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Running title: PPAR modulators in lung cancer

Peroxisome proliferator-activated receptors as novel targets of small cell lung cancer circulating tumor cells

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Small cell lung cancer (SCLC) has a dismal prognosis with a low 2-year survival rate. Chemotherapy for recurrent SCLC fails invariably, and novel tumor targets are needed. Here, the effects of agents targeting the peroxisome proliferator-activated receptors (PPARs) in SCLC are investigated. Initial screening of 96 PPAR-directed agents was performed in two SCLC CTC-derived lines (BHGc10, BHGc16). Compounds showing high cytotoxicity were subsequently tested in two pleural effusion-derived lines (S457, S1392) and the SCLC line NCI-H69. Several PPARs emerged as actionable targets: eight PPARγ ligands and nine ligands for PPARα, PPARα/δ, or PPARβ/δ. For the six most effective compounds, treatment-induced protein changes were further profiled in BHGc16 using protein arrays. Cytotoxicity varied by compound, while the PPARγ agonist pioglitazone and the PPARα agonist fenofibrate were preferentially active in CTC lines, DG172 hydrochloride was selective for pleural effusion-derived lines, while rosiglitazone maleate, cloxiquine, and agrimol B showed no selectivity. Mechanistically, in the CTC-derived cell line BHGc16, these six PPAR-directed agents increased pro-apoptotic proteins (Bax, Bad, caspase-3/9), decreased anti-apoptotic and invasion proteins (Bcl-2, Bcl-XL, c-FLIP-L, ICAM-1, CXCR4), and suppressed Akt/mTOR, MEK/ERK, p38 MAPK, and JAK2/STAT3 signaling. These findings support PPARs as clinically relevant targets in SCLC, with PPAR-directed agents showing cytotoxic effects comparable to those reported in other malignancies. Such agents may aid SCLC treatment and help delineate biological differences between CTCs and resident tumor cells.

Key words: small cell lung cancer; circulating tumor cells; peroxisome proliferator activated receptor; cytotoxicity

Peroxisomes are intracellular structures present in the majority of animal cells, involved in metabolic processes such as hydrogen peroxide-based respiration, fatty acid (FA) beta-oxidation and cholesterol metabolism [1, 2]. Transcriptional regulators controlled by FAs lead to alterations of size and number of peroxisomes present [3]. Alternatively, chemically unrelated peroxisome proliferators (PPs) can replace FAs in their effects on peroxisomes. The function of PPs is mediated by specific receptors, known as peroxisome proliferator-activated receptors (PPARs), which belong to the nuclear receptor superfamily. PPARs consist of three genetically homologous isotypes, namely PPARα, γ and β/δ, that are key metabolic regulators of the body [4]. Besides the

involvement in nutrient and energy metabolism, they control lipid and carbohydrate turnover, cell growth, and cancer development [5]. After ligand binding, PPARs bind to peroxisome proliferation reaction elements (PPREs) on the DNA and, after heterodimerization with retinol X receptors (RXR), this complex regulates the transcription of target genes in the nucleus [6, 7]. Activated PPARs may additionally exert DNA-independent transcriptional repression of transcription factors such as NFκB, STAT-1 and AP-1 signaling factors. The endogenous ligands of PPARs are mostly FAs and their derivatives [8].

PPAR ligands are regarded as potential anticancer agents with relatively low systemic toxicity [9]. PPARα activation can target cancer cells' energy balance by blocking FA synthesis and by promotion of β-oxidation. PPARα can divert energy metabolism toward FA degradation and decrease glucose uptake by inhibiting glucose transporter GLUT4 [10, 11]. PPARα activation leads to the upregulation of enzymes involved in FA uptake, transport to mitochondria, and subsequent oxidation. This enhances the breakdown of fatty acids, when glucose availability is limited and energy is required. PPARβ/δ activation is associated with tumor progression, whereas PPARα and PPARγ activation may be associated with tumor suppression. In the repressed state, the PPAR/RXR heterodimer binds to corepressor proteins, containing histone deacetylase activity, and eventually turns down target gene transcription [12]. Upon ligand binding, the heterodimer releases the corepressor enhancing the coactivator activity [13].

Antitumor effects of the PPARα, PPARβ/δ, and PPARγ ligands were reported frequently [14, 15]. In detail, inhibition of PPARα reduces cell migration and increases cell death in malignant cells. Mechanisms discussed include the downregulation of Myc, delayed G0/G1 phase transit and the downregulation of cyclin-dependent kinases (CKs), respectively. Furthermore, activation of PPARγ retards the proliferation of a glioblastoma cell line and is followed by apoptosis [16]. PPARα (e. g., clofibrate corrosive) and PPARγ agonists (e.g., pioglitazone) suppress the tumor growth, decrease angiogenesis and promote apoptosis [17]. The PPARα agonists, fenofibrate and bezafibrate were found to exert chemopreventive activity [17]. Fenofibrate impairs IGF-IR signaling resulting in increased reactive oxygen species (ROS), lower ATP production and damaged mitochondria [18]. In cancer, PPARs disturb the activity of phosphates and kinases, including ERK1/2, p38-MAPK, PKC, AMPK, and GSK3. PPARγ is frequently expressed in tumor cells and its activation leads to either inhibition of cell growth or induction of cell death [19, 20]. Although each PPAR either suppresses or promotes tumor progression, depending on the specific tumor or ligands, the mechanisms are still largely unclear [21]. Of special interest is the potential inhibitory effect of PPAR-γ ligands on the metastatic potential of cancer cells [22, 23]. In this respect, the thiazolidinediones (TZDs) class of synthetic ligands for PPARγ, including rosiglitazone, pioglitazone and others which are commonly used to lower blood sugar have been studied so far [24, 25]. Pioglitazone targets PPARγ-regulated

genes and strongly reduces cell invasiveness in addition to anti-proliferative effects in various malignancies. Normal cells appear to be largely insensitive to pioglitazone application [26, 27]. In general, PPARγ agonists hinder cancer cells migratory and invasive capabilities for successful metastasis [23]. Angiogenesis and the expression of matrix metalloproteinases and extracellular matrix (ECM) proteins seem to be modulated by PPARγ in the tumor microenvironment.

In the present study, PPAR-directed agents active against small cell lung cancer (SCLC) and circulating tumor SCLC cell lines (SCLC CTC) were detected in a screen of a compound library comprising over 700 transcription factor (TF) inhibitors. SCLC accounts for 15-20% of lung cancers and the majority of patients show tumor dissemination at first presentation [28]. SCLC exhibits exceptionally large numbers of CTCs that enabled our lab to establish a panel of permanent SCLC CTC lines that proved tumorigenic in mice and thus have metastasis-inducing capabilities [29, 30]. With help of these cell lines, effects of PPAR-directed agents on metastasis-mediating SCLC tumor cells could be checked in a direct manner and, furthermore, pleural effusion-derived SCLC lines were tested for comparison. CTCs were reported for most tumor entities, although at low numbers and are different from SCLC by a lack of derived cognate long-term tumor cell lines [31].

Materials and methods

Cell lines. The SCLC cell line NCI-H69 was acquired from the American Type Culture Collection (HTB-119, ATCC, Manassas, VA, USA). The SCLC CTC lines BHGc10 and BHGc16 were obtained from blood samples, and the SCLC cell lines S457 and S1392 were pleural effusion-derived and were successfully established at our laboratory. Samples were obtained from relapsed SCLC patients before second line chemotherapy. All SCLC cell lines belonged to the SCLC-A subtype, except for the SCLC-P line S1392, as confirmed by RNA sequencing, with gene expression values normalized to transcripts per million (TPM) (Supplementary Table S1). Pleural effusions are routinely obtained from SCLC patients since their removal is a necessary means to improve breathing for patients. All clinical specimens were obtained from patients with informed consent and according to the guidelines of the Ethics Approval 366/2003 granted by the Ethics Committee of the Medical University of Vienna, Vienna, Austria.

Cell culture. For cell culture in 75 cm^2 tissue culture flasks (#658170, Greiner Bio-One GmbH, Kremsmuenster, Austria) the cells were kept in culture medium RPMI-1640 medium (#R8758, Sigma-Aldrich, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (FBS) (#SFBS-AU, Eximus, Catus Biotech, Tutzing, Germany) and antibiotics (#P4458, Sigma-Adrich, Darmstadt, Germany). All cells were kept under tissue culture conditions of 37 °C at 5% CO_2 and regularly split by replacement of medium. All cells were harvested by pipetting except for tuft-like S1392 that

attaches loosely and can be released with cell scrapers or pipetting. Cells were counted with a LUNA automated cell counter (Biozym, Vienna, Austria).

Compounds. All compounds were used as 10 mM stock solutions in dimethyl sulfoxide (DMSO). Samples were obtained as part of the Transcription Factor Library L1380 (Batch #PHD156583), comprising 704 compounds (Targetmol, Welesely Hills, MA, USA). Due to the aim of this study, the focus was on 96 agents linked to PPAR, some which modulate it in an indirect manner (Supplementary Table S2).

MTT Cytotoxicity assays. To obtain the half-maximal inhibitory concentration values (IC_{50}-values) of the compounds, 1×10^4 cells in 100 µl complete RPMI-1640 medium (supplemented with 10% FBS and antibiotics) were distributed to the wells of 96-well flatbottom microtiter plates (92096, Techno Plastic Products AG, TPP, Trasadingen, Switzerland). Two -fold dilutions of test compounds were added in triplicate, while assays were also performed at least in triplicate. After four days of incubation under tissue culture conditions, viable cells were detected at 450 nm using a modified 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide (MTT) assay (EZ4U, Biomedica, Vienna, Austria). IC_{50}-values were calculated from dose response curves evaluated via Origin 9.1. software (OriginLab, Northampton, MA, USA). Initial screening encompassed testing of all 96 compounds on BHGc10 and BHGc16. Thereafter, if IC_{50}-values below 9 µM were achieved, these compounds were further tested in all other cell lines.

Proteome profiler oncology XL arrays. Relative expression of oncology-related proteins in BHGc16 treated with pioglitazone, rosiglitazone maleate, cloxiquine, fenofibrate, agrimol B and DG172 dihydrochloride was determined using a Proteome Profiler Human Oncology XL Array Kit (#ARY026, R&D Systems, Minneapolis, MN, USA) according to the manufacturer´s instructions. The cancer cells were lysed using the lysis buffer 17 (#895943, R&D Systems) according to the supplied instructions. Experiments were performed in duplicate and the six reference spots provided on each membrane were used to calibrate the individual chemiluminescence intensities. The arrays were evaluated using Quickspot (Ideal Eyes System, Bountiful, UT, USA) and Origin 9.1 software.

Statistical analysis. We aimed to find differences in the expression of cancer-related proteins between control and six different treatments. Therefore, we conducted repeated measures ANOVAs for control and treatment comparisons of Proteome Profiler Human Oncology XL Array data. Normality was evaluated via a Shapiro-Wilk test and sphericity via a Mauchly's Test for Sphericity. Analysis was conducted using Origin 9.1. software (OriginLab, Northampton, MA, USA).

Results

Cytotoxicity assays of PPAR-directed agents. A range of PPAR-directed agents were tested in chemosensitivity assays in 6 two-fold dilution steps starting with a 20 µM concentration (Supplementary Tables S2, S3). Pioglitazone showed similar dose-dependent activity against the SCLC CTC lines BHGc10 and BHGc16, whereas the pleural effusion-derived S457 cells showed less sensitivity. Cloxiquine exhibited cytotoxic activity against all three cell lines, BHGc10, and BHGc16 SCLC CTCs as well as against S457 cells, however with a relatively lower potency. Fenofibrate showed high cytotoxic activity against BHGc16 cells, considerable activity against BHGc10 cells but failed to exert significant cytotoxic effects on the pleural effusion-derived S457 cells. In contrast, DG172 hydrochloride showed higher cytotoxic activity against S457 cells with lower potency on BHGc16 and especially BHGc10 cells (Figure 1).

Summary of cytotoxicity tests of PPAR-directed agents. Data for the PPARγ-directed drugs are summarized in Figure 2. Mean IC_{50}-values are shown for pioglitazone, rosiglitazone maleate and cloxiquine as found in MTT tests employing the two SCLC CTC lines, the NCI-H69 SCLC cell line and two pleural effusion-derived SCLC lines S457 and S1392. While pioglitazone was active against both SCLC CTC lines, rosiglitazone maleate was cytotoxic for the BHGc16 line and cloxiquine was cytotoxic for all cell lines tested.

Data for other PPAR-directed drugs are summarized in Figure 3. Mean IC_{50}-values are shown for fenofibrate, agrimol B and DG172 hydrochloride as found in MTT tests employing the two SCLC CTC lines, the NCI-H69 SCLC cell line and two pleural effusion-derived SCLC lines S457 and S1392. While fenofibrate was active against both SCLC CTC lines, agrimol B was cytotoxic for all cell lines tested and DG172 hydrochloride showed preferential activity for the pleural effusion-derived SCLC cell lines in contrast to the BHGc16 and BHGc10 SCLC CTC cell lines. The H69 cell line was resistant to pioglitazone, rosiglitazone maleate and fenofibrate, sensitive to cloxiquine and agrimol B but highly sensitive to DG172 hydrochloride.

Changes in protein expression in response to PPAR agents. Alterations in oncology-related proteins in response to selected PPAR-directed agents were analyzed using Proteome Profiler XL Western blot arrays that capture 84 proteins. The proteins exhibiting the largest effects of the PPAR-directed compounds of the BHGc16 SCLC CTC line are shown in Figures 4A and 4B for 6 active compounds. The PPAR agents were used at their IC_{50} concentrations (Supplementary Tables S2, S3) for an incubation period of two days. Proteins showing significant changes in expression compared to controls are indicated by asterisks (statistic data available in Supplement A and B). In general, proteins involved in apoptosis, protein degradation, cell proliferation and cell adhesion are targets of the PPAR-directed agents.

Pioglitazone resulted in an upregulation of BCL-X and downregulation of ErbB3/HER3, Enloase 2, EpCAM, p27/Kip1, Serpin B5/Maspin and Survivin. Rosiglitazone maleate also led to an upregulation of BCL-X, however in line with CapG and Cathepsin S and downregulation of ErbB3/HER3, Enloase 2, EpCAM, p27/Kip1, Serpin B5/Maspin and Survivin. Cloxiquine downregulated BCL-X, Cathepsin S, DLL1, ErbB3/HER3, p27/Kip1, Serpin B5/Maspin and Survivin. Fenofibrate resulted in an upregulation CapG and downregulation of ErbB3/Her3, Enolase 2 and Survivin. Agrimol B downregulated BCL-x, Cathepsin S, DDL1, ErbB3/Her3, Serpin B5/Maspin and Survivin and upregulated CapG and p27/Kip1. DG172 dihydrochloride also led to a downregulation of BCL-x and Survivin while upregulating Cathepsin S, ErbB3/Her3 and EpCam/TROP1.

Discussion

Reprogramming of cancer cell metabolism changes the metabolization of lipids and fatty acids to increase invasiveness, metastasis, and chemoresistance [1]. These variations in FA metabolism are put into execution by peroxisomes and increased rates of FA oxidation accompany the progression of cancers in the liver, lung and breast [32, 33]. PPAR agonists have been used in clinical practice for various indications. PPAR-γ agonists, such as TZDs, first reported as insulin sensitizers in the early 1980s reduce blood glucose levels [20, 34, 35]. Generally, synthetic ligands regulate the transcription activation of PPARγ by completely displacing natural/endogenous ligands or by co-binding [36]. Full agonist TDZs have insulin-sensitizing effects but antagonists such as GW9662 suppress the transcription of PPARγ-responsive genes by competitively binding with agonists [37]. PPARα agonists, such as fibrates, are used clinically to lower lipids [7]. PPAR-β/δ activation can regulate HDL cholesterol levels and improve glycemic control [38].

Increase FA oxidation depletes levels of nicotinamide adenine dinucleotide phosphate (NADPH) and suppresses lung cancer growth by an adverse intracellular redox milieu [39]. The PPARγ agonist troglitazone in combination with trimetazidine increased fatty acid oxidation in lung cancer resulting in apoptosis [40]. Fenofibrate-mediated IGF-IR inhibition with PPARα-dependent metabolism generated ROS that suppressed glioma cell spread and survival of medulloblastoma cell lines [18, 41]. PPARγ agonists act synergistically with chemotherapy but the clinical application of PPARγ agonists remains limited due to adverse side effects [23, 42]. Apart from the inhibition of tumor growth, studies have demonstrated that PPARγ activation exerts anti-tumor effects in lung cancer by inhibition of invasion and migration [43, 44]. In colon cancer, PPARα promoted metastasis by impairing the expression of Cox-2, VEGF and matrix metalloproteinase (MMP)-9 [45, 46]. Pioglitazone suppressed pro-metastatic IL-8 and COX expression *in vitro* in pancreatic cancer cells [47].

During screening of a TF-directed compound library on SCLC and SCLC CTC cell lines, a range of PPAR-directed agents were detected and selected drugs used for further characterization. With exception of NCI-H69, the SCLC lines used were established from pleural effusions and the SCLC CTC lines from blood samples of patients with advanced disease [29, 48]. This panel of SCLC cell lines is unique and truly represents metastasis-inducing tumor cells. Here, cytotoxicity tests showed that pioglitazone impairs both SCLC CTC lines in concentrations that can be achieved in patients but spared the pleural effusion-derived cell lines [49]. Rosiglitazone maleate inhibited only BHGc16 SCLC CTCs and spared the pleural effusion-derived lines. Fenofibrate exhibited similar preference for the SCLC CTC cell lines as pioglitazone but cloxiquine showed activity against all 5 SCLC lines. Agrimol B showed no clear preference and DG172 was more active against the pleural effusion-derived cell lines compared to the SCLC CTC lines. With exception of DG172, the tested compounds revealed low activity against the NCI-H69 cell line.

The protein changes induced by the range of active PPAR-directed agents were analyzed with the help of Western blot arrays. Pioglitazone and rosiglitazone maleate downregulated ErbB3 and Enolase 2, beside alterations in proteases and p27/Kip1. In contrast, although cloxiquine revealed modifications of the same proteins, downregulation of BCL-x and Survivin point to the induction of apoptotic cell death. Downregulation of DLL1 expression in the cells result in an anti-oncogenic effect through its impairment of Notch signaling [50]. Fenofibrate showed a similar range of protein alterations with replacement of MUC-1 by EpCAM and Survivin downregulation. Essentially the same list of modified proteins is apparent in BHGc16 in response to treatment with agrimol B and DG172.

A range of 10 other PPAR-directed agents with various activities against the SCLC lines are listed in Supplement 1. GW9662 binds to the PPARγ as irreversible antagonist and inhibits adipocytic differentiation and, furthermore, suppresses growth of breast cancer cell lines and glioblastoma stem cells [37, 51-53]. This compound was cytotoxic for all cell lines used, except for BHGc10. T0070907 is an effective and highly specific PPARγ inhibitor, with > 800-fold selectivity over PPARα and PPARδ, that BHGc10 cells again showed resistance to [34]. The potent and selective PPARγ inhibitor SR1664 has antidiabetic activity and inhibits Cdk5-mediated PPARγ phosphorylation without exhibiting PPARγ agonist activity. Among the cell lines tested this compound revealed activity limited to BHGc16. SR16832 constitutes a dual-site PPARγ inhibitor that prevents the binding of endogenous ligands and the transcriptional activity of PPARγ with preferential cytotoxicity for the pleural effusion-derived SCLC cell lines [54]. GW6471 is an antagonist of PPARα with IC50 of 0.24 μ M that showed cytotoxic activity except for SCLC S1392 [34]. MA-0204 is a highly selective and orally available PPARδ modulator with anticancer activity and its activity is restricted to BHGc16 [21]. The selective PPARβ/δ antagonist CC618 showed

variable activity against the SCLC cell lines, while BHGc10 cells revealed resistance against the anti-diabetic PPARα modulator Fucosterol. The CDDO-Im (TP-235) activator of PPARγ and Nrf2 exhibited high activity against the whole panel of SCLC cell lines and breast cancer cells [55]. The PPARγ-directed agents either showed activity against the SCLC CTC lines and lacked cytotoxicity for the pleural effusion-derived lines and NCI-H69 or exhibited activity for all lines tested. There is no clear correlation between the PPAR subtype targeted and the distribution of cytotoxicities against the SCLC and SCLC CTC cell lines.

Our results are in line with previous reports dealing with cancer cell lines different from SCLC. PPARγ activation increases pro-apoptotic factors Bax and Bad, decreases anti-apoptotic factors Bcl-2 and Bcl-XL and promotes apoptosis through caspase3/9 activity and mitochondrial cytochrome c release [5, 56, 57]. Rosiglitazone-mediated PPARγ activation inhibits NSCLC cell proliferation via down-regulation of the Akt/mTOR/p70S6K signaling cascade and triggers apoptotic cell death via generation of ROS [58, 59]. PPARγ activation could also suppress the expression of invasion-related proteins, such as intercellular adhesion molecule-1 (ICAM-1) and C-X-C chemokine receptor type 4 (CXCR4) [60, 61].

TZDs have been shown to inhibit the growth of liposarcoma, breast, colon, prostatic, gastric and pancreatic cancer [62-65]. Pioglitazone treatment resulted in the inhibition of proliferation and metastasis in human pancreatic cancer cells [47, 66]. Pioglitazone mediates apoptosis in Caki cells via downregulating of the caspase regulator c-FLIP-L and reducing Bcl-2 protein stability [65]. Furthermore, it inhibits the signal transducer and activator of transcription 3 (STAT3), MEK/ERK, p38 mitogen-activated protein kinase (MAPK), BCL-2 and JAK2/STAT3 signaling pathways [67, 68]. Rosiglitazone is an orally active thiazolidinedione with antidiabetic properties and potential antineoplastic activity [69]. Cloxiquine an antituberculosis drug, markedly suppresses the growth and metastasis of melanoma cells through PPARγ without apparent toxicity in normal melanocytes and in the liver. [70]. Agrimol B suppresses adipogenesis through modulation of SIRT1-PPARγ signal pathway [71]. Fenofibrate is a PPARα agonist that exhibits antihyperlipidemic activity and antitumor activity [72, 73]. DG-172 dihydrochloride is an antagonist of PPARβ/δ that inhibits cancer cell invasion [74]. A retrospective analysis of 87,678 male diabetics demonstrated that TZD users showed a 33% lower risk of lung cancer compared to non-users [22]. Diabetes was not significantly associated with lung cancer incidence (140,395 participants) and there were no significant associations between diabetes and lung cancer risk [75]. The 1-, 2-, and 3-year survival non-diabetic versus diabetic patients with lung cancer were 43% versus 28%, 19% versus 11%, and 3% versus 1%, respectively. Adjusted for other parameters in the Cox regression model, the hazard ratio for survival in diabetic patients with lung cancer was 0.55 (95% CI, 0.41-0.75) [76]. These

findings may be explained by the inhibition of tumor dissemination in diabetic patients by PPAR-directed drugs or direct and indirect metabolic effects.

The lipidome of malignant lung pleural effusions exhibit a unique metabolic signature that can be used to discriminate benign disease [77, 78]. Thus, the pleural effusion-derived cell lines S457 and S1392 may be adapted to such special microenvironmental conditions. The CTCs seem to be released by leaky vessels in the core of the tumors and adapt to the conditions in the peripheral circulation to eventually generate secondary lesions [79, 80]. The knowledge of the biological characteristics of CTCs is incomplete and the specific responsiveness to PPAR-directed agents may provide the opportunity to find new targets and novel modes of treatment in case of SCLCs. In summary, several PPAR-directed agents impair the proliferation and viability of SCLC CTC cells and may provide a valuable contribution to the therapy for this malignancy with a survival rate below 2 years for advanced disease

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Supplementary data are available in the online version of the paper.

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Figure Legends

Figure 1. MTT cytotoxicity assays of the cell lines treated with pioglitazone, cloxiquine, fenofibrate and DG172 dihydrochloride. Data shown are mean values±SD for 6 two-fold dilutions of the compound starting at 20 µM. IC_{50}-values of pioglitazone were 5.89 µM for CTC cell line BHGc10 and 2.7 µM for CTC cell line BHGc16, respectively. No IC_{50}-value could be achieved for SCLC cell line S457 due to low cytotoxicity of the compound in this cell line. IC_{50}-values for cloxiquine were 5.89 µM for BHGc10, 4.29 µM for BHGc16, 7.77 for S457, respectively. IC_{50}-values for fenofibrate were 6.40 µM for BHGc10, 2.19 µM for BHGc16, respectively. No IC_{50}-value could be achieved for S457 due to low cytotoxicity of the compound in this cell line. IC_{50}-values for DG172 dihydrochloride were 13.52 µM for BHGc10, 7.86 µM for BHGc16 and 6.20 for S457, respectively.

Figure 2. IC_{50}-values for CTC and SCLC cell lines treated with pioglitazone, rosiglitazone maleate and cloxiquine. Each PPAR-γ directed compound was tested in triplicate (n=3) for each cell CTC cell line (BHGc16, BHGc10) and SCLC cell line (NCI-H69, S457 and S1392). Data shown are mean values±SD. Bars ending at 20 µM indicate that no IC_{50}-value could be reached up to 20 µM.

Figure 3. IC_{50}-values for CTC and SCLC cell lines treated with fenofibrate, agrimol B and DG172 dihydrochloride. Data shown are mean values±SD. The PPARα directed agent fenofibrate, PPAR-γ directed agent agrimol B and PPAR-δ/γ directed agent DG172 dihydrochloride were each tested in triplicate (n=3) for each CTC cell line (BHGc16, BHGc10) and SCLC cell line (NCI-H69, S457 and S1392). Bars ending at 20 µM indicate that no IC_{50}-value could be reached up to 20 µM.

Figure 4. Protein expression changes in BHGc16 cells after treatment with PPAR modulators. This analysis of cancer-related proteins in BHGc16 control was conducted before and after treatment with A) pioglitazone, rosiglitazone, cloxiquine and B) fenofibrate, agrimol B and DG172 dihydrochloride. Data represents mean values±SD, significant P-values are shown by an asterisk and indicate the difference of control to each group as evaluated by a repeated measures ANOVA (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). Abbreviations in the figure are as follows: BCL2 Like 1 (BCL-X), Capping Actin Protein Gelsolin Like (CapG), Delta Like Canonical Notch Ligand 1 (DLL1), Erb-B2 Receptor Tyrosine Kinase 3 (ErbB3/Her3), Epithelial Cell Adhesion Molecule (EpCAM/TROP1) and Cyclin Dependent Kinase Inhibitor 1B (p27/Kip1/CDKN1B).

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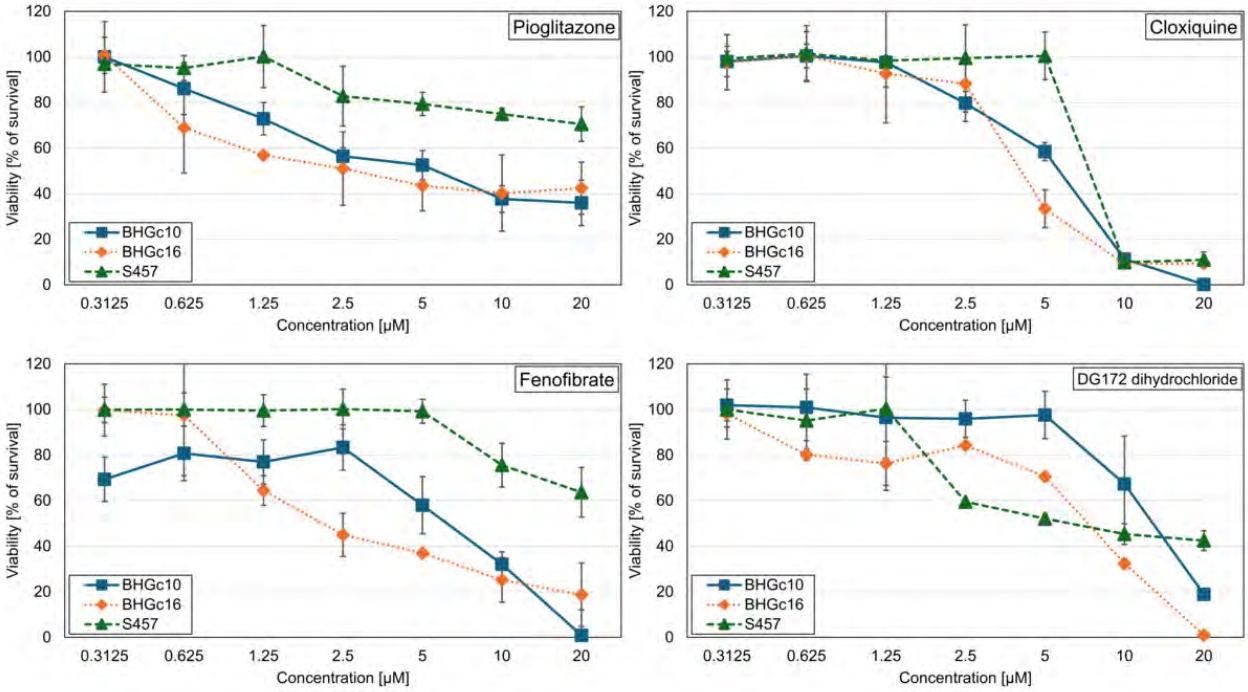

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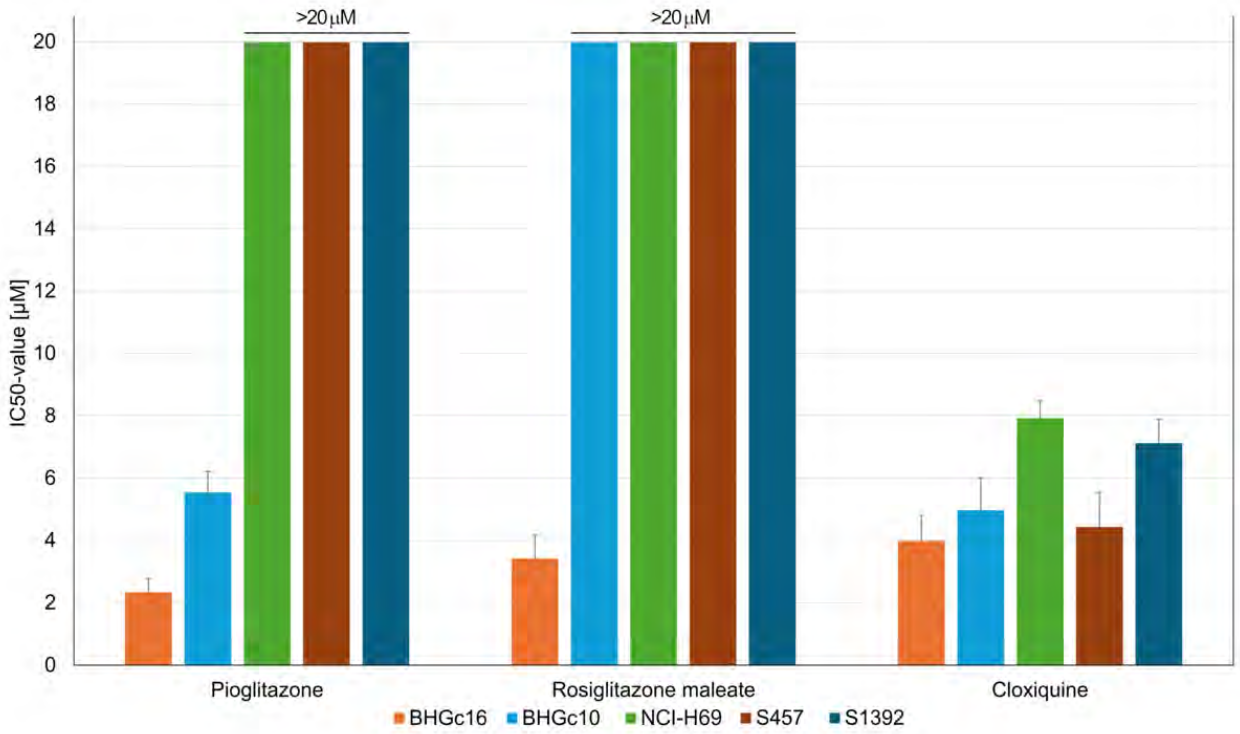

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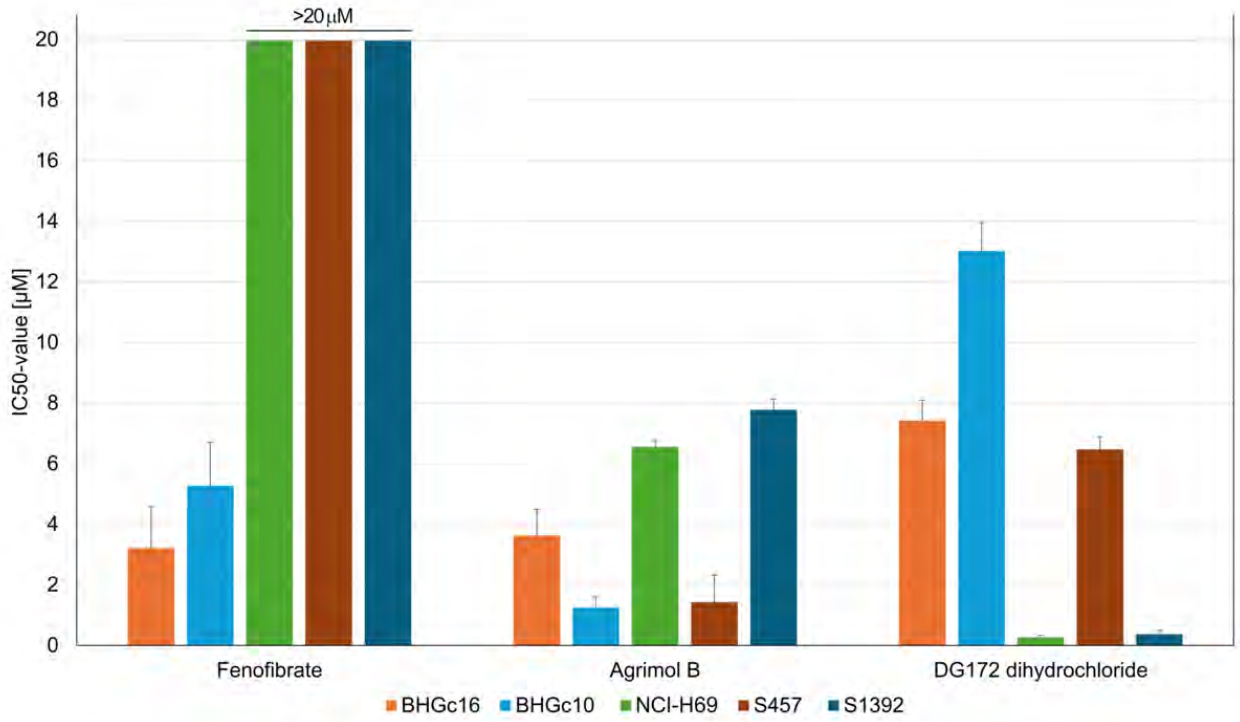

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