

# CJ14939, a Novel JAK Inhibitor, Increases Oxaliplatin-induced Cell Death Through JAK/STAT Pathway in Colorectal Cancer

JUN KI HONG<sup>1,2\*</sup>, DO YEON KIM<sup>1,2\*</sup>, JAE-SIK SHIN<sup>1\*</sup>, YEA SEONG RYU<sup>1,2</sup>, JAI-HEE MOON<sup>1</sup>, DONG-IN KOH<sup>1</sup>, SEUL LEE<sup>1,2</sup>, JINWOO LEE<sup>1</sup>, WON JUN LEE<sup>1</sup>, EUN YOUNG LEE<sup>1,2</sup>, SOO-A JUNG<sup>1,2</sup>, SEUNG CHAN KIM<sup>3</sup>, HA NA YU<sup>3</sup>, MI JIN KIM<sup>1,2</sup>, SEUNG-WOO HONG<sup>1</sup>, SANG SOO PARK<sup>1,2</sup>, JOONYEE JUNG<sup>1</sup>, SEUNG MI KIM<sup>1,2</sup>, EUN HO KIM<sup>1,2</sup>, HONG-RAE JEONG<sup>1,2</sup>, JI HEE GONG<sup>1</sup>, JIEUN KIM<sup>1</sup>, TAE WON KIM<sup>4</sup> and DONG-HOON JIN<sup>1,2</sup>

<sup>1</sup>Asan Institute for Life Science, Asan Medical Center, Seoul, Republic of Korea;

<sup>2</sup>Department of Medical Science, Asan Medical Institute of Convergence Science and Technology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea;

<sup>3</sup>CJ HealthCare R&D Center, Icheon-si, Republic of Korea;

<sup>4</sup>Department of Oncology, Asan Medical Institute of Convergence Science and Technology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

**Abstract.** *Background/Aim:* Colorectal cancer is reported to have the highest mortality rate among human malignancies. Although many research results for the treatment of colorectal cancer have been reported, there is no suitable treatment when resistance has developed. Therefore, it is necessary to develop new therapeutic agents. Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling plays an essential role in cell differentiation, proliferation, and survival. Abnormal activation of the JAK/STAT signaling pathway, by gene mutation or amplification, may induce cancer development, and sustained JAK/STAT activation is involved in chemoresistance. While many therapeutic agents have been developed to treat colon cancer, there remains no drug to overcome resistance to chemotherapies. The purpose of this study was to determine the potential of CJ14939 as a novel JAK inhibitor for the treatment of colorectal cancer. *Materials and Methods:* In this study, cell culture, cell death assay, 3-

(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium assay, colony formation assay, immunoblot analysis and tumor xenograft were applied. *Results:* CJ14939 induced cell death, and inhibited phosphorylation of JAK1 and STAT3 in colorectal cancer cells. Furthermore, CJ14939 also promoted oxaliplatin-induced cell death, up-regulated expression of cleaved caspase-3, and down-regulated expression of phospho-JAK1 and phospho-STAT3. *In vivo*, co-treatment with CJ14939 and oxaliplatin notably reduced tumor growth when compared with CJ14939 or oxaliplatin treatment alone. *Conclusion:* This study identifies the important potential of CJ14939 in colorectal cancer treatment and suggests that combining CJ14939 with oxaliplatin might be a novel therapeutic strategy for patients with colorectal cancer.

Colorectal cancer (CRC) has one of the highest mortality rates among human malignancies (1-3). Its development is believed to be caused by environmental influences and defects in gastrointestinal mucosal barriers, leading to abnormal inflammation. This increase in inflammation then contributes to tumor growth and progression through abnormal cell proliferation, anti-apoptotic cell survival, and neovascularization (4-6). Most inflammatory signals promote tumorigenesis by activating the nuclear transcription factor  $\kappa$ B and the Janus-activated kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways in tumors (7, 8).

The JAK pathway plays a crucial role in signals from cytokine production and growth factor to regulate cell proliferation and differentiation. Dysregulation of the JAK pathway is involved in the pathogenesis of autoimmune and various inflammatory disorders (9). Prognosis of cancer is

\*These Authors contributed equally to this study.

*Correspondence to:* Tae Won Kim, MD, Ph.D., Department of Oncology, Asan Medical Institute of Convergence Science and Technology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympicro-43gil, Songpa-gu, Seoul 05505, Republic of Korea. E-mail: twkimmd@amc.seoul.kr and Dong-Hoon Jin, Ph.D., Department of Medical Science, Asan Medical Institute of Convergence Science and Technology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympicro-43gil, Songpa-gu, Seoul 05505, Republic of Korea. E-mail: inno183@amc.seoul.kr

*Key Words:* JAK/STAT, CJ14939, JAK inhibitor, oxaliplatin, colorectal cancer.

poor, and chemoresistance occurs in various malignant tumors with abnormal JAK/STAT activity, including colorectal cancer. In particular, STAT3 is frequently expressed in tumors of patients with colorectal cancer, and the mortality rate of patients with high STAT3 activity is significantly greater than that of those with normal STAT3 activity (10). Moreover, recent reports show that constitutive JAK/STAT activation is involved in cell growth, survival, invasion, and migration in colorectal cancer (11-13), The JAK/STAT pathway has been shown to induce resistance to cisplatin in breast, ovarian, and prostate cancer (14-16). Therefore, more effective therapeutic options are required.

In this study, we investigated the anticancer efficacy of a JAK inhibitor (CJ14939) in colon cancer cell lines. Moreover, we examined the mechanisms underlying CJ14939-induced cell death, thus assessing its importance as a novel JAK inhibitor for CRC treatment.

## Materials and Methods

**Cell culture and reagents.** Human colon cancer cell lines KM12C, LIM1215, Colo205, RKO, HT29, Colo320HSR, SW48, Colo320DM, HCT116, LoVo, DLD1, SW480, HCT15, HCT8, SW620, LS174T and LS1034 were purchased from the American Type Culture Collection (Manassas, VA, USA) and Korean Cell Line Bank (Seoul, Republic of Korea). All cell lines were maintained in RPMI-1640 medium or Dulbecco's modified Eagle's medium (GIBCO BRL, Grand Island, NY, USA) containing 10% fetal bovine serum (GIBCO BRL) and 100 units penicillin and 100  $\mu$ l/ml streptomycin, in an incubator with 5% CO<sub>2</sub>, at 37°C. CJ14939, a novel JAK inhibitor, was kindly provided by CJ Healthcare (Seoul, Republic of Korea), and oxaliplatin was purchased from Sigma-Aldrich (St. Louis, MO, USA).

**Cell death and 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) assay.** Cells ( $3 \times 10^5$  per plate) were seeded in 60-mm plates and treated with DMSO (control) or CJ14939 (5,000 nM) with/without oxaliplatin (500 nM) for 48 h. Treated cells were then collected and counted by trypan blue exclusion. For MTS assays, colon cancer cells were seeded at  $1-3 \times 10^4$  cells/well in 96-well plates and treated with DMSO or increasing concentrations of CJ14939 for 72 h and assayed using the CellTiter 96 Aqueous one solution cell proliferation assay kit (Promega Inc., Madison, WI, USA). Half-maximal inhibitory concentrations (IC<sub>50</sub>) were then determined using GraphPad Prism v. 5.01 software (San Diego, CA, USA).

**Colony-formation assay.** Cells ( $3 \times 10^2$  per well) were seeded in 6-well plates and treated with DMSO (control) or CJ14939 (5,000 nM) with/without oxaliplatin (500 nM) and cultured for 14 days. Colonies were then fixed with 10% formalin and then stained with 0.01% crystal violet. Colonies with diameters  $\geq 1$  mm were counted.

**Immunoblot analysis.** Immunoblot analyses were conducted by preparing lysates of CJ14939-treated HCT116 or SW620 cells in RIPA lysis buffer containing protease- and phosphatase-inhibitor cocktails (Sigma-Aldrich). Protein concentrations were determined using the Bradford assay, and 20  $\mu$ g total cellular protein was then subjected to sodium dodecylsulfate-polyacrylamide gel electrophoresis and

transferred to Immobilon-P membranes (EMD Millipore, Billerica, MA, USA). Membranes were then blocked with 5% nonfat dry milk (in Tris-buffered saline with Tween<sup>®</sup> 20 buffer) and incubated with the following antibodies to: phospho-JAK1, phospho-STAT3, JAK1, STAT3, cleaved caspase-3 (Cell Signaling, Danvers, MA, USA), and  $\gamma$ -tubulin (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Primary antibodies were then detected with a horseradish peroxidase-conjugated goat anti-mouse or goat anti-rabbit secondary antibody (Cell Signaling), as appropriate, and immunoreactive proteins were visualized using an enhanced ECL Detection Reagent (GE Healthcare Bio-Sciences, Uppsala, Sweden).

**Tumor xenografts.** We obtained five 5-week-old female Balb-C nude mice from SLC laboratory (Japan Shizuoka Laboratory Animal Center, Hamamatsu, Japan) as a model for *in vivo* experiments. All experiments were approved by the Institutional Animal Care and Use Committee of the Asan Institute for Life Sciences (2018-12-209). Mice were subcutaneously injected with  $1 \times 10^7$  SW620 colorectal cancer cells, suspended in 1.0 ml phosphate-buffered saline, in the right flank. When the tumor volume had reached 100 mm<sup>3</sup>, CJ14939 (50 mg/kg) or vehicle (20% polyethylene glycol with 2% cremophor in distilled water) were administered *bid per os* for 3 weeks, or with 6.0 mg/kg oxaliplatin or vehicle (distilled water) administered intraperitoneally once per week for 3 weeks. Tumor sizes (length  $\times$  width<sup>2</sup>  $\times 0.5$ ) were measured every 3 days for 18 days, and bodyweights monitored every 3 days for 3 weeks. At day 18, tumors were excised and weighed.

**Statistical analysis.** Statistical analyses were performed using SigmaStat software v12 (Systat Software Inc., San Jose, CA, USA). Data are presented as means  $\pm$  standard deviations from three independent experiments. Significance of statistical analysis was analyzed using the Student's *t*-test. Values of  $p < 0.05$  were considered statistically significant.

## Results

**CJ14939 induced cell death and down-regulated JAK/STAT3 signaling in human colon cancer cells.** We first investigated the inhibitory effects of the novel small-molecule JAK inhibitor, CJ1493, on human colon cancer cell lines by MTS assay, demonstrating that its anticancer efficacy did not significantly differ according to the *KRAS* genotype. Anticancer effects of CJ14939 were confirmed in most colon cancer cell lines. On the other hand, SW48, Colo320DM, and LS1034 showed resistance to CJ14939 (Figure 1A). We further confirmed that JAK1 and STAT3 phosphorylation depended on the CJ14939 concentration used for *KRAS*-mutant HCT116 and SW620 cell lines, which differed in IC<sub>50</sub> values. JAK1 and STAT3 phosphorylation levels were inversely correlated with CJ14939 concentration but were not significantly different in these two cell lines. The decrease in JAK1 and STAT3 phosphorylation in these two cells upon CJ14939 treatment correlated with one another (Figure 1B). Therefore, this demonstrates that the effects of CJ14939 were through inhibition of JAK1 and STAT3 in colon cancer cell lines.

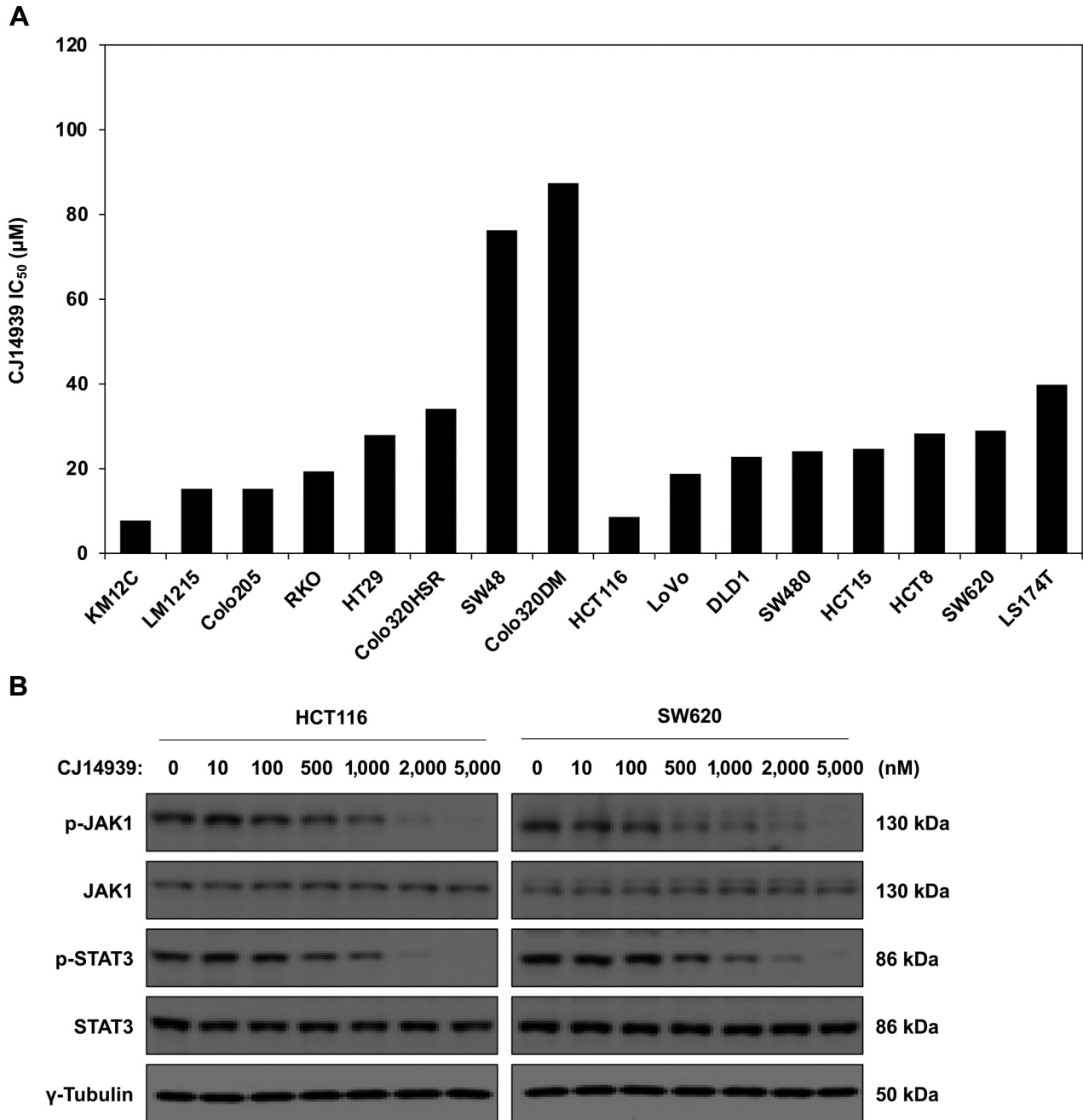


Figure 1. CJ14939 inhibited cell growth and reduced the levels of phospho (p)-Janus kinase-1 (JAK1)/signal transducer and activator of transcription-3 (STAT3) in colon cancer cell lines. A: Different colorectal cancer cell lines were seeded in 96-well plates and treated with 360 nM-100 µM CJ14939 for 72 h. 3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium assays were then performed to determine the half-maximal inhibitory concentration (IC<sub>50</sub>) of CJ14939 for each cell line. B: HCT116 and SW620 cells were treated with increasing concentrations of CJ14939, then JAK1, STAT3 and their phosphorylated forms were analyzed by western blotting. CJ14939 inhibited phosphorylation in a concentration-dependent manner.  $\gamma$ -Tubulin was used as a loading control.

Combination of CJ14939 and oxaliplatin induced additive cell death and growth inhibition. As shown in Figure 1, CJ14939 had anticancer effects on HCT116 cells. We further investigated the effects of JAK inhibitor combined with

oxaliplatin *in vitro*. The co-treatment of CJ14939 and oxaliplatin significantly sensitized colorectal cancer cells to oxaliplatin (Figure 2A and Figure 3A). Next, we investigated its effects on downstream signaling. When combined, these

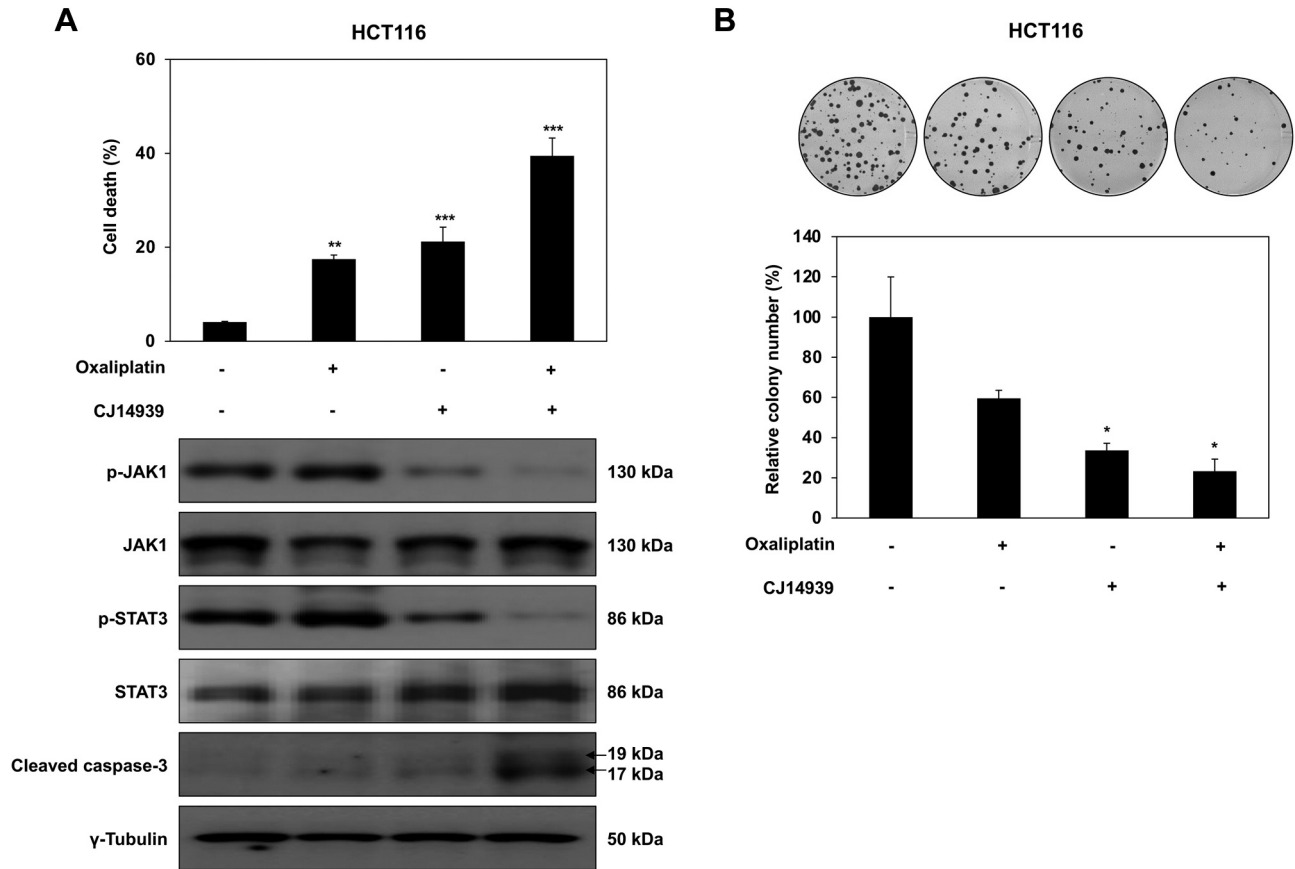


Figure 2. Synergistic effects were induced in HCT116 cells by CJ14939 and oxaliplatin combination. A: Upper panel: HCT116 cells were treated with CJ14939 (5,000 nM) with/without oxaliplatin (500 nM) for 48 h. Cell death was determined by trypan blue exclusion. Lower panel: After treatment, cells were harvested, lysed, and analyzed by western blot using antibodies against Janus kinase-1 (JAK1)/signal transducer and activator of transcription-3 (STAT3), phospho (p)-JAK1, p-STAT3, and cleaved caspase-3.  $\gamma$ -Tubulin was used as a loading control. B: Upper panel: Colony-forming assays were performed following treatment of HCT116 cells with CJ14939 (5,000 nM) with/without oxaliplatin (500 nM). After 14 days, cells were fixed, stained, and photographed. Representative photographs are shown. Lower panel: The graph shows that relative colony numbers were reduced most by the combination treatment. Data are the means  $\pm$  standard deviation of three separate experiments, performed in triplicate. Significantly different from the control at: \* $p < 0.05$ , \*\* $p < 0.01$ , and \*\*\* $p < 0.001$ .

agents strongly reduced phosphorylation of JAK1 and STAT3, while cleavage of caspase 3 increased (Figure 2A and Figure 3A). Likewise, colony-formation assays demonstrated reduced colony numbers by treatment with the combination of oxaliplatin and CJ14939 (Figure 2B and Figure 3B). Thus, CJ14939 enhanced oxaliplatin-induced cell death through JAK/STAT signaling pathway.

CJ14939 enhanced the antitumor efficacy of oxaliplatin *in vivo*. Based on the above data, we investigated whether CJ14939 enhanced the anticancer effect of oxaliplatin in SW620 tumors in nude mice. Following SW620 cell engraftment, when tumors had reached  $\sim 100 \text{ mm}^3$  in diameter, CJ14939 or oxaliplatin treatment was initiated and

continued for 3 weeks. The results showed that in the group treated with oxaliplatin alone, tumor size did not decrease significantly, while with CJ14939 treatment, tumor size was reduced by  $\sim 40\%$ , and was reduced even further by the combination of CJ14939 plus oxaliplatin (Figure 4A-C). In addition, mouse weight loss was negligible (Figure 4D). Collectively these findings show that CJ14939 notably improved the antitumor effect of oxaliplatin *in vivo*.

### Discussion

The JAK/STAT signaling pathway is involved in cell growth, proliferation, and survival in a variety of carcinoma types, including CRC (11-13), and its overactivity can result in

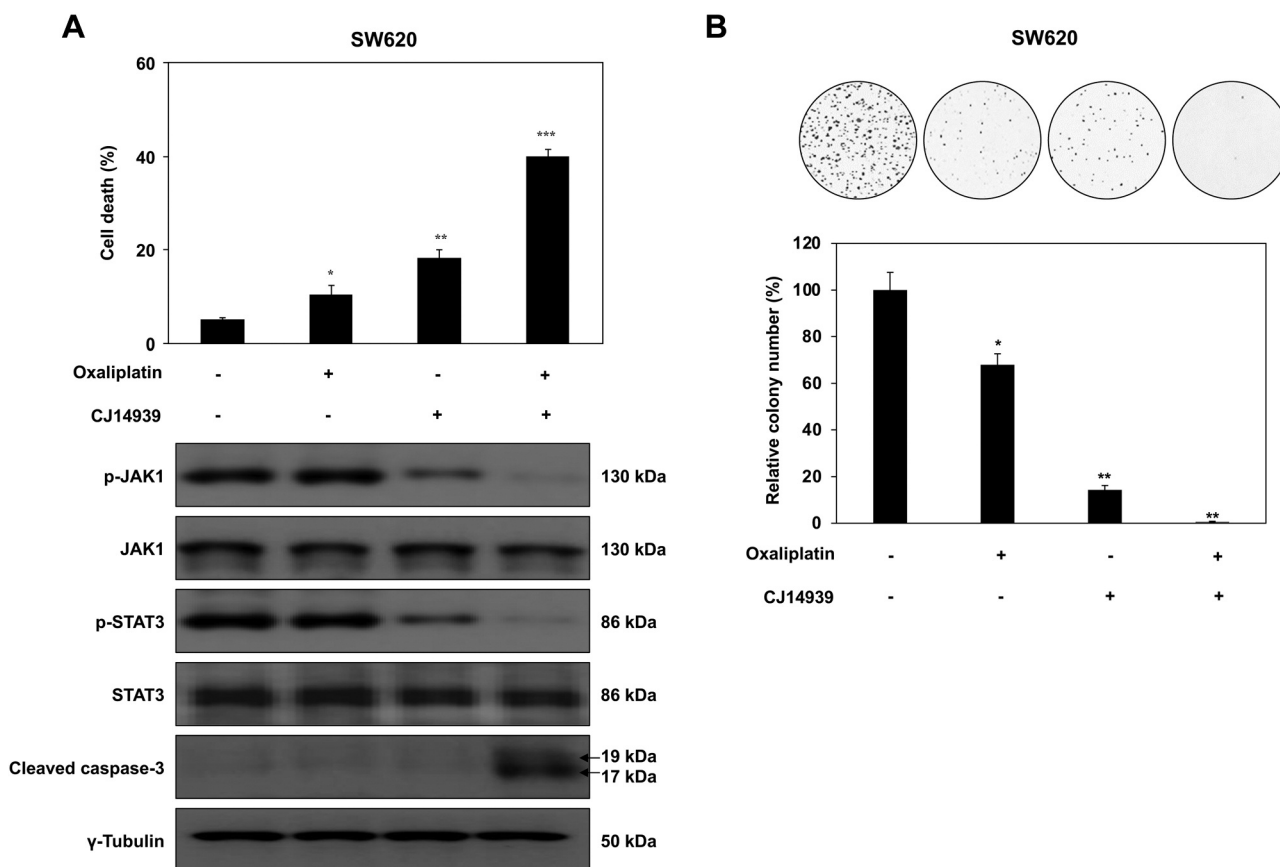


Figure 3. CJ14939 and oxaliplatin combination treatment induced death in SW620 cells. A: Upper panel: SW620 cells were treated with CJ14939 (5,000 nM) with/without oxaliplatin (500 nM) for 48 h. Cell death was determined by trypan blue exclusion. Lower panel: After treatment, cells were harvested, lysed, and analyzed by western blot using antibodies against Janus kinase-1 (JAK1)/signal transducer and activator of transcription-3 (STAT3), phospho (p)-JAK1, p-STAT3, and cleaved caspase-3.  $\gamma$ -Tubulin was used as a loading control. B: Upper panel: Colony-forming assays were performed following treatment of SW620 cells with CJ14939 (5,000 nM) with/without oxaliplatin (500 nM). After 14 days, cells were fixed, stained, and photographed. Representative photographs are shown. Lower panel: The graph shows that relative colony numbers were reduced most by the combination treatment. Data are the means  $\pm$  standard deviation of three separate experiments, performed in triplicate. \*Significantly different from the control at  $p < 0.05$ .

poor prognosis -and chemoresistance (17-19). Thus, the JAK/STAT signaling pathway is regarded as a clinically important therapeutic target in cancer, and a number of targeting drugs have been actively evaluated and recently entered clinical trials (20). One major problem with chemotherapy in various carcinomas is treatment difficulties due to side-effects and drug resistance (18, 19). In the case of CRC, one of the most common chemotherapies, oxaliplatin, often elicits intolerable side-effects and chemoresistance, requiring alternative treatment options (21-23). Here, we demonstrated that CJ14939, a novel, small-molecule JAK inhibitor, suppressed JAK1 and STAT3 activation; moreover, the efficiency of combination treatment with oxaliplatin was strong. These findings suggested that CJ14939 significantly enhanced oxaliplatin-induced cell death *via* suppressing the JAK1/STAT3 signaling pathway.

Furthermore, our *in vivo* models showed that CJ14939 increased oxaliplatin-suppression of tumor growth.

In conclusion, we evaluated the inhibitory effect of CJ14939 on the activity of JAK/STAT in human colorectal cancer cells. Such inhibitory activity enhanced oxaliplatin-induced cell death *via* JAK1/STAT3 signaling pathways, suggesting that JAK1/STAT3 signaling was the direct target of CJ14939 in an *in vitro* model. In addition, CJ14939 reduced tumor growth with administration of oxaliplatin in tumor-bearing mice. These results show that the combination of oxaliplatin treatment with CJ14939 can be effectively applied for the treatment of CRC.

### Conflicts of Interest

The Authors declare that they have no conflicts of interest.

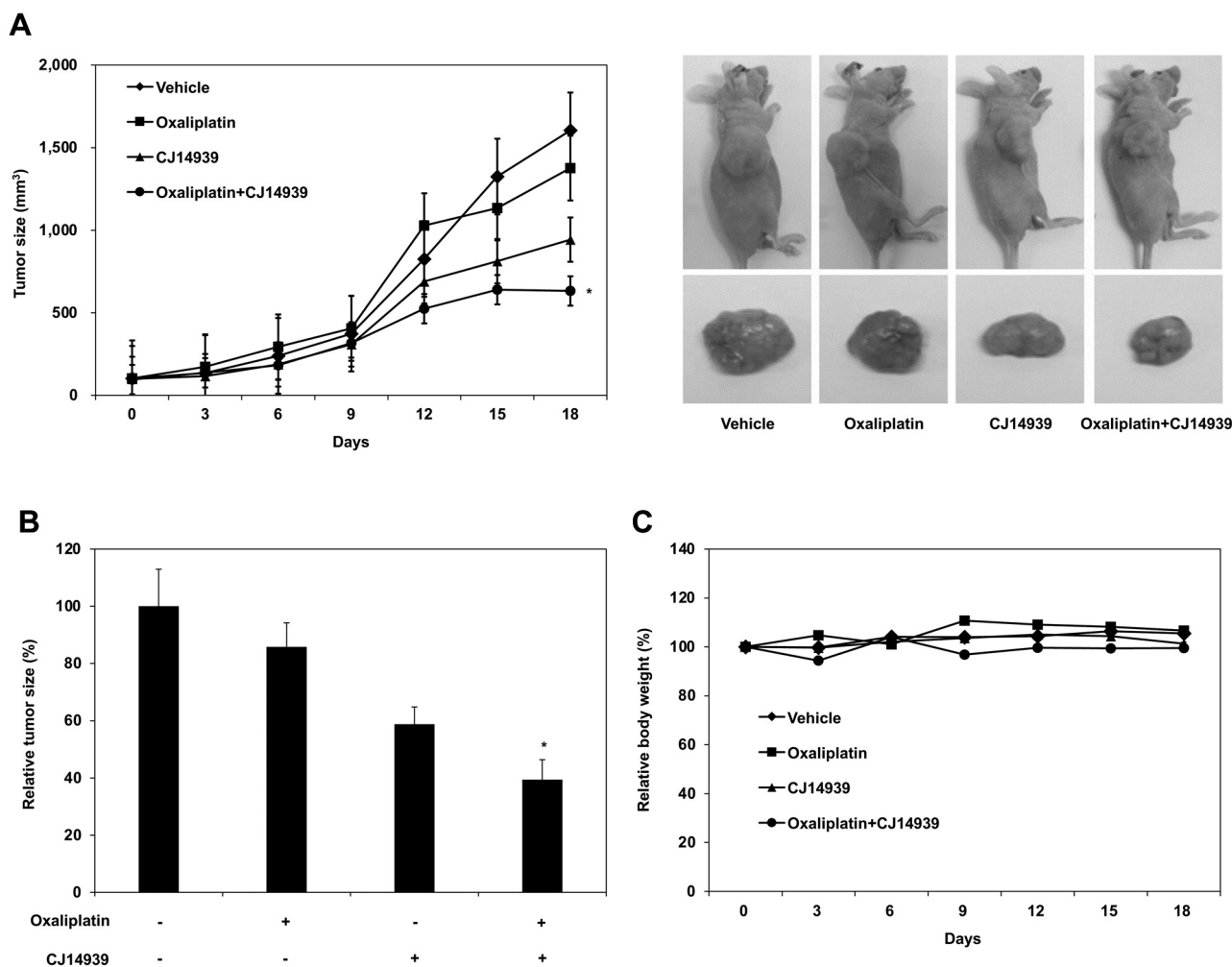


Figure 4. CJ14939 enhanced the anticancer effect of oxaliplatin in a colorectal cancer cell-derived xenograft model. Balb-C nude mice were injected subcutaneously with SW620 cells. When tumor volumes reached 100 mm<sup>3</sup>, CJ14939 (50 mg/kg) was administered by oral gavage for 18 days, with/without oxaliplatin (6 mg/kg). Tumor volumes and body weights were measured every 3 days. At the end of the experiment, mice were sacrificed, and tumor sizes checked and photographed. A: Mean tumor volumes over the experimental course. B: Relative tumor size. C: Mean relative body weights were unchanged by CJ14939, oxaliplatin, and their combination. \*Significantly different from the vehicle-treated control at  $p < 0.05$ .

**Authors' Contributions**

JKH, DYK, JSS, TWK and DHJ designed the experiments; JKH, DYK, JSS, SL, EYL, DIK, YSR, JHM, SAJ, SCK, HNY, MJK, SWH, SSP, JYJ, SMK, EHK, HRJ, JHG and JEK performed the experiments; JWJ and WJL performed statistical analysis; JKH, DYK, JSS, TWK and DHJ analyzed the results and wrote the article.

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Received December 30, 2021

Revised February 6, 2022

Accepted February 11, 2022