Telomerase-specific virotherapy in an animal model of human head and neck cancer

Oumi Nakajima,1 Atsuko Matsunaga,2 Daiju Ichimaru,3 Yasuo Urata,3 Toshiyoshi Fujiwara,4 and Koji Kawakami1,2

1Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; 2Department of Advanced Clinical Science and Therapeutics, Graduate School of Medicine, University of Tokyo; 3Oncolytic Medicine and Public Health, Kyoto University, Kyoto, Japan; 4Center for Gene and Cell Therapy, Okayama University Hospital, Okayama, Japan

Abstract

Telomerase-specific replication-competent adenovirus, Telomelysin (OBP-301), has a human telomerase reverse transcriptase promoter that regulates viral replication and efficiently kills human cancer cells. The objectives of this study are to examine the effects of OBP-301 in squamous cell carcinoma of the head and neck cells in vitro and in xenografted animals in vivo. OBP-301 was found to be cytotoxic to the YCUT892, KCCT873, KCC891, KCL871, YCUM862, HN12, and KCCOR891 cell lines in vitro. However, the level of cytotoxicity is not correlated with the expression levels of adenoviral receptors, which may be required for adenoviral infection in squamous cell carcinoma of the head and neck cells. OBP-301 shows remarkable antitumor activity against established s.c. KCCT873 tumors in immunodeficient animals in a dose-dependent manner. In addition, no significant toxicity was observed in animals receiving treatment. These results suggest that OBP-301 is a novel therapeutic agent with promise for the treatment of human head and neck cancers. [Mol Cancer Ther 2009;8(1):171–7]

Introduction

Squamous cell carcinoma of the head and neck (SCCHN) accounts for 5% of newly diagnosed adult cancers in the United States and 8% of cancers worldwide (1). Most patients are treated with various combinations of surgery, radiotherapy, and systemic agents (2). Despite major advances in the treatment of locoregionally advanced SCCHN, such as the introduction of novel chemotherapy regimens and inhibitors of the epidermal growth factor receptor, treatment fails in about half of the patients (3). The median survival of patients with recurrent or metastatic SCCHN who undergo chemotherapy is 6 to 9 months (4). Therefore, a considerable number of patients with SCCHN need additional treatment as the disease progresses.

Virotherapy, the approach to treat cancer with virus, has been done in some clinical trials; for example, clinical trials primarily using p53 gene replacement (INGN-201; a replication-competent adenoviral-based vector expressing wild-type p53) have provided the basis for the design of ongoing randomized gene therapy clinical trials in SCCHN patients in the United States (5). Although systemic administration is probably required in the case of micrometastatic disease, virotherapy has some promise when tumor is limited to the head and neck. SCCHN is a particularly attractive model because most primary and recurrent lesions are easily acceptable to direct injection (6). Potential usage of virotherapy may include the perioperative application in the surgical wound and the addition of intratumoral (i.t.) virotherapy to current standard options, such as radiotherapy and/or chemotherapy.

Telomerase is a ribonucleoprotein complex responsible for the complete replication of chromosomal ends (7). Many studies have shown the expression of telomerase activity in >85% of human cancers (8) but only in a few normal somatic cell types (9). Telomerase activation is considered to be a critical step in carcinogenesis, and its activity is closely correlated with human telomerase reverse transcriptase (hTERT) expression (10). Therefore, the hTERT proximal promoter can be used as a molecular switch for selective expression of target genes in tumor cells. Replication-selective tumor-specific adenoviruses are being developed as novel anticancer therapies (11–14). In this context, an adenoviral vector that drives E1A and E1B genes under the hTERT promoter has been developed, termed Telomelysin or OBP-301 (15). OBP-301 can replicate in and lyse only cancer cells but not normal cells, and its strong cytotoxic activity were shown in a variety human cancer cells (15–17). Also, OBP-301-mediated oncolysis induces uric acid production as a danger signal and stimulates CTL activity via proteasome activator upregulation (18).

The infection efficiency of recombinant adenoviral vectors varies widely depending on the expression of the primary receptor, the coxsackie adenovirus receptor (CAR); the secondary receptors, integrin αvβ3 and integrin αvβ5; and the tertiary receptor, heparan sulfate glycosaminoglycans (HSG; refs. 19, 20). The first step is the attachment of
cells were plated on 96-well plates at 1,000 containing 10% fetal bovine serum, 1 mmol/L HEPES, 0.12SCC, and Wmm-SCC (21) were cultured in RPMI 1640 KCCOR891, YCUL891, YCUM911, YCUMS861, YCUT891, prostate cancers in vitro death of human non-small cell lung, colorectal, and expressed in most cell types (19).

A penicillin, and 100 g/mL streptomycin. The SCCHN cell line HN12 was grown A 100 g/mL penicillin, and 100 g/mL streptomycin (Nacalai Tesuque). The virus particle (vp) titer-to-infection titer (plaque-forming units) ratios were 110:3. The virus to the cell surface through CAR (20). Following attachment, the internalization of the virus into cells occurs through the integrin receptors αvβ3 and αvβ5 that are expressed in most cell types (19).

Previously, OBP-301 has been reported to induce cell death of human non-small cell lung, colorectal, and prostate cancers in vitro and in vivo (15, 17). The present study investigates the cytotoxic activity of OBP-301 in 13 SCCHN cell lines and the association between cytotoxic activity and adenoviral receptor expression. We also assessed the in vivo antitumor activity and toxicity and tolerability of OBP-301 in an athymic nude mouse model with KCCT873 SCCHN tumors.

Materials and Methods

Adenovirus

The recombinant replication-selective, tumor-specific adenoviral vector OBP-301 was provided by Oncolyx Biopharma. The hTERT promoter element drives the expression of E1A and E1B genes linked with an internal ribosome entry site (15). The virus particle (vp) titer-to-infection titer (plaque-forming units) ratios were 110:3.

Cells

The human non-small cell lung cancer cell line H1299 was cultured in RPMI 1640 supplemented with 10% fetal bovine serum, 1 mmol/L HEPES (Nacalai Tesque), 100 μg/mL penicillin, and 100 μg/mL streptomycin (Nacalai Tesque). The SCCHN cell line HN12 was grown in MEM containing 10% fetal bovine serum, 100 μg/mL penicillin, and 100 μg/mL streptomycin. The SCCHN cell lines YCUT892, KCCT873, KCCT891, KCCOR891, YCUM862, KCCOR891, YCUL891, YCUM911, YCUMS861, YCUT891, 012SCC, and Wmm-SCC (21) were cultured in RPMI 1640 containing 10% fetal bovine serum, 1 mmol/L HEPES, 100 μg/mL penicillin, and 100 μg/mL streptomycin.

Cell Viability Assay

The XTT assay was done to measure cell viability. Briefly, cells were plated on 96-well plates at 1 × 10³ per well 24 h before viral infection. Cells were then infected with 1 to 1 × 10⁵ multiplicity of infection (vp) of OBP-301 and further cultured for 120 h. Cell viability was determined using the Cell Proliferation Kit II (Roche Diagnostics) according to the protocol provided by the manufacturer.

Flow Cytometry

Cells (1 × 10⁵) were labeled with mouse monoclonal anti-CAR (RmcB; Upstate Cell Signaling Solution), anti-integrin αvβ3 (Chemicon), anti-integrin αvβ5 (Chemicon), or anti-heparan sulfate (Seikagaku) for 60 min at 4°C, incubated with FITC-conjugated goat anti-mouse IgG secondary antibody (Chemicon), and analyzed by the FACSCalibur flow cytometer (Becton Dickinson) using CellQuest software. Control cells were incubated with anti-mouse IgG primary antibody (BD Bioscience) and FITC-conjugated goat anti-mouse IgG secondary antibody. G-means were calculated by the following formula: (G-means of antibody-treated cells) - (G-means of control cells). Correlation coefficients were obtained between the expression levels of CAR, integrin αvβ3, integrin αvβ5, HSG, and the ID₅₀ of OBP-301 in 7 SCCHN cell lines.

Quantitative Real-time PCR Analysis

Total RNA from cultured cells was obtained using the RNasey Mini kit (Qiagen). Total RNA (~ 0.1 μg) was used for reverse transcription. Reverse transcription was done at 22°C for 10 min and then at 42°C for 20 min. The hTERT mRNA copy number was determined by real-time quantitative reverse transcription-PCR using a LightCycler instrument and a LightCycler DNA TeloTAGGG kit (Roche Diagnostics). PCR amplification was run with activation at 95°C for 15 s, annealing at 58°C for 10 s, and extension at 72°C for 9 s.

Athymic Nude Mouse Models of Human Head and Neck Cancer

Five- to 6-week-old female athymic nude mice (BALB/c nu/nu) were obtained from SLC. Animal care was in

<p>| Table 1. Cytotoxic activity of adenoviral receptors on head and neck cancer cell lines |
|---------------------------------|------------------|----------------|</p>
<table>
<thead>
<tr>
<th>Cell line</th>
<th>Origin</th>
<th>ID₅₀ (vp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>YCUT892</td>
<td>Tongue</td>
<td>759</td>
</tr>
<tr>
<td>KCCCT873</td>
<td>Tongue</td>
<td>4,279</td>
</tr>
<tr>
<td>HN12</td>
<td>Lymph node</td>
<td>6,943</td>
</tr>
<tr>
<td>KCCT891</td>
<td>Hypopharynx</td>
<td>7,025</td>
</tr>
<tr>
<td>YCUM862</td>
<td>Oropharynx</td>
<td>7,512</td>
</tr>
<tr>
<td>KCCOR891</td>
<td>Larynx</td>
<td>7,599</td>
</tr>
<tr>
<td>YCUM911</td>
<td>Oral floor</td>
<td>9,204</td>
</tr>
<tr>
<td>YCUL891</td>
<td>Larynx</td>
<td>ND</td>
</tr>
<tr>
<td>YCUM911</td>
<td>Oropharynx</td>
<td>ND</td>
</tr>
<tr>
<td>YCUMS861</td>
<td>Maxillary sinus</td>
<td>ND</td>
</tr>
<tr>
<td>YCUT891</td>
<td>Tongue</td>
<td>ND</td>
</tr>
<tr>
<td>012SCC</td>
<td>Unknown</td>
<td>ND</td>
</tr>
<tr>
<td>Wmm-SCC</td>
<td>Unknown</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not done.

ID₅₀: infection dose of OBP-301 at which 50% inhibition of cell viability is observed compared with untreated cells.
accordance with the guidelines of the Kyoto University School of Medicine. A SCCHN model was established in nude mice by s.c. injection of KCCT873 tumor cells (5 × 10^6) in 150 μL PBS into the flank. Palpable tumors developed within 3 to 4 days. Tumors were measured by vernier calipers. Six to 7 mice were used for each group.

**Toxicity Assessment**

Blood samples and organs were collected from athymic nude mice at day 10 or 17 after i.t. administration of OBP-301 (3 × 10^10 vp/d for days 5-9). Organs from the experimental animals were fixed in 10% formalin, and 5 μm tissue sections were prepared and stained with H&E.

**Statistical Analysis**

Tumor volume on a given day was calculated by the following formula: (length of the tumor) × (width of the tumor)^2 / 2. The statistical significance of tumor regression was calculated by the Student’s t test.

**Results**

**Cytotoxic Activity of OBP-301 to Various SCCHN Cell Lines**

We first examined the effect of OBP-301 infection on the viability of SCCHN cell lines assessed by the XTT assay.

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**Figure 2.** Expression of the CAR in SCCHN cell lines. **A**, cells were incubated with mouse monoclonal anti-CAR (RmcB) followed by detection with FITC-labeled secondary antibody. Gray histogram, staining with anti-CAR antibody treatment. H1299 human lung cancer cells were used as a positive control. **B**, correlation between CAR expression in SCCHN cells and the ID_{50} of OBP-301 for these cells. **C**, correlation between integrins αVβ3 and αVβ5 and HSG expression in SCCHN cells and the ID_{50} of OBP-301 for these cells. The experiment was repeated three times.
Because OBP-301 showed slightly cytotoxic activity against 7 of 13 cell lines at a dose of 1,833 vp (50 plaque-forming units/cell), we assessed the ID_{50} of OBP-301 using these 7 SCCHN cell lines (Fig. 1; Table 1). As shown in Table 1, OBP-301 shows modest to strong cytotoxic activity in the 7 cell lines tested, with the ID_{50} varying from 759 to 9,204 vp. The cytotoxic activity of OBP-301 in these cell lines shows dose dependence (Fig. 1). YCUT892 cells were most sensitive to OBP-301 followed by KCCT873, HN12, KCCT891, YCUM862, KCCL871, and KCCOR871 cells, suggesting that 2 of the SCCHN cell lines are most sensitive to OBP-301.

**Expression of Adenovirus Receptors in SCCHN Cell Lines**

Because the cytotoxic activity of OBP-301 was anticipated to be correlated with efficiency of adenoviral infection through CAR, integrin \( \alpha_v \beta_3 \), integrin \( \alpha_v \beta_5 \), or HSG receptors (22), we then assessed the expression levels of CAR on SCCHN cells using flow cytometry. As shown in Fig. 2A, all 7 SCCHN cell lines have been found to express detectable levels of CAR. However, as shown in Fig. 2B, correlation between the cytotoxic activity of OBP-301 and the expression level of CAR was not significant (correlation coefficient = -0.5). In addition, we assessed the expression of integrin \( \alpha_v \beta_3 \), integrin \( \alpha_v \beta_5 \), and HSG in SCCHN cell lines; however, the expression levels were not correlated with cytotoxic activity of OBP-301 (Fig. 2C). We also assessed \( hTERT \) expression using the quantitative PCR method and found that all of the SCCHN cell lines express detectable levels of \( hTERT \) mRNA; however, there was no correlation between the expression levels and ID_{50} of OBP-301 in these cells (data not shown). These results suggest that, although 7 of 13 SCCHN cell lines are sensitive to OBP-301, its ability to enter the cell is not necessarily correlated with the degree of cytotoxicity.

**Antitumor Effect of OBP-301 in SCCHN-Bearing Animals**

To assess the antitumor effect of OBP-301 in the animal model of human SCCHN, KCCT873 cells were implanted s.c. in athymic nude mice (6, 23) to examine the effect of OBP-301 at a variety of dosages in vivo. Mice received i.t. injections of OBP-301 at \( 3 \times 10^8 \), \( 3 \times 10^9 \), or \( 3 \times 10^{10} \) vp for 3 days from days 5 to 7 after tumor implantation (Fig. 3). Tumors grew to mean tumor volume of 32.2 ± 4.5 mm³ at day 5. As shown in Fig. 3, the \( 3 \times 10^{10} \) dose of OBP-301 treatment was less effective against KCCT873 tumor growth. The mean tumor volume was 549 mm³ on day 42, which is comparable with control tumor volume (910 mm³). Higher doses of OBP-301 led to superior antitumor activity. The mean tumor volume of treated tumors was 130 mm³ at \( 3 \times 10^8 \) vp and 67 mm³ at \( 3 \times 10^{10} \) vp, which is significantly smaller compared with the control tumor at day 42 (\( P < 0.0001 \)). Remarkably, in addition to a 93% inhibition in tumor volume in mice receiving a \( 3 \times 10^{10} \) vp dosage, 3 of 7 tumors completely disappeared by day 37, which persisted through day 42. These results suggest that OBP-301 shows a remarkable antitumor effect in a dose-dependent manner in KCCT873 SCCHN tumors. Based on these findings, OBP-301 at a dosage of \( 3 \times 10^{10} \) vp per injection shows the maximum tumor reduction effect.

**Optimization of OBP-301 Injection Times in KCCT873 SCCHN Tumors**

We next evaluated the treatment schedule of OBP-301 in s.c. xenografted KCCT873 tumor-bearing mice. Mice were treated i.t. with OBP-301 for 1, 3, or 5 subsequent days. The

![Figure 3. OBP-301 acted in a dose-dependent manner in KCCT873 tumor-bearing mice. Athymic nude mice received s.c. implantation of \( 5 \times 10^5 \) KCCT873 cells on day 0. Animals then received injections of OBP-301 at the doses of \( 3 \times 10^8 \) (●), \( 3 \times 10^9 \) (▲), or \( 3 \times 10^{10} \) vp (■) on days 5 to 7 (total of three injections). Each group had 7 animals, and the injection volume was 30 μL in each tumor. Arrows, day of injections. Bars, SD. The experiment was repeated two times.](image1)

![Figure 4. Regression of KCCT873 tumors by i.t. treatment of OBP-301. Athymic nude mice receiving s.c. KCCT873 implantation were treated with OBP-301 (\( 3 \times 10^{10} \) vp) for 1 (●), 3 (▲), or 5 (■) days. Injections were made on consecutive days (QD). Each group had 6 animals, and the injection volume was 30 μL in each tumor. Arrows, day of injections. Bars, SD. The experiment was repeated two times.](image2)
OBP-301 treatment started on day 5 (mean tumor volume, 31.4 ± 7.3 mm³), as palpable tumors developed within 3 to 4 days. As shown in Fig. 4, i.t. administration of OBP-301 showed considerable antitumor activity in all groups. The mean tumor volume of animals receiving a one-time injection was 236 mm³ at day 41, 71% smaller than excipient-only injected control tumors (823 mm³; P < 0.0001). Interestingly, three or five injections of OBP-301 treatment showed superior antitumor activity. The mean tumor volume of animals in the group receiving a three-time treatment was 142 mm³ at day 41, 83% smaller than control tumors (863 mm³; P < 0.0001). Three of 6 tumors had completely regressed by day 27; however, later on, all of the tumors appeared and slowly started to grow again by day 41. Animals receiving OBP-301 for 5 days showed superior tumor response, including complete disappearance of tumors in 2 of 6 mice through day 41. The mean tumor volume measured on day 41 (121 mm³) was 86% smaller than control tumors (863 mm³; P < 0.0001). These results suggest that three- and five-time injections of OBP-301 treatment were equally effective in KCCT873 SCCHN tumor reduction.

**Toxicity Profile in Mice Treated with OBP-301**

Finally, to assess the toxicity and safety profile of OBP-301 treatment, blood and major organs including heart, liver, lung, kidney, and spleen were collected from KCCT873 tumor-bearing athymic nude mice receiving i.t. OBP-301 (3 × 10¹⁰ vp/d for 5 days) on day 10 or 17 after tumor implantation. As shown in Table 2, a blood serum chemistry analysis showed no remarkable changes in any variable in all the mice tested, except for a minor elevation of creatinine phosphokinase and aspartate aminotransferase in the OBP-301 treatment group. Similarly, no pathologic alterations were observed in any of the organs tested (data not shown). Although a slight necrosis was observed in livers from mice treated with i.t. OBP-301, all other organs from untreated control and OBP-301-treated mice did not show any evidence of toxicity. The result that all the treated mice tolerated therapy very well without any behavioral changes or toxicities in blood and pathology suggests that OBP-301 treatment leads to considerable antitumor activity without unwanted safety or toxicity issues.

**Discussion**

Although it has been reported that OBP-301 showed a strong anticancer activity in colorectal, prostate, and non-small cell lung cancer in vitro and in vivo, the effect of OBP-301 in SCCHN has not been pursued (17, 18, 24). Therefore, in this study, we planned to assess the detailed antitumor and toxicity profile of OBP-301 in an animal model of SCCHN. OBP-301 induces cell death in 7 of 13 cell lines in vitro and shows dramatic antitumor effects in an animal model bearing KCCT873 tumors without significant toxicity.

OBP-301 showed cytotoxic activity in 7 of 13 SCCHN cell lines. Because the effect of OBP-301 against SCCHN cell lines was limited compared with that previously shown against human non-small cell lung, colorectal, and prostate cancer cell lines (14, 17), we hypothesized that the limitation came from the lower viral infection rate. However, it is of interest to note that the expression levels of adenoviral receptors including CAR, integrins, and HSG are comparable between SCCHN and non-small cell lung cancer H1299 cell lines (Fig. 2; data not shown). In addition, we did not find a significant correlation between hTERT mRNA expression and the cytotoxic activity of OBP-301. These results suggest that various factors such as replication speed of viruses and the existence of unknown receptors might be involved in the cytotoxic activity of OBP-301.

The i.t. three- or five-time administration of OBP-301 dramatically inhibited the growth of KCCT873 tumors in vivo. The antitumor effect was actually superior to what we expected from our in vitro results. Previously, we reported that adenovirus present in blood of mice exists for at least 1 week after i.t. treatment with OBP-301 (15, 17), and i.t. OBP-301 showed antitumor effects both in the injected primary tumor site and in tumors located at distant sites (17). From these results, it is conceivable that OBP-301 attacked the xenografted KCCT873 tumor over and over through the bloodstream for at least 1 week after injection.

| Table 2. Changes in blood serum chemistry of mice receiving OBP-301 treatment |
|--------------------------|-----------------|------------------|------------------|
| Profile                  | Untreated control | Day 10* PBS OBP-301 | Day 17* PBS OBP-301 |
| Sodium (mEq/L)           | 156             | 153 151           | 157 156           |
| Potassium (mEq/L)        | 7.5             | 7.3 9.3           | 8.7 8.2           |
| Creatinine phosphokinase (units/L) | 4,007 | 6,895 8,790 | 4,907 6,508 |
| Lactate dehydrogenase (units/L) | 2,153 | 3,197 3,158 | 2,600 2,740 |
| Aspartate aminotransferase (units/L) | 195 | 274 445 | 349 536 |
| Alanine aminotransferase (units/L) | 38  | 48 64  | 62 71  |
| Bilirubin (mg/dL)        | 0.1             | 0.1 0.1           | 0.1 0.1           |
| Creatinine (mg/dL)      | 0.16            | 0.13 0.13         | 0.14 0.13         |

NOTE: Data are mean blood samples from 3 animals in each group.
*Blood samples were collected from athymic nude mice receiving five i.t. injections of OBP-301 (days 5-9).
It has been reported that oncolytic virus replication induces tumor-specific immune responses by stimulating uric acid production as a danger signal as well as accelerating tumor antigen cleaved by IFN-γ-inducible PA28 expression (18). Additionally, because it has been shown that telomerase is active in ~80% to 90% of SCCHN tumor tissues as assessed by immunohistochemistry (25), we speculate that SCCHN cancer preferentially responds to OBP-301 treatment. These results may be the reason why the antitumor activity of OBP-301 is more profound in KCCCT873 tumors than expected from our in vitro results. Therefore, the strong antitumor effect observed in these animal studies suggests that OBP-301 could be an attractive agent to accomplish an in situ radical cure of SCCHN patients.

Although chemoradiotherapy, radiotherapy plus concurrent chemotherapy, has become the standard care for patients with unresectable SCCHN and organ preservation (26, 27), it has recently been reported that cisplatin and fluorouracil with docetaxel plus chemoradiotherapy has a greater effect (28). Because our previous study showed that OBP-401 containing a green fluorescent protein gene for monitoring viral replication (TelomeScan) showed enhanced antitumor efficacy in an in vivo human lung cancer model when given in combination with docetaxel, it is possible that combination of OBP-301 with conventional chemotherapy may be a powerful regimen for the treatment of SCCHN in the clinic (29). Additionally, as SCCHN is easily acceptable site for direct injection (6) and i.t. OBP-301 was emerged strong antitumor effect in the xenografted KCCCT873 tumor, the i.t. OBP-301 may be a new tool for the treatment of head and neck cancer. Further directions of clinical exploration with OBP-301 are still being considered. Utilization of OBP-301 via i.t. injection appears to be associated with modest activity, although clinical utility of local regional therapy is limited. Further exploration via intrahepatic arterial infusion or i.v. infusion awaits discovery of methods to improve OBP-301 activity.

Viral replication generally results in tissue destruction. In fact, interactions between adenovirus type 5 with CAR, integrin αvβ3, integrin αvβ5, or HSG and the fiber shaft of adenovirus type 5 are known to be involved in accumulation in the liver of mice and cynomolgus monkeys when administered (30–33). In this study, a significant therapeutic effect of i.t. OBP-301 treatment was achieved without any significant liver toxicity. Histologic analyses in the brain, lung, heart, kidney, and spleen showed no toxicity profile. Oncolytic viruses have been developed as anticancer agents because controlled replication in the tumors causes selective killing of tumor cells and minimizes the effect on normal cells (34). Thus, the current results are consistent with the mechanism of action of virotherapy with oncolytic viruses.

Notably, a phase I study of OBP-301 has been initiated in the United States to test the safety and tolerability of OBP-301 in patients with various types of progressive solid cancer including SCCHN. Results from current clinical trials may further show additional information on its safety and efficacy. As for the clinical use of OBP-301 in SCCHN, the preliminary information obtained from our study is, based on the present results, considered to be useful for the planning of future clinical trials.

In conclusion, this study clearly shows that OBP-301 has remarkable in vivo anticancer effects against SCCHN. These findings suggest that the replication-selective oncolytic virus provides a new platform for treating patients with human head and neck cancer.

Disclosure of Potential Conflicts of Interest

Y. Urata and D. Ichimaru: employees of Oncolyis Biopharma Inc. T. Fujimura: consultant to Oncolyis Biopharma Inc. No other potential conflicts of interest were disclosed.

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References


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