signaling pathway has been associated with many developmental disorders and with cancer.

FGFs and their receptors

The FGF family comprises 18 secreted ligands, which can be divided into 2 subfamilies: the hormone-like FGFs (FGF19, 21, and 23) and the canonical FGFs (FGF1–10, 16–18, and 20; ref. 1). FGFs are readily sequestered to the extracellular matrix by heparan sulfate proteoglycans (HPSG). For signal propagation, FGFs are released from the extracellular matrix by proteases or specific FGF-binding proteins, with the liberated FGFs subsequently binding to a cell-surface FGFR in a ternary complex consisting of FGF, FGFR, and HPSG (1). The hormonal FGFs have a low affinity for heparin-like molecules and instead rely on Klotho proteins as essential tissue-selective cofactors for binding to their cognate FGFR (2).

There are 5 FGFRs, of which 4 (FGFRs 1–4) are highly conserved single-pass transmembrane tyrosine kinase receptors (3). The extracellular regions of these receptors comprise 3 immunoglobulin (Ig)–like domains (I–III); IgII and IgIII form the FGF ligand-binding site, with an acidic, serine-rich region located between IgI and IgII (the acid box; ref. 4). FGFRs 1 to 3, but not FGFR4, are subject to alternate splicing in IgIII, creating IIIb and IIIc variants with differing ligand-binding specificities that are expressed in a tissue-specific manner (3). The intracellular region of FGFRs 1 to 4 contains a juxtamembrane split kinase domain, which contains the classical tyrosine kinase motifs and a carboxy-terminal tail (3). The fifth receptor, FGFR5, can bind FGFs with high affinity but lacks the intracellular tyrosine kinase domain, and its role is less well understood (5).

FGF/FGFR signaling

Dimerization of the ternary FGF:FGFR:HPSG complex leads to a conformational shift in the FGFR structure, resulting in intermolecular transphosphorylation of the intracellular tyrosine kinase domain and carboxy-terminal tail (3). Subsequent downstream signaling occurs through 2 main pathways via the intracellular receptor substrates FGFR substrate 2 (FRS2) and phospholipase Cγ (PLCγ), leading ultimately to upregulation of the Ras-dependent mitogen-activated protein kinase (MAPK) and Ras-independent phosphoinositide 3-kinase (PI3K)–Akt signaling pathways (Fig. 1; ref. 5). Other pathways can also be activated by FGFRs, including STAT-dependent signaling (3).

FGF/FGFR signaling is tightly regulated by feedback mechanisms that occur at several points in the signaling pathway. For example, FGF induces SPRoutY (SPRY) proteins, which in turn are important negative regulators that bind to growth factor receptor–bound protein 2 (GRB2), thereby disrupting downstream signaling. FGF signaling also induces proteins such as MAPK phosphatase 3 (MKP3) and Similar Expression to FGF (SEF) that either compete for

Authors' Affiliation: Oncology Innovative Medicines, AstraZeneca, Alderley Park, Macclesfield, United Kingdom

Corresponding Author: Nigel Brooks, Oncology Innovative Medicines, AstraZeneca, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK. Phone: 44-(0)1625-519-347; Fax: 44-(0)-1625-582-828; E-mail: Nigel.Brooks@astrazeneca.com

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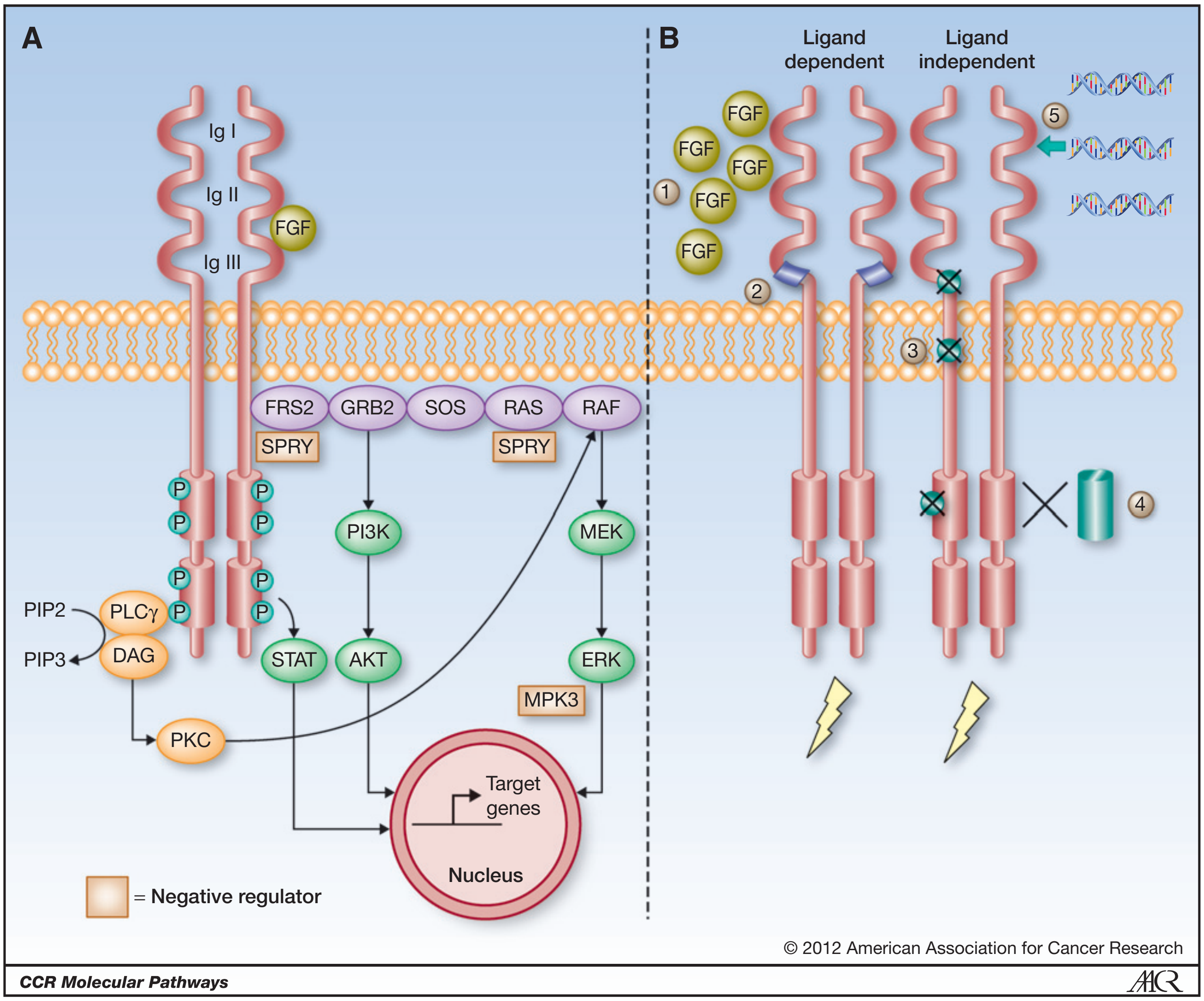

Figure 1. FGFR structure, signaling, and dysregulation in cancer. A, basic structure of an FGFR and downstream signaling. FGFRs are single-pass transmembrane receptor tyrosine kinases with an extracellular domain that comprises 3 IG-like domains (IgI–III) and an intracellular split tyrosine kinase domain. A complex is formed among the FGF ligand, heparan sulfate, and FGFR to cause receptor dimerization and transphosphorylation at several tyrosine residues in the intracellular portion of the FGFR. Subsequent downstream signaling occurs through 2 main pathways: via the intracellular receptor substrates FRS2 and PLCγ, leading ultimately to upregulation of the Ras-dependent MAPK and Ras-independent PI3K–Akt signaling pathways. Other pathways can also be activated by FGFRs, including STAT-dependent signaling. Negative regulation of the FGFR signaling pathway is mediated via FGF-regulated inhibitory factors such as SPRY and MKP3. B, FGFR dysregulation in cancer. Ligand activation of FGFRs can be dysregulated when a cell overproduces FGF ligand (1) that activates a corresponding FGFR, or when a cell produces splice-variant FGFRs (2) that have altered specificity to endogenous FGF ligands. Ligand-independent dysregulation of FGFRs can occur when an FGFR becomes mutated (3), leading to receptor dimerization or constitutive activation of the kinase, or when a gene translocation occurs (4), whereby the FGFR fuses with a transcription factor or promoter region resulting in overexpression or activation of the FGFR. A third mechanism is when a gene amplification for the receptor occurs (5), resulting in grossly exaggerated expression of the receptor. Other mechanisms of FGFR dysregulation include germline SNPs, which are associated with increased cancer risk or a poor prognosis, and impairment of the normal negative feedback mechanisms, such as reduced expression of the negative regulator SPRY.

substrate binding or cause receptor dephosphorylation (6). Other molecules have been identified that can attenuate signaling, including the cell-surface molecules *N*-CAM and *N*-cadherin and the sprouty-related enabled/vasodilator-stimulated phosphoprotein homology 1 domain-containing protein (5).

From this brief overview, it is clear that the FGF/FGFR signaling pathway is multifactorial and complex. It has evolved in a way that subserves the many different biologic functions of FGFs that occur in a tightly regulated temporal and spatial manner throughout development and in adult life.

Mechanisms of oncogenic FGF/FGFR signaling

It has long been recognized that FGFRs are overexpressed in many cancer cell types. Our understanding of the

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mechanisms by which FGFR signaling is dysregulated and drives cancer has increased significantly in recent years. Arguably, the most compelling of these mechanisms involve genetic lesions in *FGFR*s that, in some cases, define *FGFR*s as *bona fide* oncogenes to which tumors cells are addicted (7). The mechanisms of dysregulation are briefly summarized below and depicted in Fig. 1B.

Activating mutations

FGFR mutations that confer constitutive activation have been described in a number of congenital skeletal disorders (5). *FGFR*s have been identified as among the most commonly mutated kinase genes in human cancers, with mutations in *FGFR2* and *FGFR3* being most prevalent (5). For example, approximately 50% to 60% of nonmuscle invasive and 17% of high-grade bladder cancers possess *FGFR3* mutations that cause constitutive FGFR dimerization and activation (8). Activating and oncogenic *FGFR2* mutations located in the extracellular and kinase domains of the receptor have been described in 12% of endometrial carcinomas (9). Importantly, the *FGFR2* mutations found in endometrial cancer confer sensitivity to FGFR inhibition (9). More recently, *FGFR2* mutations have been described in 5% of squamous non–small cell lung cancers (NSCLC; ref. 10), although full validation of these as activating mutations has not been reported. *FGFR3* mutations in bladder cancer and *FGFR2* mutations in endometrial cancer are mutually exclusive with mutations in *HRAS* and *KRAS*, respectively. In addition, mutations in the FGFR4 kinase domain have been found in the childhood soft tissue sarcoma rhabdomyosarcoma, causing autophosphorylation and constitutive signaling (11).

FGFR gene amplification

FGFR gene amplification often leads to FGFR overexpression, which can provoke ligand-independent signaling. In breast cancer, amplification of the genomic locus of *FGFR1* (8p11–12) occurs in approximately 10% of predominantly estrogen receptor (ER)–positive patients (12). *In vitro* studies support the potential oncogenic nature of *FGFR1* amplification (13); however, due to the gene-dense nature of the 8p11-12 amplicon in breast cancer, there is continuing debate about the identity of the driving oncogene. More recently, *FGFR1* has been found to be amplified in 22% of squamous NSCLC (14), and these amplifications seem to confer dependence upon FGFR signaling. Unlike the broad amplicon containing *FGFR1* found in breast cancers, the amplicon in lung is more focal; it remains to be seen if these differences influence the degree of addiction to FGFR1. *FGFR2* amplifications have been reported in up to 10% of gastric cancers, most of which are diffuse-type with relatively poor prognosis (15). Further, in an *FGFR2*-amplified gastric cancer cell line, Snu-16, *FGFR2* downregulation led to significant inhibition of cell growth and survival that further translated into tumor growth regression *in vivo* (16). In some gastric cancer cell lines, *FGFR2* amplification is accompanied by deletion of the coding exon located proximal to the C-terminus (17). This deletion impedes receptor internalization, thereby contributing to constitutive activation of the receptor. The presence of *FGFR2* gene amplifications in gastric cancer is associated with sensitivity to inhibition of FGFR signaling by tyrosine kinase inhibitors and monoclonal antibodies in preclinical models (18, 19).

Chromosomal translocations

Several *FGFR* translocations have been identified in hematologic malignancies, whereby chromosomal rearrangement results in a protein fusing to the kinase domain of an FGFR. Fusion proteins are located in the cytosol, do not undergo lysosomal degradation, are not susceptible to feedback inhibition, and are permanently dimerized in the absence of ligand. Consequently, these translocations lead to FGFR3 overexpression, permanent dimerization of the fusion protein–FGFR complex, and continuous signaling. The mechanism of proliferation is dependent on the type of fusion protein and seems to be disease specific (20). A t(4;14) intergenic translocation, bringing *FGFR3* and the adjacent Multiple Myeloma SET domain (*MMSET*) gene under the control of the Ig heavy chain (*IGH*) promoter, has been identified in 10% to 20% of multiple myelomas and is associated with poor prognosis and dependence upon FGFR signaling (21, 22). *FGFR3* translocations are rarely found in prodromal conditions of multiple myeloma, implicating these translocations in the conversion to full multiple myeloma.

Autocrine and paracrine signaling

Although many of the mechanisms discussed so far are the result of genetic dysregulation of the FGF/FGFR signaling axis, ligand-dependent signaling is also likely to play a key role in cancer development. Autocrine FGF overproduction has been reported in many tumor types (5). *In vitro* studies have shown that FGF5 overexpression has been associated with a number of tumor cell lines (lung, esophagus, melanoma, colon, and prostate; ref. 23), and in hepatocellular carcinomas (HCC), the upregulation of FGF2, 8, 17, and 18 initiates autocrine growth stimulation, cell survival, and neoangiogenesis (24–27). Further, HCC has been found to develop in transgenic mice overexpressing the hormonal FGF19 (28), and *FGF19* is found on an amplicon on chromosome 11q that also invariably contains the adjacent *FGF3*, *FGF4*, and Cyclin D1 (*CCND1*) genes. This amplicon is found in various diseases, including head and neck squamous cell carcinoma, breast cancer, and squamous NSCLC. Although there is uncertainty about the key oncogenic gene on this amplicon or a presumption that it is *CCND1*, genetic knockdown of *FGF19* inhibits the growth of HCC cell lines carrying the amplicon (29). Autocrine FGF2–FGFR1 feedback loops have also been reported in NSCLC cell lines and in human melanomas grown as subcutaneous tumors in nude mice (30, 31).

Paracrine production of FGFs has also been reported in multiple tumor types. High levels of serum FGF2 have been observed in small cell lung cancer and are associated with a poor prognosis (32), possibly because of an FGF2-mediated cytoprotective effect, whereby the expression of

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antiapoptotic proteins are upregulated, promoting resistance to current anticancer treatments (33). Increased paracrine expression of one or more of FGF1, 2, 4, 5, 8, and 18 has been found to promote tumor neoangiogenesis in preclinical models via the main endothelial FGFRs, FGFR1 and 2 (34). Poor prognosis has been associated with neoangiogenesis in ovarian cancer and melanomas (35).

Altered FGFR splicing

In addition to overexpression of FGFs, altered gene splicing of *FGFR*s is another mechanism by which ligand-dependent signaling is upregulated. Altered *FGFR* splicing can allow tumor cells to be stimulated by a broader range of FGFs than would be capable under normal physiologic conditions (36). Altered splicing of the IgIII domains in FGFRs 1, 2, and 3 can switch receptor binding affinity in cancer cells towards FGFs found in the healthy stroma, creating an aberrant paracrine signaling loop (37). In bladder and prostate cancer cell lines, a switch from the FGFR2-IIIb isoform to the IIIc isoform has been associated with tumor progression, epithelial–mesenchymal transition, and increased invasiveness (37).

Other Mechanisms of Oncogenic FGF/FGFR Signaling

In addition to the predominant mechanisms of FGF/FGFR dysregulation summarized above, several other mechanisms have been identified that may also contribute to cancer development.

Germline single-nucleotide polymorphisms

Genome-wide association studies have identified several single nucleotide polymorphisms (SNP) located within *FGFR2* intron 2 that are associated with an increased risk of breast cancer (38). Due to the strong linkage disequilibrium between these SNPs, it remains unclear which are mechanistically important, although one of these SNPs (rs2981582) has been reported to be more strongly linked to the development of ER-positive rather than ER-negative breast cancer (39). An SNP located within *FGFR4* causing a G388R substitution has been associated with poor prognosis following the onset of cancer (40). The arginine substitution increases receptor stability and induces a migratory phenotype resulting in a more aggressive behavior in multiple cancer types, including breast cancer, colon cancer, and lung adenocarcinoma.

Dysregulation of signal attenuation

Increased FGF/FGFR signaling can also result from impairment of the normal attenuation and negative feedback steps. Mutations in proteins involved in FGFR internalization can cause increased or prolonged signaling (41). Mutations causing alterations in the structure of FGFRs may also prevent efficient internalization and degradation of the receptors; the FGFR3 G380R substitution identified in bladder cancer increases recycling of the receptor, thereby escaping degradation and resulting in signal prolongation (42). In a splice variant of FGFR2 found to be overexpressed in several cancer cell lines, deletion of the C-terminal tail, including an endocytic motif, contributes to inefficient signal downregulation (43). Loss of expression of negative regulators, including SPRY1, SPRY2, and SEF, has been associated with increased FGF/FGFR signaling in a number of cancers, including prostate and breast cancer (5).

Overall, a consistent finding from these preclinical studies is that dysregulation of FGFR-dependent signaling can contribute to tumor growth and angiogenesis through a variety of mechanisms. These insights have spurred further investigation of the FGF/FGFR pathway as a potential therapeutic target.

Clinical–Translational Advances

On the basis of the evidence for their dysregulation in human cancers, several approaches are being pursued to generate agents to disrupt FGF-ligand/receptor activity, including small-molecule tyrosine kinase inhibitors, monoclonal antibodies, and FGF-ligand traps.

Small-molecule tyrosine kinase inhibitors

Several companies have generated small-molecule tyrosine kinase inhibitors targeting the ATP-binding site of the intracellular tyrosine kinase domain of FGFRs. The most clinically advanced of these are mainly mixed kinase inhibitors, including brivanib, dovitinib, lenvatinib, ponatinib, and nintedanib (Table 1), with dominant anti-VEGF receptor (VEGFR) and/or anti–platelet-derived growth factor receptor (PDGFR) pharmacology. Activity of most of these agents against FGFRs is weak. Although the broader specificity of these compounds could add to efficacy, the inhibition of several tyrosine kinases will likely result in increased side effects, which may limit the ability to achieve doses required for effective FGFR inhibition. Recently, a phase II trial of the mixed VEGFR/FGFR inhibitor dovitinib in *FGFR1*-amplified and nonamplified metastatic breast cancer failed to reach its primary endpoint of improved overall response rate, although it was reported that activity was observed primarily in the subgroup of patients with *FGFR1* gene amplification (44). The implications of this result for the therapeutic potential of FGFR inhibition in *FGFR1* gene amplified breast cancer will remain uncertain until more selective FGFR inhibitors are tested in this setting.

The second-generation compounds are potent FGFR inhibitors with a greater margin for selectivity versus VEGFR and other tyrosine kinases. The first of these have now entered early clinical development: AZD4547 (AstraZeneca; ref. 45); BGJ398 (Novartis; ref. 46); and LY2874455 (Eli Lilly; ref. 18). *In vitro* studies show that AZD4547 and BGJ398 are more potent inhibitors of FGFR1, FGFR2, and FGFR3 than FGFR4, whereas LY2874455 is a pan-FGFR inhibitor (18, 45, 46). In contrast to VEGFR inhibitors, efficacious doses of AZD4547 and LY2874455 do not induce elevations in blood pressure in several tumor xenograft models, including lung, gastric, multiple myeloma, and bladder cancers (18, 45). All 3 agents have shown antitumor activity in xenograft models with FGFR dysregulation, including

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Table 1. Current clinical development status of FGF/FGFR-targeting anticancer agents

Compound	Company	Target	Clinical development (indication)
Small-molecule tyrosine kinase inhibitors: mixed pharmacology			
Brivanib	Bristol-Myers Squibb	FGFR, VEGFR	Phase III (CRC, HCC, liver)
Dovitinib	Novartis	FGFR, PDGFR, VEGFR, FLT3, c-KIT	Phase III (RCC)
Lenvatinib	Eisai	FGFR, PDGFR, VEGFR	Phase III (melanoma, thyroid)
Masitinib	AB Science	FGFR3, PDGFR, c-KIT	Phase III (GIST, melanoma, MM, pancreatic)
Nintedanib	Boehringer Ingelheim	FGFR, PDGFR, VEGFR	Phase III (NSCLC, ovarian)
Pazopanib	GlaxoSmithKline	FGFR1, FGFR3, VEGFR, PDGFR, c-KIT	Phase III (breast, lung, ovarian, RCC, STS)
PI-88	Progen	FGF1, FGF2, VEGF	Phase III (HCC, liver)
Regorafenib	Bayer	FGFR, PDGFR, VEGFR, c-KIT, RET	Phase III (GIST, CRC)
TSU 68	Pfizer	FGFR, KDR, PDGFR, VEGFR2	Phase III (HCC)
ENMD-2076	Entremed	FGFR1, KDR, FGFR2, PDGFR, VEGFR, FLT3, c-KIT, Aurora K, FLT3	Phase II (ovarian)
Ponatinib	Ariad	FGFR, PDGFR, VEGFR	Phase II (AML, CML)
E3810	Eisai	FGFR1, VEGFR	Phase I (solid tumors)
PBI-05204	Phoenix Bio	FGF2, AKT, NF-κB, p70S6K	Phase I (solid tumors)
Small-molecule tyrosine kinase inhibitors: FGFR selective			
AZD4547	AstraZeneca	FGFR1–3	Phase II (breast, gastric)
BGJ398	Novartis	FGFR1–3	Phase I (solid tumors)
LY2874455	Eli Lilly	FGFR1–4	Phase I (solid tumors)
FGFR antibodies			
RG7444	Roche	FGFR3	Phase I (MM)
FGF-ligand traps			
FP-1039	Five Prime Therapeutics	FGF1, FGF2, FGF4	Phase II (endometrial)

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CRC, colorectal cancer; FLT3, fms-like tyrosine kinase receptor-3; GIST, gastrointestinal stromal tumor; KDR, kinase insert domain receptor; MM, multiple myeloma; RCC, renal cell carcinoma; RET, REarranged during Transfection; STS, soft tissue sarcoma.
Source: www.ClinicalTrials.gov (accessed December 15, 2011).

KMS11 and OPM-2 (*FGFR3* chromosomal translocation/mutation multiple myeloma); SNU16 (*FGFR2*-amplified gastric cancer); and RT112 (FGFR3 high-expressing bladder cancer; refs. 16, 18, 45, 46). Preclinical evidence not only suggests that these compounds have potential as cancer therapies but also indicates the need to identify those patient populations most likely to benefit from therapy based on the presence of tumor *FGFR* mutations or gene amplification and FGFR expression levels. Currently, AZD4547 is being tested in phase I clinical trials in *FGFR1* and *FGFR2* gene–amplified patients (NCT00979134) and in phase IIa trials in *FGFR2* gene–amplified gastric cancer and *FGFR1* gene–amplified ER-positive breast cancer (NCT01457846 and NCT01202591, respectively), whereas BGJ398 is being tested in phase I trials in solid tumors with *FGFR1* and *FGFR2* gene amplification or *FGFR3* mutation (NCT01004224), and LY2874455 is in phase I trials in an unselected cancer patient population (NCT01212107).

Given the broad expression of FGFRs and their key role in development and physiology, toxicity issues are to be expected from FGFR inhibition. The FGFR pathway is involved in normal phosphate and vitamin D homeostasis, and preclinical development of FGFR inhibitors has been complicated by hyperphosphatemia-mediated tissue calcification, owing to blockade of FGF23 release from bone and of the FGF23 signal in kidney (47). FGF23 binds FGFR4 and the IIIc isoforms of FGFR1 and FGFR3 (2, 48), but uncertainty remains about the relative contribution of individual FGFR subtypes to hyperphosphatemia (49–52). In preclinical models, FGFR inhibition results in dynamic modulation of circulating FGF23 levels, with suppressed levels observed during periods of drug exposure (attributable to direct inhibition of FGF23 release from bone) and elevated levels upon drug withdrawal (driven by increased plasma phosphate and vitamin D levels acting on bone to stimulate FGF23 production; ref. 53). Hence, modulation of circulating FGF23, together with elevated vitamin D levels, and the incidence of hyperphosphatemia are potential biomarkers for effective FGFR inhibition. The challenge for specific FGFR inhibitors in the clinic is to determine a therapeutic dose that will balance efficacy against gene-addicted tumors with a manageable tolerability profile.

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Monoclonal antibodies

Therapeutic monoclonal antibodies are being developed in the hope of delivering agents highly specific for a particular FGF ligand or FGFR isoform, thus improving the side-effect profile associated with inhibition of multiple FGFR isoforms. Antibodies can offer the additional advantage of recruiting the immune system to contribute to the antitumor activity via antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity (54). Several anti-FGFR monoclonal antibodies have been assessed in preclinical studies. GP369 (Aveo) and HuGAL-FR21 (Galaxy) anti-FGFR2 monoclonal antibodies have shown efficacy in mouse xenograft models of *FGFR2*-amplified gastric cancer (SNU16) and breast cancer (MFM-223; refs. 19, 55). Antibodies raised against FGFR3 have been shown to be efficacious in the KMS11 t(4;14) translocated multiple myeloma model and in the RT112 bladder cancer model (22). Recently, a humanized anti-FGFR4 monoclonal antibody was reported to inhibit tumor growth in the HUH7 HCC xenograft model (56), and antibodies against the FGFR4-ligand FGF19 have shown efficacy in preclinical models of colorectal cancer and HCC (57). Little information is available on the tolerability profile of any of these agents. Administration of an anti-FGFR1-IIIc antibody resulted in profound weight loss in preclinical *in vivo* models (58), and this has prevented evaluation of its efficacy. The first FGFR antibody to enter clinical development is the anti-FGFR3 antibody MFGR1877S (Genentech) currently in phase I trials in t(4;14) translocated multiple myeloma patients (NCT01122875). Continued clinical research may identify which FGFR isoforms have the greatest efficacy potential and whether inhibition of particular isoforms can avoid side effects associated with broad specificity small-molecule FGFR inhibitors.

FGF-ligand traps

Another approach for inhibiting FGF:FGFR signaling is by using a ligand trap to sequester FGF ligand and thus preventing it from binding to FGFRs. FP-1039 (Five Prime Therapeutics, Inc.) is a soluble fusion protein consisting of the extracellular FGFR1-IIIc domain fused to the Fc portion of IgG1 that prevents the binding of FGF1, FGF2, and FGF4 to their associated FGFRs (59). A key question is whether this agent sequesters the hormonal FGFs, including FGF23; if not, its use could potentially avoid the hyperphosphatemia side effects observed with small-molecule FGFR inhibitors. FP-1039 is currently being evaluated in a phase II trial in patients with endometrial cancers carrying specific *FGFR2* mutations (NCT01244438).

Conclusions

Dysregulation of FGF signaling in cancer is now well understood, and it is becoming increasingly likely that certain tumors become dependent on activation of this pathway for their growth and survival. FGF/FGFR dependence offers the hope of developing new therapeutic approaches that selectively target the FGF/FGFR axis in patients whose tumors are known to harbor FGF/FGFR dysregulation. This research fulfills the ambition of many: to treat the right patient with the right drug for the right target. However, there are significant challenges in developing such an approach, not the least of which is the fact that the FGF/FGFR signaling axis is so intimately involved in many normal biologic processes that will also be disturbed by therapeutic intervention. Additionally, it is currently far from clear how to select patients whose tumors are likely to respond to inhibitors of FGF/FGFR signaling. Overcoming these challenges will require considerable focused effort in the coming years if we are to successfully develop this new therapeutic opportunity in cancer.

Disclosure of Potential Conflicts of Interest

A. Nigel Brooks, E. Kilgour, and P.D. Smith are employees of and hold shares in AstraZeneca.

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A. Nigel Brooks, Elaine Kilgour and Paul D. Smith

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