Farnesyltransferase Inhibitor as Anticancer Agent

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Abstract: Ras protein plays pivotal roles in control of normal and transformed cell growth. These *ras* genes are mutated in 30% of human cancer. For functioning of Ras protein its prenylation (farnesylation) is required. Therefore targeting Ras farnesylation is valuable approach for cancer treatment. Farnesyltransferase inhibitor (FTI) has been developed as anticancer drug and is currently evaluated in clinical trials. Different types of FTI have been identified that inhibit Ras farnesylation. FTI in combination with some cytotoxic antineoplastic drugs, exhibit additive effects.

Key Words: Farnesyltransferase, ras protein, farnesyltransferase inhibitor.

INTRODUCTION

Cancer is a class of diseases characterized by uncontrolled cell division and the ability of these cells to invade other tissues, either by direct growth into adjacent tissue or by migration of cells to distant sites. This unregulated growth is caused by a series of acquired or inherited mutations to DNA within cells, damaging genetic information that define the cell functions and removing normal control of cell division. To prevent this unregulated growth various anticancer drug (Table **1**) [1, 2] have been developed. Structures of some of the available drug are given in Fig. (**1**). But these drugs have severe toxicity and are not well tolerated in the patient. Therefore, the major goal in anticancer drug discovery is to develop innovative therapies that exhibit a real improvement in effectiveness and/or tolerability. In cancer therapy, remarkable progress has been made in the identification of 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 [3-5]. 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 [6-8].

Ras PROTEIN

Ras is the name of a protein, the gene that encodes it, and the family and superfamily of proteins to which it belongs. The Ras superfamily includes the Ras, Rho, and Rab families. There are three Ras proto-oncogenes: the H-*ras* gene (homologous to the oncogene of the Harvey murine sarcoma virus), the K-*ras* gene (homologous to the oncogene of the Kirsten murine sarcoma virus), and the N-*ras* gene (which does not have a retroviral homolog and was first isolated from a neuroblastoma cell line) [9-14]. 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) [6,8,15], 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.

Except for K-Ras 4B (189 amino acids), all the Ras proteins comprise 188 amino acids and exhibit high sequence homology, with the first 86 amino acids being identical, the next 78 having 79% homology, and the following 25 amino acids being highly variable [10, 11]. 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. 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 box, in which "C" refers to the cysteine, "A" to any aliphatic amino acid, usually valine, leucine, or isoleucine and "X" to any amino acid, usually methionine or serine [16-18].

Ras is a G protein and functions as a molecular switch that cycle between an inactive GDP-bound form and an active GTP-bound state. It is activated by guanine exchange factors (GEFs) which are themselves activated by mitogenic signals and through feedback from Ras itself. It is inactivated by GTPase-activating protein (GAP), which increases the rate of GTP hydrolysis, returning Ras to its GDP-bound form, simultaneously releasing an inorganic phosphate. They transmit various extracellular signals from the cell surface, including growth factors that activate cell-surface receptors (e.g. epidermal growth factor receptor, plateletderived growth factor receptor), cytokines (e.g. interleukins 2 and 3, granu-

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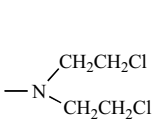
Table 1. Various Anticancer Drugs

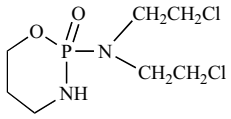
Type of Agent	Nonproprietary Name	Disease	Mechanism of Action	Usual Adult Dose
Alkylating Agents				
Nitrogen mustards	Mechlorethamine	Hodgkin's disease; non-Hodgkin's lymphoma	Disturb DNA synthesis and cell division	400 µg
	Cyclophosphamide	Acute and chronic lymphocytic leukemia		40-50 mg
	Melphalan	Multiple myeloma; breast, ovarian cancer		150 µg
	Chlorambucil	Chronic lymphocytic leukemia		100- 200 µg
Ethyleneimines and methylmelamines	Altretamine	Ovarian cancer		260 mg
	Thiotepa	Bladder, breast, Ovarian cancer		30 mg
Methylhydrazine derivative	Procarbazine	Hodgkin's disease		2-4 mg
Alkyl sulfonate	Busulfan	Chronic myelogenous leukemia		4-6 mg
Nitrosoureas	Carmustine	Hodgkin's disease; non-Hodgkin's lymphoma		150-200 mg
	Streptozocin	Malignant pancreatic insulinoma		500 mg
Triazenes	Dacarbazine, temozolomide	Malignant melanoma; Hodgkin's disease		3.5 mg
Platinum coordination complexes	Cisplatin, carboplatin	Testicular, ovarian, bladder, colon cancer		20 mg
Antimetobolites				
Folic acid analogs	Methotrexate	Acute lymphocytic leukemia	Inhibits dihydrofolate reductase	15- 50 mg
	Pemetrexed	Mesothelioma, lung cancer		--
Pyrimidine analogs	Fluorouracil	Breast, colon, stomach, esophageal	Inhibits thymidylate synthetase	12 mg
	Cytarabine	Acute myelogenous leukemia	Inhibits DNA polymerase	0.5-1 mg
	Gemcitabine	Pancreatic, ovarian, lung cancer	Inhibits DNA synthesis	1-1.2 g
Type of Agent	Nonproprietary Name	Disease	Mechanism of Action	Usual Adult Dose
Purine analogs and related inhibitors	Mercaptopurine	Acute lymphocytic and myelogenous, leukemia	Inhibit purine ring biosynthesis	2.5 mg
	Pentostatin	Hairy cell leukemia	Inhibit adenosine deaminase	4 mg
	Fludarabine	Chronic lymphocytic leukemia	Inhibits DNA synthesis	20-30 mg
Natural Products				
Vinca alkaloids	Vinblastine, Vinorelbine	Hodgkin's disease, Non-Hodgkin's lymphoma, testis cancer	Inhibit β-tubulin and block its polymerisation into microtubules	3.7 mg
	Vincristine	Acuter lymphocytic leukemia		1.4 mg
Taxanes	Paclitaxel, Docetaxel	Ovarian, breast, head and neck cancer	Stabilise microtubules	100 mg

(Table 1. Contd….)

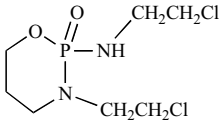
Type of Agent	Nonproprietary Name	Disease	Mechanism of Action	Usual Adult Dose
Epipodo-phyllotoxins	Etoposide, teniposide	Testis, small cell lung, and other lung cancer	Form complex with topoi-somerase	35- 50 mg
Camptothecins	Topotecan, irinotecan	Ovarian cancer, small cell lung cancer	Inhibit the function of topoi-somerase	1.5 mg
Antibiotics	Dactinomycin	Choriocarciloma, wilms, tumor	Prevent the transcription	10- 15 µg
	Daunorubicin	Acute myelogenous, acute lymphocitic leukemia	Block topoisomerase func-tion	60 mg
	Doxorubicin	Soft tissue, osteogenic and other sarcoma	Inhibits DNA and RNA synthesis	60-75 mg
Anthracenedione	Mitoxantrone	Acute mylogenous leukemia	Causes DNA chain breakage	12 mg
	Bleomycin	Testis and cervical cancer, Hodgkin's disease	Cause single- and double-standed break in DNA	10-30 units
	Mitomycin	Stomach, anal, lung cancer	Inhibit DNA synthesis	20 mg
Enzymes	L-asparginase	Acute lymphocytic leukemia	Deaminates asparagines	200 IU
Miscellaneous agents				
Substituted urea	Hydroxyurea	Cronic myelogenous leukemia	Inhibits ribo-nucleoside diphosphate reductase	80 mg
Type of agent	Nonproprietary Name	Disease	Mechanism of Action	Usual Adult Dose
Differentiating agents	Tretinoin, Arsenic trioxide	Acute promyelocytic leukemia,	Cause differentiation of cancer cells	45 mg
Protein tyrosine kinase in-hibitors	Imatinib	Cronic myelocytic leukemia	Inhibit gene transcription and/ or DNA synthesis	400 mg
	Gefiltinib	Non small cell lung cancer		250 mg
Proteaome inhibitors	Bortezomib	Multiple myeloma	Disturb signa-ling in cell	1.3 mg
Biological response modifier	Interferon-alfa, Interleukin-2	Heary cell leukemia , Kaposi's sarcoma	Amplify killer T-cell response	3 milli-on IU
Hormones and antagonists				
Adrenocortilcal supressants	Mitotane	Adrenal cortex cancer	Damages mitochondria	8-10 g
	Aminoglutethi mide	Breast cancer	Inhibit adrenocortical steroids	250 mg
Adreno-corticosteroids	Prednisone	Acute and cronic lymphocytic leukemia	Suppress mitosis in lymphocytes	20-40 mg
Progestin	Hydroxyl progesterone caproate	Endometrial, breast cancer	Exert antiestrogenic effect	1 g
Estrogens	Diethyl-stilbesterol, Ethinylestradiol	Breast, Prostate cancer	Interfere with peripheral androgens	--
Antiestrogens	Tamoxifen, Toremifene	Breast cancer	Antiestrogens	--
Aromatase inhibitors	Anastozole, Letrozole	Breast cancer	Inhibit aromatase	1 mg
Androgens	Testosterone propionate, Fluoximesterone	Breast cancer	Inhibit pituitary gonadotropins	--
Anti androgens	Flutamide,	Prostate cancer	Inhibit androgen receptor	250 mg
Gonadotdrophin releasing hormone analogue	Leuprolide	Prostate cancer	Reduce testosterone production level	1 mg



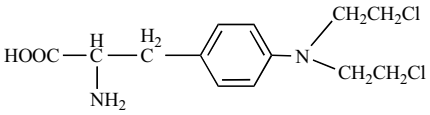
Mechlorethamine



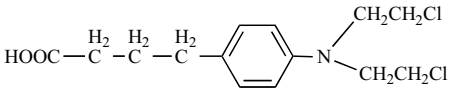
Cyclophosphamide



Ifosfamide

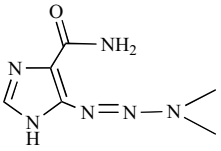


Melphalan

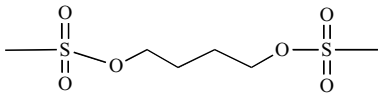


Chlorambucil

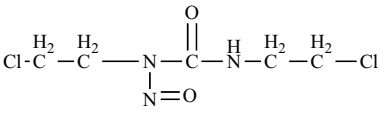
Nitrogen mustards



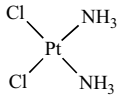
Dacarbazine



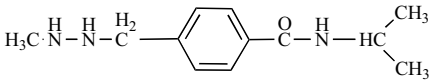
Busulfan



Carmustine

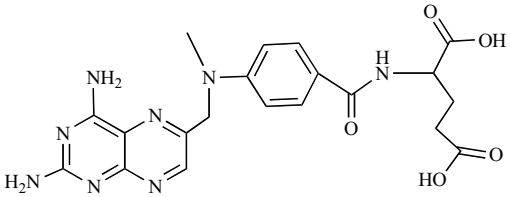


Cisplatin

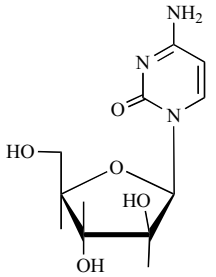


Procarbazine

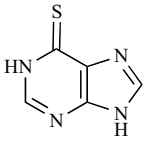
Other Alkylating Agents



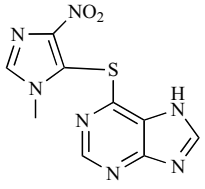
Methotrexate



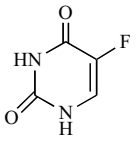
Cytosine arabinoside



Mercaptopurine

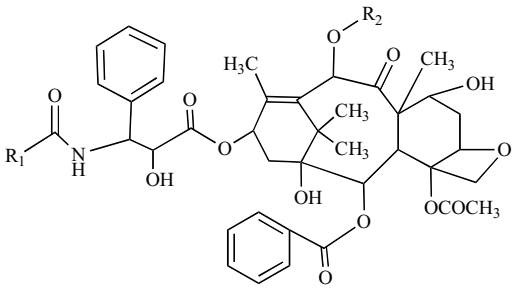


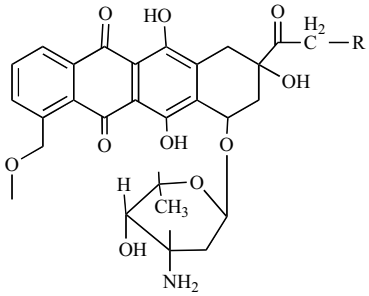
Azathioprine



5-Fluorouracil

Antimetabolite Agents





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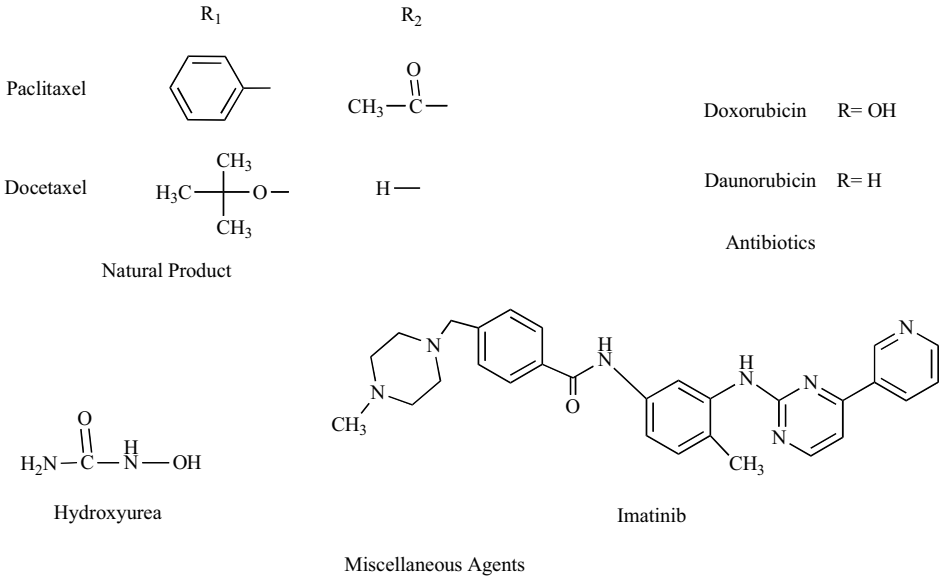


Fig. (1). Structures of some of the available drugs.

locyte–macrophage colony-stimulating factor), and hormones (e.g. insulin, insulin-like growth factor) [19].

Ras is synthesized 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. 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 [20-23], 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 and is catalyzed by Farnesyl trasnferase (FTase).

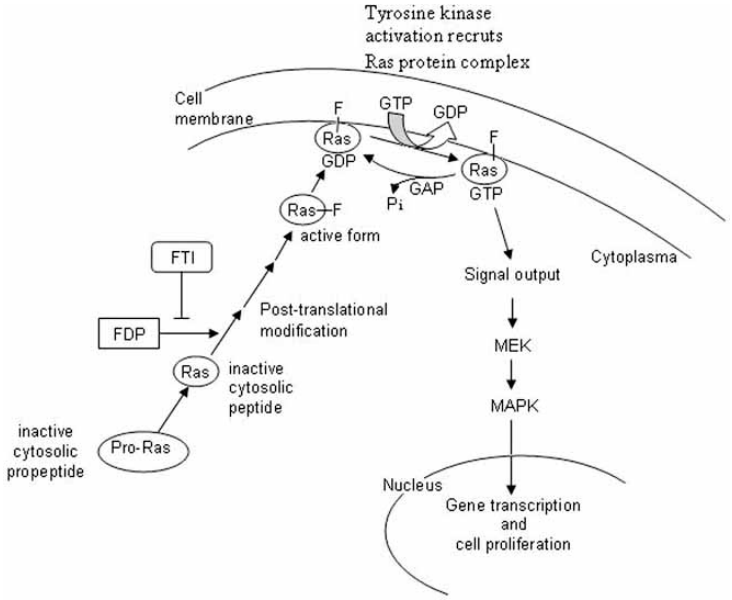


Fig. (2). Ras-dependent signal transduction with Farnesyltransferase inhibitor (FTI) target.

Mutations of Ras in Human Cancers

Ras and Ras-related proteins are often deregulated in cancers, 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. The encoded Ras protein include an altered amino acid sequence, most commonly at one of the critical positions 12, 13, or 61 that rendered the protein permanently activated because the mutated form was unable to interact with the enzymes that normally bring about rapid hydrolysis and inactivation of Ras-bound GTP to its GDP form [24].

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. In human tumors, the mutation at residue 12, in which the glycine residue is mutated to serine, cysteine, arginine, asparagine, alanine, or valine, is the most commonly found [25-27]. The glycine to valine mutation at residue 12 renders Ras insensitive to inactivation by GAP and thus stuck in the "on state". Ras requires a GAP for inactivation as it is a relatively poor catalyst on its own, as opposed to other G-domain-containing proteins such as the alpha subunit of heterotrimeric G proteins. Residue 61 is responsible for stabilizing the transition state for GTP hydrolysis. Because enzyme catalysis in general is achieved by lowering the energy barrier between substrate and product, mutation of Q61 necessarily reduces the rate of intrinsic Ras GTP hydrolysis to physiologically meaningless levels.

Mutations of *ras* occur in approximately 30% of all human cancers, including a significant proportion of pancreatic and colorectal carcinomas [28-30]. 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 particularly associated with myeloid malignancies and carcinomas of the colon, pancreas, lung, and thyroid, they have also been detected in many other types of cancer [31]. No major functional differences appear among the three Ras proteins when mutated, and in most tumor types there does not appear to be absolute specificity for any particular type of *ras* mutation.

POST-TRANSLATIONAL MODIFICATION OF RAS

For the Ras protein to function in the signal transduction cascade provided by growth factors and cytokines, it must become associated with the inner surface of the plasma membrane, which involves 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 [32-40], 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**).

The processed farnesylated Ras protein becomes more hydrophobic and readily associates with the lipid bilayer of the plasma membrane. This enables farnesylated Ras to cycle from its inactive GDP-bound state to the active GTP-bound state in response to upstream tyrosine kinase signaling.

In addition, there are other prenyltransferase enzymes, including geranylgeranyltransferases 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 proteins modified by geranylgeranylation are more hydrophobic than are those modified by farnesylation, and geranylgeranylation may also serve as part of a recognition sequence for protein-protein interactions. Geranylgeranyltransferases preferentially prenylate proteins in which X in the CAAX motif is leucine, although substrate specificity with FTase is not absolute [41]. Thus, geranylgeranyltransferase-1 can modify K-Ras4B and other proteins (ie the small G protein family) that are typically farnesylated [42], but it can both farnesylate and geranylgeranylate the same protein, such as RhoB protein (RhoB is a member of the Rho family of small GTPases, which regulates the actin cytoskeleton and cell adhesion signaling. RhoB is localized in early endosomes and nuclear membranes and has a specialized role in intracellular receptor trafficking) [43]. The potential for cross-prenylation of proteins such as Ras suggests that geranylgeranyltransferase could restore the function of these proteins if FTase was inhibited [44]. However, not all Ras proteins are prenylated by geranylgeranyltrans-

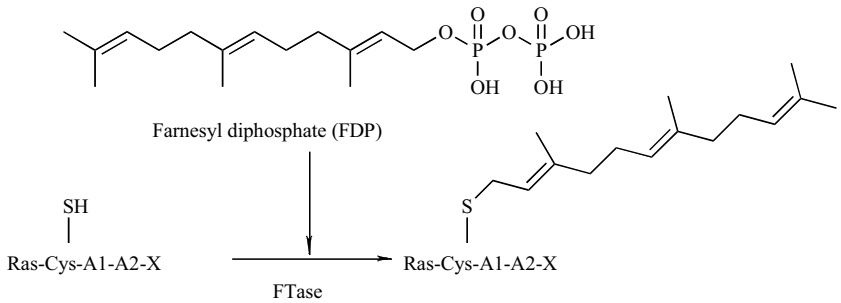


Fig. (3). The first step in Ras posttranslational modification is mediated by FTase, which transfers a farnesyl moiety from FDP to the cysteine moiety in the CAAX motif at the carboxyl terminus of Ras.

ferase, 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.

FARNESYL TRANSFERASE

Farnesyl trasnferase 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. FTase adds a 15 carbon [45] 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 heterodimer that has two distinct subunits denoted as α and β, having molecular weights of 48 kDa and 46 kDa respectively [46]. Both subunits are primarily composed of alpha helices. The α subunit is made of a double layer of paired alpha helices stacked in parallel which wraps partly around the beta subunit like a blanket. The alpha helices of the β subunit form a barrel. The active site is formed by the center of the β subunit flanked by part of the α subunit. FTase is a zinc metalloenzyme requiring zinc (Zn^{2+}) for substrate CAAX binding [47], also magnesium (Mg^{2+}) is required for catalysis [48]. The substrate specificity for FTase is determined by the amino acids that make up the CAAX motif, in particular the X residue [49]. Thus, proteins in which X is methionine or serine are preferred substrates (eg, N-Ras with Cys-Val-Val-Met, K-Ras4A with Cys-Ile-Ile-Met, K-Ras4B with Cys-Val-Ile-Met, and H-Ras with Cys-Val-Leu-Ser). The affinity for the enzyme is 10- to 30-fold higher for substrates in which X is methionine (eg, K-Ras4B) than for substrates in which X is either serine or glycine (H-Ras) [50, 51].

The X-ray crystal structures of FTase indicate that it has binding sites for both the CAAX peptide and the FDP [52]. At the intersection of the α and β-subunits lies a single zinc ion, which coordinates the thiol group of the cysteine into a ternary complex. Cross-linking studies showed that both FDP and the CAAX region bind the β-subunit, whereas the α-subunit stabilize the β-subunit and catalyzes the transfer of the farnesyl isoprenoid moiety [53]. The α-subunit then undergoes phosphorylation, which controls the activity of the enzyme [54]. The rate limiting step in enzyme catalysis is product dissociation, which occurs only in the presence of additional substrate [55, 56]. It has been shown that geranylgeranyltransferase can prenylate some of the substrates of FTase and vice versa.

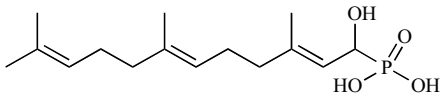
FARNESYLTRANSFERASE INHIBITORS

The detailed kinetic information about the FTase reaction and the physicochemical nature of FTase substrates has led to the rational design of farnesyltransferase inhibitor (FTI) [57, 58]. 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 [59]. While these inhibitors were designed to target Ras [60], it is evident in many instances that Ras may not be the only target of FTI. In many tumor cell lines the antitumor activity of FTI does not correlate with mutated Ras status [61, 62]. FTIs are also potent activators of apoptosis in *ras*-transformed cells [63]. The finding that K-Ras and N-Ras can be prenylated by geranylgeranyl transferase also argues against Ras as the dominant target, as preclinical models bearing these mutations are sensitive to FTI treatments [64]. FTIs interfare with bipolar spindle formation during transition from prophase to metaphase in mitosis [65, 66]. To date, many proteins have been suggested as potential FTI targets [67]. Therefore, in theory, the inhibition of farnesylation of any of these peptides can explain the antiproliferative effects of FTIs in human tumors.

Currently known FTIs can be divided into three categories based on their mechanism of action: compound competitive with FDP, compound competitive with CAAX, and bisubstrate analogues that combine features of both [68]. 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.

FDP Analogs

Inhibitors of FTase have been 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. An overview of the chemical structures of most of the thus far developed FDP analogues is given in Fig. (**4**). Although the compounds that competed with FDP and inhibited Ras processing in H-Ras- transformed NIH 3T3 fibroblasts at micromolar concentrations, they showed no antitumour activity in animal models [69]. 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 [70]. Therefore clinically useful compounds need to be much more selective for FTase than other FDP using enzymes in the cell.



(α-hydroxyfarnesyl) phosphonic acid

Fig. (4). Farnesyl diphosphate analogues.

Peptidomimetics

The finding that CAAX tetrapeptides contain the primary determinants for enzyme recognition led to the synthesis of a number of peptides as FTIs, using the approach of rational drug design. Tetrapeptides with inhibitory activity against FTase contain structural modifications at the AA amino acid locations of CAAX. 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 [71, 72]. Although CAAX tetrapeptides were found to be potent inhibitors of FTase in acellular systems, they shared a limited chemical stability due to susceptibility to proteolytic cleavage and poor cellular permeability due to their negative charge that limited their use. These problems were overcome by the synthesis of ester prodrugs such as L-744,832, which inhibited the growth of more than 70% of tumour cell lines [73] and significantly inhibited the growth of spontaneous mammary tumours in H-*ras* transgenic mice, without any systemic toxicity [74]. This represented one of the first reports of FTI induced tumour regression in an *in vivo* model. Other prodrugs, such as FTI-277, have been synthesised, in which the central portion of the CAAX mimetic is replaced with a rigid spacer group [75]. Some chemical structures of peptide CAAX peptidomimetics is given in Fig. (**5**).

Nonpeptidomimetic

Random, high-volume screening of histamine-receptor antagonists from compound libraries led to the identification of 8-chlorobenzocycloheptapyridines a class of novel nonpeptidic, nonsulfhydryl tricyclic selective inhibitors of FTase (Fig. **6**). This led to the discovery of two unrelated compounds, R115777 and SCH66336, both of which are orally active and have now entered clinical development. R115777 is an imidazole-containing heterocyclic compound [76], initially developed as antifungals and possess high enzyme specificity and interesting levels of growth inhibition [77, 78]. *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* [79]. In human xenograft studies, various tumours, including those of colon, bladder, lung, prostate, and pancreas, showed dose-dependent growth inhibition [80, 81]. Interestingly, the growth inhibitory effects of SCH66336 appear to be at least partly independent of *ras*-mutational status. This agent prevented the occurrence of newly formed tumours and is one of the few FTIs inducing tumour size reduction in animal models in a dose-dependent way [82]. The prototypical tricyclic FTI SCH44342 actively competes with the CAAX substrate [83, 84]. It has a high specificity for FTase over geranylgeranyl transferase I, and could block Ras induced morphological changes of malignant cells *in vitro*. Unfortunately, *in vivo* antitumour activity was poor [85]. 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.

Bisubstrate Analogs

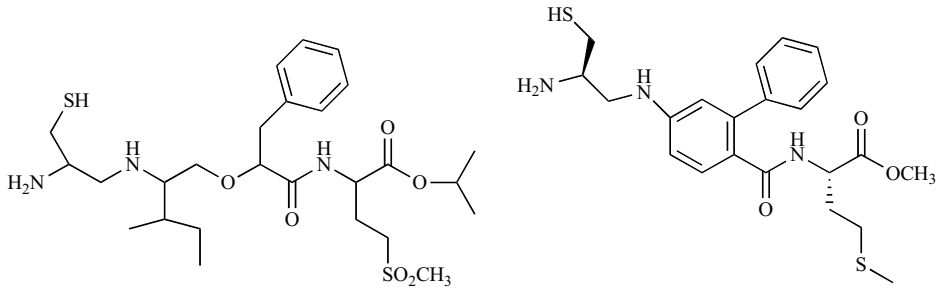
Structural and kinetic analyses of FTase revealed a sequential mechanism whereby an enzyme-FDP-CAAX ternary complex is formed before catalysis and lead to the possibility that bisubstrate analogs that mimic the transition state of the enzyme might be both potent and specific inhibitors of the enzyme. Bisubstrate 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 [86, 87].

Natural Products

A number of compounds with inhibitory activities against FTase have been identified by screening natural products isolated from microorganisms [88], plants 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 [89-93]. 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 [94]. Other natural products, such as fusidienol, preussomerin, gliotoxin, 10'-desmethoxystreptonigrin, and cylindrol A, inhibit FTase noncompetitively.

CLINICAL DEVELOPMENT OF FTIS

The FTIs entered in clinical development, so far, are R115777 (Zarnestra), SCH-66336 (Sarasar), L-778, 123 and BMS-214662 [95, 96]. Among these, R115777 is the most advanced in the clinical development since some phase III studies have been already completed. BMS-214662 and L-778, 123 are administrated intravenously, whereas the two other agents, R115777 and SCH66336, are given orally with different schedules. Dose-limiting toxicities have included myelosuppression, gastrointestinal disorders, peripheral neuropathy and fatigue. Because of cardiac conduction abnor-



L- 744,832 FTI-277

Fig. (5). Peptide CAAX peptidomimetics.

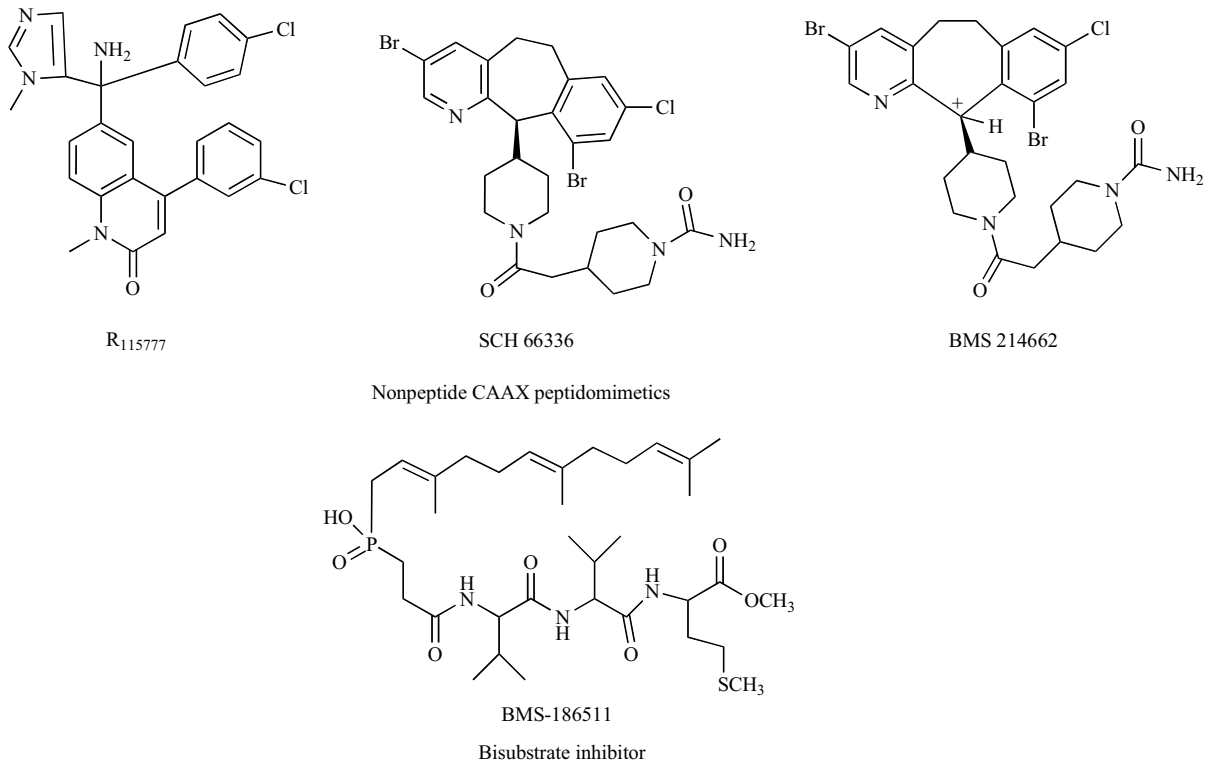


Fig. (6). Nonpeptide CAAX peptidomimetics and Bisubstrate inhibitor.

malities, 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 nonsmall- cell lung cancer (NSCLC), colorectal cancer and pancreatic cancer [97]. Phase I studies showed that myelosuppression and neurotoxicity were dose-limiting toxicities. Gastrointestinal toxicities and fatigue were also observed [98-100]. In phase II study, it has been evaluated as single agent in advanced breast cancer achieving a response rate of 11% and disease stabilization in 35% of patients [101]. Other trials are conducted in patients with malignant glioma and haematological malignancies and interesting results are documented [102]. A phase III study was conducted in patients with advanced refractory colorectal cancer who had failed two prior chemotherapy regimens. Unfortunately, median survival was comparable if R115777 (Zarnestra) or placebo was administered [103-105]. The activity of R115777 was also tested in hematologic malignancies [106]; a Phase I trial of R1115777 in patients with refractory or relapsed Acute Myeloid Leukemia (AML) or Acute Lymphocytic Leukemia, blast phase Chronic myeloid Leukemia, or high-risk previously untreated AML is reported [107], the response rate was of 29% including complete responses.

SCH66336 is orally active [108] and its first phase I trial was started in 1997. In the following years, different administration schedules were tested to determine the minimum therapeutic dose and the highest achievable plasma concentrations [109, 110]. 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 [111]. Using prelamin A as a surrogate marker for FTase inhibition, SCH66336 was shown to inhibit farnesylation at clinically relevant doses [112]. In the phase II study in transitional cell carcinomas, myelosuppression was dose limiting with patients experiencing additional toxicities of fatigue, anorexia, nausea, vomiting, confusion, dyspnoea and dehydration. Despite significant toxicities, no responses were observed [113]. Also, in a second phase II study investigating the effect of SCH66336 in patients with metastatic colorectal cancer, no responses were observed, 14% patients had stable disease for at least 4 months [114, 115]. Phase III studies with SCH66336 have just been started.

BMS-214662 was investigated in phase I single agent studies by infusion, as the oral formulation exhibits dose-dependent gastrointestinal toxicity, which limits its oral dosing [116]. Evidence of activity was observed by tumor regressions in patients with colorectal and breast cancer. In addition a reduction in tumor size greater than 40% occurred in patient with NSCLC. Furthermore, several other patients had disease stabilisation for up to 10 cycles [117]. In a recent phase I study, preliminary evaluation of the efficacy demonstrated a minor response in patient with NSCLC with bony metastases. Stable disease, as best protocol response, was reported in 64% of patients. Of these, 60% experienced disease stabilization for a period longer than 12 weeks. A prolonged stabilization of disease was reported for 28% patients with thyroid carcinoma [118]. Dose-limiting toxicities were nausea, vomiting, diarrhoea, hypokalemia, cardiovascular problems, creatinine elevation, acute pancreatitis, and renal failure. There are currently no published phase II trials with this agent.

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 [119]. 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. 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 [120, 121]. 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. 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 [122].

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 [123, 124]. The most common toxicities were myelosuppression and diarrhoea. Promising preliminary evidence of efficacy was documented with 38% patients demonstrating partial response [125]. 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 [126]. In phase II when SCH66336 was given with imatinib, 33% patients had a clinical response or improvement with combination therapy [127]. Responses were encouraging also in another study of SCH66336 combined with gemcitabine in patients with advanced urothelial tract cancer: 29% patients responded partially and 3% gave a complete response achieving an overall response rate of 32% [128]. It also resulted in impressive long-term stable disease in 44% patients [129].

On the other side, no benefit is reported with the combination of gemcitabine and R115777, in pancreatic cancer [130, 131]. 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 [132]. The R115777 was combined with 5-fluorouracil and leucovorin in patients with advanced colorectal and pancreatic cancers [133, 134]. Phase I study of R115777 with imatinib mesylate combination is well tolerated and demonstrates antileukemia activity [135].

BMS-214662 and taxol combination have shown 33% response in larynx and prostate cancer, with neutropenia, nausea as dose limiting toxicity [136]. One phase I combination study has been reported for the BMS-214662 [137], 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 [138-140]. One phase I study combining gamma radiation with the FTI L778, 123 demonstrated that such a combination with gamma radiation was feasible with minimal toxicity. More importantly it showed complete responses in NSCLC, head and neck cancer [141, 142].

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.

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. Although their true mechanism of action remains unclear, ongoing clinical trails are assessing their potential to enhance the efficacy of current cytotoxic therapies in cancer. Further clinical studies will examine the clinical activity of this agent in combination with other cytotoxics or as maintenance therapy in cancer. 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.

ABBREVIATIONS

GDP = Guanosine 5'-diphosphate

GTP = Guanosine 5'-triphosphate

CAAX = "C" cysteine, "A" any aliphatic amino acid, "X" any amino acid

GEF = Guanine exchange factors

GAP = GTPase-activating protein

FTase = Farnesyl trasnferase

FTI = Farnesyltransferase inhibitor

FDP = Farnesyl diphosphate

NSCLC = Non small cell lung cancer

AML = Acute Myeloid Leukemia

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Received: 05 January, 2009 **Revised: 03 February, 2009** **Accepted: 02 March, 2009**

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