



## REVIEW

## Open Access

# Safe and targeted anticancer therapy for ovarian cancer using a novel class of curcumin analogs

Kellie S Rath<sup>1</sup>, Georgia A McCann<sup>1</sup>, David E Cohn<sup>1</sup>, Brian K Rivera<sup>2</sup>, Periannan Kuppusamy<sup>2</sup> and Karuppaiyah Selvendiran<sup>1\*</sup>

## Abstract

A diagnosis of advanced ovarian cancer is the beginning of a long and arduous journey for a patient. Worldwide, approximately half of the individuals undergoing therapy for advanced cancer will succumb to the disease, or consequences of treatment. Well-known and widely-used chemotherapeutic agents such as cisplatin, paclitaxel, 5-fluorouracil, and doxorubicin are toxic to both cancer and non-cancerous cells, and have debilitating side effects. Therefore, development of new targeted anticancer therapies that can selectively kill cancer cells while sparing the surrounding healthy tissues is essential to develop more effective therapies. We have developed a new class of synthetic curcumin analogs, diaryliденyl-piperidones (DAPs), which have higher anticancer activity and enhanced bio-absorption than curcumin. The DAP backbone structure exhibits cytotoxic (anticancer) activity, whereas the N-hydroxypyrroline (-NOH) moiety found on some variants functions as a cellular- or tissue-specific modulator (antioxidant) of cytotoxicity. The anticancer activity of the DAPs has been evaluated using a number of ovarian cancer cell lines, and the safety has been evaluated in a number of non-cancerous cell lines. Both variations of the DAP compounds showed similar levels of cell death in ovarian cancer cells, however the compounds with the -NOH modification were less toxic to non-cancerous cells. The selective cytotoxicity of the DAP-NOH compounds suggests that they will be useful as safe and effective anticancer agents. This article reviews some of the key findings of our work with the DAP compounds, and compares this to some of the targeted therapies currently used in ovarian cancer therapy.

**Keywords:** Ovarian cancer, Targeted therapy, STAT3, Curcumin analog, Curcumin

## Introduction

"Targeted therapy" is a relatively modern term that is commonly used to describe new drugs that are specifically designed to take advantage of known molecular pathways involved in the pathophysiology to be treated. Targeted therapies include small molecules and monoclonal antibodies. A number of new small molecules and immunotherapeutic agents for cancer treatment are currently in clinical trials or in advanced development phase. This review will focus on our research efforts, specifically diaryliденyl piperidone (DAP) analogs, in the development of new targeted agents for the treatment of ovarian and other solid tumors. We will highlight the selective cytotoxicity of

these agents toward cancer cells, sparing the surrounding healthy tissues. We will discuss the current challenges of ovarian cancer drug discovery, and finally identify the potential future of targeted therapy for ovarian cancer.

## New approaches for ovarian cancer therapeutics

Ovarian cancer is the leading cause of death from gynecologic cancer in North American women. In the US alone 22,280 new cases of ovarian cancer will be diagnosed and 15,500 women will die in 2013 [1]. Initial management consists of aggressive surgical cytoreduction followed by adjuvant platinum and taxane-based chemotherapy. Despite initial response in many women, 70-80% will relapse and ultimately die of their disease. Therapy at the time of relapse is less effective, and recurrent disease is uniformly fatal. Unfortunately, clinical response to second-line therapy is usually short-lived,

\* Correspondence: [selvendiran.karuppaiyah@osumc.edu](mailto:selvendiran.karuppaiyah@osumc.edu)

<sup>1</sup>Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Ohio State University, Columbus, OH 43210, USA  
Full list of author information is available at the end of the article

and women with recurrent disease will die of ovarian cancer [2-4]. Finding new therapies that can reduce the rate of recurrence through overcoming resistance is essential.

With advancing technology and access to biospecimens, the ability to obtain a genetic and molecular profile of cancers has led to the understanding of cancer pathways and the development of targeted therapies [5]. The goal of these therapies is to specifically target cancer cells, while leaving normal tissues unaffected. In many solid tumors these agents have led to improvements in both progression-free and overall survival. For example, in metastatic colorectal cancer, the addition of bevacizumab to standard chemotherapy added 8 months to overall survival with a 30 month improved overall survival [6,7], unfortunately, the goal of sparing normal tissues has not been fully realized. As more patients are treated with these targeted therapies, the adverse events associated with these agents are becoming better understood. While the traditional toxicities of cytotoxic chemotherapy are less common, adverse events such as rash, gastrointestinal toxicity (diarrhea and bowel perforation) and pulmonary toxicities are observed.

The poor prognosis associated with ovarian cancer (given that it is usually diagnosed after metastatic disease is present) makes it an optimal disease in which targeted therapies can be developed. The genetic and molecular profile of epithelial ovarian cancer (EOC) is complex, making a single molecular target difficult to identify. In EOC, overexpression of VEGF-A has been associated with advanced disease, poor prognosis, and ascites formation [8-10]. Given this, bevacizumab has been studied in both primary and recurrent settings netting an improvement of 4 months in progression free survival [11,12]. However, this did not translate to an improvement in overall survival [13]. Poly(ADP-ribose) polymerase (PARP) inhibitors were initially considered a potential treatment specifically for tumors with germline BRCA mutations due to the inherent defect in homologous recombination that occurs in BRCA-deficient tumors [14-16]. Trials are ongoing testing both of these promising targeted therapies in patients with ovarian cancer [17-19]; however, to date no targeted agent has been shown to improve overall survival in ovarian cancer nor been granted FDA approval. Table 1 reviews targeted agents of interest in ovarian cancer that have been evaluated in either Phase II or III trials. Additionally, data regarding disease site of FDA approval, response rates, and common adverse events are reported.

#### **Curcumin and its anti-cancer property**

Curcumin (diferuloylmethane) is a major constituent of turmeric powder, a spice used extensively in Southeast Asia for centuries. This yellow pigment is extracted

from the rhizomes of the plant *Curcuma longa*, and is recognized for its medicinal properties including anti-inflammatory, anti-oxidant, anti-proliferative, anti-angiogenic, and anti-tumor activities [38-43]. The anti-carcinogenic properties of curcumin have been demonstrated in animal models and human studies have shown the chemo-preventive properties of curcumin against breast, prostate, colon, and lung cancer [44-50]. Curcumin's anti-neoplastic activity, along with its low molecular weight and apparent lack of toxicity (use of up to 8 g/day), makes it an ideal foundation for the development of new, synthetic chemotherapeutic agents [51].

#### **Problems with solubility and bioavailability of curcumin**

Despite curcumin's activity as an anti-cancer agent with minimal side effects, it is notorious for poor bioavailability, low solubility in aqueous solutions, and low potency [52-55]. The majority of curcumin is processed by the gut and very little is absorbed into the vascular system [56-58]. When administered orally, doses of up to 8 grams per day produce very low serum concentrations of curcumin, about 1.77  $\mu\text{M}$  [59], limiting curcumin's potential as a chemotherapeutic agent. To address this, some investigators have attempted to modify the delivery method, including the use of a nanoparticle-encapsulated form of curcumin (nanocurcumin) [60,61]. Another approach to circumvent the limitations presented by curcumin is the development of synthetic chemical analogs with enhanced solubility, bioabsorption and potency. We have published several reports on a novel class of curcumin analogs, diarylidenylpiperidones (DAPs), which have been synthesized by shortening and incorporation of a piperidone ring within the beta-diketone backbone structure of curcumin and additional fluorination of the phenyl groups [62]. In this review, we will focus on two compounds DAP-F(p) and DAP-F(p)NOH which were synthesized by our group [63].

#### **DAPs have superior bioavailability than curcumin**

The DAP compounds, while structurally similar to curcumin (Figure 1), do not share the limitations of low bioabsorption and bioavailability. Two DAP compounds, DAP-F(p)-NOH and DAP-F(p), have been examined *in vitro* to determine their bioabsorption [62,64,65]. Bioabsorption of DAP-F(p)-NOH, was compared to curcumin using UV/Vis and electron paramagnetic resonance (EPR) spectrometry of cell or tissue lysates. Ovarian cancer cells grown in medium containing 10  $\mu\text{M}$  of DAP-F(p)-NOH, demonstrated absorption of 220 pmol/million cells after 1 hour. In contrast, cells exposed to 100  $\mu\text{M}$  of curcumin only absorbed about 20 pmol/million. Additionally, after removal of DAP-F(p)-NOH-containing culture medium and replacement with standard media, the EPR active form of DAP-F(p)-NOH was

**Table 1 Selected targeted agents for ovarian cancer evaluated in phase II studies\***

Targeted molecular agents	Primary molecular target	FDA approved cancer sites	Response rate in ovarian cancer	Toxicities
Imatinib	KIT, PDGF-R (TKI)	GIST	0% ORR, 33% SD [20,21]	Fatigue, diarrhea, rash, nausea, cardiotoxicity, granulocytopenia
Trastuzumab	HER-2 (mAB)	Breast, gastroesophageal	7.3% ORR [22]	Fatigue, diarrhea, rash, cardiotoxicity, anemia, dyspnea, neutropenia
Pertuzumab	HER-2 (TKI)	Breast cancer	4.3% ORR, 6.8% SD [23]	Diarrhea, neutropenia, nausea, LV dysfunction, VTE, vomiting, renal failure
Bevacizumab	VEGF (mAB)	Glioblastoma, NSCLC, mBreast, mCRC, mRCC	15-21% ORR, 25-52% SD [24,25]	Fatigue, diarrhea, anorexia, hypertension, gastrointestinal perforation, proteinuria, hemorrhage, congestive heart failure, arterial thromboembolism, wound healing problems
Gefitinib	EGFR (TKI)	NSCLC	0-4% ORR, 29-37% SD [26-28]	Diarrhea, rash, nausea, vomiting, mucositis, dyspnea
Erlotinib	EGFR (TKI)	NSCLC	6% ORR, 44% SD [29]	Fatigue, diarrhea, rash, anorexia
Temsirolimus	mTOR inhibitor	RCC	9.3% ORR, 24.1% mPFS [30]	Fatigue, diarrhea, rash, nausea, anorexia, stomatitis, anemia, hypertension, dyspnea
Vandetanib	EGFR, TEGF, RET (TKI)	Medullary thyroid cancer	0% ORR/SD [31]	Diarrhea, rash, hypertension, proteinuria, asymptomatic, QT prolongation
Sorafenib	VEGF, PDGF, c-Raf (TKI, Raf KI)	RCC, hepatocellular carcinoma	3% ORR, 34% SD [32]	Fatigue, diarrhea, rash, nausea, vomiting, anorexia, hypothyroidism, cardiotoxicity, hand-foot syndrome
Sunitinib	VEGF, PDGF, KIT (TKI)	RCC, GIST, pancreatic neuroendocrine tumor	3% ORR, 53% SD [33]	Fatigue, diarrhea, nausea, vomiting, hypothyroidism, hypertension, cardiotoxicity
Pazopanib	TKI VEGF, PDGFR (TKI)	RCC, soft tissue sarcoma	31% ORR, 56% SD (Ca-125 response) [34]	Fatigue, diarrhea, nausea, anorexia, hypertension, abdominal pain, arrhythmia, hepatotoxicity, hemorrhage
Lapatinib	HER2, EGFR (TKI)	Breast Cancer	0% ORR, 8 SD [35]	QT prolongation, CYP3A4, GI toxicity
Olaparib	PARP inhibitor	n/a	24-41% ORR, 35%-59% SD (BRCA carriers) [36,37]	fatigue, somnolence, nausea, loss of appetite, thrombocytopenia

\*There are no FDA approved targeted agents in ovarian cancer.

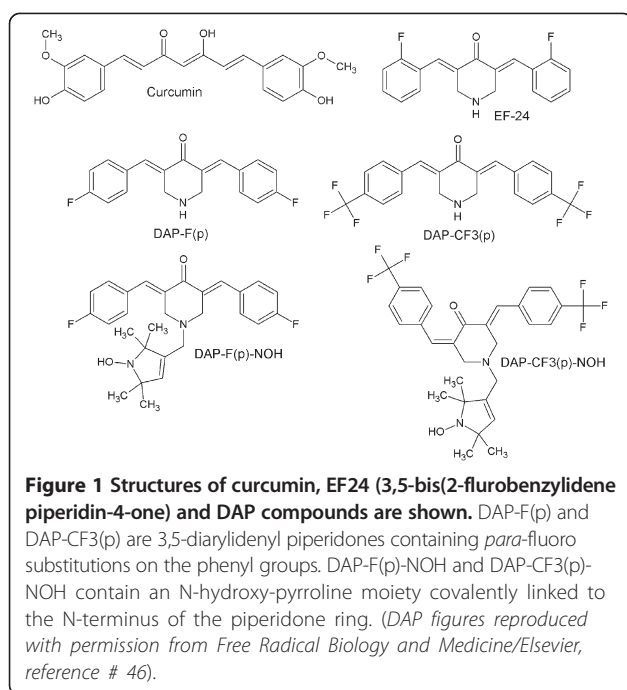
**Abbreviations:** TKI = tyrosine kinase inhibitor, mAB (monoclonal antibody), mTOR (mammalian target of rapamycin), PARP (Poly ADP-ribose polymerase), GIST (Gastrointestinal stromal tumor), NSCLC (non-small cell lung cancer), CRC (colorectal cancer), RCC (renal cell carcinoma), m (metastatic), ORR (overall response rate, REIST criteria if not specified), SD (stable disease).

detected in cells for at least 72 hours. However, curcumin was not present in the cells at this time point. The distribution of DAP-F(p)-NOH *in vivo* was also examined using EPR spectrometry of plasma, liver, kidney and stomach tissue samples of rats exposed to the compound. These samples were collected 3 hours after intraperitoneal (IP) injection of either 10 mg/kg or 25 mg/kg of DAP-F(p)-NOH. A measurable EPR spectrum was found in liver, kidney, blood, and stomach samples, indicating the presence of DAP-F(p)-NOH in paramagnetic nitroxide form. Quantification revealed that the liver concentration of HO-3867 was twice that of other organs. Further, in a murine tumor xenograft model of ovarian cancer, animals were given DAP-F(p)-NOH in feed, and tumor tissue samples were subsequently examined with EPR. In these samples, an EPR signal was

detected, indicating that oral administration of DAP-F(p)-NOH is an effective delivery method [62].

#### Biological activity of DAPs

DAPs incorporate several well-established strategies to enhance metabolic stability, and increase bioavailability within the tissues [43,62,66,67]. This, in turn, translates to increased anticancer efficacy when treating cancer cells both *in vitro* and *in vivo* when compared to curcumin [65,68-70]. We investigated a number of DAP compounds using biochemical and molecular studies with the aim of identifying the connections between the structure and mode of action. Other groups have also reported upon DAP-type compounds. In 2004, Adams, et al, reported the synthesis and anticancer/antiangiogenesis screening of a number of curcumin analog



compounds, including DAPs [71]. Subramaniam, et al, later focused upon one of these compounds, EF24 for an *in vivo* study, and reported high anticancer potency in colon cancer tumor xenografts [69]. Lagisetty, et al, synthesized a number of derivatives or similar compounds to EF24, and conducted structure-activity screenings [72]. One of these derivatives, CLEFMA, exhibited significantly higher cancer cell-killing potential than EF24.

#### DAPs are effective against multiple human cancers

Diphenyl difluoroketone (EF24), an ortho-fluorinated DAP, is toxic to a variety of cancer cells *in vitro* [64,66,73,74]. This has been attributed to cell-cycle arrest and

apoptosis in both colon and ovarian cancer cell lines [66,69]. Interestingly, this toxicity was not seen when mouse embryo fibroblasts were treated with EF24, suggesting a component of selective cytotoxicity. This activity was confirmed *in vivo* with a xenograft colon cancer model, showing tumors treated with EF24 were smaller than control [69]. We have observed that DAP-F(p), is more potent than EF24 for inducing cytotoxicity in ovarian cancer cells [70]. In our own work, we studied multiple DAP compounds, and found that they exhibit similar if not greater toxicity than cisplatin to multiple cancer cell lines *in vitro*. However, those compounds with the -NOH moiety were not toxic to non-cancer cell lines (Table 2). We also confirmed these findings *in vivo* with an ovarian cancer xenograft model [70]. In mice treated with 100 ppm DAP-F(p)-NOH, the tumors size was reduced 70 to 80% compared to untreated. In addition the mice did not show any gross signs of toxicity measured by two profiles; body weight and feed intake [70].

#### Metabolic conversion of DAPs in cells

The N-hydroxypyrroline (-NOH) moiety is capable of undergoing a reversible, one-electron oxidation to its nitroxide form, which is paramagnetic and detectable by EPR spectroscopy. Hence, we determined whether or not DAP-F(p)-NOH is converted its corresponding nitroxide form in cells. The EPR spectrum measured from a 100  $\mu$ M solution of DAP-F(p)-NOH incubated with cancer cells showed a characteristic triplet feature attributable to the nitroxide form [64]. This was verified using a known nitroxide as a control. A five-fold increase in the EPR signal intensity of the nitroxide metabolite was observed in cancer cells incubated with DAP-F(p)-NOH when compared to cells treated with DMSO alone. Under these conditions, DAP-F(p), which possess

**Table 2 Growth-inhibition efficacy data on ovarian cancer cell lines and normal cell lines treated with DAP compounds compiled from individual MTT assay**

Cell lines	Cisplatin 10 $\mu$ g/ml (%)	Curcumin 100 $\mu$ M (%)	DAP-F (p) 10 $\mu$ M (%)	DAP-F(p)-NOH 10 $\mu$ M (%)	DAP-CF3(P) 10 $\mu$ M (%)	DAP-CF3(P)-NOH 10 $\mu$ M (%)
A2780	75-85	65-75	80-90	75-85	80-90	80-90
A2780R*	50-60	55-65	85-90	70-80	75-85	70-80
SKOV3	80-90	65-75	80-90	75-85	85-90	75-80
OVCAR3	70-80	65-70	75-80	80-85	75-85	70-80
OV-4	75-80	60-65	75-80	70-80	80-85	80-85
PA-1	65-75	50	65-75	70-75	75-80	75-80
hOSE	⊕	⊕	⊕	⊕	⊕	⊕
CHO	⊕	⊕	⊕	⊕	⊕	⊕
H9C2	⊕	⊕	⊕	⊕	⊕	⊕
HSMC	⊕	⊕	⊕	⊕	⊕	⊕

Cell viability, cell survival and cell proliferation were quantified as means  $\pm$  SE (N = 8,  $p \leq 0.05$  versus control) and expressed as percentage of respective untreated controls. ⊕ = Moderately toxic; ⊙ = Non-toxic; - = not tested.



the DAP backbone structures of NOH respectively, but lacks the pro-nitroxide moiety, did not show any EPR signal, suggesting that the N-hydroxypyrrrole moiety is the source of the observed EPR signal. The results show the presence of a significant level of the antioxidant nitroxide form in the cells tested, and that the metabolite level was significantly higher (25–30%) in noncancerous cells when compared to cancer cells (7–16%). This difference can be explained by the intracellular environment of the cancer cells which is characterized by hypoxia, acidemia, and presence of glutathione. Cancer cells are more reducing than their normal, non-cancerous, analogues. Since HO-3867 exists in both oxidized and reduced forms, is particularly susceptible to changes in the redox state of the cellular environment. Therefore, HO-3867 undergoes loss of an electron and a greater shift from the antioxidant to anti-proliferative form in cancer cells.

#### Superoxide radical-scavenging activity of DAPs

Many chemotherapeutic agents act by producing free radicals, which increases the oxidative stress [75,76]. N-hydroxypyrrrole-bearing compounds and other nitroxides are generally known to have antioxidant properties including superoxide dismutase- and catalase-mimetic activities [77]. The superoxide radical scavenging ability of DAPs was evaluated using a competitive reaction in the presence of DEPMPO (5-(diethoxyphosphoryl)-5-methyl-1-pyrroline-N-oxide), an EPR spin-trap commonly used for this assay [78,79]. Superoxide radicals were generated using an aerobic solution of xanthine and xanthine oxidase (X/XO) and detected as DEPMPO-OOH adduct by EPR spectroscopy. The DAP compounds (100  $\mu$ M) were used to compete with 1 mM DEPMPO for the superoxide ions. SOD (4.2  $\mu$ M) was used as a positive control. The EPR studies clearly demonstrated that the N-hydroxypyrrrole modified DAPs are capable of scavenging superoxide radicals.

#### Selective induction of ROS by DAP-F(p)-NOH

Several studies have shown that curcumin and curcumin analogs induce apoptosis and inhibit growth in human cancer cells [66,73,80-82]. Curcumin is also known for its antioxidant properties and ability to act as a free-radical scavenger by inhibiting lipid peroxidation and oxidative DNA damage [83]. Several *in vitro* studies, however, suggest that curcumin analog-induced apoptosis is associated with ROS production and/or oxidative stress in cells [64,73,84,85]. Curcumin also has demonstrated anticancer activity by decreased mitochondrial membrane potential and induced reactive oxygen species (ROS) in pancreatic cancer cells [86]. Apoptosis is induced through an increase in intracellular ROS concentration through reduction of the mitochondrial membrane

potential (MMP), alterations in MAPK (Mitogen-activated protein kinases) expression, and activation of JNK (Jun-amino-terminal kinase), p38 and ERK (Extracellular signal-regulated kinases) [87-89]. GSH (Glutathione) and NAC (N-acetylcysteine), both antioxidants, have been shown to block curcumin-induced ROS production and MMP loss, and rescue cells from curcumin-induced apoptosis. This suggests that curcumin induces apoptosis in cancer cells through a ROS-dependent mitochondrial signaling pathway, and alterations in signaling pathways. In addition, it has been reported that curcumin is a weak stimulator of differentiation and shows synergistic effects on retinoid acid induced differentiation of cancer cells [89]. The production of ROS has been linked to the anti-proliferative effects of most agents [90-92].

We further determined whether the DAPs could have a similar effect upon cancer cells. Cancer cells were incubated with 5 or 10  $\mu$ M of the DAP compounds DAP-F(p)-NOH, and DAP-F(p) for 12 h, and intracellular ROS generation was measured by DCF (dichlorofluorescein) fluorescence [64]. The fluorescence intensity observed in cancer cells was significantly higher in the cells treated with both DAP compounds when compared to untreated controls. The DCF fluorescence intensity in human smooth muscle cells (HSMCs) treated with DAP-F(p)-NOH was not significantly different from that of the untreated cells. In contrast, DAP-F(p) induced significant ROS generation in HSMC cells. The results show that DAP-F(p) and DAP-F(p)-NOH are comparable in inducing ROS generation in cancer cells. However, in normal cells (HSMCs), DAP-F(p)-NOH generated significantly less ROS when compared to DAP-F(p) [64]. Taken together, the results imply that DAP-F(p)-NOH is capable of inducing oxidative stress in cancer cells while sparing healthy cells. These cells are spared because in the normal cellular environment, unlike the cancer cellular environment, the equilibrium shift to loss of an electron and an increase in the anti-oxidant form of the compound.

#### Efficacy in treating *in vivo* ovarian carcinoma xenografts

The anti-cancer efficacy of curcumin was first confirmed in a model of Dalton's lymphoma cells grown as ascites, and curcumin was found to reduce the development of animal tumors [93]. Curcumin has been shown to prevent cancer of the skin, colon, stomach, liver, lung, and breast through oral administration using *in vivo* rodent models of these cancers [94-97]. The effects of dietary curcumin on colon carcinogenesis, in particular, have been demonstrated in both chemically-induced and genetically-modified animal models [98]. Furthermore, curcumin has been shown to be a chemopreventive agent by inhibiting tumorigenesis during the initiation phase in chemical models [99]. Based on our *in vitro*

results, which showed significant cytotoxicity of DAPs to human various cancer cell lines, we evaluated the efficacy of DAPs in a human ovarian tumor xenograft grown on the back of immunocompromised mice. A significant reduction in the tumor volume was observed in a dose-dependent manner [70]. Doses of 50 and 100 parts-per-million (ppm) were effective in reducing tumor growth when compared to vehicle-treated controls. Tumor weight in untreated animals measured 1.2g compared to 0.6g and 0.2g in the 50 and 100 ppm groups respectively. This translates to a 70 to 80% reduction of tumor growth observed in the group treated with 100 ppm of HO-3867. Animals treated through oral administration of DAP-F(p)-NOH did not show any gross signs of toxicity and/or possible adverse side effects as measured by two parameters: body weight and diet consumption. Many cancer patients exposed to modern chemotherapeutics experience the undesirable side effects of a loss of appetite and subsequent weight loss, often extreme. Our results demonstrated *in vivo* antitumor efficacy using DAP-F(p)-NOH without any toxicity complications. The results of our *in vitro* and *in vivo* studies using DAP-F(p)-NOH imply that the induction of apoptosis may be an additional means by which DAP-F(p)-NOH inhibits ovarian tumor growth.

### Understanding the molecular targets of DAPS in ovarian cancer

Recent evidence suggests that curcumin analogs have a wide range of molecular targets, which supports the notion that curcumin analogs influence numerous biological and molecular cascades [45,100]. Included among the DAP molecular targets are transcription factors, growth factors and their receptors, and genes regulating cell proliferation and apoptosis. We have shown that the DAP compounds target the signal transducer and activator of transcription 3 (STAT3) signaling pathways in various cancer cells when compared to other pro-oncogenic signaling pathways [64,70].

### Induction of cell-cycle arrest by activation of p53

Cell-cycle control plays a critical role in the regulation of tumor cell proliferation. Cell-cycle is tightly controlled in normal cells by checkpoints and these checkpoints can become disrupted by damaged DNA [101]. The cell-cycle consists of four phases (G1, S, G2 and M). p53 is a nuclear transcription factor that accumulates in response to cell-cycle arrest and DNA damage [102]. This triggers transcriptional trans-activation of p53 target genes such as p21, and p27, leading to cell-cycle arrest, or apoptosis [103]. Another p53 transcriptional target is the Mdm2 gene, whose protein product ubiquitinates p53 and targets it for proteasome-mediated degradation [102].

The failure of many chemotherapeutic agents reflects an inability of these drugs to induce cell-cycle arrest and apoptosis [104]. The cell-cycle and programmed cell death are intimately related, as evidenced by the central role of p53 in both cell-cycle arrest and in the induction of apoptosis. Many cytotoxic agents arrest the cell cycle at the G1, S, or G2-M phase [105-107]. DAPs induced G1/G2-M cell cycle arrest in cisplatin-resistant ovarian cancer cells and serum-stimulated vascular smooth muscle cells [66,67]. Previous studies have shown that the G2-M-phase progression is regulated by a number of Cdk/cyclins as well as Cdk inhibitors such as p21 and p27. We have observed that the curcumin analog-induced G2-M cell-cycle arrest is mediated by the induction of p53 and p21 and downregulation of cyclin A and Cdk2 [108]. Previous studies also have shown that the synthetic curcumin analog, EF24, induces G2/M cell-cycle arrest by means of a redox-dependent mechanism in human breast cancer cells and human prostate cancer cells [73].

### Induction of apoptosis

The induction of apoptosis is believed to be the main mechanism of action for the anticancer effects of flavonoids, although other mechanisms have been proposed [109,110]. Some of these alternatives include cell-cycle inhibition by inactivation of cyclin-dependent kinase 2 (CDK-2), and attenuation of angiogenesis by inhibition of vascular endothelial growth factor (VEGF)-induced phosphatidylinositol-3-kinase (PI3K) activity [111]. Many curcumin derivatives induce apoptosis in cancer cells, but the mechanisms by which they do so differ [66,70, 112-114]. The death receptor-associated mechanism has been recently receiving much attention for the anticancer activity of curcumin derivatives [82,115]. We reported that the death receptor gene Fas/CD95 and FASL were activated in cancer cells by curcumin analogs [66,70]. We further observed that the expression level of TNF-R1, the receptor of tumor necrosis factor- $\alpha$ , was unchanged in DAPs-treated cancer cells. It has been reported that curcumin promoted tumor necrosis factor- $\alpha$ -induced apoptosis in a variety of cancer cells, but without a significant increase in the TNF-R1 expression level. Curcumin and curcumin analogues have also been shown to upregulate death receptor 5 and FasL expression, thereby inducing apoptosis in human cancer cells [82,115,116]. Upregulation of the death receptor superfamily-mediated signaling appear to be critical involvement in the stimulation of apoptosis following curcumin analog exposure.

Several reports have shown that some anticancer agents induced apoptosis, in part, by blocking the activation of Akt [117,118]. Akt prevents cells from undergoing apoptosis by inhibiting pro-apoptotic factors and suppressing death-receptor signals such as Fas and FasL [66]. The role

of Akt signaling in regulating death receptor signaling is not fully understood. In a recent study using prostate cancer cells and T-lymphocytes, blocking Akt-signaling has been shown to increase caspase-8 activity, resulting ultimately in FasL-dependent apoptosis [119]. It reported that the curcumin analogs also downregulate Akt signaling and induces apoptosis [66,120]. Akt activation appears to be a critical downstream target of the death receptor-mediated apoptotic pathway, and should provide opportunities as a target for future anticancer therapeutics.

### Targeting STAT3 and PTEN

Signal transducer and activator of transcription 3 (STAT3) has been implicated in the pathogenesis of a variety of human malignancies, including head and neck cancer, myeloma, prostate cancer, breast cancer, colon cancer, and ovarian cancer [121]. Activation of STAT3 can be accomplished by the Janus kinases (JAKs; including tyrosine kinase 2, TYK2), activated epidermal growth factor receptor (EGFR), and Src kinase [122-124]. STAT3 is constitutively activated in many tumor types and this activation promotes acceleration of cell proliferation, upregulation of survival factors, and activation of anti-apoptotic proteins [125]. Activated STAT3 imparts cellular resistance to chemotherapy by inhibiting apoptosis in epithelial malignancies, including ovarian cancer [126-128]. Currently, the oncogenic transcription factor STAT3 has attracted much attention as a pharmacologic target, although *in vivo* evidence demonstrating that inhibition of STAT3 could counteract cancer remains incomplete [129].

Curcumin and curcumin analogs induce apoptosis by inhibiting pSTAT3 Tyr<sup>705</sup> and Ser<sup>727</sup> expression in various cancer cells [65]. Flavonoids and other analogs have been shown to target STAT3 indirectly, by inhibiting STAT3-regulating genes such as the JAK1 and JAK2 pathways [64,81,130]. We have reported that the DAPs caused a substantial inhibition of phospho-JAK1 (Tyr<sup>1022/1023</sup>), suggesting that DAPs can inhibit the constitutive activation of STAT3, which may be caused, at least in part, by the inhibition of pJAK1 [70]. Further, evidence showed that DAPs activates cleaved caspase-3 and induces apoptotic markers of PARP in various cancer cell lines, suggesting that DAPs induce apoptosis in cancer cells by targeting STAT3 proteins [64]. Many reports have shown that blockage of constitutive STAT3 activation and signaling results in growth inhibition and induction of apoptosis in tumor cells both *in vitro* and *in vivo* [131-133]. However, DAP-F(p)-NOH may also inhibit STAT3 activation through JAK2, Src, Erb2, and epidermal growth factor receptor (EGFR), which are implicated in STAT3 activation as well. Cisplatin resistance is associated with the altered activation of signaling pathways which include phosphatidylinositol 3-kinase PI3K/Akt and MAPK, or the suppression of tumor

suppressor genes, p53 and PTEN [134,135]. The tumor suppressor gene PTEN encodes a multifunctional phosphatase that is mutated in a variety of human cancers [136,137]. PTEN is considered to be a central regulator of cell proliferation and apoptosis [138]; inactivation of PTEN results in increased Akt activity in many cancers [135,139,140]. The overexpression of PTEN in cancer cells carrying mutant or deletion-type PTEN can inhibit cell proliferation and tumorigenicity via induction of cell cycle arrest at the G1 phase and apoptosis.

Previously, we have reported that the curcumin analog EF24 downregulated pAkt Ser<sup>473</sup> and Thr<sup>308</sup> through the upregulation of PTEN expression in cisplatin-resistant (CR) ovarian cancer cells [66]. Overexpression of PTEN showed inhibition of Akt activation, further supporting the idea that PTEN upregulates p53 through the Akt pathway, and how it might be involved in cell-cycle arrest and apoptosis in CR ovarian cancer cells. Further we showed that EF24 might inhibit PTEN proteasomal degradation, leading to the accumulation of polyubiquitinated proteins in the cells. These results suggest that EF24 may exert its cytotoxic effect on cancer cells through inhibition of the pPTEN and PTEN proteasome degradation [66]. This is consistent with previous studies, which showed that the turnover of PTEN in cultured COS-7 cells was dependent mainly on proteasomal degradation [141]. The oncogenic potential of PTEN is further highlighted by its roles in integrin signaling and ability to dephosphorylate FAK that can reduce cell adhesion and enhance migration [142]. Curcumin analogs which initiate PTEN stabilization may play a role in the regulation of cell proliferation in cancer and smooth muscle cells.

### Effects on migration/invasion and FAS/FAK pathways

Tumor progression involves complex processes that include malignant transformation, proliferation, invasion, and metastasis of cancer cells. Particularly, cancer-cell invasion and metastasis are the critical processes that define the aggressive phenotype of human cancers and pose major impediments to treatment [143,144]. Tumor cell migration requires the concerted effort of a number of molecules such as integrins, ion channels, cell adhesion molecules, soluble cytokines and growth factors, matrix-degrading proteases, and Rho GTPases [143]. The migration process involves the assembly and disassembly of focal adhesions. This process is stimulated extracellularly and is initiated by integrins and intracellular signaling proteins located in focal adhesions [145]. Focal adhesion kinase (FAK), a tyrosine receptor kinase, is activated in focal adhesions and is important in cell-extracellular matrix (ECM) interactions that affect cell migration, proliferation, and survival [145]. DAPs effectively inhibit ovarian cancer cell migration and invasion



by altering the FASN and FAK expression. Further, it also exhibits the potential to inhibit vascular endothelial growth factor (VEGF)-induced invasion and migration of these cell lines [65].

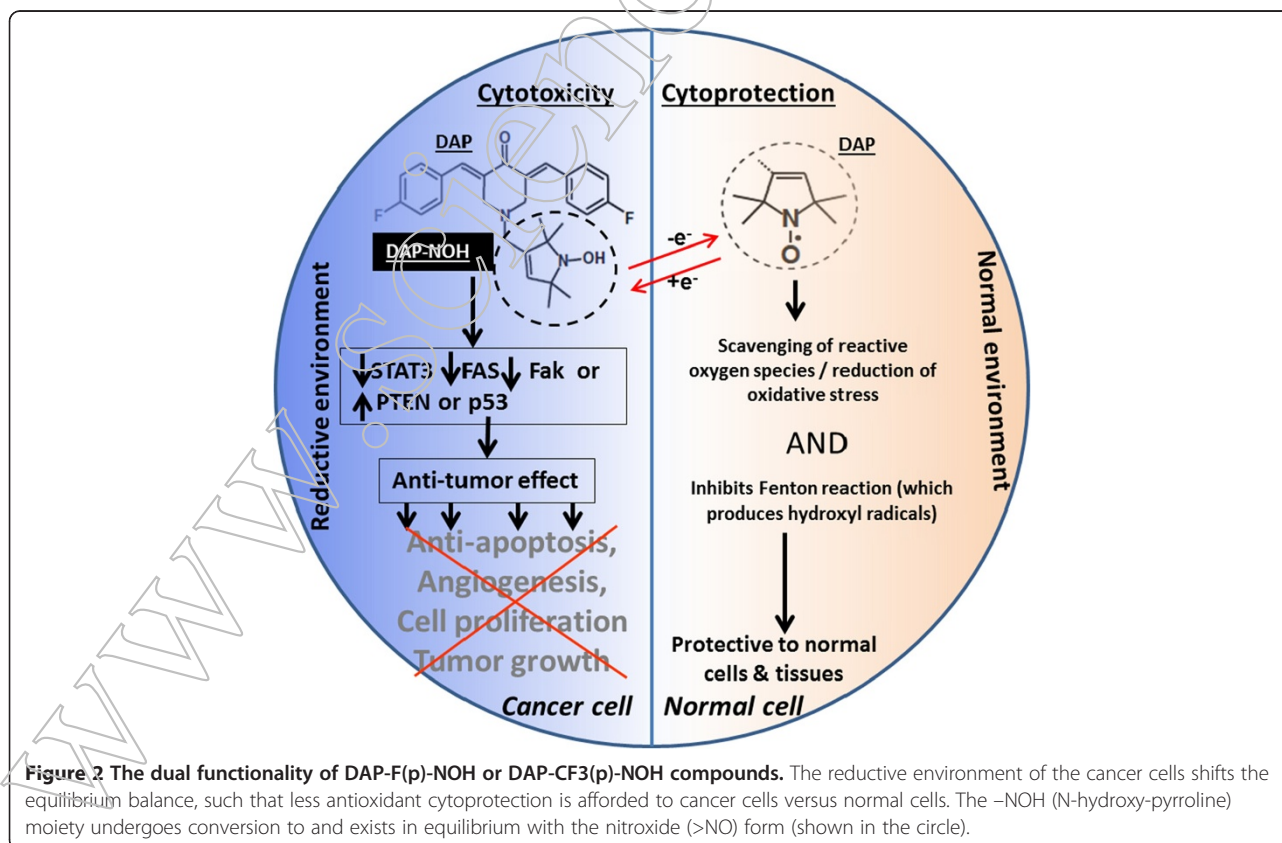
FASN is overexpressed in ovarian cancer, and overexpression has been related with aggressive biologic behavior, suggesting a functional role for fatty acid synthesis in the growth, survival, and expansion/proliferation of cancer cells [146]. Recent evidence shows that FASN inhibition induces apoptosis, via inactivation of pAKT and dephosphorylation of Bad in human cancer cells, including ovarian cancer cells [147]. DAP-F(p)-NOH targets FASN, resulting in inhibition of migration and invasion in ovarian cancer cell lines [65]. A recent report also showed that suppression of growth and invasiveness of renal cancer cells by targeting FASN using a synthetic pharmacological inhibitor [148].

### Conclusion & future direction

The diagnosis of an advanced cancer, such as ovarian, means multi-modality therapy for most patients, which typically includes chemotherapy. Unfortunately, most chemotherapy is toxic not only to tumors, but also to healthy tissue. This adversely impacts quality of life both during and after therapy. In addition, most ovarian cancer patients will ultimately recur, and die of their disease

Current cancer research focuses on developing new therapies to both improve survival and decrease toxicity. Given the anti-cancer properties of curcumin we have focused on developing compounds based that are not restricted by poor bioavailability, limited solubility, and low potency. One of these compounds DAP-F(p)-NOH shows promise not only in its toxicity toward cancer cells through a variety of mechanisms, but also its protection of healthy tissue. We show that the -NOH moiety provides an antioxidant protection to healthy cells minimizing damage to normal tissues *in vivo*. The cytotoxicity is mediated through the STAT3 and FAS/FAK signaling pathways (Figure 2).

While much has been learned from the collective work involving curcumin derivatives and DAP compounds in particular, it is clear that many questions are left unanswered. In the future, it will be critical to expand the existing knowledge of the mechanism of action of DAP compounds; in particular the other cancer-promoting pathways on which it may act. Additional *in silico* studies may be conducted to optimize the structure of the DAP compounds with the intent of maximizing interaction with known and future molecular targets. Further *in vivo* work is needed with head-to-head comparisons of DAP compounds against both standard chemotherapies and targeted agents as progress is made toward





possible clinical trials. Because of the complexity and variety of cancers found in the modern world, the idea of a “silver bullet” treatment or cure is unlikely to be found. However, the continued development of new therapies such as those described here will lead to improved survival and quality of life for cancer patients.

#### Competing interests

The authors declare that they have no competing interests.

#### Authors' contributions

This is a review article of previously-published work. KR, GM, DC, BR, PK, and KS all contributed to the writing, proofreading and editing of this review. All authors have read and approved the final manuscript.

#### Acknowledgment

This work was supported by a grant from the Ovarian Cancer Research Foundation (OCRF) - (K.S.)

#### Author details

<sup>1</sup>Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Ohio State University, Columbus, OH 43210, USA.

<sup>2</sup>Department of Internal Medicine, The Ohio State University, Columbus, OH 43210, USA.

Received: 8 February 2013 Accepted: 1 May 2013

Published: 11 May 2013

#### References

- Siegel R, Naishadham D, Jemal A: **Cancer statistics, 2012.** *CA Cancer J Clin* 2012, **62**(1):10–29.
- Yap TA, Carden CP, Kaye SB: **Beyond chemotherapy: targeted therapies in ovarian cancer.** *Nature reviews* 2009, **9**(3):167–181.
- Zaman MS, Maher DM, Khan S, Jaggi M, Chauhan SC: **Current status and implications of microRNAs in ovarian cancer diagnosis and therapy.** *J Ovarian Res* 2012, **5**(1):44.
- Gubbels JA, Claussen N, Kapur AK, Connor JP, Patankar MS: **The detection, treatment, and biology of epithelial ovarian cancer.** *J Ovarian Res* 2010, **3**:8.
- Kohn EC, Lu Y, Wang H, Yu Q, Yu S, Hall H, Smith DL, Meric-Bernstam F, Hortobagyi GN, Mills GB: **Molecular therapeutics: promise and challenges.** *Semin Oncol* 2004, **31**(1 Suppl 3):39–53.
- Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, et al: **Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.** *N Engl J Med* 2004, **350**(23):2335–2342.
- Lane D, Matte I, Rancourt C, Piche A: **The prosurvival activity of ascites against TRAIL is associated with a shorter disease-free interval in patients with ovarian cancer.** *J Ovarian Res* 2010, **3**:1.
- Burger RA: **Experience with bevacizumab in the management of epithelial ovarian cancer.** *J Clin Oncol* 2007, **25**(20):2902–2908.
- Nagy JA, Meyers MS, Masse EM, Herzberg KJ, Dvorak HF: **Pathogenesis of ascites tumor growth: fibrinogen influx and fibrin accumulation in tissues lining the peritoneal cavity.** *Cancer Res* 1995, **55**(2):369–375.
- Yoshiji H, Kuriyama S, Hicklin DJ, Huber J, Yoshii J, Ikenaka Y, Noguchi R, Nakatani T, Tsujimoto H, Fukui H: **The vascular endothelial growth factor receptor KDR/Flk-1 is a major regulator of malignant ascites formation in the mouse hepatocellular carcinoma model.** *Hepatology* 2001, **33**(4):841–847.
- Keefe DM, Bateman EH: **Tumor control versus adverse events with targeted anticancer therapies.** *Nat Rev Clin Oncol* 2012, **9**(2):98–109.
- Mansi L, Thiery-Vuillemin A, Nguyen T, Bazan F, Calcagno F, Rocquain J, Demarchi M, Villanueva C, Maurina T, Pivot X: **Safety profile of new anticancer drugs.** *Expert Opin Drug Saf* 2010, **9**(2):301–317.
- Villanueva MT: **Gynaecological cancer: OCEANS' three: the ovarian job.** *Nat Rev Clin Oncol* 2012, **9**(6):305.
- Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, Sovak MA, Yi J, Nycum LR: **OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer.** *J Clin Oncol* 2012, **30**(17):2039–2045.
- Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, Mannel RS, Homesley HD, Fowler J, Greer BE, et al: **Incorporation of bevacizumab in the primary treatment of ovarian cancer.** *N Engl J Med* 2011, **365**(26):2473–2483.
- Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, Carey MS, Beale P, Cervantes A, Kurzeder C, et al: **A phase 3 trial of bevacizumab in ovarian cancer.** *N Engl J Med* 2011, **365**(26):2484–2496.
- Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, Mortimer P, Swaisland H, Lau A, O'Connor MJ, et al: **Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers.** *N Engl J Med* 2009, **361**(2):123–134.
- Helm CW, States JC: **Enhancing the efficacy of cisplatin in ovarian cancer treatment - could arsenic have a role.** *J Ovarian Res* 2009, **2**:2.
- Komarova S, Roth J, Alvarez R, Curjel DT, Pereboeva L: **Targeting of mesenchymal stem cells to ovarian tumors via an artificial receptor.** *J Ovarian Res* 2010, **3**:12.
- Coleman RL, Broaddus RR, Bodurka DC, Wolf JK, Burke TW, Kavanagh JJ, Levenback CF, Gershenson DM: **Phase II trial of imatinib mesylate in patients with recurrent platinum- and taxane-resistant epithelial ovarian and primary peritoneal cancers.** *Gynecol Oncol* 2006, **101**(1):126–131.
- Noguera IR, Sun CC, Broaddus RR, Branham D, Levenback CF, Ramirez PT, Sood AK, Coleman RL, Gershenson DM: **Phase II trial of imatinib mesylate in patients with recurrent platinum- and taxane-resistant low-grade serous carcinoma of the ovary, peritoneum, or fallopian tube.** *Gynecol Oncol* 2012, **125**(3):640–645.
- Bookman MA, Darcy KM, Clarke-Pearson D, Boothby RA, Horowitz IR: **Evaluation of monoclonal humanized anti-HER2 antibody, trastuzumab, in patients with recurrent or refractory ovarian or primary peritoneal carcinoma with overexpression of HER2: a phase II trial of the Gynecologic Oncology Group.** *J Clin Oncol* 2003, **21**(2):283–290.
- Gordon MS, Matei D, Aghajanian C, Matulonis UA, Brewer M, Fleming GF, Hainsworth JD, Garcia AA, Pegram MD, Schilder RJ, et al: **Clinical activity of pertuzumab (rhuMAB 2C4), a HER dimerization inhibitor, in advanced ovarian cancer: potential predictive relationship with tumor HER2 activation status.** *J Clin Oncol* 2006, **24**(26):4324–4332.
- Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JL: **Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study.** *J Clin Oncol* 2007, **25**(33):5165–5171.
- Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, Douglas J, Burger RA, Armstrong D, Wenham R, et al: **Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer.** *J Clin Oncol* 2007, **25**(33):5180–5186.
- Posadas EM, Liel MS, Kwitkowski V, Minasian L, Godwin AK, Hussain MM, Espina V, Wood BJ, Steinberg SM, Kohn EC: **A phase II and pharmacodynamic study of gefitinib in patients with refractory or recurrent epithelial ovarian cancer.** *Cancer* 2007, **109**(7):1323–1330.
- Schilder RJ, Sill MW, Chen X, Darcy KM, Decesare SL, Lewandowski G, Lee RB, Arciero CA, Wu H, Godwin AK: **Phase II study of gefitinib in patients with relapsed or persistent ovarian or primary peritoneal carcinoma and evaluation of epidermal growth factor receptor mutations and immunohistochemical expression: a Gynecologic Oncology Group Study.** *Clin Cancer Res* 2005, **11**(15):5539–5548.
- Wagner U, du Bois A, Pfisterer J, Loibl S, Luck HJ, Sehouli J, Gropp M, Stahle A, Schmalfeldt B, et al: **Gefitinib in combination with tamoxifen in patients with ovarian cancer refractory or resistant to platinum-taxane based therapy—a phase II trial of the AGO Ovarian Cancer Study Group (AGO-OVAR 2.6).** *Gynecol Oncol* 2007, **105**(1):132–137.
- Gordon AN, Finkler N, Edwards RP, Garcia AA, Crozier M, Irwin DH, Barrett E: **Efficacy and safety of erlotinib HCl, an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, in patients with advanced ovarian carcinoma: results from a phase II multicenter study.** *Int J Gynecol Cancer* 2005, **15**(5):785–792.
- Behbakht K, Sill MW, Darcy KM, Rubin SC, Mannel RS, Waggoner S, Schilder RJ, Cai KQ, Godwin AK, Alpaugh RK: **Phase II trial of the mTOR inhibitor, temsirolimus and evaluation of circulating tumor cells and tumor biomarkers in persistent and recurrent epithelial ovarian and primary**

- peritoneal malignancies: a Gynecologic Oncology Group study. *Gynecol Oncol* 2011, **123**(1):19–26.
31. Annunziata CM, Walker AJ, Minasian L, Yu M, Kotz H, Wood BJ, Calvo K, Choyke P, Kimm D, Steinberg SM, et al: **Vandetanib, designed to inhibit VEGFR2 and EGFR signaling, had no clinical activity as monotherapy for recurrent ovarian cancer and no detectable modulation of VEGFR2.** *Clin Cancer Res* 2010, **16**(2):664–672.
  32. Matei D, Sill MW, Lankes HA, DeGeest K, Bristow RE, Mutch D, Yamada SD, Cohn D, Calvert V, Farley J, et al: **Activity of sorafenib in recurrent ovarian cancer and primary peritoneal carcinomatosis: a gynecologic oncology group trial.** *J Clin Oncol* 2011, **29**(1):69–75.
  33. Biagi JJ, Oza AM, Chalchal HI, Grimshaw R, Ellard SL, Lee U, Hirte H, Sederias J, Ivy SP, Eisenhauer EA: **A phase II study of sunitinib in patients with recurrent epithelial ovarian and primary peritoneal carcinoma: an NCIC Clinical Trials Group Study.** *Ann Oncol* 2011, **22**(2):335–340.
  34. Friedlander M, Hancock KC, Rischin D, Messing MJ, Stringer CA, Matthys GM, Ma B, Hodge JP, Lager JJ: **A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer.** *Gynecol Oncol* 2010, **119**(1):32–37.
  35. Garcia AA, Sill MW, Lankes HA, Godwin AK, Mannel RS, Armstrong DK, Carolla RL, Liepmann MK, Spiratos NM, Fischer EG, et al: **A phase II evaluation of lapatinib in the treatment of persistent or recurrent epithelial ovarian or primary peritoneal carcinoma: a gynecologic oncology group study.** *Gynecol Oncol* 2012, **124**(3):569–574.
  36. Gelmon KA, Tischkowitz M, Mackay H, Swenerton K, Robidoux A, Tonkin K, Hirte H, Huntsman D, Clemons M, Gilks B, et al: **Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study.** *Lancet Oncol* 2011, **12**(9):852–861.
  37. Kaye SB, Lubinski J, Matulonis U, Ang JE, Gourley C, Karlan BY, Amnon A, Bell-McGuinn KM, Chen LM, Friedlander M, et al: **Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer.** *J Clin Oncol* 2012, **30**(4):372–379.
  38. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB: **Curcumin and cancer: an "old-age" disease with an "age-old" solution.** *Cancer Lett* 2008, **267**(1):133–164.
  39. Ammon HP, Wahl MA: **Pharmacology of Curcuma longa.** *Planta Med* 1991, **57**(1):1–7.
  40. Weir NM, Selvendiran K, Kutala VK, Tong L, Vishwanath S, Rajaram M, Tridandapani S, Anant S, Kuppasamy P: **Curcumin induces G2/M arrest and apoptosis in cisplatin-resistant human ovarian cancer cells by modulating Akt and p38 MAPK.** *Cancer Biol Ther* 2007, **6**(2):178–184.
  41. Ghosh SS, Massey HD, Krieger R, Fazlshoy ZA, Ghosh S, Sica DA, Fakhry I, Gehr TW: **Curcumin ameliorates renal failure in 5/6 nephrectomized rats: role of inflammation.** *Am J Physiol Renal Physiol* 2009, **296**(5):F1146–F1157.
  42. Aggarwal BB, Sundaram C, Malani N, Ichikawa H: **Curcumin: the Indian solid gold.** *Adv Exp Med Biol* 2007, **595**:1–75.
  43. Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, Tharakan ST, Misra K, Priyadarsini IK, Rajasekharan KN, et al: **Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature.** *Biochem Pharmacol* 2008, **76**(11):1590–1611.
  44. Ravindran J, Prasad S, Aggarwal BB: **Curcumin and cancer cells: how many ways can curry kill tumor cells selectively?** *AAPS J* 2009, **11**(3):495–510.
  45. Singh S, Khar A: **Biological effects of curcumin and its role in cancer chemoprevention and therapy.** *Anticancer Agents Med Chem* 2006, **6**(3):259–270.
  46. Ren S, Lien EJ: **Natural products and their derivatives as cancer chemopreventive agents.** *Prog Drug Res* 1997, **48**:147–171.
  47. Half E, Arber N: **Colon cancer: preventive agents and the present status of chemoprevention.** *Expert Opin Pharmacother* 2009, **10**(2):211–219.
  48. Elsharkawy AM, Oakley F, Mann DA: **The role and regulation of hepatic stellate cell apoptosis in reversal of liver fibrosis.** *Apoptosis* 2005, **10**(5):927–939.
  49. Johnson JJ, Mukhtar H: **Curcumin for chemoprevention of colon cancer.** *Cancer Lett* 2007, **255**(2):170–181.
  50. Molina-Vijon E, Tapia E, Zazueta C, El Hafidi M, Zatarain-Barron ZL, Hernandez-Pando R, Medina-Campos ON, Zarco-Marquez G, Torres I, Pedraza-Chaverri J: **Curcumin prevents Cr(VI)-induced renal oxidant damage by a mitochondrial pathway.** *Free Radic Biol Med* 2011, **51**(8):1543–1557.
  51. Sampaio FJ: **Anti-neoplastic activity of curcumin in PCA.** *Int Braz J Urol* 2009, **35**(3):254–255.
  52. Marczylo TH, Verschoyle RD, Cooke DN, Morazzoni P, Steward WP, Gescher AJ: **Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine.** *Cancer Chemother Pharmacol* 2007, **60**(2):171–177.
  53. Sharma RA, Steward WP, Gescher AJ: **Pharmacokinetics and pharmacodynamics of curcumin.** *Adv Exp Med Biol* 2007, **595**:453–470.
  54. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB: **Bioavailability of curcumin: problems and promises.** *Mol Pharm* 2007, **4**(6):807–818.
  55. Yang CS, Sang S, Lambert JD, Lee MJ: **Bioavailability issues in studying the health effects of plant polyphenolic compounds.** *Mol Nutr Food Res* 2008, **52**(Suppl 1):S139–S151.
  56. Wahlstrom B, Blennow G: **A study on the fate of curcumin in the rat.** *Acta Pharmacol Toxicol (Copenh)* 1978, **43**(2):86–92.
  57. Ravindranath V, Chandrasekhara N: **Absorption and tissue distribution of curcumin in rats.** *Toxicology* 1980, **16**(3):259–265.
  58. Garcea G, Berry DP, Jones DJ, Singh B, Dennison AR, Farmer PB, Sharma RA, Steward WP, Gescher AJ: **Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences.** *Cancer Epidemiol Biomarkers Prev* 2005, **14**(1):120–125.
  59. Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, Boggs ME, Crowell J, Rock CL, Brenner DE: **Dose escalation of a curcuminoid formulation.** *BMC Complement Altern Med* 2006, **6**:10.
  60. Bisht S, Feldmann G, Soni S, Ravi R, Karikar C, Maitra A: **Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): a novel strategy for human cancer therapy.** *J Nanobiotechnology* 2007, **5**:3.
  61. Boockck DJ, Patel KR, Faust GE, Normolle DP, Marczylo TH, Crowell JA, Brenner DE, Booth TD, Gescher A, Steward WP: **Quantitation of trans-resveratrol and detection of its metabolites in human plasma and urine by high performance liquid chromatography.** *J Chromatogr B Analyt Technol Biomed Life Sci* 2007, **848**(2):182–187.
  62. Dayton A, Selvendiran K, Kuppasamy ML, Rivera BK, Meduru S, Kalai T, Hideg K, Kuppasamy P: **Cellular uptake, retention and bioabsorption of HO-3867, a fluorinated curcumin analog with potential antitumor properties.** *Cancer Biol Ther* 2010, **10**(10):1027–32.
  63. Kalai T, Kuppasamy ML, Balog M, Selvendiran K, Rivera BK, Kuppasamy P, Hideg K: **Synthesis of N-substituted 3,5-bis(arylidene)-4-piperidones with high antitumor and antioxidant activity.** *J Med Chem* 2011, **54**(15):5414–5421.
  64. Selvendiran K, Ahmed S, Dayton A, Kuppasamy ML, Tazi M, Bratasz A, Tong L, Rivera BK, Kalai T, Hideg K, et al: **Safe and targeted anticancer efficacy of a novel class of antioxidant-conjugated difluoroarylidene piperidones: differential cytotoxicity in healthy and cancer cells.** *Free Radic Biol Med* 2010, **48**(9):1228–1235.
  65. Selvendiran K, Ahmed S, Dayton A, Ravi Y, Kuppasamy ML, Bratasz A, Rivera BK, Kalai T, Hideg K, Kuppasamy P: **HO-3867, a synthetic compound, inhibits the migration and invasion of ovarian carcinoma cells through downregulation of fatty acid synthase and focal adhesion kinase.** *Mol Cancer Res* 2010, **8**(9):1188–1197.
  66. Selvendiran K, Tong L, Vishwanath S, Bratasz A, Trigg NJ, Kutala VK, Hideg K, Kuppasamy P: **EF24 induces G2/M arrest and apoptosis in cisplatin-resistant human ovarian cancer cells by increasing PTEN expression.** *J Biol Chem* 2007, **282**(39):28609–28618.
  67. Selvendiran K, Kuppasamy ML, Bratasz A, Tong L, Rivera BK, Rink C, Sen CK, Kalai T, Hideg K, Kuppasamy P: **Inhibition of vascular smooth-muscle cell proliferation and arterial restenosis by HO-3867, a novel synthetic curcuminoid, through up-regulation of PTEN expression.** *J Pharmacol Exp Ther* 2009, **329**(3):959–966.
  68. Robinson TP, Hubbard RB, Ehlers TJ, Arbiser JL, Goldsmith DJ, Bowen JP: **Synthesis and biological evaluation of aromatic enones related to curcumin.** *Bioorg Med Chem* 2005, **13**(12):4007–4013.
  69. Subramaniam D, May R, Sureban SM, Lee KB, George R, Kuppasamy P, Ramanujam RP, Hideg K, Dieckgraefe BK, Houchen CW, et al: **Diphenyl difluoroketone: a curcumin derivative with potent in vivo anticancer activity.** *Cancer Res* 2008, **68**(6):1962–1969.
  70. Selvendiran K, Tong L, Bratasz A, Kuppasamy ML, Ahmed S, Ravi Y, Trigg NJ, Rivera BK, Kalai T, Hideg K, et al: **Anticancer efficacy of a**

- difluorodiarylidene piperidone (HO-3867) in human ovarian cancer cells and tumor xenografts. *Mol Cancer Ther* 2010, **9**(5):1169–1179.
71. Adams BK, Ferstl EM, Davis MC, Herold M, Kurtkaya S, Camalier RF, Hollingshead MG, Kaur G, Sausville EA, Rickles FR, et al: **Synthesis and biological evaluation of novel curcumin analogs as anti-cancer and anti-angiogenesis agents.** *Bioorg Med Chem* 2004, **12**(14):3871–3883.
  72. Lagisetty P, Vilekar P, Sahoo K, Anant S, Awasthi V: **CLEFMA-an anti-proliferative curcuminoid from structure-activity relationship studies on 3,5-bis(benzylidene)-4-piperidones.** *Bioorg Med Chem* 2010, **18**(16):6109–6120.
  73. Adams BK, Cai J, Armstrong J, Herold M, Lu YJ, Sun A, Snyder JP, Liotta DC, Jones DP, Shoji M: **EF24, a novel synthetic curcumin analog, induces apoptosis in cancer cells via a redox-dependent mechanism.** *Anti-Cancer Drugs* 2005, **16**(3):263–275.
  74. Tierney BJ, McCann GA, Cohn DE, Eisenhauer E, Sudhakar M, Kuppusamy P, Hideg K, Selvendiran K: **HO-3867, a STAT3 inhibitor induces apoptosis by inactivation of STAT3 activity in BRCA1-mutated ovarian cancer cells.** *Cancer Biol Ther* 2012, **13**(9):766–775.
  75. Kakar SS, Jala VR, Fong MY: **Synergistic cytotoxic action of cisplatin and withaferin A on ovarian cancer cell lines.** *Biochem Biophys Res Commun* 2012, **423**(4):819–825.
  76. Solomon LA, Ali S, Banerjee S, Munkarah AR, Morris RT, Sarkar FH: **Sensitization of ovarian cancer cells to cisplatin by genistein: the role of NF-kappaB.** *J Ovarian Res* 2008, **1**(1):9.
  77. Samuni AM, DeGraff W, Krishna MC, Mitchell JB: **Cellular sites of H2O2-induced damage and their protection by nitroxides.** *Biochim Biophys Acta* 2001, **1525**(1–2):70–76.
  78. Krishna MC, Samuni A, Taira J, Goldstein S, Mitchell JB, Russo A: **Stimulation by nitroxides of catalase-like activity of hemoproteins. Kinetics and mechanism.** *J Biol Chem* 1996, **271**(42):26018–26025.
  79. Krishna MC, Russo A, Mitchell JB, Goldstein S, Dafni H, Samuni A: **Do nitroxide antioxidants act as scavengers of O2- or as SOD mimics?** *J Biol Chem* 1996, **271**(42):26026–26031.
  80. Watson JL, Greenshields A, Hill R, Hilchie A, Lee PW, Giacomantonio CA, Hoskin DW: **Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and downregulation of Bcl-2 and survivin expression and Akt signaling.** *Mol Carcinog* 2010, **49**(1):13–24.
  81. Hutzen B, Friedman L, Sobo M, Lin L, Cen L, De Angelis S, Yamakoshi H, Shibata H, Iwabuchi Y, Lin J: **Curcumin analogue GO-Y030 inhibits STAT3 activity and cell growth in breast and pancreatic carcinomas.** *Int J Oncol* 2009, **35**(4):867–872.
  82. Jung EM, Lim JH, Lee TJ, Park JW, Choi KS, Kwon JK: **Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through reactive oxygen species-mediated upregulation of death receptor 5 (DR5).** *Carcinogenesis* 2005, **26**(11):1905–1913.
  83. Goud VK, Polasa K, Krishnaswamy K: **Effect of turmeric on xenobiotic metabolising enzymes.** *Plant Foods Hum Nutr* 1993, **44**(1):87–92.
  84. Chan DK, Miskimins WK: **Metformin and phenethyl isothiocyanate combined treatment in vitro is cytotoxic to ovarian cancer cultures.** *J Ovarian Res* 2012, **5**(1):19.
  85. Yallapu MM, Maher DM, Sundram V, Bell MC, Jaggi M, Chauhan SC: **Curcumin induces chemo/radio-sensitization in ovarian cancer cells and curcumin nanoparticles inhibit ovarian cancer cell growth.** *J Ovarian Res* 2010, **3**:11.
  86. Jutooru I, Chadalapaka G, Lei P, Safe S: **Inhibition of NFkappaB and pancreatic cancer cell and tumor growth by curcumin is dependent on specificity protein down-regulation.** *J Biol Chem* 2010, **285**(33):25332–25344.
  87. Collett GP, Campbell FC: **Curcumin induces c-jun N-terminal kinase-dependent apoptosis in HCT116 human colon cancer cells.** *Carcinogenesis* 2004, **25**(11):2183–2189.
  88. Choudhuri T, Pal S, Das T, Sa G: **Curcumin selectively induces apoptosis in deregulated cyclin D1-expressed cells at G2 phase of cell cycle in a p53-dependent manner.** *J Biol Chem* 2005, **280**(20):20059–20068.
  89. Chen Q, Wang Y, Xu K, Lu G, Ying Z, Wu L, Zhan J, Fang R, Wu Y, Zhou J: **Curcumin induces apoptosis in human lung adenocarcinoma A549 cells through a reactive oxygen species-dependent mitochondrial signaling pathway.** *Oncol Rep* 2010, **23**(2):397–403.
  90. Yang JC, Lu MC, Lee CL, Chen GY, Lin YY, Chang FR, Wu YC: **Selective targeting of breast cancer cells through ROS-mediated mechanisms potentiates the lethality of paclitaxel by a novel diterpene, gelomulide K.** *Free Radic Biol Med* 2011, **51**(3):641–657.
  91. Choi CH, Jung YK, Oh SH: **Selective induction of catalase-mediated autophagy by dihydrocapsaicin in lung cell lines.** *Free Radic Biol Med* 2010, **49**(2):245–257.
  92. Nagai M, Vo NH, Shin Ogawa L, Chimmanamada D, Inoue T, Chu J, Beaudette-Zlatanova BC, Lu R, Blackman RK, Barsoum J, et al: **The oncology drug elesclomol selectively transports copper to the mitochondria to induce oxidative stress in cancer cells.** *Free Radic Biol Med* 2012, **52**(10):2142–2150.
  93. Kuttan R, Bhanumathy P, Nirmala K, George MC: **Potential anticancer activity of turmeric (*Curcuma longa*).** *Cancer Lett* 1985, **29**(2):197–202.
  94. Agrawal DK, Mishra PK: **Curcumin and its analogues: potential anticancer agents.** *Med Res Rev* 2010, **30**(5):818–860.
  95. Su CC, Yang JS, Lu CC, Chiang JH, Wu CL, Lin JJ, Lai KC, Hsia TC, Lu HF, Fan MJ, et al: **Curcumin inhibits human lung large cell carcinoma cancer tumour growth in a murine xenograft model.** *Phytother Res* 2010, **24**(2):189–192.
  96. Somasundaram S, Edmund NA, Moore DT, Small GW, Shi YY, Orłowski RZ: **Dietary curcumin inhibits chemotherapy-induced apoptosis in models of human breast cancer.** *Cancer Res* 2002, **62**(13):3868–3875.
  97. Milacic V, Banerjee S, Landis-Piowar KR, Sarkar FH, Majumdar AP, Dou QP: **Curcumin inhibits the proteasome activity in human colon cancer cells in vitro and in vivo.** *Cancer Res* 2008, **68**(18):7283–7292.
  98. Kawamori T, Lubet R, Steele VE, Kelloff GJ, Kaskay RB, Rao CV, Reddy BS: **Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion/progression stages of colon cancer.** *Cancer Res* 1999, **59**(3):597–601.
  99. Ushida J, Sugie S, Kawabata K, Pham QV, Tanaka T, Fujii K, Takeuchi H, Ito Y, Mori H: **Chemopreventive effect of curcumin on N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats.** *Jpn J Cancer Res* 2000, **91**(9):893–898.
  100. Moiseeva EP, Manson MM: **Dietary chemopreventive phytochemicals: too little or too much?** *Cancer Prev Res (Phila)* 2009, **2**(7):611–616.
  101. Vermeulen K, Van Bockstaele DR, Berneman ZN: **The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer.** *Cell Prolif* 2003, **36**(3):131–149.
  102. Amundson SA, Myers TG, Fornace AJ Jr: **Roles for p53 in growth arrest and apoptosis: putting on the brakes after genotoxic stress.** *Oncogene* 1998, **17**(25):3287–3299.
  103. Vousden KH, Prives C: **Blinded by the Light: The Growing Complexity of p53.** *Cell* 2009, **137**(3):413–431.
  104. Vermeulen K, Berneman ZN, Van Bockstaele DR: **Cell cycle and apoptosis.** *Cell Prolif* 2003, **36**(3):165–175.
  105. Damia G, Broggin M: **Cell cycle checkpoint proteins and cellular response to treatment by anticancer agents.** *Cell Cycle* 2004, **3**(1):46–50.
  106. Zhu H, Huang M, Yang F, Chen Y, Miao ZH, Qian XH, Xu YF, Qin YX, Luo HB, Shen X, et al: **R16, a novel amonafide analogue, induces apoptosis and G2/M arrest via poisoning topoisomerase II.** *Mol Cancer Ther* 2007, **6**(2):484–495.
  107. Bignon J, Benechie M, Herlem D, Liu JM, Pinault A, Khuong-Huu F, Wdziecizak-Bakala J: **A novel iodomethylene-dimethyl-dihydropyranone induces G2/M arrest and apoptosis in human cancer cells.** *Anticancer Res* 2009, **29**(6):1963–1969.
  108. Ouchi M, Ouchi T: **Role of IFI16 in DNA damage and checkpoint.** *Front Biosci* 2008, **13**:236–239.
  109. Newcomb EW: **Flavopiridol: pleiotropic biological effects enhance its anti-cancer activity.** *Anticancer Drugs* 2004, **15**(5):411–419.
  110. Pan MH, Ho CT: **Chemopreventive effects of natural dietary compounds on cancer development.** *Chem Soc Rev* 2008, **37**(11):2558–2574.
  111. Arcaro A, Guerreiro AS: **The phosphoinositide 3-kinase pathway in human cancer: genetic alterations and therapeutic implications.** *Curr Genomics* 2007, **8**(5):271–306.
  112. Ferrari E, Lazzari S, Marverti G, Pignedoli F, Spagnolo F, Saladini M: **Synthesis, cytotoxic and combined cDDP activity of new stable curcumin derivatives.** *Bioorg Med Chem* 2009, **17**(8):3043–3052.
  113. Hail N Jr: **Mitochondrial reactive oxygen species affect sensitivity to curcumin-induced apoptosis.** *Free Radic Biol Med* 2008, **44**(7):1382–1393.
  114. Cao J, Liu Y, Jia L, Zhou HM, Kong Y, Yang G, Jiang LP, Li QJ, Zhong LF: **Curcumin induces apoptosis through mitochondrial hyperpolarization**



- and mtDNA damage in human hepatoma G2 cells. *Free Radic Biol Med* 2007, **43**(6):968–975.
115. Bush JA, Cheung KJ Jr, Li G: Curcumin induces apoptosis in human melanoma cells through a Fas receptor/caspase-8 pathway independent of p53. *Exp Cell Res* 2001, **271**(2):305–314.
  116. Liu H, Zhou BH, Qiu X, Wang HS, Zhang F, Fang R, Wang XF, Cai SH, Du J, Bu XZ: T63, a new 4-arylidene curcumin analogue, induces cell cycle arrest and apoptosis through activation of the reactive oxygen species-FOXO3a pathway in lung cancer cells. *Free Radic Biol Med* 2012, **53**(12):2204–2217.
  117. Krystal GW, Sulanke G, Litz J: Inhibition of phosphatidylinositol 3-kinase-Akt signaling blocks growth, promotes apoptosis, and enhances sensitivity of small cell lung cancer cells to chemotherapy. *Mol Cancer Ther* 2002, **1**(11):913–922.
  118. Liu X, Shi Y, Giranda VL, Luo Y: Inhibition of the phosphatidylinositol 3-kinase/Akt pathway sensitizes MDA-MB468 human breast cancer cells to cerulenin-induced apoptosis. *Mol Cancer Ther* 2006, **5**(3):494–501.
  119. Garrison JB, Kyprianou N: Doxazosin induces apoptosis of benign and malignant prostate cells via a death receptor-mediated pathway. *Cancer Res* 2006, **66**(1):464–472.
  120. Mishra S, Kapoor N, Mubarak Ali A, Pardhasaradhi BV, Kumari AL, Khar A, Misra K: Differential apoptotic and redox regulatory activities of curcumin and its derivatives. *Free Radic Biol Med* 2005, **38**(10):1353–1360.
  121. Devarajan E, Huang S: STAT3 as a central regulator of tumor metastases. *Curr Mol Med* 2009, **9**(5):626–633.
  122. Leonard WJ: Role of Jak kinases and STATs in cytokine signal transduction. *Int J Hematol* 2001, **73**(3):271–277.
  123. Aaronson DS, Horvath CM: A road map for those who don't know JAK-STAT. *Science* 2002, **296**(5573):1653–1655.
  124. Wilken JA, Webster KT, Mailhe NJ: Trastuzumab Sensitizes Ovarian Cancer Cells to EGFR-targeted Therapeutics. *J Ovarian Res* 2010, **3**:7.
  125. Yu H, Jove R: The STATs of cancer—new molecular targets come of age. *Nat Rev Cancer* 2004, **4**(2):97–105.
  126. Duan Z, Foster R, Bell DA, Mahoney J, Wolak K, Vaidya A, Hampel C, Lee H, Seiden MV: Signal transducers and activators of transcription 3 pathway activation in drug-resistant ovarian cancer. *Clin Cancer Res* 2006, **12**(17):5055–5063.
  127. Selvendiran K, Bratasz A, Kuppusamy ML, Tazi MF, Rivera BK, Kuppusamy P: Hypoxia induces chemoresistance in ovarian cancer cells by activation of signal transducer and activator of transcription 3. *Int J Cancer* 2009, **125**(9):2198–2204.
  128. Selvendiran K, Bratasz A, Tong L, Ignarro LJ, Kuppusamy P: NCX-4016 a nitro-derivative of aspirin, inhibits EGFR and STAT3 signaling and modulates Bcl-2 proteins in cisplatin-resistant human ovarian cancer cells and xenografts. *Cell Cycle* 2008, **7**(1):81–88.
  129. Yue P, Turkson J: Targeting STAT3 in cancer: how successful are we? *Expert Opin Investig Drugs* 2009, **18**(1):45–56.
  130. Saydmohammed M, Joseph D, Syed V: Curcumin suppresses constitutive activation of STAT-3 by up-regulating protein inhibitor of activated STAT-3 (PIAS-3) in ovarian and endometrial cancer cells. *J Cell Biochem* 2010, **110**(2):447–456.
  131. Selvendiran K, Koga H, Ueno T, Yoshida T, Maeyama M, Torimura T, Yano H, Kojiro M, Sata M: Luteolin promotes degradation in signal transducer and activator of transcription 3 in human hepatoma cells: an implication for the antitumor potential of flavonoids. *Cancer Res* 2006, **66**(9):4826–4834.
  132. Singh RP, Raina K, Deep G, Chari D, Agarwal R: Silibinin suppresses growth of human prostate carcinoma PC-3 orthotopic xenograft via activation of extracellular signal-regulated kinase 1/2 and inhibition of signal transducers and activators of transcription signaling. *Clin Cancer Res* 2009, **15**(2):613–621.
  133. Liu Y, Li PK, Li C, Lin J: Inhibition of STAT3 signaling blocks the anti-apoptotic activity of IL-6 in human liver cancer cells. *J Biol Chem* 2010, **285**(35):27429–27439.
  134. Yang X, Fraser M, Moll UM, Basak A, Tsang BK: Akt-mediated cisplatin resistance in ovarian cancer: modulation of p53 action on caspase dependent mitochondrial death pathway. *Cancer Res* 2006, **66**(6):3126–3136.
  135. Lee S, Choi EJ, Jin C, Kim DH: Activation of PI3K/Akt pathway by PTEN reduction and PIK3CA mRNA amplification contributes to cisplatin resistance in an ovarian cancer cell line. *Gynecol Oncol* 2005, **97**(1):26–34.
  136. Okumura K, Zhao M, DePinho RA, Furnari FB, Cavenee WK: PTEN: a novel anti-oncogenic function independent of phosphatase activity. *Cell Cycle* 2005, **4**(4):540–542.
  137. Li Y, Guessous F, Kwon S, Kumar M, Ibdapo O, Fuller L, Johnson E, Lal B, Hussaini I, Bao Y, et al: PTEN has tumor-promoting properties in the setting of gain-of-function p53 mutations. *Cancer Res* 2008, **68**(6):1723–1731.
  138. Yan X, Fraser M, Qiu Q, Tsang BK: Over-expression of PTEN sensitizes human ovarian cancer cells to cisplatin-induced apoptosis in a p53-dependent manner. *Gynecol Oncol* 2006, **102**(2):348–355.
  139. Yao D, Alexander CL, Quinn JA, Porter MJ, Wu H, Greenhalgh DA: PTEN loss promotes rasHa-mediated papillomatogenesis via dual up-regulation of AKT activity and cell cycle deregulation but malignant conversion proceeds via PTEN-associated pathways. *Cancer Res* 2006, **66**(3):1302–1312.
  140. Lee JY, Kang MB, Jang SH, Qian T, Kim HJ, Kim CH, Kim Y, Kong G: Id-1 activates Akt-mediated Wnt signaling and p27(Kip1) phosphorylation through PTEN inhibition. *Oncogene* 2009, **28**(6):824–831.
  141. Torres J, Pulido R: The tumor suppressor PTEN is phosphorylated by the protein kinase CK2 at its C terminus. Implications for PTEN stability to proteasome-mediated degradation. *J Biol Chem* 2001, **276**(2):993–998.
  142. Tamura M, Gu J, Danen EH, Takino T, Miyamoto S, Yamada KM: PTEN interactions with focal adhesion kinase and suppression of the extracellular matrix-dependent phosphatidylinositol 3-kinase/Akt cell survival pathway. *J Biol Chem* 1999, **274**(29):20693–20703.
  143. Yamaguchi H, Wyckoff J, Condeelis J: Cell migration in tumors. *Curr Opin Cell Biol* 2005, **17**(5):559–564.
  144. Eccles SA, Box C, Court W: Cell migration/invasion assays and their application in cancer drug discovery. *Biotechnol Annu Rev* 2005, **11**:391–421.
  145. Golubovskaya VM, Kweh FA, Cance WG: Focal adhesion kinase and cancer. *Histol Histopathol* 2009, **24**(4):503–510.
  146. Kuhajda FP: Fatty acid synthase and cancer: new application of an old pathway. *Cancer Res* 2006, **66**(12):5977–5980.
  147. Zhou W, Han WF, Landree LE, Thupari JN, Pinn ML, Billington T, Kim EK, Vadlamudi A, Medghalchi SM, El Meskini R, et al: Fatty acid synthase inhibition activates AMP-activated protein kinase in SKOV3 human ovarian cancer cells. *Cancer Res* 2007, **67**(7):2964–2971.
  148. Horiguchi A, Asano T, Asano T, Ito K, Sumitomo M, Hayakawa M: Fatty acid synthase over expression is an indicator of tumor aggressiveness and poor prognosis in renal cell carcinoma. *J Urol* 2008, **180**(3):1137–1140.

doi:10.1186/1757-2215-6-35

Cite this article as: Rath et al.: Safe and targeted anticancer therapy for ovarian cancer using a novel class of curcumin analogs. *Journal of Ovarian Research* 2013 **6**:35.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)