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Farnesyltransferase Inhibitor in Cancer Treatment

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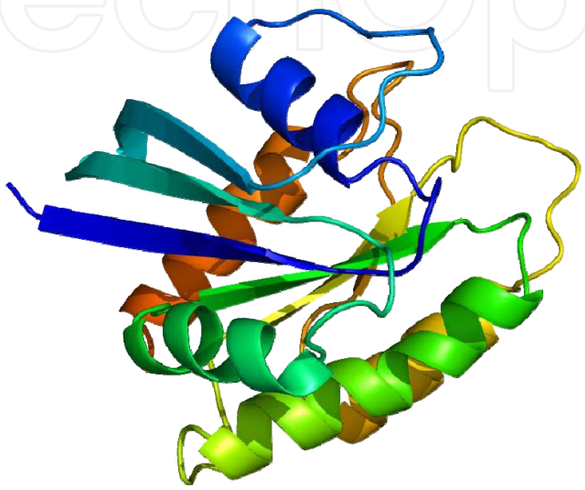
1. Introduction

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).

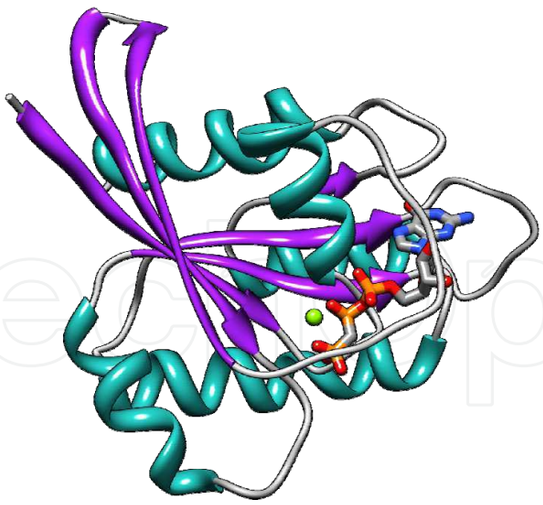
2. Ras protein

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).

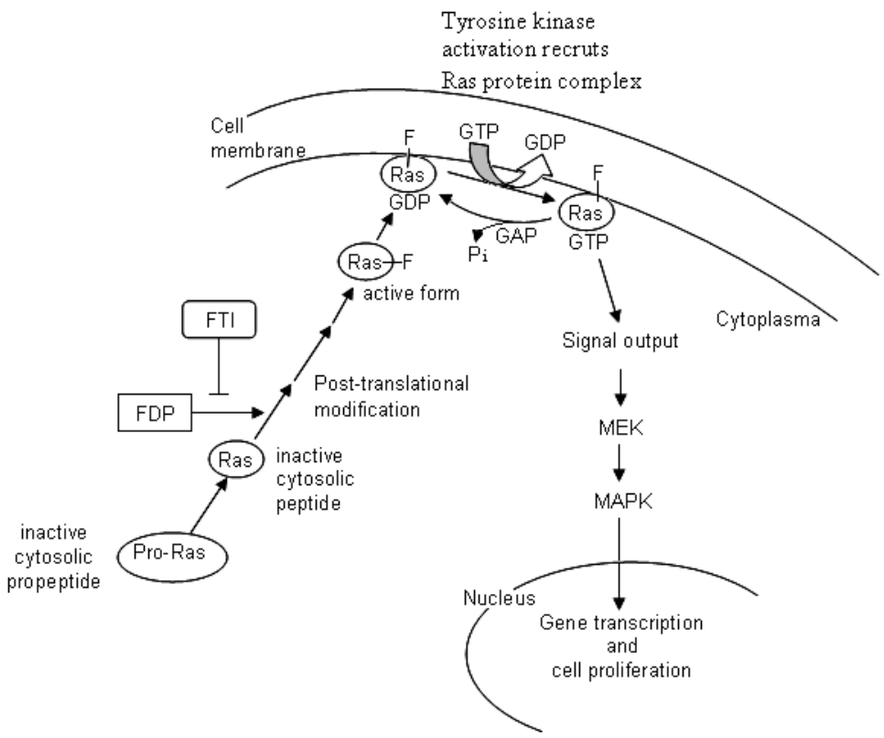


Fig. 2. Ras-dependent signal transduction with Farnesyltransferase inhibitor (FTI) target.

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**).

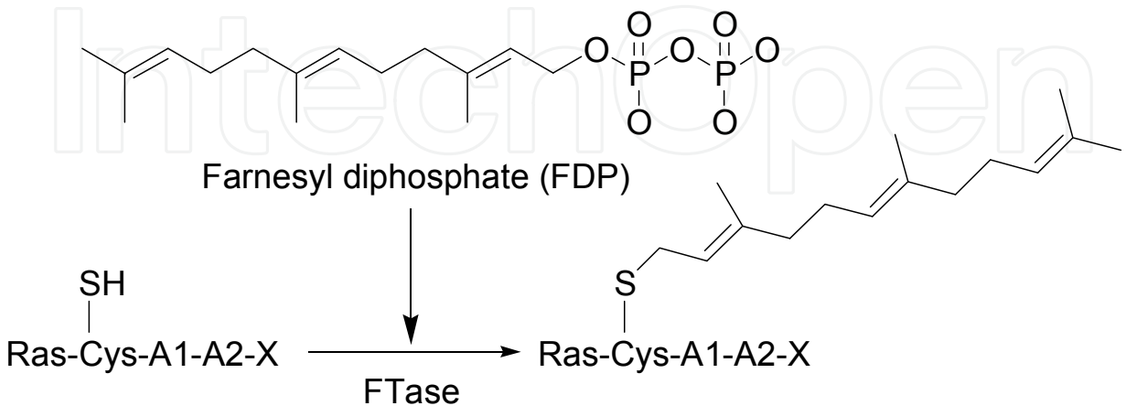


Fig. 3. The first step in Ras posttranslational modification is mediated by FTase, which transfers a farnesyl moiety from FDP to the cysteine moiety in the CAAX motif at the carboxyl terminus of Ras.

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.

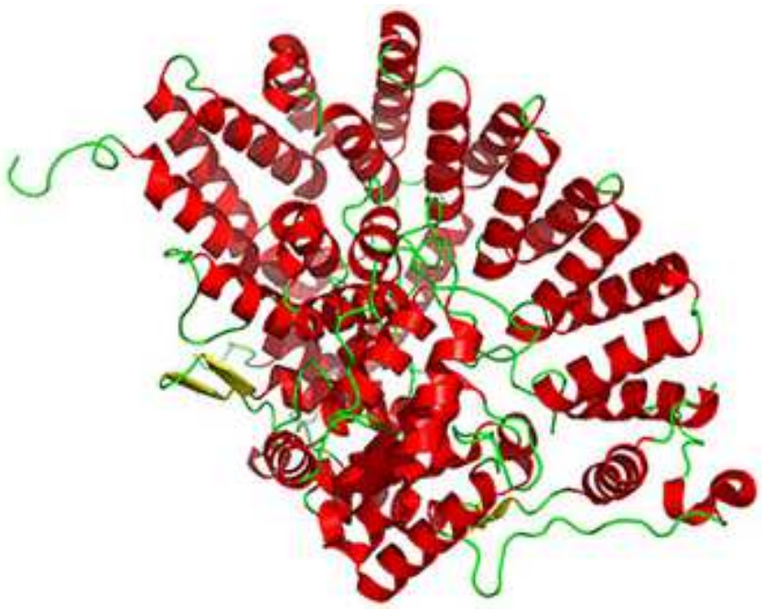


Fig. 4. Structure of Farnesyltransferase (Berman et al., 2000)

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.

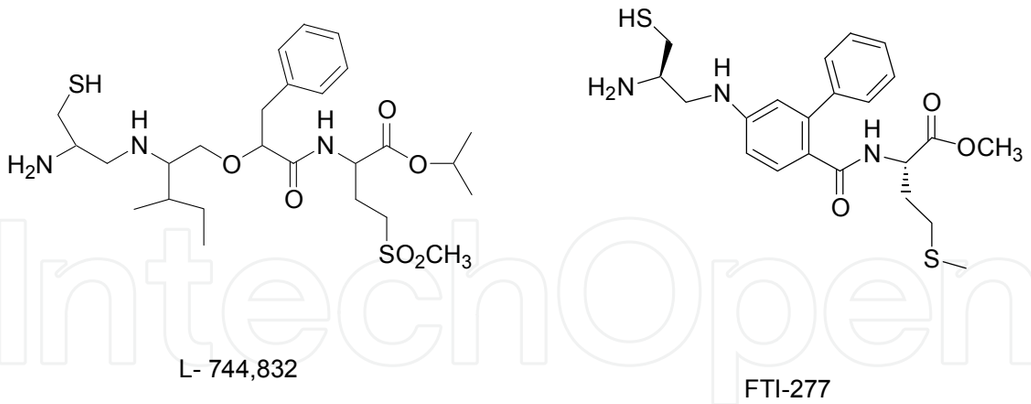


Fig. 5. Peptide CAAX peptidomimetics.

6.3 Nonpeptidomimetic

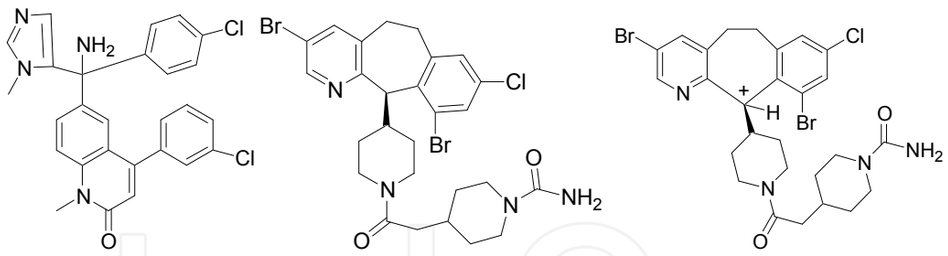
The molecules of this class are potentially able to inhibit almost selectively the farnesylation of different target proteins involved in malignant cell signalling processes. These class of inhibitors constitute a heterogeneous group of FTIs with different action profiles for each target cell type (Manne 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.,



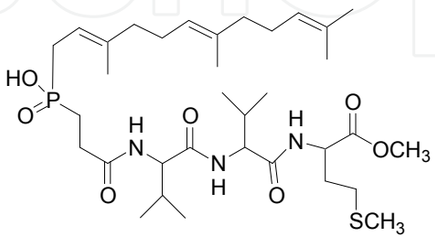


Fig. 6. Nonpeptide CAAX peptidomimetics and Bisubstrate inhibitor.

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

Adjei, A.A. (2006). Farnesyltransferase inhibitors. *Update on Cancer Ther*, Vol.1, (2006), pp. 17-23.

Adjei, A.A., Erlichman, C., Davis, J.N., Reid, J., Sloan, J., Statkevich, P., Zhu, Y., Randolph, M., Henry, P., Goldberg, R., Hanson, L., Alberts, S., Cutler, D. & Scott, K. (1999). A phase I and pharmacologic study of the farnesyl protein transferase (FPT) inhibitor SCH 66336 in patients with locally advanced or metastatic cancer. *Proc Am Soc Clin Oncol*, Vol.18, (1999), pp. 156a (abstr).

Ageberg, M., Rydström, K., Lindén, O., Linderoth, J., Jerkeman, M., Drott, K. (2011). Inhibition of geranylgeranylation mediates sensitivity to CHOP-induced cell death of DLBCL cell lines. Exp Cell Res, Vol.317, No.8, (2011), pp. 1179-1191.

Appels, N.M., Bolijn, M.J., van Eijndhoven, M.A., Stephens, T.C., Beijnen J.H., & Schellens, J.H. (2011). Characterization of the in vitro activity of AZD3409, a novel prenyl transferase inhibitor. *Cancer Chemother Pharmacol,* Vol.67, No.1, (2011), pp. 137-45.

Appels, N.M.G.M., Beijnen, J.H. & Schellens, J.H.M. (2005). Development of farnesyl transferase inhibitors: A review. *Oncologist,* Vol.10, (2005), pp. 565–578.

Ashar, H.R., James, L., Gray, K., Car, D., Black, S., Armstrong, L., Bishop, W.R., & Kirschmeier, P. (2000). Farnesyl transferase inhibitors block the farnesylation of CENP-E and CENP-F and alter the association of CENP-E with the microtubules. *J Biol Chem*, Vol.275, (2000), pp. 30451-30457.

Babcock, J.T. & Quilliam, L.A. (2011). Rheb/mTOR activation and regulation in cancer: Novel treatment strategies beyond rapamycin. *Curr Drug Targets*, (May 2011), [Epub ahead of print].

Baer, M.R. & Gojo, I. (2011). Novel agents for the treatment of acute myeloid leukemia in the older patient. *J Natl Compr Canc Netw*, Vol.9, No.3, (2011), pp. 331-5.

Bailey, H.H., Alberti, D.B., Thomas, J.P., Mulkerin, D.L., Binger, K.A., Gottardis, M.M., Martell, R.E. & Wilding, G. (2007). Phase I trial of weekly paclitaxel and BMS-214662 in patients with advanced solid tumors. *Clin Cancer Res*, Vol.13, No.12, (2007), pp. 3623-9.

Bailey, H.H., Marnocha, R., Arzoomanian, R., Alberti, D., Binger, K., Volkman, J., Feierabend, C., Ellingen, S., Black, S., Hampton, K., Cooper, M., Hott, T. & Wilding, G. (2001). Phase I trial of weekly paclitaxel and BMS214662 in patients with advanced solid tumors. *Proc Am Soc Clin Oncol*, Vol.20, (2001), pp. 314(abstr).

Barbacid, M. (1987). ras genes. *Ann Rev Biochem*, Vol.56, (1987), pp. 779-827.

Beaupre, D.M. & Kurzrock, R. (1999). Ras and leukemia: From basic mechanisms to gene-directed therapy. *J Clin Oncol*, Vol.17, (1999), pp. 1071-1079.

Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, I.N., & Bourne P.E. (2000). *The Protein Data Bank. Nucleic Acids Research*, 28 pp. 235-242 (2000) Accessed on 21st April 2011, Retrieved from: http://www.3dchem.com/imagesofmolecules/1d8d.jpg

Biagi, C., Astolfi, A., Masetti, R., Serravalle, S., Franzoni, M., Chiarini, F., Melchionda, F. & Pession, A. (2010). Pediatric early T-cell precursor leukemia with NF1 deletion and high-sensitivity in vitro to tipifarnib. *Leukemia,* Vol.24, No.6, (2010), pp. 1230-3.

Bishop, W.R., Bond, R., Petrin, J., Wang, L., Patton, R., Doll, R., Njoroge, G., Catino, J., Schwartz, J., Windsor, W., Syto, R., Schwartz, J., Carr, D., James, L. & Kirschmeier, P. (1995). Novel tricyclic inhibitors of farnesyl protein transferase. Biochemical characterization and inhibition of Ras modification in transfected Cos cells. *J Biol Chem*, Vol.270, (1995), pp. 30611-30618.

Boguski, M.S. & McCormick, F. (1993). Proteins regulating Ras and its relatives. *Nature*, Vol.366, (1993), pp. 643-654.

Bollag, G. & McCormick, F. (1991). Regulators and effectors of ras proteins. *Ann Rev Cell Bio*, Vol.17, (1991), pp. 601-632.

Bos, J.L. (1989). ras oncogenes in human cancer: a review. *Cancer Res*, Vol.49, (1989), pp. 4682-4689.

Brown, M.S., Goldstein, J.L., Paris, K.J., Burnier, J.P. & Marsters, J.C. (1992). Tetrapeptide inhibitors of protein farnesyltransferase: Amino-terminal substitution in phenylalanine-containing tetrapeptides restores farnesylation. *Proc Natl Acad Sci*, Vol.89, (1992), pp. 8313-8316.

Camacho, L.H., Soignet, S., Pezzuli, S., Canales, C., Aghajanian, C., Spriggs, D.S., Damle, B. & Sonnichsen, D. (2001). Dose escalation study of oral farnesyl transferase inhibitor (FTI) BMS-214662 in patients with solid tumors. *Proc Am Soc Clin Oncol*, Vol.20, (2001), pp. 311 (abstr).

Casey, P.J. (1989). p21 Ras is modified by a farnesyl isoprenoid. *Proc Natl Acad Sci*, Vol.86, (1989), pp. 8323-8327.

Castaneda, C., Meadows, K.L., Truax, R., Morse, M.A., Kaufmann, S.H., Petros, W.P., Zhu, Y., Statkevich, P., Cutler, D.L. & Hurwitz, H.I. (2011). Phase I and pharmacokinetic study of lonafarnib, SCH 66336, using a 2-week on, 2-week off schedule in patients with advanced solid tumors. *Cancer Chemother Pharmacol,* Vol.67, No.2, (2011), pp. 455-63.

Cengel, K.A. & McKenna, W.G. (2005). Molecular targets for altering radiosensitivity: lessons from Ras as a pre-clinical and clinical model. *Crit Rev Oncol Hematol*, Vol.55, (2005), pp. 103-116.

Chaponis, D., Barnes, J.W., Dellagatta, J.L., Kesari, S., Fast, E., Sauvageot, C., Panagrahy, D., Greene, E.R., Ramakrishna, N., Wen, P.Y., Kung, A.L., Stiles, C. & Kieran, M.W. (2011). Lonafarnib (SCH66336) improves the activity of temozolomide and radiation for orthotopic malignant gliomas. *J Neurooncol*, (January 2011), [Epub ahead of print].

Chen, C., Zhang, Y., Wang, Y., Huang, D., Xi, Y. & Qi, Y. (2011). Synergic effect of 3'-azido-3'-deoxythymidine and arsenic trioxide in suppressing hepatoma cells. *Anticancer Drugs,* Vol.22, No.5, (2011), pp. 435-43.

Clark, G.J., Der, C.J. In Cellular cancer, Markers, C.T., Garret, T. & Sell, S. Ed., Humana Press: Totowa, NJ, 1995, pp 17-52.

Copland, M., Pellicano, F., Richmond, L., Allan, E.K., Hamilton, A., Lee, F.Y., Weinmann, R. & Holyoake, T.L. (2008). BMS-214662 potently induces apoptosis of chronic myeloid leukemia stem and progenitor cells and synergizes with tyrosine kinase inhibitors. *Blood,* Vol.111, No.5, (2008), pp. 2843-53.

Cox, A.D. & Der, C.J. (1997). Farnesyltransferase inhibitors and cancer treatment: Targeting simply Ras?. *Biochim Biophys Acta*, Vol.1333, (1997), pp. F51-F71.

Crespo, N.C., Ohkanda, J., Yen, T.J., Hamilton, A.D. & Sebti, S.M. (2001). The farnesyltransferase inhibitor, FTI-2153, blocks bipolar spindle formation and chromosome alignment and causes prometaphase accumulation during mitosis of human lung cancer cells. *J Biol Chem*, Vol.276, (2001), pp. 16161-16167.

Crul, M., de Klerk, G.J., Beijnen, J.H. & Schellens, J. (2001). Ras biochemistry and farnesyl transferase inhibitors: A literature survey. *Anticancer Drugs*, Vol.12, (2001), pp. 163-184.

Crul, M., de Klerk, G.J., Swart, M., van't Veer, L.J., de Jong, D., Boerrigter, L., Palmer, P.A., Bol, C.J., Tan, H., de Gast, G.C., Beijnen, J.H. & Schellens, J.H. (2002). Phase I clinical and pharmacologic study of chronic oral administration of the farnesyl protein transferase inhibitor R115777 in advanced cancer. *J Clin Oncol*, Vol.20, (2002), pp. 2726-2735.

David, E., Kaufman, J.L., Flowers, C.R., Schafer-Hales, K., Torre, C., Chen, J., Marcus, A.I., Sun, S.Y., Boise, L.H. & Lonial, S. (2010). Tipifarnib sensitizes cells to proteasome

inhibition by blocking degradation of bortezomib-induced aggresomes. *Blood*, Vol.116, No.24, (2010), pp. 5285-8.

Druker, B.J. (2003). Overcoming resistance to imatinib by combining targeted agents. *Mol Cancer Ther*, Vol.2, No.3, (2003), pp. 225-226.

Duque, G., Vidal, C., Rivas, D. (2011). Protein isoprenylation regulates osteogenic differentiation of mesenchymal stem cells: effect of alendronate, and farnesyl and geranylgeranyl transferase inhibitors. *Br J Pharmacol*, Vol.162, No.5, (2011), pp. 1109-1118.

Dy, G.K., Bruzek, L.M., Croghan, G.A., Mandrekar, S., Erlichman, C., Peethambaram, P., Pitot, H.C., Hanson, L.J., Reid, J.M., Furth, A., Cheng, S., Martell, R.E., Kaufmann, S.H. & Adjei, A.A. (2005). A phase I trial of the novel farnesyl protein transferase inhibitor, BMS-214662 in combination with paclitaxel and carboplatin in patients with advanced cancer. *Clin Cancer Res*, Vol.11, (2005), pp. 1877-1883.

Eder, J.P., Ryan, D.P., Appleman, L., Zhu, A.X., Puchalski, T., He, X., Sonnichsen, D.S., Cooper, M., Wright, J., Clark, J.W. & Supko, J.G. (2006). Phase I clinical trial of the farnesyltransferase inhibitor BMS-214662 administered as a weekly 24 h continuous intravenous infusion in patients with advanced solid tumors. *Cancer Chemother Pharmacol*, Vol.58, No.1, (2006), pp. 107-16.

Elaine Meng. (December 2009). Protein HRAS PDB 121p, In: Wikimedia Commons, Accessed on 21st April 2011, Retrieved from: http://upload.wikimedia.org /wikipedia/commons/4/49/Protein_HRAS_PDB_121p.png

Elaine Meng. (January 2010). Hras secondary structure ribbon, In: Wikimedia Commons, Accessed on 21st April 2011, Retrieved from: http://upload.wikimedia.org /wikipedia/commons/6/60/Hras_secondary_structure_ribbon.png

Ellis, R.W., Defeo, D., Shih, T.Y., Gonda, M.A., Young, H.A., Tsuchida, N., Lowy, D.R. & Scolnick, E.M. (1981). The p21 src genes of Harvey and Kirsten sarcoma viruses originate from divergent members of a family of normal vertebrate genes. *Nature*, Vol.292, (1981), pp. 506-511.

End, D.W., Smets, G., Todd, A.V., Applegate, T.L., Fuery, C.J., Angibaud, P., Venet, M., Sanz, G., Poignet, H., Skrzat, S., Devine, A., Wouters, W. & Bowden, C. (2001). Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. *Cancer Res*, Vol.61, (2001), pp. 131-137.

End, E., Skrzat, S. G., Devine, A., Angibaud, P., Venet, M., Saz, G. & Bowden, C. (1998). R115777, a novel imidazole farnesyl protein transferase inhibitor (FTI): Biochemical and cellular effects in H-ras and K-ras dominant systems. *Proc Am Ass Cancer Res*, Vol.39, (1998), pp. 269 (abstr).

Epifano, F., Curini, M., Genovese, S., Blaskovich, M., Hamiltonc, A. & Sebtic, S.M. (2007). Prenyloxyphenylpropanoids as novel lead compounds for the selective inhibition of geranylgeranyl transferase I. *Bioorg Med Chem*, Vol.17, (2007), pp. 2639-2642.

Epling-Burnette, P.K. & Loughran, T.P. (2010). Suppression of farnesyltransferase activity in acute myeloid leukemia and myelodysplastic syndrome: current understanding and recommended use of tipifarnib. *Expert Opin Investig Drugs*, Vol.19, No.5, (2010), pp. 689-98.

Eskens, F.A.L.M. & Stoter, G., Verweij, J. (2000). Farnesyl transferase inhibitors: current developments and future perspectives. *Cancer Treat Rev*, Vol.26, (2000), pp. 319-332.

Field, K.A., Charoenthongtrakul, S., Bishop, J.M. & Refaeli, Y. (2008). Farnesyl transferase inhibitors induce extended remissions in transgenic mice with mature B cell lymphomas. *Mol Cancer*, Vol.7, (2008), pp. 39-51.

Gelb, M.H. (1997). Protein prenylation, et cetera: Signal transduction in two dimensions. *Science*, Vol.275, (1997), pp. 1750-1751.

Geryk-Hall, M., Yang, Y. & Hughes, D.P. (2010). Driven to death: inhibition of farnesylation increases Ras activity in osteosarcoma and promotes growth arrest and cell death. *Mol Cancer Ther*, Vol.9, No.5, (2010), pp. 1111-9.

Gibbs, J.B. GTPases in Biology, Springer-Verlag: New York, 1993. Goldstein JL, Brown MS, Stradley SJ, Reiss Y, Gierasch LM (1991): Nonfarnesylated tetrapeptide inhibitors of protein farnesyltransferase. *J Biol Chem,* Vol.266 (1993), pp. 15575–15578.

Gibbs, J.B. & Oliff, A. (1997). The potential of farnesyltransferase inhibitors as cancer chemotherapeutics. *Ann Rev Pharmacol Toxicol*, Vol.37, (1997), pp. 143-166.

Goldstein, J.L., Brown, M.S., Stradley, S.J., Reiss, Y. & Gierasch, L.M. (1991). Nonfarnesylated tetrapeptide inhibitors of protein farnesyltransferase. *J Biol Chem*, Vol.266, (1991), pp. 15575–15578.

Gridelli, C., Rossi, A. & Maione, P. (2003). Treatment of non-small-cell lung cancer: state of the art and development of new biologic agents. *Oncogene*, Vol.22, (2003), pp. 6629-6638.

Haas-Kogan, D.A., Banerjee, A., Poussaint, T.Y., Kocak, M., Prados, M.D., Geyer, J.R., Fouladi, M., Broniscer, A., Minturn, J.E., Pollack, I.F., Packer, R.J., Boyett, J.M. & Kun, L.E. (2011). Phase II trial of tipifarnib and radiation in children with newly diagnosed diffuse intrinsic pontine gliomas. *Neuro Oncol*, Vol.13, No.3, (2011), pp. 298-306.

Hancock, J.F., Magee, A.I., Childs, J.E. & Marshall, C. (1989). All ras proteins are polyisoprenylated but only some are palmitoylated. *Cell*, Vol.57, (1989), pp. 1167-1177.

Hancock, J.F., Paterson, H. & Marshall, C.J. (1990). A polybasic domain or palmitoylation is required for the addition of the CAAX motif to localize p21 to the plasma membrane. *Cell*, Vol.63, (1990), pp. 133-139.

Hanrahan, E.O., Kies, M.S., Glisson, B.S., Khuri, F.R., Feng, L., Tran, H.T., Ginsberg, L.E., Truong, M.T., Hong, W.K .& Kim, E.S. (2009) A phase II study of Lonafarnib (SCH66336) in patients with chemorefractory, advanced squamous cell carcinoma of the head and neck. *Am J Clin Oncol*. Vol.32, No.3, (2009), pp. 274-9.

Hara, M., Akasaka, K., Akinaga, S., Okabe, M., Nakano, H., Gomez, R., Wood, D., Uh, M. & Tamanoi, F. (1993). Identification of Ras farnesyl transferase inhibitors by microbial screening. *Proc Natl Acad Sci*, Vol.90, (1993), pp. 2281-2285.

Heimbrook, D.C. & Oliff, A. (2009). Therapeutic intervention and signaling. *Curr Opin Cell Biol*, Vol.10, (1998), pp. 284-288.

Hochhaus, A. (2004). Imatinib mesylate (Glivec, Gleevec) in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). *Ann Hematol*, Vol.83, No.1, (2004), pp. S65-S66.

Hong, D.S., Cabanillas, M.E., Wheler, J., Naing, A., Tsimberidou, A.M., Ye, L., Waguespack, S.G., Hernandez, M., El Naggar, A.K., Bidyasar, S., Wright, J., Sherman, S.I. & Kurzrock, R. (2011). Inhibition of the Ras/Raf/MEK/ERK and RET Kinase Pathways with the Combination of the Multikinase Inhibitor Sorafenib and the Farnesyltransferase Inhibitor Tipifarnib in Medullary and Differentiated Thyroid Malignancies. *J Clin Endocrinol Metab,* Vol.96, No.4, (2011), pp. 997-1005.

Hourigan, C.S. & Karp, J.E. (2010). Development of therapeutic agents for older patients with acute myelogenous leukemia. *Curr Opin Investig Drugs,* Vol.11, No.6, (2010), pp. 669-77.

Jabbour, E., Kantarjian, H., Ravandi, F., Garcia-Manero, G., Estrov, Z., Verstovsek, S., O'Brien, S., Faderl, S., Thomas, D.A., Wright, J.J. & Cortes, J. (2011). A phase 1-2 study of a farnesyltransferase inhibitor, tipifarnib, combined with idarubicin and cytarabine for patients with newly diagnosed acute myeloid leukemia and high-risk myelodysplastic syndrome. *Cancer*, Vol.117, No.6, (2011), pp. 1236-44.

Jackson, J.H., Cochrane, C.G., Bourne, J.R., Solski, P.A., Buss, J.E. & Der, C.J. (1990). Farnesyl modification of Kirsten-ras exon 4B protein is essential for transformation. *Proc Natl Acad*, Vol.87, (1990), pp. 3042-3046.

James, G., Joseph, L., Goldstein, & Michael, S. (1996). Brown Resistance of K-RasBVl2 proteins to farnesyltransferase inhibitors in Ratl cell. *Proc Natl Acad Sci USA,* Vol.93, (April 1996), pp. 4454-4458.

Johnston, S.R., Hickish, T., Ellis, P., Houston, S., Kelland, L., Dowsett, M., Salter, J., Michiels, B., Perez-Ruixo, J.J., Palmer, P. & Howes, A. (2003). Phase II study of the efficacy and tolerability of two dosing regimens of the farnesyl transferase inhibitor, R115777, in advanced breast cancer. *J Clin Oncol*, Vol.21, (2003), pp. 2492-2499.

Juan, C., Varela, I., Mandel, D.A., Schmidt, W.K., Diaz-Perales, A., Lopez-Otin, C. & Freij, J.M.P. (2003). AtFACE-2, a functional Prenylated Protein Protease from Arabidopsis thaliana Related to Mammalian Ras-converting Enzymes. *J Bio Chem*, Vol.278, No.43, (2003), pp. 2091–42097.

Kainuma, O., Asano, T., Hasegawa, M., Kenmochi, T., Nakagohri, T., Tokoro, Y. & Isono, K. (1997). Inhibition of growth and invasive activity of human pancreatic cancer cells by a farnesyltransferase inhibitor, manumycin. *Pancreas*, Vol.15, (1997), pp. 379-383.

Kato, K., Cox, A.D., Hisaka, M.M., Graham, S.M., Bus, J.E. & Der, C.J. (1992). Isoprenoid addition to Ras protein is the critical modification for its membrane association and transforming activity. *Proc Natl Acad Sci,* Vol.89, (1992), pp. 6403-6407.

Kauh, J., Chanel-Vos, C., Escuin, D., Fanucchi, M.P., Harvey, R.D., Saba, N., Shin, D.M., Gal, A., Pan, L., Kutner, M., Ramalingam, S.S., Bender, L., Marcus, A., Giannakakou, P. & Khuri, F.R. (2011). Farnesyl transferase expression determines clinical response to the docetaxel-lonafarnib combination in patients with advanced malignancies. *Cancer,* (March 2011), doi: 10.1002/cncr.26004. [Epub ahead of print]

Khan, A.H., Prakash, A., Kumar, D., Rawat, A.K., Srivastava, R., Srivastava, S. (2010). Virtual screening and pharmacophore studies for ftase inhibitors using Indian plant anticancer compounds database. *Bioinformation*, Vol.5, No.2, (2010), pp. 62-66.

Kho, Y., Kim, S.C., Jiang, C., Barma, D., Kwon, S.W., Cheng, J., Jaunbergs, J., Weinbaum, C., Tamanoi, F., Falck, J. & Zhao, Y. (2004). A tagging-via-substrate technology for

detection and proteomics of farnesylated proteins. *PNAS,* Vol.101, No.34, (August 2004), pp. 12479-12484.

Khosravi-Far, R. & Der, C.J. (1994). The Ras signal transduction pathway. *Cancer Metastasis Rev*, Vol.13, (1994), pp. 67-89.

Khuri, F.R., Glisson, B.S., Kim, E.S., Statkevich, P., Thall, P.F., Meyers, M.L., Herbst, R.S., Munden, R.F., Tendler, C., Zhu, Y., Bangert, S., Thompson, E., Lu, C., Wang, X.M., Shin, D.M., Kies, M.S., Papadimitrakopoulou, V., Fossella, F.V., Kirschmeier, P., Bishop, W.R. & Hong, W.K. (2004). Phase I study of the farnesyltransferase inhibitor lonafarnib with paclitaxel in solid tumors. *Clin Cancer Res*, Vol.10, (2004), pp. 2968-2976.

Khuri, F.R., Glisson, B.S., Meyers, M.L., Herbst, R.S., Thall, P.F., Munden, R.F., Bangert, S., Cascino, M., Blumenschein, G., Pisters, K. & Hong, W.K. (2000). Phase I study of farnesyl transferase inhibitor (FTI) SCH66336 with paclitaxel in solid tumors: dose finding, pharmacokinetics, efficacy/safety. *Proc Am Soc Clin Oncol,* Vol.19, (2000), pp. 799 (abstr).

Kim, C.K., Choi, Y.K., Lee, H., Ha, K.S., Won, M.H., Kwon, Y.G. & Kim, Y.M. (2010). The farnesyltransferase inhibitor LB42708 suppresses vascular endothelial growth factor-induced angiogenesis by inhibiting ras-dependent mitogen-activated protein kinase and phosphatidylinositol 3-kinase/Akt signal pathways. *Mol Pharmacol*, Vol.78, No.1, (2010), pp. 142-50.

Kim, I.A., Fernandes, A.T., Gupta, A.K., McKenna, W.G. & Bernhard, E.J. (2004). The influence of Ras pathway signaling on tumor radiosensitivity. *Cancer Metastasis Rev*, Vol.23, (2004), pp. 227-236.

Kim, S.H. & Dass, C.R. (2011). p53-targeted cancer pharmacotherapy: move towards small molecule compounds. *J Pharm Pharmacol*, Vol.63, No.5, (2011), pp. 603-10.

Kohl, N.E. (1999). Farnesyltransferase inhibitors: preclinical development. *Ann N Y Acad Sci*, Vol.886, (1999), pp. 91-102.

Kurzrock, R., Kantarjian, H.M., Cortes, J.E., Singhania, N., Thomas, D.A., Wilson, E.F., Wright, J.J., Freireich, E.J., Talpaz, M. & Sebti, S.M. (2003). Farnesyltransferase inhibitor R115777 in myelodysplastic syndrome: clinical and biologic activities in the phase I setting. *Blood*, Vol.102, (2003), pp. 4527-4534.

Kyathanahalli, C.N. & Kowluru, A. (2011). A farnesylated G-protein suppresses Akt phosphorylation in INS 832/13 cells and normal rat islets: Regulation by pertussis toxin and PGE(2). *Biochem Pharmacol*, Vol.81, No.10, (2011), pp. 1237-1247.

Lancet, J.E., Duong, V.H., Winton, E.F., Stuart, R.K., Burton, M., Zhang, S., Cubitt, C., Blaskovich, M.A., Wright, J.J., Sebti, S. & Sullivan, D.M. (2011). A phase I clinical-pharmacodynamic study of the farnesyltransferase inhibitor tipifarnib in combination with the proteasome inhibitor bortezomib in advanced acute leukemias. *Clin Cancer Res,* Vol.17, No.5, (2011), pp. 1140-6.

Lau, C.P., Huang, L., Tsui, S.K., Ng, P.K., Leung, P.Y., Kumta, S.M. (2011). Pamidronate, farnesyl transferase, and geranylgeranyl transferase-I inhibitors affects cell proliferation, apoptosis, and OPG/RANKL mRNA expression in stromal cells of giant cell tumor of bone. *J Orthop Res*, Vol.29, No.3, (2011), pp. 403-413.

Le Moulec, S., Loriot, Y. & Soria, J.C. (2009). Targeting KRAS pathway in NSCLC therapy. *Bull Cancer*, Vol.96, No.1, (2009), pp. S69-74.

Liu, G., Taylor, S.A., Marrinan, C.H., Hsieh, Y., Bishop, W.R., Kirschmeier, P. & Long, B.J. (2009). Continuous and intermittent dosing of lonafarnib potentiates the therapeutic efficacy of docetaxel on preclinical human prostate cancer models. *Int J Cancer*, Vol.125, No.11, (2009), pp. 2711-20.

Ljuca, F., Drevenšek, G., Zerem, E. (2011). Contribution of Ras farnesyl transferase , MAP kinase and cytochrome P-450 metabolites to endothelin-1 induced hypertension. *Bosn J Basic Med Sci*, Vol.11, No.2, (2011), pp. 84-86.

Lowry, D.R. & Willumsen, B.M. (1993). Function and regulation of Ras. *Ann Rev Biochem*, Vol.62, (1993), pp. 851-891.

Machida, S., Kato, N., Harada, K., Ohkanda, J. (2011). Bivalent inhibitors for disrupting protein surface-substrate interactions and for dual inhibition of protein prenyltransferases. *J Am Chem Soc*, Vol.133, No.4, (2011), pp. 958-963.

Manne, V., Yan, N., Carboni, J.M., Tuomari, A.V., Ricca, C.S., Brown, J.G., Andahazy, M.L., Schmidt, R.J., Patel, D. & Zahler, R. (1995). Bisubstrate inhibitors of farnesyl transferase: A novel class of specific inhibitors of Ras transformed cells. *Oncogene,* Vol.10, (1995), pp. 1763-1779.

Marcos, M. & Barbacid, M. (2003). RAS oncogenes: The first 30 years. *Nat RevCancer,* Vol.3, (2003), pp. 459–465.

Marks, R.E., Ho, A.W., Robbel, C., Kuna, T., Berk, S. & Gajewski, T.F. (2007). Farnesyltransferase inhibitors inhibit T-cell cytokine production at the posttranscriptional level. *Blood*, Vol.110, (2007), pp. 1982-1988.

McCormick, F. (1993). How receptors turn Ras on. *Nature*, Vol.363, (1993), pp. 15-17.

McKenna, W.G., Weiss, M.C., Endlich, B., Ling, C.C., Bakanauskas, V.J., Kelsten, M.L. & Muschel, R.J. (1990). Synergistic effect of the v-myc oncogene with H-Ras on radioresistance. *Cancer Res*, Vol.50, (1990), pp. 97-102.

Minna, J.D., Gazdar, A.F., Sprang, S.R. & Herz, J. (2004). Cancer: A bull's eye for targeted lung cancer therapy. *Science*, Vol.304, (2004), pp. 1458-1461.

Moasser, M.M., Sepp-Lorenzino, L., Kohl, N.E., Oliff, A., Balog, A., Su, D.S., Danishefsky, S.J. & Rosen, N. (1998). Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epithelones. *Proc Natl Acad Sci*, Vol.95, (1998), pp. 1369-1374.

Morgillo, F. & Lee, H. (2007). Development of farnesyl transferase inhibitors as anticancer agents: current status and future. *Cancer Therapy*, Vol.5, (2007), pp. 11-18.

Nghiemphu, P.L., Wen, P.Y., Lamborn, K.R., Drappatz, J., Robins, H.I., Fink, K., Malkin, M.G., Lieberman, F.S., Deangelis, L.M., Torres-Trejo, A., Chang, S.M., Abrey, L., Fine, H.A., Demopoulos, A., Lassman, A.B, Kesari, S., Mehta, M.P., Prados, M.D. & Cloughesy, T.F. (2009). A Phase I Trial of Tipifarnib with Radiation Therapy, with and without temozolomide, for Patients with Newly Diagnosed Glioblastoma. *Int J Radiat Oncol Biol Phys*, (October 2009), [Epub ahead of print].

Niessner, H., Beck, D., Sinnberg, T., Lasithiotakis, K., Maczey, E., Gogel, J., Venturelli, S., Berger, A., Mauthe, M., Toulany, M., Flaherty, K., Schaller, M., Schadendorf, D., Proikas-Cezanne, T., Schittek, B., Garbe, C., Kulms, D. & Meier, F. (2011). The farnesyl transferase inhibitor lonafarnib inhibits mTOR signaling and enforces

sorafenib-induced apoptosis in melanoma cells. *J Invest Dermatol*, Vol.131, No.2, (2011), pp. 468-79.

Omer, C.A., Anthony, N.J., Buser-Doepner, C.A., Burkhardt, A.L., deSolms, S.J., Dinsmore, C.J., Gibbs, J.B., Hartman, G.D., Koblan, K.S., Lobell, R.B., Oliff, A., Williams, T.M. & Kohl, N.E. (1997). Farnesyl: Proteintransferase inhibitors as agents to inhibit tumor growth. *Biofactors*, Vol.6, (1997), pp. 359-366.

Park, H.W., Boduouri, S.R., Moomaw, J.F., Casey, P.J. & Beese, L.S. (1997). Crystal structure of protein farnesyltransferase at 2.25 angstrom resolution. *Science*, Vol.275, (1997), pp. 1800-1804.

Patel, D.V., Schmidt, R.J., Biller, S.A., Gordon, E.M., Robinson, S.S. & Manne, V. (1995). Farnesyl diphosphate-based inhibitors of Ras farnesyl protein transferase. *J Med Chem* Vol.38, (1995), pp. 2906-2921.

Peeters, M., VanCustem, E., Marse, H., Palmer, P., Walraven, V. & Willems, L. (1999). Phase I combination trial of the farnesyl transferase inhibitor (FTI) R115777 with a 5FU/LV regimen in advanced colorectal and pancreatic cancer. *Proc Am Soc Clin Oncol,* Vol.18, (1999), pp. 223a (abstr).

Pellicano, F., Copland, M., Jorgensen, H.G., Mountford, J., Leber, B. & Holyoake, T.L. (2009). BMS-214662 induces mitochondrial apoptosis in chronic myeloid leukemia (CML) stem/progenitor cells, including CD34+38- cells, through activation of protein kinase Cbeta. *Blood,* Vol.114, No.19, (2009), pp. 4186-96.

Pellicano, F., Simara, P., Sinclair, A., Helgason, G.V., Copland, M., Grant, S. & Holyoake, T.L. (2011). The MEK inhibitor PD184352 enhances BMS-214662-induced apoptosis in CD34+ CML stem/progenitor cells. *Leukemia*, (April 12, 2011), [Epub ahead of print].

Poussaint, T.Y., Kocak, M., Vajapeyam, S., Packer, R.I., Robertson, R.L., Geyer, R., Haas-Kogan, D., Pollack, I.F., Vezina, G., Zimmerman, R., Cha, S., Patay, Z., Boyett, J.M. & Kun, L.E. (2011). MRI as a central component of clinical trials analysis in brainstem glioma: a report from the Pediatric Brain Tumor Consortium (PBTC). *Neuro Oncol*, Vol.13, No.4, (April 2011), pp. 417-27.

Punt, C.J., van Maanen, L., Bol, C.J., Seifert W.F. & Wagener D.J. (2001). Phase I and pharmacokinetic study of the orally administered farnesyl transferase inhibitor R115777 in patients with advanced solid tumors. *Anticancer Drugs*, Vol.12, (2001), pp. 193-197.

Raza, S., Kornblum, N., Kancharla, V.P., Baig, M.A., Singh, A.B., Kalavar, M. (2011). Emerging therapies in the treatment of locally advanced squamous cell cancers of head and neck. *Recent Pat Anticancer Drug Discov*, Vol.6, No.2, (2011), pp. 246-257.

Robak, T., Szmigielska-Kapłon, A., Pluta, A., Grzybowska-Izydorczyk, O., Wolska, A., Czemerska, M. & Wierzbowska, A. (2011). Novel and emerging drugs for acute myeloid leukemia: pharmacology and therapeutic activity. *Curr Med Chem*, Vol.18, No.5, (2011), pp. 638-66.

Roberts, P.J., Mitin, N., Keller, P.J., Chenette, E.J., Madigan, J.P., Currin, R.O., Cox, A.D., Wilson, O., Kirschmeier, P. & Der, C.J. (2008). Rho family GTPase modification and dependence on CAAX motif-signaled posttranslational modification. *J Biol Chem*, Vol.283, No.37, (2008), pp. 25150-25163.

Rose, W.C., Lee, F.Y., Fairchild, C.R., Lynch, M., Monticello, T., Kramer, R.A. & Manne, V. (2001). Preclinical antitumor activity of BMS-214662, a highly apoptotic and novel farnesyltransferase inhibitor. *Cancer Research*, Vol.61, (2001), pp. 7507–7517.

Rowinsky, E.K. (2006). Lately, it occurs to me what a long, strange trip it's been for the farnesyltransferase inhibitors. *J Clin Oncol*, Vol.24, No.19, (2006), pp. 2981-2984.

Rowinsky, E.K., Windle, J.J. & VonHoff, D.D. (1999). Ras protein farnesyltransferase: A strategic target for anticancer therapeutic development. *J Clin Oncol*, Vol.17, (1999), pp. 3631-3652.

Ruta, M., Wolford, R., Dhar, R., Defeo-Johnson, D., Ellis, R.W. & Scolnick, E.M. (1986). Nucleotide sequence of the two rat cellular H-ras genes. *Mol Cell Bio*, Vol.16, (1986), pp. 1706-1710.

Salaun, M.C., Deweer, S., Goossens, J.F., Houssin, R., Pommery, J. & Henichart, J.P. (1999). New Non-peptidic Inhibitors of Ras Farnesyltransferase. *Pharm Pharmacol Comm,* Vol.5, No.3, (1999), pp. 173–176.

Schafer, W.R., Kim, R., Sterne, R., Thorner, J., Kim, S. & Rine, J. (1989). Genetic and pharmacological suppression of oncogenic mutations in ras genes of yeast and humans. *Science*, Vol.245, (1989), pp. 379-385.

Schellens, J.H., de Klerk, G., Swart, M., Palmer, P.A., Bol, C.J., van't Veer, L.J., Tan, S., de Gast, G.C., Beijnen, J.H. & ten Bokkel Huinink, W.W. (2000). Phase I and pharmacologic study with the novel farnesyl transferase inhibitor (FTI) R115777. *Proc Am Soc Clin Oncol*, Vol.19, (2000), pp. 184a (abstr).

Sebti, S.M. & Hamilton, A.D. (1998). New approaches to anticancer drug design based on the inhibition of farnesyltransferase. *Drug Discov Today*, Vol.3, (1998), pp. 26-33.

Seki, T., Hayashi, N. and Nishimoto, T. (1996). RCC1 in the Ran Pathway. *J Biochem,* Vol.120, No.2, (1996), pp. 207-214.

Sharma, S., Britten, C., Spriggs, D., Rosen, N., Soignet, S., Pezzulli, S., Patnik, A., Kher, U., Arena, C., Deutsch, P., Yao, S. & Rowinsky, E. (2000). A phase I and PK study of farnesyl transferase inhibitor L-778,123 administered as a seven day continuous infusion in combination with paclitaxel. *Proc Am Soc Clin Oncol*, Vol.19, (2000), pp. 719 (abstr).

Shi, B., Gurnani, M., Yaremko, B., Lee, S., Chen, J., Lipari, P., Ferrari, E., Malkowski, M., Liu, M., Gerald Haijan, G. & Nielsen, L.L. (1999). Enhanced efficacy of the farnesyl protein transferase inhibitor SCH 66336 in combination with paclitaxel. *Proc Am Ass Cancer Res*, Vol.40, (1999), pp. 524 (abstr).

Shimizu, K., Goldfarb, M., Suard, Y., Perucho, M., Li, Y., Kamata, T., Feramisco, J., Stavnezer, E., Fogh, J. & Wigler, M.H. (1983). Three human transforming genes are related to the viral oncogenes. *Proc Natl Acad Sci*, Vol.80, (1983), pp. 2112-2116.

Shimoyama S. (2011). Statins are logical candidates for overcoming limitations of targeting therapies on malignancy: their potential application to gastrointestinal cancers. *Cancer Chemother Pharmacol*, Vol.67, No.4, (2011), pp. 729-739.

Singh, S.B., Jones, E.T., Goetz, M.A., Bills, G.F., Nallin-Omstead, M., Jenkins, R.G., Lingham, R.B., Silverman, K.C. & Gibbs, J.G. (1994). Fusidieno: A novel inhibitor of Ras farnesyl-protein transferase from fusidium griseum. *Tetrahedron Lett*, Vol.35, (1994), pp. 4693-4696.

Singh, S.B., Liesch, J.M., Lingham, R.B., Silverman, K.C., Sigmund, J.M. & Goetz, M.A. (1995). Structure, chemistry, and biology of actinoplanic acids: potent inhibitors of Ras farnesyl protein transferase. *J Org Chem*, Vol.60, (1995), pp. 7896-7901.

Singh, S.B., Zinc, D.L., Liesch, J.M., Goetz, M.A., Jenkins, R.G., Nallin-Omstead, M., Silverman, K.C., Bills, G.F., Mosley, R.T., Gibbs, J.B., Albers-Schonberg, G. & Lingham, R.B. (1993). Isolation and structure of chaetomelic acids a and b from chaetomell acutiseta: farnesyl pyrophosphate mimic inhibitors of Ras farnesyl-protein transferase. *Tetrahedron*, Vol.49, (1993), pp. 5917-5926.

Singh, S.B., Zink, D.L., Bills, G.F., Jenkins, R.G., Silverman, K.C. & Lingham, R.B. (1995). Cylindrol A: A novel inhibitor of Ras farnesyl-protein transferase from cylindrocarpon lucidum. *Tetrahedron Lett*, Vol.36, (1995), pp. 4935-4938.

Skrzat, S., Angibaud, P., Venet, M., Sanz, G., Bowden, C. & End, D.W. (1998). R115777, a novel imidazole farnesyl protein transferase inhibitor (FTI) with potent oral antitumour activity. *Proc Am Assoc Cancer Res*, Vol.39, (1998), pp. 317 (abstr).

Skrzat, S., Bowden, C. & End, D. (1999). Interaction of the farnesyl protein transferase inhibitor (FTI) R115777 with cytotoxic chemotherapeutics in vitro and in vivo. *Proc Am Ass Cancer Res*, Vol.40, (1999), pp. 523 (abstr).

Smets, G., van Eyck, N., Devine, A., Bowden, C., Wouters, W. & End, D.W. (1999). R115777, a selectice farnesyl protein transferase inhibitor (FTI), induces predominantly apoptotic activity in C32 melanoma tumor xenografts. *Proc Am Ass Cancer Res*, Vol.40, (1999), pp. 522 (abstr).

Subramanian, T., Liu, S., Troutman, J.M., Andres, D.A. & Spielmann, H.P. (2008). Protein farnesyltransferase-catalyzed isoprenoid transfer to peptide depends on lipid size and shape, not hydrophobicity. *Chembiochem*, Vol.9, No.17, (2008), pp. 2872-2882.

Sun, J., Blaskovich, M.A., Knowles, D., Qian, Y., Ohkanda, J., Bailey, R.D., Hamilton, A.D. & Sebti, S.M. (1999). Antitumor efficacy of a novel class of non-thiol-containing peptidomimetic inhibitors of farnesyltransferase and geranylgeranyltransferase I: combination therapy with the cytotoxic agents cisplatin, taxol, and gemcitabine. *Cancer Res*, Vol.59, (1999), pp. 4919-4926.

Symons, M. (1995). The Rac and Rho pathways as a source of drug targets for Ras-mediated malignancies. *Curr Opin Biotechnol*, Vol.6, (1995), pp. 668-774.

Tamanoi, F. & Mitsuzawa, H. (1995). Use of yeast for identification of farnesyltransferase inhibitors and for generation of mutant farnesyltransferases. *Methods Enzymol*, Vol.255, (1995), pp. 82-91.

Theodore, C., Geoffrois, L., Vermorken, J.B., Caponigro, F., Fiedler, W., Chollet, P., Ravaud, A., Peters, G.J., de Balincourt, C., Lacombe, D. & Fumoleau, P. (2005). Multicentre EORTC study 16997: Feasibility and phase II trial of farnesyl transferase inhibitor & gemcitabine combination in salvage treatment of advanced urothelial tract cancers. *Eur J Cancer*, Vol.41, (2005), pp. 1150-1157.

Tomillero, A. & Moral, M.A. (2010). Gateways to clinical trials. *Methods Find Exp Clin Pharmacol*, Vol.32, No.8, (2010), pp. 599-620.

Tsimberidou, A.M., Chandhasin, C. & Kurzrock, R. (2010). Farnesyltransferase inhibitors: where are we now? *Expert Opin Investig Drugs*, Vol.19, No.12, (2010), pp. 1569-80.

Verslype, C., Van Steenbergen, W. & Humblet, Y. (2001). Phase I trial of 5-FU/LV in combination with the farnesyltransferase inhibitor (FTI) R115777. *Proc Am Soc Clin Oncol*, Vol.20, (2001), pp. 681 (abstr).

Wasko, B.M., Dudakovic, A., Hohl, R.J. (2011). Bisphosphonates induce autophagy by depleting geranylgeranyl diphosphate. *J Pharmacol Exp Ther*, Vol.337, No.2, (2011), pp. 540-546.

Weber, F., Siska, P., Kramer, M., Zulehner, N., Hackl, S., Wesierska-Gádek, J. (2011). Combining an FPTase inhibitor with cisplatin facilitates induction of apoptosis in human A549 lung cancer cells. *J Exp Ther Oncol*, Vol.9, No.1, (2011), pp. 53-65.

Wei, H.Y., Chen, G.J., Chen, C.L., Lin, T.H. (2011). Developing consensus 3D-QSAR and pharmacophore models for several beta-secretase, farnesyl transferase and histone deacetylase inhibitors. *J Mol Model*, (May 2011), [Epub ahead of print].

Widemann, B.C., Arceci, R.J., Jayaprakash, N., Fox, E., Zannikos, P., Goodspeed, W., Goodwin, A., Wright, J.J., Blaney, S.M., Adamson, P.C. & Balis, F.M. (2011). Phase 1 trial and pharmacokinetic study of the farnesyl transferase inhibitor tipifarnib in children and adolescents with refractory leukemias: a report from the Children's Oncology Group. *Pediatr Blood Cancer*, Vol.56, No.2, (2011), pp. 226-33.

Widemann, B.C., Salzer, W.L., Arceci, R.J., Blaney, S.M., Fox, E., End, D., Gillespie, A., Whitcomb, P., Palumbo, J.S., Pitney, A., Jayaprakash, N., Zannikos, P. & Balis, F.M. (2006). Phase I trial and pharmacokinetic study of the farnesyltransferase inhibitor tipifarnib in children with refractory solid tumors or neurofibromatosis type I and plexiform neurofibromas. *J Clin Oncol*, Vol.24, No.3, (2006), pp. 507-516.

Winquist, E., Moore, M.J., Chi, K.N., Ernst, D.S., Hirte, H., North, S., Powers, J., Walsh, W., Boucher, T., Patton, R. & Seymour, L. (2005). A multinomial phase II study of lonafarnib (SCH 66336) in patients with refractory urothelial cancer. *Urol Oncol*, Vol.23, (2005), pp. 143-149.

Yamane, H.K., Farnsworth, C.C., Xie, H.Y., Howald, W., Fung, B.K., Clarke, S., Gelb, M.H. & Glomset, J.A. (1990). Brain G protein gamma subunits contain all-trans-geranylgeranylcysteine methyl ester at their carboxyl termini. *Proc Natl Acad Sci*, Vol.87, (1990), pp. 5868-5872.

Yan, N., Ricca, C., Fletcher, J., Glover, T., Seizinger, B.R. & Manne, V. (1995). Farnesyltransferase inhibitors block the neurofibromatosis type I (NF1) malignant phenotype. *Cancer Res*, Vol.55, (1995), pp.3569-3575.

Yanamandra, N., Buzzeo, R.W., Gabriel, M., Hazlehurst, L., Mari, Y., Beaupre, D. & Cuevas, J. (2011). Tipifarnib-induced apoptosis in acute myeloid leukemia and multiple myeloma cells is dependent on Ca2+ influx through plasma membrane Ca2+ channels. *J Pharmacol Exp Ther*, (March 2011), [Epub ahead of print].

Yasui, W., Nishiyama, M., Tsuruo, T. & Tahara, E. (2003). Molecular targeting therapy for cancer: the twelfth international symposium of the hiroshima cancer seminar, November 2002. *Cancer Sci*, Vol.94, (2003), pp. 221-223.

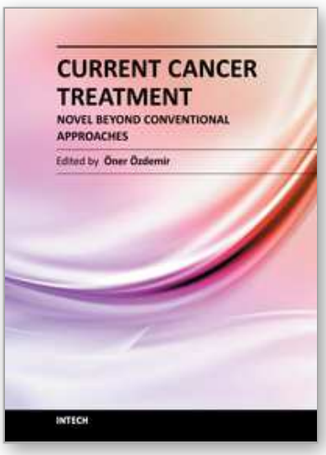
Zhang, F.L. & Casey, P.J. (1996). Protein prenylation: Molecular mechanisms and functional consequences. *Ann Rev Biochem*, Vol.65, (1996), pp. 241-269.

Zhao, J., Zhu, Y.J., Zeng, L., Wang, Q., Jiang, F.C. (2011). The design of muti-target antitumor drugs affecting on FTase and Raf-1 kinase (Article in Chinese). *Yao Xue Xue Bao*, Vol.46, No.2, (2011), pp. 170-178.

Zheng, H., Liu, A., Liu, B., Li, M., Yu, H. & Luo, X. (2010). Ras homologue enriched in brain is a critical target of farnesyltransferase inhibitors in non-small cell lung cancer cells. *Cancer Lett*, Vol.297, No.1, (2010), pp. 117-25.

Zujewski, J., Horak, I.D., Bol, C.J., Woestenborghs, R., Bowden, C., End, D.W., Piotrovsky, V.K., Chiao, J., Belly, R.T., Todd, A., Kopp, W.C., Kohler, D.R., Chow, C., Noone, M., Hakim, F.T., Larkin, G., Gress, R.E., Nussenblatt, R.B., Kremer, A.B. & Cowan, K.H. (2000). Phase I and pharmacokinetic study of farnesyl transferase inhibitor R1157777 in advanced cancer. *J Clin Oncol*, Vol.18, (2000), pp. 927-941.

Zukotynski, K.A., Fahey, F.H., Kocak, M., Alavi, A., Wong, T.Z., Treves, S.T., Shulkin, B.L., Haas-Kogan, D.A., Geyer, J.R., Vajapeyam, S., Boyett, J.M., Kun, L.E. & Poussaint, T.Y. (2011). Evaluation of 18F-FDG PET and MRI associations in pediatric diffuse intrinsic brain stem glioma: a report from the Pediatric Brain Tumor Consortium. *J Nucl Med*, Vol.52, No.2, (2011), pp. 188-95.



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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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