dose ketoconazole normalized PCN (mPXR ligand) induced changes in paclitaxel metabolism.
Conclusions: These studies demonstrate that ketoconazole and commonly used anti-fungal analogs repress the co-ordinated activation of several genes involved in drug metabolism by blocking PXR activation. We show a completely novel mechanism of inhibitor action on PXR by ketoconazole. Our observation may lead to the development of new strategies to improve the clinical efficacy of drugs, reduce therapeutic side effects and prevent unwanted drug-drug interactions during cancer treatment by specifically targeting liganded orphan nuclear receptors.

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TKI258 is an effective multitargeted receptor tyrosine kinase (RTK) inhibitor against prostate cancer models via potent inhibition of FGFR kinase

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Background: TKI258 (formerly CHIR-258) is an oral, multitargeted RTK inhibitor of FGFR, VEGFR, PDGFRβ, FLT3 and cKIT currently in clinical trials. FGFs and their cognate receptors FGFR1–4 are dysregulated in multiple cancer types and have been implicated in tumorigenesis and angiogenesis. Previous studies have confirmed the antiangiogenic activity and inhibition of other target RTKs. Preclinical evaluation of TKI258 against FGFR was undertaken in prostate cancer models to investigate the therapeutic rationale for clinical studies in this patient population.
Materials and Methods: Prostate (PXRF 1369, DU145, PC3M, MRIH 1579, 22RV1, PNT1A) cell lines and tumor xenografts were characterized for expression levels of FGFR1–4 by Western blot analyses. Mutational analyses and FGFR4 gene polymorphism (Arg388) were evaluated by PCR sequencing. To dissect the mechanism of TKI258 against FGFR, anti-proliferative activity (using clonogenic assays) and signaling (pFRS2 and pERK) was examined. Anti-tumor activity of TKI258, Taxotere and the combination was evaluated in DU145 and 22RV1 xenograft models *in vivo*.
Results: Prostate cells differentially expressed FGFR1–4. All prostate cells were generally responsive to TKI258, modulated downstream FGFR signaling of pFRS2 and pERK, and sensitivity independent of expression pattern of FGFRs and/or FGFR4 (Arg388) polymorphism. The addition of TKI258 increased the sensitivity (decreased EC50) of DU145, 22RV1 and MRIH 1579 cells to Taxotere. Single agent activity (tumor inhibition and regressions) with TKI258 (10–100 mg/kg, daily) was observed in all prostate xenograft models tested (PC3, DU145 and 22RV1), including inhibition of metastatic growth of PC3M-luc cells *in vivo*. TKI258 was more potent than selective kinase inhibitors ZD1839 (EGFR inhibitor), and SU5416 (VEGFR and PDGFRβ inhibitor) in the DU145 tumor model. The addition of Taxotere (20 or 30 mg/kg once/week) to TKI258 (20 – 40 mg/kg, daily) augmented anti-tumor responses in both DU145 and 22RV1 xenograft models, resulting in additive drug effects. In the PSA-secreting 22RV1 tumor model, drug efficacy (tumor volumes) correlated with reduction of serum PSA levels.
Conclusion: The multitargeted activity of TKI258, arising from the direct inhibition of FGFR in addition to its anti-angiogenic activity, contributes significantly to its effectiveness as both a monotherapy or combined with Taxotere in $FGFR^+$ cancers.

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A potential for combining the mTOR inhibitor RAD001 (everolimus) with the ErbB2 receptor tyrosine kinase inhibitory antibody trastuzumab in breast cancer

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RAD001 (everolimus) is an mTOR pathway inhibitor exhibiting potent, antiproliferative/antitumor activity, which is currently in phase II clinical trials in oncology. Trastuzumab, is a humanized monoclonal antibody registered for the treatment of cancer patients with ErbB2-overexpressing, metastatic breast cancer. To investigate the potential for RAD001/trastuzumab combinations, trastuzumab-sensitive ErbB2-overexpressing breast carcinoma cells (BT474, SKBR3), with known sensitivity to RAD001 (IC50 for antiproliferative activity: 0.55±0.12 and 0.74±0.34 nM, respectively), were incubated with increasing concentrations of trastuzumab in the presence of an optimal RAD001 concentration (2 nM) and effects on proliferation were analyzed. In both lines, increased antiproliferative effects were observed with the combination as compared to the single agents. For example, as assessed by direct cell counting following 6 days incubation, treatment of BT474 cells with 10 nM (optimal) trastuzumab or 2 nM RAD001 resulted in a 64 % and 73 % decrease in cell number, respectively, as compared to control cultures. Interestingly, a more striking decrease (83 %) in cell number was observed with the combination. Similar results were obtained with SKBR3 cells, with a 33 % and 61 % decrease in cell number occurring with trastuzumab or RAD001 alone, and a 71 % decrease with the combination. In both cell lines, statistical analysis indicated significant positive interactions between RAD001 and trastuzumab ($p < 0.001$ BT474; $p = 0.035$ SKBR3, two-way ANOVA). Based on this promising in vitro data, the combination was also assessed in an athymic mouse BT474 orthotopic mammary tumor model. Ten estrogen pellet-bearing animals per group were treated three times per week (MWF) with RAD001 (5 mg/kg p.o.), trastuzumab (2 mg/kg i.p.), the combination or vehicle control. Antitumor activity (expressed as % T/C: mean increase of tumor volumes of treated animals divided by the mean increase of tumor volumes of control animals multiplied by 100) was observed with the single agents (T/C = 40 % for RAD001, 42 % for trastuzumab) and was increased with the combination (T/C = 14 %); a result indicating positive interaction between the two agents that reached near significance ($p = 0.060$, two-way ANOVA). A second experiment also showed increased activity of the combination. Based on body weights, treatments were well tolerated. Taken together, these data suggest that combinations of RAD001 and trastuzumab may have application in the treatment of ErbB2-overexpressing breast cancer patients, although further dose/regimen optimization may be required.

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NVP-TAE226, an inhibitor of FAK, induces regression of solid tumor

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Background: Focal Adhesion Kinase (FAK) is a non-receptor cytoplasmic tyrosine kinase that regulates multiple cell functions. Activation of integrins and the growth factor receptors result in FAK autophosphorylation at Y397 and the presentation of suitable binding sites for proteins containing either SH2 or phosphotyrosine binding domains. Elevated expression levels of FAK have been detected in various tumor samples and are closely correlated with invasive potential. Recent evidences indicate that FAK plays important roles in cancer cell proliferation and survival. Therefore, an inhibitor of FAK may selectively block the growth, migration, and survival of tumor cells.
Methods: In the present study, anti-cancer activity of a potent and selective FAK inhibitor, NVP-TAE226, was evaluated in cancer cell lines panel and various tumor models. All procedures in this study were in compliance with the regulations of Animal Welfare Committee in Novartis Institutes for BioMedical Research Tsukuba.
Results: NVP-TAE226 inhibited various cancer cell lines with mean GI_{50} value of 0.76 μmole/L. Expression of P-glycoprotein did not affect inhibition of cancer cell proliferation by NVP-TAE226, suggesting that the inhibitor is not served as a substrate of P-glycoprotein. Pancreas, colon tumors and melanoma growth were inhibited by oral administration of NVP-TAE226. Tumor stasis was observed at a dose of 30 mg/kg, furthermore regression of a pancreatic tumor was observed at a higher dose. The compound was also effective in an orthotopic model. All animals tolerated NVP-TAE226 treatment up to 100 mg/kg with no body weight loss. Inhibition of downstream signaling such as phosphorylation of Akt at Serine473 was accompanied by inhibition of FAK phosphorylation in human tumor cell lines.

Group	Regimen/Route	Dose (mg/kg)	ΔT/C (%)	Regression (%)	ΔBW[a] (%)	Dead/ Total
Vehicle	qd, po, 7×/wk	–	–	–	10±0.9	0/7
TAE226	qd, po, 7×/wk	10	50**	None	9.9±0.3	0/7
		30	13**	None	6.2±0.9	0/7
	qd, po, 5×/wk	100	<0	17##	7.0±1.2	0/7

MAI PaCa-2 model, efficacy in primary tumor, n = 7 @day 14
[a]BW, body weight. *$P < 0.05$, **$P < 0.01$ vs. vehicle control (Dunnett's test); #$P < 0.05$, ##$P < 0.01$ (paired t-test.)

Conclusion: NVP-TAE226 is a novel class of selective and small molecule kinase inhibitors with a potent in vivo activity and potential therapeutic application.