Breast Cancer RESEARCH

REVIEW

Challenges and opportunities in the targeting of fibroblast growth factor receptors in breast cancer

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Abstract

Activation of the fibroblast growth factor receptor pathway is a common event in many cancer types. Here we review the role of fibroblast growth factor receptor signalling in breast cancer, from SNPs in *FGFR2* that influence breast cancer risk and SNPs in *FGFR4* that associate with breast cancer prognosis, and potential therapeutic targets such as receptor amplification and aberrant autocrine and paracrine ligand expression. We discuss the multiple therapeutic strategies in preclinical and clinical development and the current and future challenges to successfully targeting this pathway in cancer.

Introduction

Activation of tyrosine kinase growth factor receptors presents one of the most common oncogenic events in cancer. Targeting these receptors is a proven therapeutic strategy, as exemplified by the efficacy of trastuzumab in *HER2* amplified breast cancer. However, in the ~85% of breast cancers that do not have *HER2* amplification there has been limited progress with targeting other growth factor receptors. Studies have found potential evidence of efficacy targeting epidermal growth factor receptor (EGFR) in combination with endocrine therapy [1], and insulin-like growth factor 1 receptor in combination with mammalian target of rapamycin inhibitors [2], although none of these approaches have as yet proceeded beyond phase II trials.

Preclinical evidence suggests that activation of fibroblast growth factor receptor (FGFR) signalling is a common event in cancer [3]. Yet the clinical development of therapies targeting the FGFR signalling pathway presents multiple challenges, with diverse mechanisms of pathway activation combined with multiple inhibitors of differing potency and with antibodies in preclinical development. In the present review we discuss the multiple mechanisms through which FGFR signalling contributes to the pathogenesis of breast cancer, and also review the challenges of translating this evidence into clinical trials of therapies targeting the FGFRs.

The fibroblast growth factor signalling system

The fibroblast growth factors (FGFs) and their receptors (FGFRs) play an important role in a wide range of biological functions, controlling developmental events such as brain patterning, morphogenesis and limb development [4,5] with multiple physiological functions in the adult including angiogenesis, wound repair and endocrine functions [6].

The FGF family consists of 18 ligands; FGF ligand nomenclature extends to FGF23 although only 18 FGFs function as ligands, which signal through four high-affinity FGFRs (FGFR1 to FGFR4) [3,6,7]. The majority of FGFs bind to heparan sulphate glycosaminoglycans on the cell surface or in the extracellular matrix, and consequently do not diffuse far from the site of production acting as paracrine or autocrine growth factors – although one FGF ligand family (FGF19, FGF21, FGF23) function as hormones and bind to FGFRs in complex with Klotho proteins [6]. As well as this spatial regulation of ligand–receptor interaction, alternative splicing of the third immunoglobulin domain in the receptor generates two different receptors with highly different ligand specificity (reviewed in [6]).

The majority of FGFs bind receptor in a trimeric complex with heparins, triggering a conformational change in the receptor that leads to activation of the FGFR that results in phosphorylation of multiple sites on the intracellular domain, adapter protein binding and intracellular signalling (reviewed in detail elsewhere [8]). Under physiological conditions, the highly complex FGF signalling pathway is tightly regulated [3]. The deregulation of FGF signalling in cancer results in activation of the pathway without appropriate regulation leading to/contributing to development of cancer, promoting cancer cell proliferation, survival and migration [9-13].

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FGFR signalling in breast cancer pathogenesis

The mouse mammary tumour virus was a major cause of mammary tumours in multiple laboratory mouse strains, vertically transmitted from mother to pup. Mouse mammary tumour virus is a retrovirus that is oncogenic through integration into the genome activating the expression of nearby genes, with *FGF3* and *FGF8* being, along with *WNT* genes, the commonest site of integration [14,15]. The link between FGF activation and mammary carcinoma was subsequently confirmed by experiments with transgenic mice, with both epithelial FGF3 overexpression [16] and FGFR1 activation [17] leading to epithelial proliferation and invasive lesions [17].

Genome-wide association studies have subsequently identified SNPs within the second intron of the *FGFR2* gene that are associated with increased risk of developing breast cancer [18,19]. The minor, predisposing, allele is present in approximately 40% of western populations, although the associated increased risk is relatively small: 1.26-fold for heterozygotes and 1.63-fold for homozygotes [18]. The minor allele increases the risk of developing oestrogen receptor (ER)-positive breast cancer, with only a minor effect on ER-negative breast cancer [20]. Multiple SNPs in the second intron are in very high linkage disequilibrium, and from genetic data it is not possible to pinpoint the causative SNP(s) – although strong biochemical evidence suggests that rs2981578 may be causative through creation of an OCT1/RUNX2 binding site [21], potentially resulting in increased FGFR2 expression in breast cancers with the minor allele variant [21]. Whether this reflects increased epithelial or stromal expression is less clear [22]. *FGFR2 IIIb* knockout mice have a gross failure of branching morphogenesis in the breast [23], raising the possibility that increased FGFR2 expression may simply result in nonspecific changes in breast epithelium that predispose to breast cancer. Further research with transgenic models is required to establish how increased FGFR2 expression results in breast cancer predisposition.

A SNP in *FGFR4* (G388R, Gly338–Arg338) has been shown to confer a more aggressive behaviour and poor prognosis in multiple cancer types, including breast cancer [24-28]. This SNP may increase invasion and motility through altering receptor internalisation, potentially leading to abnormally sustained signalling [29-31]. Recent data have suggested in addition that the FGFR4 Arg388 allele may be associated with a pathological complete response to chemotherapy [32], although potentially conflicting data have also been reported [27]. Although the SNPs in both *FGFR2* and *FGFR4* illustrate the potential importance of FGF signalling in breast cancer pathogenesis, there is no current evidence that either SNP presents a therapeutic target in established breast cancer.

Potential therapeutic targets in breast cancer

There are multiple mechanisms through which FGFR signalling may be activated in breast cancer, that may present potential therapeutic targets (Figure 1).

FGFR2 gene amplification

Amplification of the *FGFR2* gene occurs in a small subset of breast cancer, although in these cancers preclinical evidence suggests this gene is potentially an excellent therapeutic target. Breast cancer cell lines with *FGFR2* amplification show high sensitivity to FGFR inhibitors *in vitro* [33,34], and the *FGFR2*-amplified MFM223 cell line is sensitive *in vivo* to an FGFR2 targeting antibody [35]. FGFR2 is highly overexpressed in amplified cell lines, along with expression of a C-terminal truncated form that results in impaired receptor internalisation [36], and FGFR2 is constitutively active and ligand independent in the amplified cell lines. *FGFR2* amplification is rare in breast cancer, however, present in only 1 to 2% of breast cancer overall [37], although this is enriched to an estimate of ~4% of breast cancers with the aggressive triple-negative breast cancers [33]. *FGFR2* amplifications have also been described in approximately 10% of gastric cancers usually associated with the poor-prognosis diffuse-type histology [38].

FGFR1 *gene amplification*

The *FGFR1* gene is one of the most commonly amplified genes in cancer [39]. Amplification of the chromosomal region 8p11-12, the genomic location of *FGFR1*, is seen in approximately 10% of the breast cancers, predominantly in the ER-positive breast cancers [40-44]. The oncogenic driver of 8p11-12 amplifications has been a source of substantial discord in the scientific literature for the last 15 years, although in the last few years clarity has finally emerged.

Prior misunderstandings have arisen in part from attempts to find a single oncogenic driver within the region, a view that follows the paradigm of *HER2* and 17q21 amplification. Evidence that this simplified model is incorrect emerged from high-resolution comparative genomic hybridisation analysis of breast cancer suggesting two major cores, or peaks, of amplification (core A1 distal at 36.5 to 37.8 Mb, and core A2 proximal at 38.1 to 38.9 Mb; Genome Build 35) [41]. Although the most common pattern was for amplification of both cores, amplification of either core alone occurred in a minority of cancers. Further evidence supporting the existence of two separate cores, and therefore at least two driver oncogenes, has subsequently come from cross-cancer comparisons. Amplification of 8p11-12 is also found in ~10% of squamous lung cancers but with a different genomic structure, with, at least in the published datasets, a frequent pattern of amplification of the proximal A2 core without amplification of the distal A1 core [13].

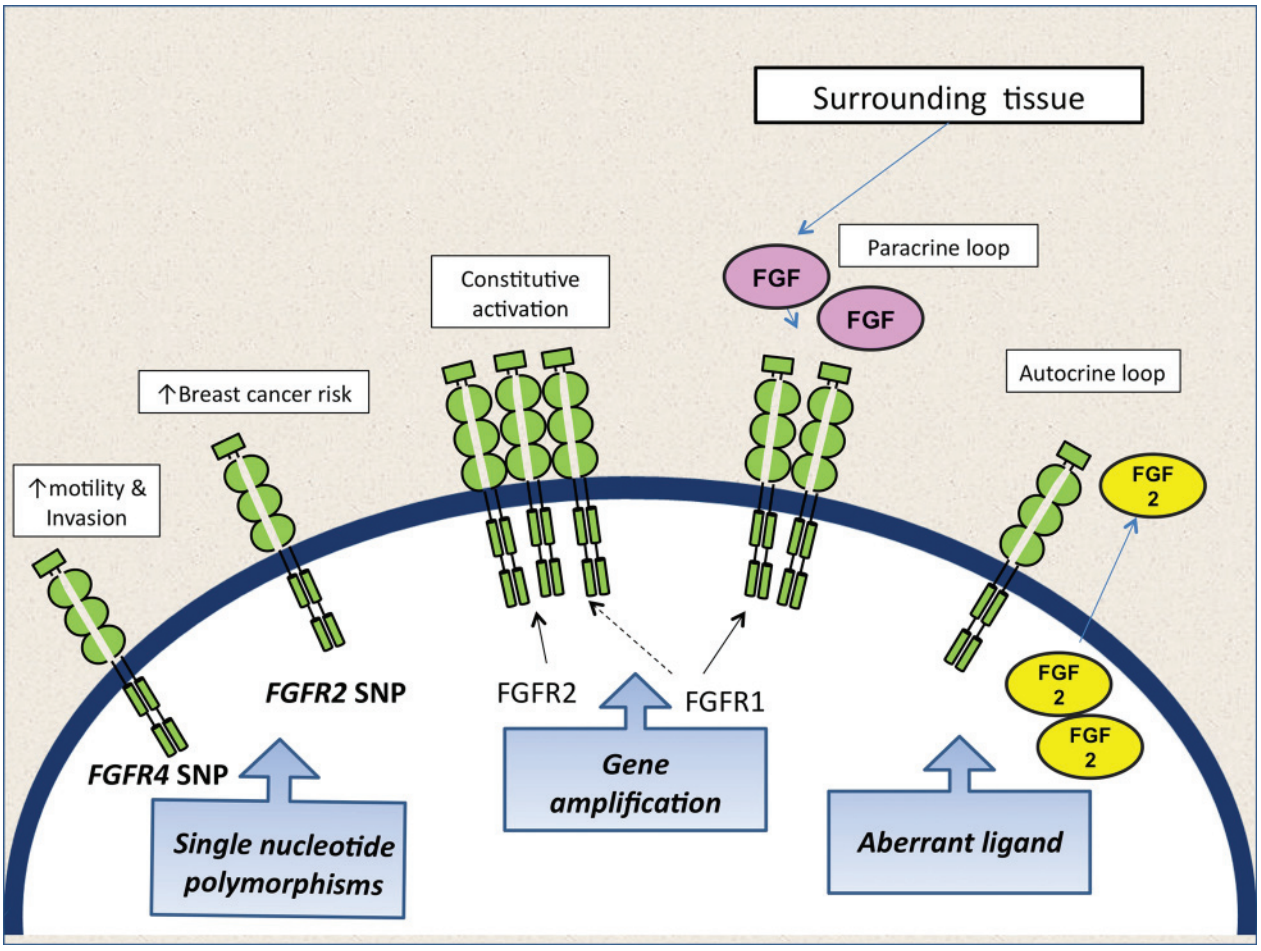

Figure 1. Alterations in the FGFR signalling pathway that influence breast cancer. Single nucleotide polymorphisms (SNPs) influence breast cancer risk (*FGFR2*), and prognosis in established cancers likely through effects on motility and invasive capacity (*FGFR4*). Somatic alterations presenting potential therapeutic targets include amplification of *FGFR1* and *FGFR2*, and aberrant FGF2 ligand expressed in a paracrine or autocrine fashion.

Following on from clarity on the genomic structure, pointing to at least two oncogenic drivers, has come further clarity on the likely oncogenic drivers for each amplification core. ZNF703 has been demonstrated, with high likelihood, to be the principle oncogenic driver of the distal A1 core [45,46], resulting in induction of stem-cell-like phenotypes, potentially also suppressing ER and promoting E2F1 transcriptional activity [47]. In contrast, FGFR1 is the likely target of proximal A2 amplifications – although other genes have been implicated, such as the phosphatase PPAPDC1B [47]. FGFR1 promotes the growth of both breast cancer and lung cancer cell lines with *FGFR1* amplification [13,43,48], with *FGFR1* mRNA overexpression tightly linked to *FGFR1* amplification [12,13], although cases of *FGFR1* amplification without receptor overexpression have been demonstrated [12].

Amplification of *FGFR1* is associated with a marked poor prognosis in breast cancer, specifically in ER-positive breast cancer [11]. We have recently provided evidence that *FGFR1* amplification promotes resistance to endocrine therapy [12], potentially through enhanced ligand-dependent signalling in *FGFR1* amplified cell lines. FGFR1 signalling promoted cyclin D_1 expression and suppressed progesterone receptor expression, and similarly *FGFR1* overexpressed cancers were more likely to be progesterone receptor negative and high in proliferation. Up to 25% of luminal-B-type breast cancers potentially have amplification of *FGFR1* [12], and in these cancers FGFR1 may present an alternative growth/survival signal to escape the effects of endocrine therapy. An association has been reported between increased FGFR1 expression [49], *FGFR1* amplification [43], and lobular breast cancer, although the enrichment for *FGFR1* amplification in lobular cancers is relatively weak [11].

Some important questions remain, however, regarding the role of FGFR1 as an oncogene and therapeutic target. In contrast to *FGFR2*, where an aberrant form of the receptor is expressed, all data currently suggest that

wild-type FGFR1 is overexpressed in amplified cancers. Ligand-independent signalling can be seen at very high levels of wild-type FGFR1 expression, presumably from local crowding of the receptors at the cell surface promoting transient receptor dimerisation [12]. There is little evidence of ligand-independent signalling in amplified breast cell lines or tumours, however, with the limited evidence suggesting enhanced ligand-dependent signalling [12]. This raises important, and unanswered, questions regarding which extracellular splice variants are expressed, and which of the multiple potential ligands activate the receptor.

Cooperative effects of FGFR gene amplification

There is substantial evidence that FGFR signalling co-operates with other oncogenic drivers to drive tumorigenesis. FGFR1 activation substantially accelerated the development of mammary carcinomas in a murine Wnt1 model of mammary carcinoma, and in this model FGFR signalling potentially accelerated tumour development through the promotion of cap-dependent translation [50]. FGFR signalling has also been shown to upregulate the EGFR ligands amphiregulin and epiregulin in mouse mammary cells and MCF7 breast cancer cells [51], and FGFR2 activates EGFR family receptors in *FGFR2* amplified gastric cell lines [38], suggesting cooperation of FGFR and EGFR signalling in oncogenesis. Whether EGFR family signalling is important in the pathogenesis of *FGFR* amplified breast cancers is unknown. In certain contexts, *FGFR1* transformed cells have been shown to be dependent on ribosomal S6 kinase signalling [49] – potentially because FGFR may directly phosphorylate RSK2 and possibly other ribosomal S6 kinase isoforms [52].

FGFR1 is frequently co-amplified with *CCND1* on 11q, and *in vitro* evidence suggests substantial functional interaction between the genes on 8p11-12 and 11q [53]. An uncertain area around FGFR1 as a potential therapeutic target, however, is the relationship between *FGFR1* and *ZNF703*. Whether co-amplification of ZNF703 affects sensitivity to FGFR inhibition in breast cancer will be an important question for future research.

FGFR mutations

Although FGFR activating mutations are found in multiple other cancer types, including *FGFR2* in endometrial cancer [54] and *FGFR3* in bladder cancer [55], there is no evidence for common mutational activation of the FGFRs in breast cancer.

Aberrant autocrine and paracrine signalling

Extending the evidence that *FGFR2* amplifications are enriched in triple-negative breast cancer cell lines, we recently demonstrated that a number of triple-negative breast cancer cell lines are sensitive to FGFR inhibitors *in vitro* [33]. Sensitive cells lines were of the claudin-low subtype, and expressed autocrine FGF2 ligand. Sensitivity was found predominantly in anchorage-independent conditions *in vitro*, and CAL51 cell line xenografts were also sensitive *in vivo* [33]. Expression of cytoplasmic FGF2 ligand was also found to be specific to basal-like breast cancers by immunohistochemistry [33]. This raises the possibility that autocrine FGF2 ligand may be a therapeutic target in basal-like breast cancer, although there is uncertainty as to whether this is specific to the subset of basal-like breast cancers with a claudin-low-type expression pattern.

Assessment of the tumour stromal ligand concentration has shown FGF2 ligand to be expressed at high levels in tumour stroma [56]. Indeed, assessment of elevated FGF2 content in nipple aspirates has been suggested to be a potential diagnostic test for breast cancer [57]. Presumably FGF2 is secreted by activated stromal fibroblasts, but there is no direct evidence for the cell of origin and how this relates to cancer biology is unclear. Elevated FGF2 ligand may potentially be a source for signalling by amplified and overexpressed FGFR1. FGF2 is an angiogenic signalling peptide that is also released in an autocrine/paracrine fashion from activated endothelial cells [58]. There is, however, no association between FGF2 ligand concentrations and microvessel density [56], which has been interpreted as evidence that FGF2 does not promote *de novo* angiogenesis in breast cancer [56]. FGF2 has been shown to cause resistance to VEFGR targeting *in vitro* [59], although it is unknown whether promotes resistance to bevacizumab in breast cancer.

A potential role for paracrine FGF9/FGFR signalling has also been identified in the oestrogen-mediated expansion of a breast cancer stem-cell-like subpopulation *in vitro,* potentially through promoting expression of the Tbx3 transcription factor [60]. The full potential role of FGF autocrine and paracrine signalling in breast cancer is therefore yet to be fully elucidated.

Targeting FGFR signalling

The past decade has seen a marked increase in our understanding of the FGF signalling pathway. Given its role in the pathogenesis of various cancers, several pharmaceutical companies have developed agents targeting FGFs or FGFRs, the most common being small-molecule receptor tyrosine kinase inhibitors targeting the FGFR (Table 1).

Tyrosine kinase inhibitors

Multiple FGFR tyrosine kinase inhibitors are currently in early clinical development, although the inhibitors vary substantially in potency (Table 1). The first generation of inhibitors are multi-targeting ATP competitive inhibitors,

Table 1. Fibroblast growth factor targeting therapies in clinical development

Drug class	Drug name	Target	Stage of clinical development
First-generation TKIs	TKI258 (dovitinib) [64]	FGFR, PDGFR and VEGFR	Phase III
	BMS540215 (brivanib) [71]	FGFR and VEGFR	Phase II
	BIBF 1120 [72]	FGFR, PDGFR and VEGFR	Phase III
	Ponatinib [73]	ABL, FGFR, VEGFR2, PDGFRα, FLT3	Phase II
	E7080 [74]	VEFGR, PDGFR, FGFR, KIT and RET	Phase I
	E3810 [75]	VEGFR1 to VEGFR3 and FGFR1 inhibitor	Phase I
	Sulfatinib [76]	VEGFR and FGFR inhibitor	Phase I
Second-generation TKIs	AZD 4547 [77,78]	Selective FGFR1, FGFR2 and FGFR3 inhibitor	Phase II
	BGJ398 [79]	Selective pan-FGFR inhibitor	Phase I
FGFR antibodies	IMC-A1 [62]	FGFR1-IIIc-specific antibody	Preclinical
	GP369 [35]	FGFR2 blocking antibody	Preclinical
	PRO-001 [80]	FGFR3-specific blocking antibody	Preclinical
	R3Mab [61]	FGFR3-specific antibody	Preclinical
FGFR ligand traps	FP-1039 [81]	FGF ligand trap (blocks multiple FGFs)	Phase I

ABL, c-abl oncogene 1, non-receptor tyrosine kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FLT3, fms-related tyrosine kinase 3; KIT, Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PDGFR, platelet-derived growth factor receptor; RET, ret proto-oncogene; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

with most originally developed as VEGFR inhibitors that also inhibit the FGFRs due to similarity in the ATP binding pocket structure. These inhibitors have varying potency against the FGFRs, and in cellular assays, in particular, have relatively low potency. Consequently, a number of pharmaceutical companies have developed second-generation inhibitors, developing inhibitors that specifically target FGFRs with selectivity over VEGFR and other kinases, with substantially increased potency (Table 1). A number of additional selective FGFR inhibitors are in preclinical development. The kinase domains of FGFR1 to FGFR3 are highly similar and the kinase inhibitors in development inhibit all three members, to a lesser or greater extent. FGFR4 has diverged from the other kinases, and consequently many inhibitors are less potent against FGFR4.

Antibodies

Multiple FGFR antibodies are in preclinical development, with evidence of efficacy for FGFR2 targeting antibodies in *FGFR2* amplified breast cancer models [35] and FGFR3 targeting antibodies in *FGFR3*-driven models [61]. FGFR1 inhibitory antibodies are in preclinical development, but have not proceeded beyond preclinical toxicity testing due to appetite suppression and weight loss, potentially due to FGFR1 targeting in the hypothalamus [62]. A second potential approach is to develop antibodies against specific FGFs, such as FGF2, although none of these antibodies have yet emerged from the early preclinical development. The potential disadvantage of targeting a single FGF is the potential for rescue of any effect by alternative ligands.

Ligand traps

Another approach to targeting ligand-dependent signalling has been to develop ligand traps – such as FP-1039 based on a modified extracellular domain of FGFR1 fused to Fc, which has the potential to sequester multiple ligands including FGF2 [63]. Whether such approaches can work on autocrine ligand production is yet to be fully addressed.

Early clinical trial evidence

The first clinical trial evidence to support FGFR1 as a potential therapeutic target was presented at the 2011 American Society of Clinical Oncology annual meeting. Andre and colleagues presented the results of the phase II (n = 81) multicentre trial of dovitinib, a multi-tyrosine kinase inhibitor that targets FGFR, VEGFR and platelet-derived growth factor receptor in patients with metastatic breast cancer prescreened for *FGFR1* amplification [64]. An unconfirmed response was observed in 15% of women with *FGFR1* amplified ER-positive breast cancer, with no responses in nonamplified ER-positive breast cancer, although this level of response failed to meet the predefined criteria for a positive study [64]. Many patients withdrew from the study for reasons other than disease progression, with the drug less well tolerated than expected in a very heavily pretreated population [64]. Interestingly this study suggested that co-amplification of the 11q genomic region, encompassing *CCND1*, *FGF3*, *FGF4* and *FGF19*, possibly identified sensitive tumours, potentially supporting *in vitro* evidence of cooperation between CCND1 and FGFR1 in oncogenesis [53,65].

Recently a second multi-targeting inhibitor has reported very preliminary evidence of activity, with responses reported in FGFR1 amplified cancers in the dose escalation study of E3810 [66]

Roadmap for clinical development

The multiple different mechanisms through which FGF signalling can be activated necessitate a complex approach to clinical development. Only a subset of breast cancers are likely to be sensitive to FGFR inhibitors, and screening will be required to specifically identify cancers with amplification, or potentially with FGF2 ligand expression.

Yet this complex approach presents substantial challenges for rare targets such as *FGFR2* amplification. One approach is to screen a very large number of patients, as has been done for *ELM4–ALK* translocations in nonsmall-cell lung cancer leading to the licence of crizotinib [67]. Another approach is to potentially combine different cancer types with the same genetic aberration into a single trial – but this requires the target to be the same in different cancer subtypes. *FGFR2* amplification occurs in both breast cancer and gastric cancer, and based on current evidence appears to be a similarly good potential target in both cancers. In contrast, it is not clear that *FGFR1* amplification found in breast cancers, squamous lung cancers [13] as well as oral squamous cell carcinomas [68] is similar in the different cancers, as we have discussed previously.

Matching therapeutic approaches to targets

Multiple different therapeutics are in clinical development, so it is important to consider whether different therapeutic approaches lend themselves to specific oncogenic aberrations. Different FGFR tyrosine kinase inhibitors vary substantially in potency against FGFRs. Kinases with constitutive ligand-independent activation, through mutation or amplification, are generally more sensitive to tyrosine kinase inhibitors than wild-type receptors. Consequently, for targeting oncogenic aberrations such as *FGFR2* amplification, which results in constitutive activation, it is likely that multi-targeted first-generation inhibitors will be of sufficient potency to induce tumour shrinkage. For most of the multi-targeted inhibitors, however, the maximum tolerated dose is not defined by the side effects of FGFR inhibition, and consequently may be administered at a dose below that required to achieve full wild-type FGFR inhibition. Targets such as FGF2 ligand autocrine expression, and potentially *FGFR1* amplification, which signal through a wild-type receptor, may therefore be best approached through antibodies or more potent second-generation inhibitors.

The only first-generation inhibitor that has been shown, at the time of writing, to have inhibitory properties in clinical trials against wild-type FGFR signalling is dovitinib/TKI258, which results in a moderate increase in FGF23 ligand. FGF23 is secreted in bone, and hormonally regulates phosphate excretion from the kidney [64], and inhibition of FGFR in the kidney is expected to increase FGF23 levels. Recent data, however, have suggested that FGFR signalling also promotes FGF23 expression in bone, making interpretation of FGF23 levels complex [69]. This observation emphasises the importance of assessing further biomarkers in inhibitor development, although at present there are no biomarkers that can be used on clinical tumour material to assess FGFR directly, and this is an area that requires urgent attention to direct future development.

The second-generation inhibitors have potentially different challenges around high potency inhibition of multiple FGFRs, which have important physiological roles such as phosphate excretion (bone-derived FGF23 hormonally acting on renal FGFR1) [6]. The potential toxicity of pan-FGFR inhibition could therefore be avoided by use of FGFR inhibitory antibodies whose side effects would be limited to those of a single FGFR member, although FGFR1/FGFR2 antibodies have yet to progress beyond preclinical development.

Challenges to study design

Conducting clinical trials in small subsets presents challenges of recruitment in a study that only enrols a small proportion of potentially eligible patients. For example, considering the 10% rate of *FGFR1* amplification in breast cancer, nearly 1,000 patients would need to be screened for a 100-patient phase II trial; and an even larger number would be needed for a phase III trial. The complexity of targets such as *FGFR1* amplification potentially also requires even larger trials to identify within amplified cancers those cancers that are sensitive to FGFR inhibition. This factor potentially argues for a different approach to clinical development, focused on biomarker analysis – ideally with biopsy at study entry, as biomarkers may alter through prior therapy, paired with biopsy on study completion to confirm target inhibition and to identify potential determinants of sensitivity.

Conclusion

Substantial progress is being made in understanding how FGF signalling may impact breast cancer pathogenesis and progression, but we are only at the beginning of understanding how, and in which cancers, FGF signalling might be targeted for therapeutic benefit. Should FGFR inhibitors be developed in combination with conventional therapies? How does FGFR signalling effect respond to chemotherapy? With everolimus heading towards licensing in metastatic breast cancer [70], how will mammalian target of rapamycin inhibition impact on

FGFR signalling? We look forward to further scientific and clinical research to clarify the potential role of FGFR targeting in breast cancer treatment.

Abbreviations
FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; SNP, single nucleotide polymorphism.

Competing interests
NCT has consulted for and received honoraria from Novartis, and has received research funding from AstraZeneca. VKJ declares that he has no competing interests.

Acknowledgements
NCT is funded by a Cancer Research UK Clinician Scientist fellowship. The authors acknowledge National Health Service funding from the National Institute for Health Research Biomedical Research Centre.

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Published: 19 June 2012

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doi:10.1186/bcr3139
Cite this article as: Jain VK, Turner NC: **Challenges and opportunities in the targeting of fibroblast growth factor receptors in breast cancer.** *Breast Cancer Research* 2012, **14:**208.