PXD101. Moreover, a combination of low, sub-effective doses of PXD101 and the AR antagonist, bicalutamide, resulted in a synergistic reduction in cell proliferation and increase in caspase-dependent cell death. In similar conditions but in acute treatment, this combination was not effective in AR negative PC3 cells. However, chronic administration of PXD101 at subeffective doses restored AR expression and sensitized to the activity of bicalutamide. In vivo, PXD101 showed higher effects when administered in castrated mice bearing both 22rv1 and PC3 cells and this seem to be associated also to the reduction of Her2 expression and Her2-mediated AR transactivation.
Conclusions: Taken together, our results demonstrate that HDAC inhibition can increase the sensitivity of antagonists resulting attractive in the treatment of hormone refractory prostate cancers. Further information, we need to develop clinical treatment strategies for prostate cancer.

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Anti-tumor activity of CU-201, an inhibitor of HDAC, SFK and Abl kinases

R. Bao[1], C. Lai[2], H. Qu[1], D. Wang[1], L. Ying[1], X. Tao[2], J. Wang[2], H. Zhai[3], H. Cai[3], C. Qian[4]. *[1]Curis Inc, Oncology, Cambridge Massachusetts, USA; [2]Curis Inc, Biology, Cambridge Massachusetts, USA; [3]Curis Inc, Chemistry, Cambridge Massachusetts, USA; [4]Curis Inc, Drug Discovery, Cambridge Massachusetts, USA*

Recent evidence has established Src Family Kinases (SFKs) as a critical component of multiple signaling pathways that regulate proliferation, survival, angiogenesis and metastasis. Increased levels of SFK protein and activity have been widely reported in human cancers. Dasatinib and bosutinib, multi-kinase inhibitors of Bcr-Abl and SFKs, are undergoing multiple clinical trails for the treatment of hematological and solid tumors associated with Src kinase. On the other hand, HDAC inhibitors downregulate oncoproteins and disrupt signaling pathways of tumor growth and metastasis via epigenetic modification. Synergy between HDAC and Src inhibition has previously been demonstrated in cancer cell lines. We have designed CU-201, a single small molecule that displays potent inhibition of HDAC (IC50 6.8 nM), Src (IC50 2.4 nM) and Brc-Abl (25.8 nM). In cell based assays CU-201 exhibits potent anti-proliferation and apoptosis-inducing effects in hematological as well as solid tumor cell lines. CU-201 displays preferential exposure to tumor tissues compared with plasma in tumor-bearing mice with a prolonged half life following intravenous administration. CU-201 displays antitumor efficacy in various xenograft models of hematological and solid tumors. MOA (mechanism-of-action) studies demonstrate that CU-201 is able to inhibit Src family kinases and upregulate acetylated histones. Importantly CU-201 is able to downregulate essential molecular mediators of the Src signaling pathways through epigenetic regulation, which may partially account for its synergistic effects. In summary, as a single agent with potent non-kinase and kinase inhibitory activities, CU-201 exhibits potent antitumor activity in preclinical models of cancer and deserves further investigation.

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Dasatinib blocks cetuximab- and radiation-induced nuclear translocation of the epidermal growth factor receptor in head and neck squamous cell carcinoma

C. Li[1], M. Iida[1], E.F. Dunn[1], T.M. Brand[1], C.R. Peet[1], D.L. Wheeler[1]. *[1]University of Wisconsin, Human Oncology, Madison, USA*

The aberrant expression of epidermal growth factor receptor (EGFR) has been linked to the etiology of head and neck squamous cell carcinoma (HNSCC). The first major phase III trial combining cetuximab with radiation confirmed a strong survival advantage. However, both cetuximab and radiation can promote EGFR translocation to the nucleus where it enhances resistance to both of these modalities. In this study we sought to determine how to block cetuximab- and radiation-induced translocation of EGFR to the nucleus in HNSCC cell lines. We utilized three established HNSCC cell lines, SCC1, SCC6 and SCC1483 and measured nuclear translocation of EGFR after treatment with cetuximab or radiation. We then utilized dasatinib (BMS-354825, sprycel®), a potent, orally bioavailable inhibitor of several tyrosine kinases, including the Src Family Kinases, to determine if SFKs blockade could abrogate cetuximab- and radiation-induced nuclear EGFR translocation. The results of these experiments showed that cetuximab and radiation treatment of all three HNSCC lines lead to translocation of the EGFR to the nucleus. Further, blockade of SFKs abrogated cetuximab and radiation-induced EGFR translocation to the nucleus. The data presented in this study suggests that both cetuximab and radiation can promote EGFR translocation to the nucleus and dasatinib can inhibit this process. Collectively these findings may suggest that dasatinib can limit EGFR translocation to the nucleus and may enhance radiotherapy plus cetuximab in HNSCC.

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The effect of KRAS mutations on the rectal cancer transcriptome: clinical implications

J. Gaedcke[1], M. Grade[1], K. Jung[2], J. Camps[3], P. Jo[4], H. Becker[4], T. Beißbarth[5], T. Ried[3], M. Ghadimi[4]. *[1]Georg-August University Göttingen, General Surgery, Gottingen, Germany; [2]Georg-August University Göttingen, Medical Statistics, Gottingen, Germany; [3]National Cancer Institute, Section of Cancer Genomics Genetics Branch, Bethesda MD, USA; [4]Georg-August University Göttingen, General Surgery, Göttingen, Germany; [5]Georg-August University Göttingen, Medical Statistics, Göttingen, Germany*

Background: Mutations of the KRAS oncogene are predictive for resistance to treatment with antibodies against the epithelial growth factor receptor in patients with colorectal cancer. Overcoming this therapeutic dilemma could potentially be achieved by the introduction of drugs that inhibit signaling pathways that are activated by KRAS mutations.
Material: To comprehensively identify such signaling pathways we profiled pretreatment biopsies and normal mucosa from 65 patients with locally advanced rectal cancer − 30 of which carried mutated KRAS − using global gene expression microarrays.
Results: By comparing all tumor tissues exclusively to matched normal mucosa, we could improve assay sensitivity, and identified a total of 22,297 features that were differentially expressed (adjusted p-value $p < 0.05$) between normal mucosa and cancer, including several novel potential rectal cancer genes. We then used this comprehensive description of the rectal cancer transcriptome as the baseline for identifying KRAS-dependent alterations. The presence of activating KRAS mutations resulted in significant upregulation of 13 genes (adjusted p-value <0.05), among them DUSP4, a MAP-kinase phosphatase, and SMYD3, a histone methyltransferase. Inhibition of the expression of both genes has previously been shown using the MEK1-inhibitor PD98059 and the antibacterial compound Novobiocin, respectively.
Conclusion: These findings first have to be validated in rectal cancer, however, they suggest a potential approach to overcome resistance to treatment with antibodies against the epithelial growth factor receptor in patients with KRAS-mutant rectal carcinomas.

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Synergistic activity of the novel apoptosis-inducing compound KP1339 with the tyrosine kinase inhibitor sorafenib in cancer cell lines of diverse origin

P. Heffeter[1], B. Atil[1], U. Jungwirth[1], E. Gal[1], J. Gojo[1], M. Micksche[1], B.K. Keppler[2], W. Berger[1]. *[1]Institute of Cancer Research, Medical University, Vienna, Austria; [2]Institute of Inorganic Chemistry, University, Vienna, Austria*

KP1339 is a promising novel apoptosis-inducing anti-cancer compound. The aim of this study was to test the in vitro and in vivo activity of KP1339 in combination with sorafenib. The combination of KP1339 and sorafenib was initially tested against a tumor cell line panel (n = 10) by MTT assay. The combination of the two drugs resulted in additive to synergistic effects in all cell lines tested. Particularly strong synergism with CI values between 0.1 and 0.5 were observed at higher sorafenib concentrations (10 μM). The synergistic activity of sorafenib and KP1339 was observed in sorafenib-resistant as well as sorafenib-sensitive cell lines. Recently, we have presented that KP1339 treatment led to cell cycle arrest in G2/M Phase and induced the phosphorylation of P38, JNK, and ERK. We therefore analyzed the effects of KP1339-sorafenib combination on the phosphorylation of these proteins and cell cycle arrest. Western blot analyses revealed that, compared to KP1339 monotherapy, KP1339-sorafenib combination exhibits significantly reduced phosphorylation of P38 and ERK. Moreover, addition of sorafenib shifted KP1339-induced G2/M arrest into a G0/G1 arrest. The activity of the KP1339-sorafenib combination was also evaluated in xenograft experiments (Hep3B cells). KP1339 monotherapy led to a 2.4-fold increase in life span (mean survival 80 days vs. 33 days in control) and thus was superior to sorafenib monotherapy, which induced a 1.9-fold survival increase compared to control (60 days vs. 33 days). Combination of KP1339 with sorafenib increased the mean survival by 3.9-fold to 96 days. Together, our data indicate that the combination of KP1339 with sorafenib displays promising activity in vitro and in vivo especially against human hepatoma cells.
This work was supported by the Herzfelder'sche Familienstiftung and the Austrian Science Fond (FWF) grant L212.