this approach appears related to the molecular alterations of tumour cells including the down-regulation of specific DUSPs and may be reduced in cell systems with acquired drug resistance.

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Mechanisms associated with Sunitinib-resistance in human breast carcinomas

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Background: Despite potent activity in several tumor types, sunitinib showed disappointingly no benefit when combined with cytotoxics in patients with breast cancer. Aiming understanding resistance in breast cancer, we examined molecular changes in carcinoma models protractedly exposed to sunitinib.
Materials and Methods: MCF-7 models were selected to investigate the effects of sunitinib in vitro (MTT and Matrigel assay) and in xenografts. RT-PCR and western blot assays were used to assess a panel of 75 genes and proteins possibly affected by exposure to sunitinib.
Results: The MCF-SUNI cell line was established from the parental MCF-7 cell line using a stepwise exposure to increasing sunitinib concentrations for more than 6 months. Exposure to 48-hour sunitinib led to IC_{50}s of 8.6 and 17.8 μM in MCF7 and MCF-SUNI cells, respectively. Protracted exposure to sunitinib led to a 3-fold increase mRNA expression of VEGFC, VEGFR1, VEGFR3, Neuropilin-1, CXCL12 (SDF-1), CXCR4, HIF1-alpha, PDGFRA, endothelin-1, RET in MCF-SUNI as compared to parental MCF-7 cells. We also observed a basal up regulation of MAPK and AKT survival signalling pathways as measured by p-ERK1/2 and p-AKT levels in MCF-SUNI cells. Interestingly, MCF-SUNI cells also displayed an increased invasive capacity in matrigel as compared to MCF-7 cells. Consistent with the potential role of SDF-1/CXCR4 cell signalling in spontaneous invasion, we observed that AMD3100, a CXCR4 inhibitor, was capable of inhibiting invasion in MCF-SUNI cells. In MCF-7 xenografts protractedly exposed to cytostatic doses of sunitinib, tumor resistance occurred around day 30 and was associated with increased expressions of SDF-1, CXCR4, and PDGFRA mRNAs.
Conclusions: Our data suggest that acquired resistance to sunitinib involves an increased expression of several survival molecules such as SDF-1/CXCR4 (chemokine/GPCR signalling also involved in resistance to cytotoxics) in MCF-7 breast carcinomas. Our data provide a rationale to further investigate inhibitors of SDF-1/CXCR4 to prevent and/or counteract resistance to sunitinib.

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Food does not affect the pharmacokinetics of CS-7017 in healthy subjects: results from an open label, phase I, two-treatment, three-period, crossover study

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Background: CS-7017 is a novel, highly selective peroxisome proliferator activated receptor gamma (PPARγ) agonist which has shown anti-cancer effects in preclinical studies. The aim of this phase I clinical study was to evaluate the effect of a high fat meal on the pharmacokinetics and safety of CS-7017 in healthy subjects.
Methods: This was a phase I, single-centre, open-label, randomized, two-treatment, three period, crossover study in healthy subjects. Subjects received single doses of 0.5 mg (2 × 0.25 mg) of CS-7017 under fasting conditions (A) or following a high fat meal (B) in an ABB or BAA sequence. Each treatment was separated by 6 days. PK samples for CS-7017 were collected on Days 1−4 (Period 1), Days 7−10 (Period 2) and Days 13−16 (Period 3). The primary endpoint was the *ln*-transformed PK parameters of CS-7017 (AUC_{last}, AUC_{0-inf} and C_{max}) when CS-7017 was administered with food (B), relative to when CS-7017 was administered without food (A). Furthermore, intra-subject variability of CS-7017 pharmacokinetics in the fed and fasted state was also determined. The secondary endpoint included a safety assessment.
Results: Twenty-one subjects were enrolled and randomized, two discontinued due to personal reasons. Based on the bioequivalence criteria (90% confidence interval to be within 80−125% of the control), the total exposure (AUC) of CS-7017 was equivalent and the peak exposure (Cmax) of CS-7017 was almost equivalent under fasting and fed conditions (Table). Based on ANOVA results, the intra-subject CVs were 1.6−2.7 folds lower when CS-7017 was given with a high fat meal (Treatment B). No deaths, serious adverse events (SAEs) or discontinuations due to AEs occurred in this study. Four subjects reported treatment-emergent AEs, all of which were mild and resolved by the end of the study without medication.
Conclusions: If CS-7017 is administered with food there may be a slight decrease in CS-7017 exposure. However, this reduction in exposure is not considered clinically significant and therefore, no dose modification is recommended. The administration of a single oral dose of 0.5 mg CS-7017 appeared to be well tolerated in this group of healthy subjects.

Table. Pharmacokinetic parameters of CS-7017 under fasting and fed conditions.

Parameter CS-7017	Geometric LSM Single oral 0.5 mg dose of CS-7017 under		Ratio B/A, % (95% CI)	Intra-subject CV (%) Single oral 0.5 mg dose of CS-7017 under	
	fasting conditions (A)	fed conditions (B)		fasting conditions (A)	fed conditions (B)
AUC_{last} (ng·h/mL)	368.4	314.8	85.4 (80.3, 90.9)	15.8	9.8
AUC_{0-inf} (ng·h/mL)	396.1	341.3	86.2 (81.3, 91.3)	16.2	6.0
C_{max} (ng/mL)	30.5	25.6	84.1 (79.3, 89.2)	15.3	8.9

AUC_{last}, area under the plasma concentration curve from the time of dosing to last measurable concentration; AUC_{0-inf}, AUC from the time of dosing extrapolated to infinity, calculated as: $AUC_{0-inf} = AUC_{last} + Clast/\lambda z\ C_{max}$, Maximum (peak) observed plasma concentration; LSM, least-squares-means.

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Co-administration of a CYP3A4 inhibitor (ketoconazole) increased the bioavailability of CS-7017 but did not affect tolerability: results from an open-label, phase I, two-way crossover study in healthy subjects

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Background: CS-7017 is a novel, highly selective, peroxisome proliferator activated receptor gamma agonist (PPARγ) agonist showing anticancer activity in preclinical models. CS-7017 is metabolized via the CYP3A4 enzyme. The aim of this phase I clinical study was to determine the effect of concomitant administration of a CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics and safety of CS-7017 in healthy volunteers.
Methods: Healthy male subjects aged 20−40 years were eligible for enrolment in this phase I, open label, randomized, two-treatment period, two-way crossover study. Subjects were randomized to receive two treatment sequences either in the order AB or BA. Treatment A comprised of a single oral dose of 0.25 mg CS-7017 (1 × 0.25 mg tablet) on the morning of day 4. In treatment B, subjects received an oral dose of ketoconazole, 400 mg (2 × 200 mg tablets) in the morning of days 1 to 6 and a single oral dose of 0.25 mg CS-7017 (1 × 0.25 mg tablet) in the morning of day 4. There was a washout period of 14 days between treatments. The primary endpoint of this study was the geometric mean ratio of the PK parameters of CS-7017 in combination with ketoconazole compared with CS-7017 administered alone. The safety and tolerability of CS-7017 with and without concomitant ketoconazole administration were also evaluated.

Table 1. Pharmacokinetic parameters of CS-7017 with and without concomitant administration of ketoconazole

Parameter CS-7017	Geometric LSM		Ratio B/A (%)	90% Confidence interval (%)	95% Confidence interval (%)
	Treatment A (Reference)	Treatment B (Test)			
AUC_{last} (ng·h/mL)	193.4	330.4	170.81	(161.57, 180.58)	(159.69, 182.70)
AUC_{0-inf} (ng·h/mL)	214.3	367.5	171.48	(161.62, 181.94)	(159.62, 184.21)
C_{max} (ng/mL)	14.9	16.2	108.8	(102.46, 115.61)	(101.17, 117.09)
	Medians				
	Treatment A (Reference)	Treatment B (Test)	Hodges-Lehmann Estimator for B-A	90% Confidence interval (%)	95% Confidence interval (%)
t_{max} (hours)	2.000	2.000	0.4917	(-0.008, 0.983)	(-0.017, 0.992)
$t_{1/2}$ (hours)	10.50	15.31	6.0717	(5.213, 6.749)	(5.118, 6.931)

$AUC_{0-inf} = AUC_{last} + C_{last}/\lambda_z$.; LSM, least-squares-means.

Results: A total of 22 patients completed the study and were evaluable. The PK parameters of CS-7017 as monotherapy or in combination with ketoconazole are summarized in Table 1. Concomitant administration of CS-7017 with ketoconazole significantly increased total exposure to CS-7017 by approximately 71% and extended the half-life of CS-7017 by 46%