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Farnesyltransferase Inhibitor in Cancer Treatment

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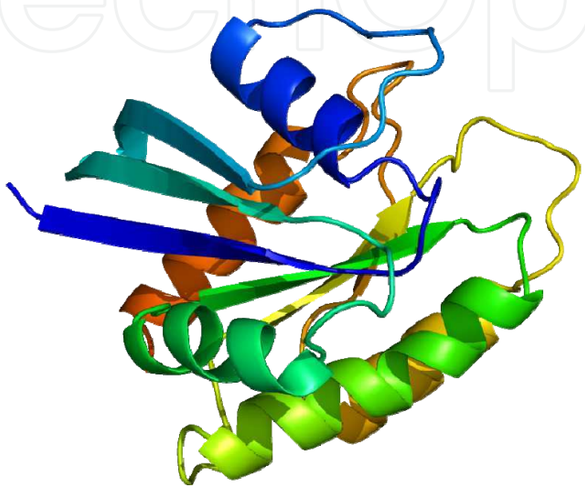
1. Introduction

Cancer is a class of diseases characterized by uncontrolled growth of abnormal cells anywhere in the body and the ability of these cells to invade other locations in the body, either by direct growth into adjacent tissue or by migration of cells to distant sites. This unregulated growth is caused by damage to DNA, resulting in mutations to genes that encode proteins controlling cell division. To prevent this unregulated growth various anticancer drug (Chen et al., 2011; Kim & Dass 2011) have been developed. But these drugs have severe toxicity and are not well tolerated in the patient. Therefore, the major goal in anticancer drug discovery process is to discover and develop innovative therapies that exhibit a real improvement in effectiveness and/or tolerability. In cancer therapy, continuous effort has been made to explore the new targets. Cancer research is largely focused on prospective targets identified by basic science such as the oncogenic signal transduction pathway, oncogenes, tumor suppressor genes, and genes involved in the regulation of the cell cycle and apoptosis or programmed cell death (Gridelli et al., 2003; Hochhaus et al., 2004; Lau et al., 2011; Minna et al., 2004). Proteins mediating their effects are obvious targets for cancer therapy because, by definition, these proteins are involved in the primary transformation of normal cells. Proteins that transmit abnormal growth signals offer enticing points of intervention for the treatment of cancer. One potential target is the Ras family of proteins, which are mutationally activated in a wide range of human tumor types and are important contributors to the neoplastic phenotype (Barbacid et al., 1987; Biagi et al., 2010; Bollag et al., 1991; Bos et al., 1989).

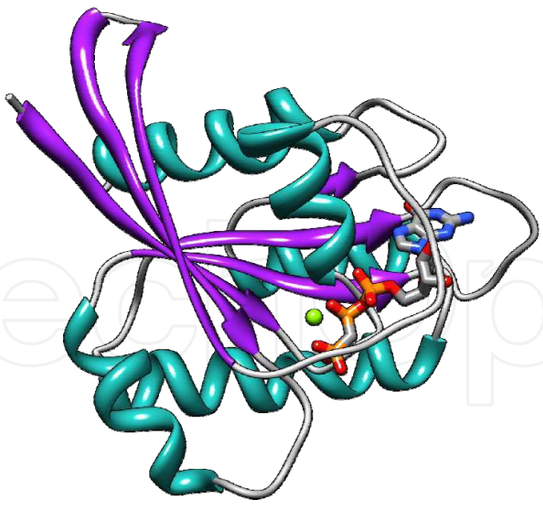
2. Ras protein

Ras proteins have been the subject of intense research investigation by the biomedical research community since 1982 (James et al., 1996). Ras is the name of a protein, the gene that encodes it, and the family and superfamily of proteins to which it belongs. Ras proteins are guanine nucleotide–binding proteins that play pivotal roles in the control of normal and transformed cell growth. The Ras superfamily includes the Ras, Rho, and Rab families. There are three Ras proto-oncogenes: the H-*ras* gene (Harvey murine sarcoma viral

oncogene homolog, Fig. 1), the K-*ras* gene (Kirsten murine sarcoma viral oncogene homolog), and the N-*ras* gene (neuroblastoma oncogene homolog) (Boguski et al., 1993; Ellis et al., 1981; Marcos et al., 2003; Ruta et al., 1986; Shimizu et al., 1983). The *ras* oncogenes encode four low molecular weight (21 kDa) proteins, Ras (H-Ras, N-Ras, and K-Ras4A and K-Ras4B, resulting from two alternatively spliced K-*ras* gene products) (Morgillo et al., 2007), that, in normal untransformed cells, cycle between an inactive guanosine 5'-diphosphate (GDP)-bound state and active guanosine 5'-triphosphate (GTP)-bound state at the inner surface of the plasma membrane in mammalian cells.



(a)



(b)

Fig. 1. a. Structure of the HRAS protein (Elaine 2009), b. Ribbon diagram of H-ras (Elaine 2010).

The highly conserved nature of the variable region across mammalian species indicates that Ras proteins serve specific functions. They are very important molecular switches for a wide

variety of signal pathways that control such processes as cytoskeletal integrity, proliferation, cell adhesion, apoptosis, and cell migration (Zhao et al., 2011). The final four amino acids play an important role in specifying subcellular localization of the Ras protein. All Ras proteins have a specific amino acid sequence motif at the carboxyl (C) terminus, commonly referred to as the CAAX sequence (C, cysteine; A, aliphatic amino acid; X, any amino acid usually methionine or serine) which signals for posttranslational modifications (Cadinanos et al., 2003; Epifano et al., 2007; Roberts et al., 2008; Rowinsky et al., 2006).

Ras is a G protein and functions as a molecular switch cycling between GTP- bound "on" and GDP-bound "off" states (Seki et al., 1996). It is activated by guanine exchange factors which are themselves activated by mitogenic signals and through feedback from Ras itself. It is inactivated by GTPase-activating protein, which increases the rate of GTP hydrolysis, returning Ras to its GDP-bound form, simultaneously releasing an inorganic phosphate. Ras is synthesized in the cytoplasm as a biologically inactive cytosolic propeptide (Pro-Ras) and undergoes a series of closely linked posttranslational modifications by the covalent addition of a non-polar farnesyl group to the COOH-terminal, thereby increasing its hydrophobicity (Kyathanahalli & Kowluru, 2011). The C-termini triplet of amino acids is cleaved off, leaving a farnesylated, methylated cysteine residue at the carboxyterminus. Ras is then localized to the inner surface of the plasma membranes (Gibbs et al., 1993; Hancock et al., 1989, 1990; Jackson et al., 1990; Salaun et al., 1999), in which Ras cycles from an inactive GDP-bound state to an active GTP-bound state. Once in its GTP-bound form, Ras activates several downstream effector pathways that mediate increased gene transcription and rapid cell proliferation (Fig. 2). The most critical step, farnesylation, adds a 15-carbon farnesyl isoprenoid group to H-, K-, and N-Ras through a thioether bond and is catalyzed by Farnesyl transferase (FTase) (Kho et al., 2004; Ljuca et al., 2011).

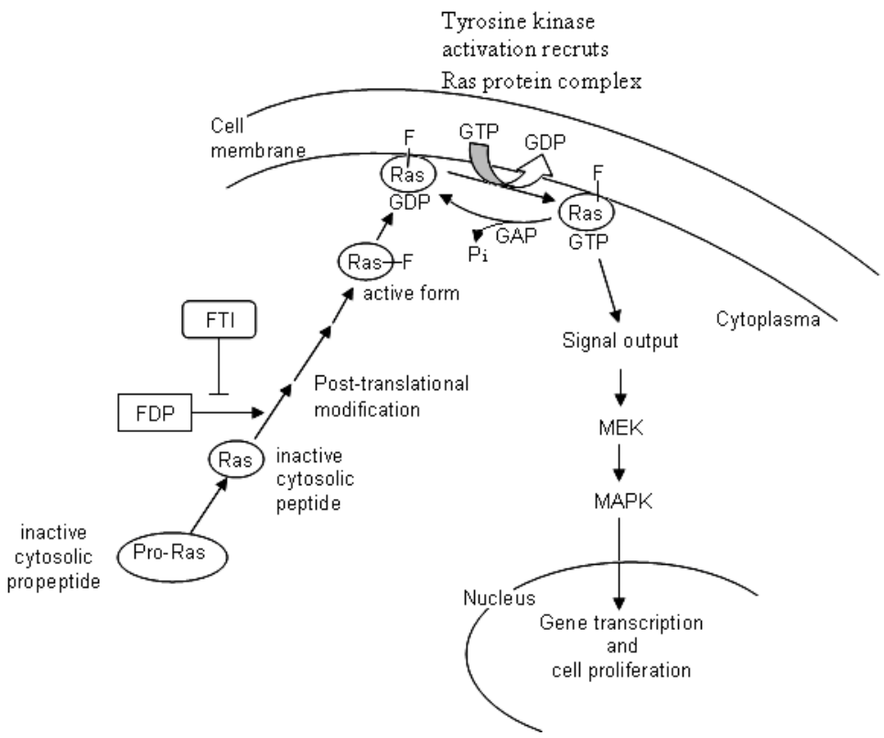


Fig. 2. Ras-dependent signal transduction with Farnesyltransferase inhibitor (FTI) target.

3. Mutations of Ras in human cancers

Ras is mutated to an oncogenic form in cancer, so the Ras and Ras-related proteins are often deregulated, leading to increased invasion and metastasis, and decreased apoptosis. In part of the human tumors, one of the three *ras* genes harbored a point mutation, they result in a permanently active GTP-bound form of Ras (Le Moulec et al., 2009; Lowry & Willumsen et al., 1993).

Mutant Ras proteins transform cells because they continuously activate the downstream effector pathways, including those involved in cell proliferation, in the absence of any upstream growth factor stimulation. Mutations of *ras* occur in approximately 30% of all human cancers, including a significant proportion of pancreatic and colorectal carcinomas (Clark et al., 1995; Khosravi-Far et al., 1994; Shimoyama, 2011; Widemann et al. 2006). With regard to the three *ras* genes, mutation of K-*ras* is most commonly found in human tumors, whereas N-*ras* mutations are encountered less often and H-*ras* mutations rarely. The type of *ras* mutation seems to correlate with tumor type. Although activating *ras* mutations are mainly involved with myeloid malignancies and carcinomas of the breast, colon, pancreas, lung, and thyroid, they have also been detected in many other types of cancer (Beaupre et al., 1999; Zheng et al., 2010).

4. Post-translational modification of Ras

Ras proteins are tethered to the inner face of the membrane by posttranslational modifications that make them more hydrophobic (Ageberg et al., 2011), which involve prenylation (addition of a lipid moiety) of the protein. After its synthesis as cytoplasmic Pro-Ras, Ras is sequentially modified by farnesylation of the cysteine residue, proteolytic cleavage of the AAX peptide by proteases, and carboxymethylation of the new C-terminal carboxylate by carboxymethyl transferase. As the first step in this sequence, farnesylation is the most critical part of the process (Casey et al., 1989; Cox & Der, 1997; Gibbs & Oliff, 1997; Gelb et al., 1997; Kato et al., 1992; McCormick et al., 1993; Omer et al., 1997; Schafer et al., 1989; Yamane et al., 1990), in which a 15-carbon farnesyl isoprenoid group is transferred from farnesyl diphosphate (FDP) to form a thioether bond with the cysteine moiety in the C terminal tetrapeptide sequence of the Ras protein (Fig. **3**).

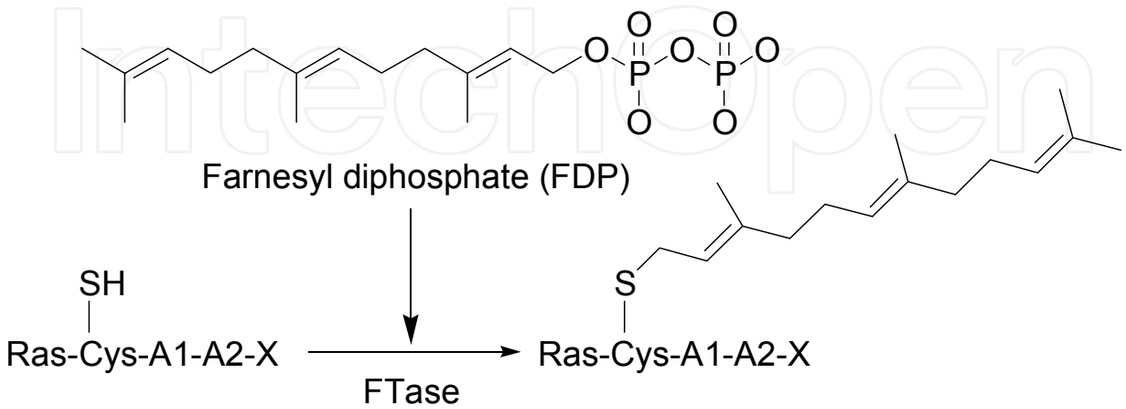


Fig. 3. The first step in Ras posttranslational modification is mediated by FTase, which transfers a farnesyl moiety from FDP to the cysteine moiety in the CAAX motif at the carboxyl terminus of Ras.

In addition, there are other prenyltransferase enzymes, including geranylgeranyl transferases which transfer one or two 20-carbon geranylgeranyl isoprenoid lipid moieties to proteins, again facilitating membrane incorporation. Both farnesylation and geranylgeranylation result in more hydrophobic proteins. The potential for cross-prenylation of proteins such as Ras suggests that geranylgeranyltransferase could restore the function of these proteins if FTase was inhibited (Kim et al., 2010; Marks et al., 2007). However, not all Ras proteins are prenylated by geranylgeranyltransferase, and it is not clear that the function of geranylgeranylated Ras is the same as that of farnesylated Ras, as suggested by the fact that geranylgeranylated normal Ras may be inhibitory. Strategies that are capable of blocking FTase and preventing farnesylation may be expected to inhibit the maturation of Ras into a biologically active molecule, thus turning off signal transduction (Appels et al., 2011; Geryk-Hall et al., 2010).

5. Farnesyl transferase

Farnesyl transferase is located in cell cytosol. FTase is one of the three enzymes in the prenyltransferase group that catalyzes most prenylation reactions and differs in their isoprenoid substrates and protein targets (Fig. 4). FTase adds a 15 carbon (Subramanian et al., 2008) isoprenoid lipid called a farnesyl group to proteins bearing a CAAX motif and its targets include members of the Ras superfamily of small GTP binding proteins critical to cell cycle progression.

FTase is a zinc metalloenzyme that exists as a heterodimer. This heterodimer has two distinct subunits denoted as α and β, having molecular weights of 48 kDa and 46 kDa respectively (Machida et al., 2011; Zhang & Casey, 1996). The X-ray crystal structure of FTase reveals that it has binding sites for both the CAAX peptide and the FDP (Kauh et al., 2011; Park et al., 1997; Wei et al., 2011). It has been shown that geranylgeranyltransferase can prenylate some of the substrates of FTase and vice versa.

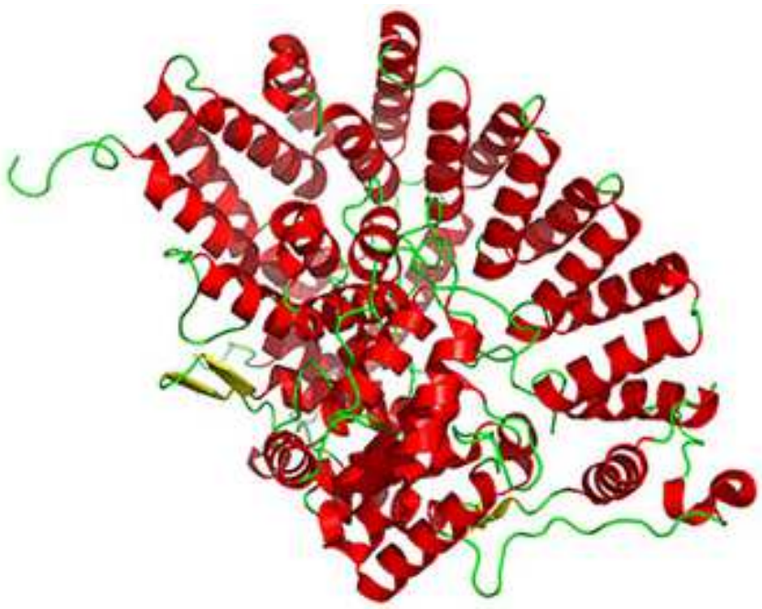


Fig. 4. Structure of Farnesyltransferase (Berman et al., 2000)

6. Farnesyltransferase inhibitors

The introduction of the first 'anti-Ras' agents, the farnesyl transferase inhibitor (FTI), which were proposed to interrupt the crucial post-translational modification of Ras, led to much anticipation of their potential therapeutic benefits (Niessner et al., 2011). The detailed kinetic information about the FTase reaction and the physicochemical nature of FTase substrates has led to the rational design of FTI (Heimbrook & Oliff, 1998; Sebti & Hamilton, 1998). FTI comprise a novel class of antineoplastic agents recently developed to inhibit FTase with the downstream effect of preventing the proper functioning of the Ras protein, which is commonly abnormally active in cancer (Babcock & Quilliam, 2011; Hourigan & Karp, 2010; Kohl et al., 1999). FTIs interfare with bipolar spindle formation during transition from prophase to metaphase in mitosis (Ashar et al., 2000; Crespo et al., 2001).

Currently known FTIs can be divided into three categories based on their mechanism of action: FDP competitive inhibitors, CAAX competitive inhibitors and compounds that inhibit both CAAX and FDP (so-called "bisubstrate analogues") (Crul et al., 2001; Wasko et al., 2011). The second class of compounds in particular has shown promising results. This group can be divided into two subclasses comprising peptidomimetic and nonpeptidomimetic agents, respectively. The high-throughput screening of natural products or compound libraries also led to the discovery of some FTIs which possess good activity.

A number of specific inhibitors have been developed in each of these categories, and subjected to rigorous testing in pre-clinical studies. In the laboratory setting, FTIs revealed the ability to inhibit growth of a wide range of human tumour cell lines, as well as in xenograft and transgenic models (Appels et al., 2005). The anti-tumour outcome has been linked with pleiotropic effects on apoptosis, angiogenesis and the cell cycle.

6.1 FDP analogs

FDP analogs were the first reported active inhibitors of FTase and were designed based on the farnesyl moiety of the FDP substrate. FDP based inhibitors of FTase offer several advantages over bisubstrate analogs or CAAX peptidomimetics in that they are small and non-peptides. Although the compounds that competed with FDP and inhibited Ras processing showed no antitumour activity in animal models (Rowinsky et al., 1999). However, the use of FDP inhibitors in chemotherapy raises several concerns about toxic side effects, since FDP is involved in several biological pathways including cholesterol biosynthesis (Patel et al., 1995). Therefore clinically useful compounds need to be much more selective for FTase than other FDP using enzymes in the cell.

6.2 Peptidomimetics

Development of peptidomimetic inhibitors was initiated upon discovering that FTase activity can be inhibited by a tetrapeptide having the CAAX motif. This was followed by the finding that introduction of an aromatic residue such as phenylalanine at the second ''A'' position of the CAAX tetrapeptide destroys the ability of the peptide to serve as a substrate while maintaining its ability to inhibit FTase reaction (Goldstein et al., 1991).

When this modification contains an aromatic residue at the terminal A position, the tetrapeptide is a non-substrate inhibitor, and this aroused interest in developing low-molecular-weight CAAX peptidomimetics as a principal strategy for FTase inhibition (Brown et al., 1992; Duque et al., 2011; Symons, 1995). Some chemical structures of peptide CAAX peptidomimetics is given in Fig. 5.

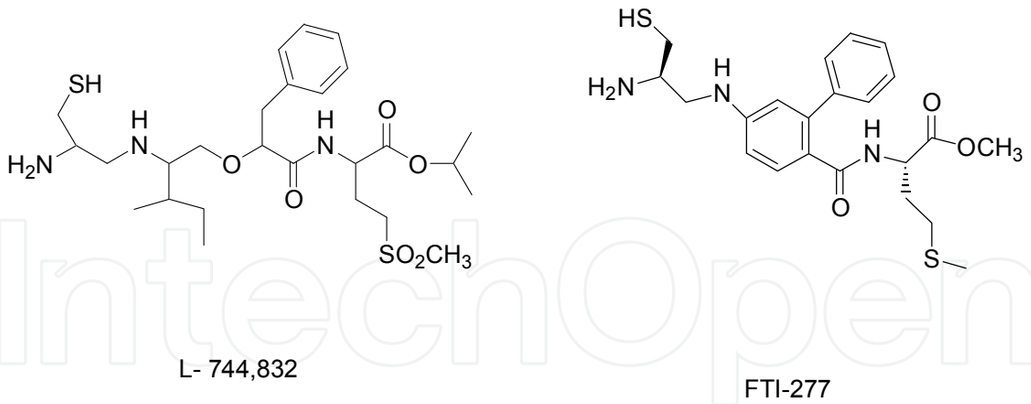


Fig. 5. Peptide CAAX peptidomimetics.

6.3 Nonpeptidomimetic

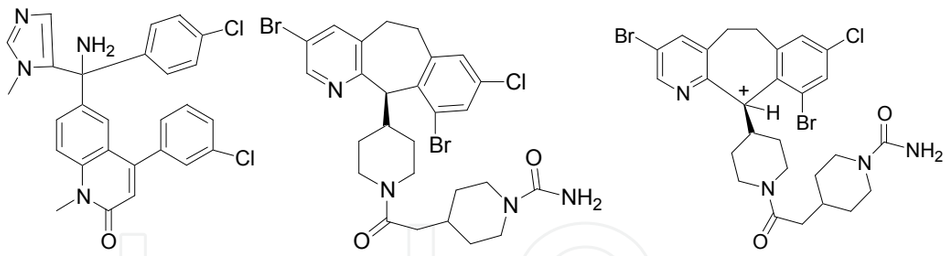
The molecules of this class are potentially able to inhibit almost selectively the farnesylation of different target proteins involved in malignant cell signalling processes. These class of inhibitors constitute a heterogeneous group of FTIs with different action profiles for each target cell type (Manne et al., 1995). R115777 and SCH66336 (Fig. 6), both of which are orally active nonpeptidomimetic, have now entered clinical development (Castaneda et al., 2011). R115777 is an imidazole-containing heterocyclic compound (Epling-Burnette & Loughran 2010; Skrzat et al., 1998), initially developed as antifungals and possess high enzyme specificity and interesting levels of growth inhibition (End et al., 1998; Smets et al., 1999). *In vitro* tests of human tumor cell lines showed 80% overall sensitivity to R115777. SCH66336 is a tricyclic halogeneted compound, which inhibits the growth of several tumour cell lines as well as K-*ras*-transformed xenografts *in vivo* (Bishop et al., 1995). BMS-214662 is an example of a new class of nonpeptide imidazol FTIs, showing high affinity for FTase over geranylgeranyltransferase and it exhibits complete tumour regressions in various tumor xenograft models after both oral and intraperitoneal administration. This compound has recently entered clinical studies.

6.4 Bisubstrate analogs

Bisubstrate analog inhibitors of FTase combine the features of FDP analogues and non-peptide CAAX peptidomimetics and are highly potent in vitro. The bisubstrate analog BMS-186511 (Fig. 6), which is 3-log-fold more selective for FTase than for geranylgeranyltransferase, inhibits Ras signalling and transformed growth with a minimal effect on normal cells. Cytotoxic effects were not seen (Manne et al., 1995; Yan et al., 1995).

6.5 Natural products

A variety of compounds with inhibitory activities against FTase have been identified by screening of natural products isolated from microorganisms (Hara et al., 1993), plants (Khan et al., 2010) and soils. This led to the identification of manumycin, chaetomellic acids, actinoplanic acid A, pepticinnamins, fusidienol, cylindrol A, preussomerin, gliotoxin, 10'-desmethoxystreptonigrin and related analogues as inhibitors of FTase (Singh et al., 1993, 1994, 1995a, 1995b; Tamanoi & Mitsuzawa 1995). Natural compounds, such as Manumycin, which is isolated from Streptomyces sp., act on the FDP-CAAX complex (Leonard et al.,



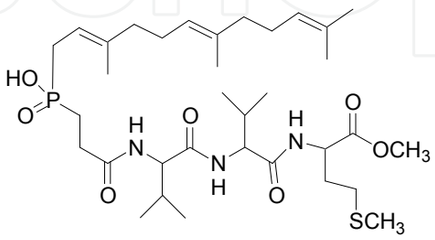


Fig. 6. Nonpeptide CAAX peptidomimetics and Bisubstrate inhibitor.

1997). Some natural products, including the chaetomellic acids, actinoplanic acid A, and manumycin analogs, compete with FDP, whereas other inhibitors, such as the pepticinnamins, compete with the Ras CAAX tetrapeptide (Kainuma et al., 1997). Other natural products, such as fusidienol, preussomerin, gliotoxin, 10'-desmethoxystreptonigrin, and cylindrol A, inhibit FTase noncompetitively.

7. Clinical development of FTIs

The FTIs entered in clinical development, so far, are R115777 (Zarnestra) (Tomillero & Moral 2010), SCH-66336 (Sarasar), L-778, 123 and BMS-214662 (Eskens et al., 2000; Yasui et al., 2002). Among these, R115777 is the most advanced in the clinical development (Fig. **9**) since some phase III studies have been already completed (Tsimberidou et al., 2010). BMS-214662 and L-778, 123 are administrated intravenously, whereas the two other agents, R115777 and SCH66336, are given orally with different schedules (Widemann et al., 2011). Dose-limiting toxicities have included myelosuppression, gastrointestinal disorders, peripheral neuropathy and fatigue. Because of cardiac conduction abnormalities, the clinical development of L-778, 123 has been discontinued. The results from Phase I studies are encouraging. R115777 has given evidence of clinical activity in a minority of patients including those with non small cell lung cancer (NSCLC), colorectal cancer and pancreatic cancer (Zujewski et al., 2000). Phase I studies showed that myelosuppression and neurotoxicity were dose-limiting toxicities. Gastrointestinal toxicities and fatigue were also observed (Crul et al., 2002; Punt et al., 2001; Schellens et al., 2000). A phase II trial in breast cancer with R115777 showed a modest activity with a low toxicity profile and achieving a response rate of 11% and disease stabilization in 35% of patients (Johnston et al., 2003). Other trials are conducted in patients with malignant glioma and haematological malignancies and interesting results are documented (Kurzrock et al., 2003). A phase III

study was conducted in patients with advanced refractory colorectal cancer who had failed two prior chemotherapy regimens. R115777 is currently under study in acute myeloid leukemia (Baer & Gojo, 2011; Robak et al., 2011). Because of its relatively low toxicity profile, R115777 provides an important alternative to traditional cytotoxic approaches for elderly patients who are not likely to tolerate or even benefit from aggressive chemotherapy. SCH66336 is orally active (Field et al., 2008) and its first phase I trial was started in 1997. SCH66336 has shown to inhibit the in vitro anchorage-independent growth of many human tumour cell lines and the growth of a number of human xenografts in a dose-dependent manner (Castaneda et al., 2011). In the first phase I study with SCH66336, 5% NSCLC patient experienced a partial response, disease stabilization in 40% were also described for 5-10 cycles (Adjei et al., 1999). Phase II study of SCH66336 in patients with chemorefractory, advanced squamous cell carcinoma of the head and neck was well-tolerated at a dose of 200 mg twice daily (Hanrahan et al., 2009, Raza et al., 2011). In the phase II study in transitional cell carcinomas, myelosuppression was dose limiting with patients experiencing additional toxicities. Despite significant toxicities, no responses were observed (Winquist et al., 2005). Also, in a second phase II study investigating the effect of SCH66336 in patients with metastatic colorectal cancer, no responses were observed. Phase III studies with SCH66336 have just been started.

Drugs	**Trial Stage**
R115777 (Zarnestra)	Phase III (leukemia, refractory colorectal) Phase II (bladder, brain, breast, malignant glioma, colorectal, leukemia, lymphoma, melanoma, myeloma, pancreatic, sarcoma, haematological malignancies)
SCH-66336 (Sarasar)	Phase II (brain, breast, genitourinary, head and neck)
BMS-214662	Phase II (leukemia)
L778, 123[a]	Phase I

[a] Denotes agents which have been withdrawn because of concerns over demonstrated or potential toxicity

Table 1. FTIs in clinical development

BMS-214662 is administered intravenously and has shown significant activity against several tumour lines in preclinical models as well as potent cytotoxic effects in vitro and in human tumour xenografts (Rose et al, 2001). The oral formulation exhibits dose-dependent gastrointestinal toxicity, which limits its oral dosing (Camacho et al., 2001). BMS-214662 is unique in inducing apoptosis in hematopoietic stem cells. BMS-214662 significantly and selectively induced apoptosis in chronic myeloid leukemia stem cells compared with normal cells [Pellicano, et al 2009]. Phase I clinical trial of the BMS-214662 has shown promising suggestions of single agent activity in patients with advanced solid tumors. There are currently no published phase II trials with this agent. [Eder et al., 2006]

8. Combination with other anticancer drug

As multiple pathways are important for the proliferation, invasion, and metastases of malignant cells, and because combination therapies are often far more effective than are

single-agent regimens, the FTase inhibitors may complement other anticancer agents that may or may not affect Ras-mediated pathways. FTIs target different downstream effectors according to host–tumor interactions, histological tumor type and stage of the tumor and their anti-tumor effects are quite heterogeneous from a prominent anti-angiogenic to an anti-proliferative and an apoptotic effect in different tumors (End et al., 2001). Moreover, resistance to FTIs is reported probably by overexpression of antiapoptotic proteins. Thus, as a single agent, FTIs appear to have modest clinical effects that are not sufficient to induce a long-term tumor inhibition. Additionally, although FTIs demonstrated the capacity to rapidly reduce and nearly ablate large tumors in preclinical studies (rather than simply prevent tumor growth), residual tumors proliferated after withdrawal of the agents. Therefore, combination with other well-chosen targeted therapy might synergize with FTIs and may reduce the need for protracted therapy (David et al., 2010). The overlapping antitumor spectra and nonoverlapping toxicity profiles of FTIs and cytotoxic agents provide a rationale for assessing the efficacy and feasibility of combination regimens. Pre-clinical studies confirm that FTIs can be useful in combination therapy and have showed that combination with cisplatine, taxanes or gemcitabine can improve response (Adjei et al., 2006; Sun et al., 1999 Weber et al., 2011). Although the choice of chemotherapeutic agents to be evaluated in combination with FTIs will ultimately be dependent on the logistics and appropriateness of the agents for the particular clinical setting, the selection may also be based on a unique mechanistic rationale (Table 2). For example, the combination of FTI L-744,832 and taxanes is sustained by the fact that FTIs sensitize tumor cells to paclitaxel-induced mitotic arrest (Moasser et al., 1998).

Therapy	**Trial Stage**	
Cytotoxic chemotherapy		
Alkylating agents	I/II	Glioblastoma
Antimetabolites	I/II	Breast
Taxanes	I/II	Breast
Topoisomerase Inhibitors	I	AML advanced solid tumours
Endocrine therapy		
Aromatase inhibitors	II	Breast
Anti-oestrogen	II	Breast
Targeted therapy		
Trastuzumab	I	Breast
Sorafenib	I	Advanced solid tumours
Bortezomib	I/II	Myeloma
Imatinib	I	CML
Ionizing radiation		
External beam radiotherapy	I	Pancreas/lung/ glioblastoma

Table 2. Current combination studies employing FTIs (R115777 or SCH66336)

SCH66336 potentate the activity of temozolomide and radiation for orthotopic malignant gliomas (Chaponis et al., 2011). Combination of SCH66336 with paclitaxel has been reported, which demonstrated either synergistic or additive activity against a broad panel of human tumor cell lines, except for one breast cancer cell line against which the combination demonstrated antagonism (Khuri et al., 2004; Sharma et al., 2000). Promising preliminary

evidence of efficacy was documented with 38% patients demonstrating partial response (Khuri et al., 2000). The study revealed that the inhibitor SCH66336 did not sensitise cells to all anticancer drugs; whereas the combination with cisplatin was synergistic, for melphalan was additive and no potentiation was observed with 5-FU. Moreover this study reported that the synergism between cisplatin and SCH66336 was cell lines specific and did not appear to correlate with the status of Ras. In addition, in many models the effect of SCH66336 was additive to the effect of cytotoxic agents such as vincristine and cytoxan (Shi et al., 1999). Docetaxel- SCH66336 combination therapy in refractory solid tumors was tolerated in all cohorts with the exception of a 28% incidence of diarrhea (Kauh et al., 2011). Coadministration of continuous and intermittent SCH66336 enhanced the antitumor activity of docetaxel in a panel of prostate cancer models (Liu et al., 2009). In phase II when SCH66336 was given with imatinib, 33% patients had a clinical response or improvement with combination therapy (Druker et al., 2003). Responses were encouraging also in another study of SCH66336 combined with gemcitabine in patients with advanced urothelial tract cancer (Theodore et al., 2005).

The combination of R115777 with cytotoxic agents such as cisplatin and paclitaxel induced additional antiproliferative activity against human breast, pancreatic, and melanoma cells growing in tissue culture and as well-established tumor xenografts. The interaction between R115777 and paclitaxel was additive irrespective of the order of drug administration, and the duration of the response to R115777 was not enhanced by paclitaxel. The addition of R115777 to irinotecan failed to enhance the antitumour effect of this topoisomerase inhibitor (Skrzat et al., 1999). The R115777 was combined with 5-fluorouracil and leucovorin in patients with advanced colorectal and pancreatic cancers (Peeters et al., 1999; Verslype et al., 2001)). Phase I study of R115777 with imatinib mesylate combination is well tolerated and demonstrates antileukemia activity (Verslype et al., 2001). Phase II trial of R115777 and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas offered no clinical advantage over historical controls (Haas-Kogan et al., 2011; Poussaint et al., 2011; Zukotynski et al., 2011). The combination of R115777 with bortezomib, a proteosome inhibitor, in patients with advanced leukemias was well-tolerated, demonstrated relevant target inhibition, promoted synergistic death, overcomes de novo drug resistance and was associated with signals of clinical activity in patients with advanced and refractory acute leukemias (Lancet et al., 2011; Yanamandra et al., 2011). Sorafenib, a vascular endothelial growth factor receptor kinase inhibitor, combined with R115777 is well tolerated and active against thyroid cancer (Hong et al., 2011). A phase I-II study of R115777combined with idarubicin and cytarabine for patients with newly diagnosed acute myeloid leukemia and high-risk myelodysplastic syndrome showed a better complete remission (Jabbour et al., 2011). R115777 was well tolerated when given with radiation therapy and temozolomide in patients with newly diagnosed glioblastoma (Nghiemphu et al., 2010).

BMS-214662 in combination with imatinib mesylate or dasatinib, potently induced apoptosis of both proliferating and quiescent chronic myeloid leukemia stem/progenitor cells (Copland et al., 2008). Also combination with PD184352, a MEK inhibitor, improves the ability of BMS-214662 to selectively target chronic myeloid leukemia cells (Pellicano et al., 2011). BMS-214662 and taxol combination have shown 33% response in larynx and prostate cancer, with neutropenia, nausea as dose limiting toxicity (Bailey et al., 2001). One phase I combination study has been reported for the BMS-214662 (Dy et al., 2005; Bailey et al., 2007), in combination with paclitaxel and carboplatin, in patients with advanced solid tumors. This

combination was well tolerated, with broad activity in solid tumors. In parallel, combination of FTI with radiotherapy is under investigation. *ras* oncogenes have been reported to confer resistance to ionizing radiation (Cengel et al., 2005; Kim et al., 2004; McKenna et al., 1990). Presently, many other combinations in phase I/II trials are ongoing, the results of which will hopefully soon be reported. FTIs are a promising class of novel antineoplastic agents. As single agents have significant activity in myeloid leukemias, but in solid tumors their activity seems to be modest and these drugs probably need to be studied in combination with cytotoxic agents, ionizing radiation and other novels targeted drugs, such as antiangiogenic agents.

9. Conclusion

FTIs are a new class of agents and have been developed rapidly as potential cancer therapeutic drugs. They can be quoted as the rolling stones to some of the current generation of cancer research. They have shown promise in early preclinical and clinical studies as a novel anticancer agent. Combinations with other signal transduction inhibitors may be an additional strategy that merits further research. However, FTIs represent one of the first small molecule signal transduction inhibitors to enter the clinic and show promise for the future.

10. List of abbreviations

GDP = Guanosine 5'-diphosphate
GTP = Guanosine 5'-triphosphate
CAAX = "C" cysteine, "A" any aliphatic amino acid, "X" any amino acid
FTase = Farnesyl transferase
FTI = Farnesyltransferase inhibitor
FDP = Farnesyl diphosphate
NSCLC = Non small cell lung cancer

11. References

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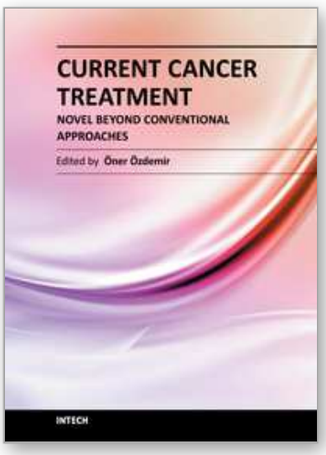

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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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