Interstitial Infusion of Glioma-Targeted Recombinant Immunotoxin 8H9scFv-PE38

Neal Luther1, Nai-Kong Cheung2, Eleni P. Souliopoulos1, Ioannis Karempelas1, Daniel Bassiri1, Mark A. Edgar3, Hong-fen Guo2, Ira Pastan3, Philip H. Gutin4, and Mark M. Souweidane1,4

Abstract

Monoclonal antibodies have the potential to target therapy for high-grade gliomas. Monoclonal antibody 8H9 is specific for membrane protein B7H3 and is reactive with most human high-grade gliomas. We tested the 8H9scFv-PE38 recombinant Pseudomonas immunotoxin in a preclinical model of high-grade glioma. The half maximal inhibitory concentration (IC50) of 8H9scFv-PE38 in vitro was determined using glioblastoma cell lines U87 and U251. Maximum tolerated infusion dose of 8H9scFv-PE38 following interstitial infusion to the striatum and pons was defined using athymic rats. Maximum tolerated infusion dose of 8H9scFv-PE38 or PBS control were interstitially delivered to athymic rats xenografted with U87 in the striatum or brain stem. Radiographic response and survivals were measured and compared between treatment groups. The in vitro IC50 of 8H9scFv-PE38 for U87 was 1.265 ng/mL and, for U251, 91 ng/mL. The maximum tolerated infusion doses of interstitially infused 8H9scFv-PE38 to the striatum and brain stem were 0.75 and 1.8 μg, respectively. For rats harboring intracranial U87 xenografts, infusion of 8H9scFv-PE38 increased mean survival (striatum, 43.4 versus 24.6 days; brain stem, 80.6 versus 45.5 days; n = 28 total) and produced three long-term survivors past 120 days. None of the 14 placebo-treated animals survived >54 days. Tumors also showed volumetric response to infusion of 8H9scFv-PE38 by magnetic resonance imaging. Interstitial infusion of 8H9scFv-PE38 shows potential for the treatment of hemispherical and brain stem glioma. Mol Cancer Ther; 9(4); 1039–46. ©2010 AACR.

Introduction

High-grade gliomas are the most common primary brain tumors in adults. Given the poor prognosis of these tumors with conventional forms of therapy, a critical need exists for the development of novel therapy (1–4). Monoclonal antibody (mAb)–mediated immunotherapy has met with success and enthusiasm in oncology and has been proposed as a potential avenue for treating high-grade glioma (5, 6). The murine mAb 8H9 is immunoreactive to most human high-grade gliomas without cross-reactivity to normal brain (7, 8). This antibody has produced compelling results following intrathecal delivery for stage IV neuroblastoma (9). The recombinant immunotoxin 8H9scFv-PE38, which uses the Fv subunit of 8H9 as the targeting domain for Pseudomonas exotoxin PE38, has shown preclinical in vitro and in vivo efficacy against human neuroblastoma, breast cancer, and osteosarcoma (10). The use of such macromolecules for brain tumors, however, has been problematic given their limited delivery across the blood-brain barrier.

Intratumoral delivery of such targeted agents may be accomplished through interstitial infusion, also referred to as convection-enhanced delivery. This mode of local delivery uses a pressure-dependent gradient to enhance drug uniformity and volume of distribution (11–14). Interstitial infusion bypasses the blood-brain barrier, a natural obstacle to delivery of systemically administered therapeutics to the brain. This delivery modality holds particular potential for deeply situated unresectable high-grade gliomas and has in fact been postulated as an attractive therapy for diffuse intrinsic pontine glioma (15–18). Successful interstitial infusion of mAb 8H9 has recently been shown in immunoreactive glioma xenografts (8).

In the present study, the tumoricidal activity of 8H9scFv-PE38 is evaluated in vitro against human glioblastoma cell lines. The safety of 8H9scFv-PE38 following interstitial infusion to the rodent striatum and brain stem is evaluated, and the efficacy of this therapy in vivo against supratentorial and brain stem glioma xenografts is assessed.

Materials and Methods

Immunotoxin preparation

The production of 8H9scFv-PE38 was done at the laboratory of Ira Pastan, M.D., and has been previously described (10, 19, 20). In brief, a fusion protein consisting of
the single-chain Fv component of mAb 8H9 and a truncated form of the Pseudomonas exotoxin (PE38) was expressed in Escherichia coli BL21. Bacterial inclusion bodies were solubilized in guanidine hydrochloride solution, reduced with dithioerythritol, and refolded by dilution in a refolding buffer containing arginine to prevent aggregation. Active monomeric protein was purified from the refolding solution by ion-exchange and size-exclusion chromatography. Protein concentration was determined by Bradford Assay (Coomassie Plus, Pierce).

Cytotoxicity assay

The in vitro tumoricidal activity of 8H9scFv-PE38 was assayed against human glioblastoma cell lines U87 and U251, both found to be 8H9 immunoreactive by previous fluorescence-activated cell sorter analysis (8). The rat glioblastoma cell line F98, which is 8H9 antigen negative, was used as a negative control. Cell lines were cultured in DMEM supplemented with 10% fetal bovine serum. Cells were harvested at 50% to 70% confluency, concentrated to 1.0 to 4.0 × 10⁶ cells/mL, and plated in 100 μL volumes per well in 96-well plates. Following 20-h incubation, a 50 μL volume of 8H9scFv-PE38 in sterile PBS was added in triplicate serial dilutions to a maximum concentration of 2,000 ng/mL. The plates were then incubated for 3 d; after which, the WST-8 reagent was added (Medical and Biological Laboratories) to determine cell proliferation. The WST-8 reagent uses a tetrazolium salt that is cleaved to formalan by living cells, quantifiable by an enzyme-linked immunosorbent assay spectrophotometer at 440 nm. For each cell line, the half maximal inhibitory concentration (IC₅₀) was then determined by analysis of plots of optical density for all dose groups.

In vivo toxicity assays

All animal procedures were approved by the Institutional Animal Care and Use Committee at Weill Cornell Medical College at Cornell University. To determine maximum tolerated infusion dose, groups of five athymic rats per dose weighing 200 to 400 g underwent interstitial infusion of 8H9scFv-PE38 to either the striatum or brain stem. An additional ten rats underwent infusion of sterile PBS to striatum or brain stem (n = 5 animals per group) as placebo. The surgical procedure is done as previously described (8, 17, 21). The animal is anesthetized by inhalational isoflurane and placed in a stereotact frame (Kopf Instruments). Following administration of s.c. lidocaine, a midline scalp incision is created, and subperiosteal dissection is carried out to expose the coronal and sagittal sutures. For striatal infusion, a burr hole is created 1 mm anterior and 3 mm lateral to bregma. A 0.2-mm blunt titanium tip cannula is then lowered to a depth of 6 mm below the skull. For brain stem infusion, the burr hole is created 1.4 mm lateral to lambda, and the cannula is lowered to a depth of 9 mm beneath the skull to the pons.

Delivery of the therapeutic agent is done at a rate of 0.1 μL/min. The infusion volume was 5μL for all animals. Infusion doses to the striatum were 0.5, 0.75, 1.0, and 2.0 μg, and doses to the pons were 1.2, 1.8, and 2.4 μg. At the end of infusion, the cannula is left in place for 5 min and then slowly withdrawn. The skin is closed, and the animal is allowed to recover.

Animals were then observed clinically for 4 wk for signs of toxicity. Assessment for toxicity included daily neurologic examinations (consist of cranial nerve, motor, and sensory examination) and weight measurements every 3rd day. If any animal experience debilitating toxicity, they were humanely euthanized. Otherwise, 4 wk after surgery, the rats were euthanized by i.p. pentobarbital injection. All brains were harvested, embedded in paraffin, and sectioned in coronal series. Hematoxylin and eosin staining was done, and slides were then analyzed by a blinded neuropathologist for evidence of histotoxicity (M.A. Edgar). The maximum tolerated infusion dose was defined as the highest dose at which most animals experienced no debilitating clinical toxicity.

In vivo tumoricidal assay

The glioblastoma cell line U87 was cultured as above, and cells were harvested at 60% to 80% confluency. Rodent surgery and intracranial targeting were done as previously described. A total of 28 athymic rats underwent U87 implantation to either the striatum or pons (n = 14 for each). A total of 1.0 × 10⁶ cells in a 5 μL volume were inoculated. Following implantation of xenografts, serial magnetic resonance imaging (MRI) was done to confirm tumor growth before treatment with 8H9scFv-PE38 and to evaluate for radiographic response following therapy.

Time points for imaging and treatment of striatal and pontine tumors were distinct on account of differential growth rates seen for tumors at each site. For all animals with striatal tumors, imaging was done 1, 2, 3, and 5 wk following U87 implantation. These animals all underwent interstitial infusion of either the maximum tolerated dose of 8H9scFv-PE38 or PBS control (n = 7 animals per group; chosen at random) on day 8 following tumor implantation. For animals with brain stem tumors, MRI was done 1, 2, 4, 6, and 8 wk following xenografting. These animals all underwent interstitial infusion of the maximum tolerated infusion dose of 8H9scFv-PE38 or PBS (n = 7 for each) on day 29 following U87 implantation. Two animals with pontine tumors died of anesthetic complications during exposure for convection-enhanced delivery, and these animals were excluded from statistical analysis. Tumor volume measurements were determined manually for each animal. Animals were then followed for surviviorship in days following tumor inoculation. Those who survived >120 d were considered long-term survivors.

Results

In vitro cytotoxicity

Results of U87, U251, and F98 growth following treatment with 8H9scFv-PE38 are depicted in Fig. 1, with
optical density used as a correlate for cell population. From this analysis, it was determined that the IC\textsubscript{50} of 8H9scFv-PE38 for U87 was 1,265 \pm 28 ng/mL and, for U251, 91 \pm 8 ng/mL. Growth of nonimmunoreactive F98 was not inhibited by 8H9scFv-PE38 at doses up to 2,000 ng/mL. Previously reported IC\textsubscript{50} of 8H9scFv-PE38 with breast cancer, osteosarcoma, and neuroblastoma cell lines have ranged from 5 to 90 ng/mL (10). Dose concentrations of 8H9scFv-PE38 selected for \textit{in vivo} toxicity assays in rodents were \textasciitilde 100-fold greater than these IC\textsubscript{50} measurements for U87 and U251.

**Maximum tolerated infusion dose determination**

For infusions to the striatum, rats underwent interstitial infusion of 0.5, 0.75, 1.0, and 2.0 \(\mu\)g of 8H9scFv-PE38 or PBS in a 5-\(\mu\)L volume (Table 1). Animals in the 1.0-\(\mu\)g dose group all showed hyperaggressive behavior. Three of the animals who received the 1.0-\(\mu\)g dose also experienced significant weight loss. All five animals administered the 2.0-\(\mu\)g dose suffered significant weight loss, became lethargic, and required sacrifice between 1 to 2 weeks following treatment. Histologic assessments revealed increasing degrees of necrosis and inflammation with dose escalation, most pronounced at the 1.0 and 2.0 \(\mu\)g doses. Based on these data, the maximum tolerated infusion dose of 0.75 \(\mu\)g (150 \(\mu\)g/mL) of 8H9scFv-PE38 was selected for striatal infusion.

For pontine infusion, rats underwent interstitial infusion of 1.2, 1.8, and 2.4 \(\mu\)g of 8H9scFv-PE38 or PBS in a 5-\(\mu\)L volume (Table 1). Two of the animals who received 1.8 \(\mu\)g suffered cranial nerve palsies but no other clinical deficit or toxicity. All five animals administered the 2.4 \(\mu\)g dose suffered significant hemiparesis and weight loss, necessitating sacrifice between 1 and 2 weeks following treatment. Histology again revealed necrosis and inflammation increasing with dose (Fig. 2). A maximum tolerated infusion dose of 1.8 \(\mu\)g of 8H9scFv-PE38 (360 \(\mu\)g/mL) was selected for infusion to the pons.

**In \textit{vivo} efficacy determination**

To evaluate the potential \textit{in vivo} antiglioma efficacy of interstitial infusion of 8H9scFv-PE38, the maximum

<table>
<thead>
<tr>
<th>Infusion site</th>
<th>(n)</th>
<th>Dose ((\mu)g)</th>
<th>Histopathology</th>
<th>Clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>5</td>
<td>0.5</td>
<td>Minimal inflammation/necrosis</td>
<td>No neurologic/behavioral findings</td>
</tr>
<tr>
<td>Striatum</td>
<td>5</td>
<td>0.75</td>
<td>Moderate necrosis and inflammation</td>
<td>No neurologic/behavioral findings</td>
</tr>
<tr>
<td>Striatum</td>
<td>5</td>
<td>1.0</td>
<td>Significant necrosis and inflammation</td>
<td>Behavioral changes in all 5 animals, weight loss in 3 of 5</td>
</tr>
<tr>
<td>Striatum</td>
<td>5</td>
<td>2.0</td>
<td>Significant necrosis and inflammation</td>
<td>Lethargy, behavioral change, and weight loss in all animals</td>
</tr>
<tr>
<td>Striatum</td>
<td>5</td>
<td>PBS</td>
<td>Minimal cystic change at infusion site</td>
<td>No neurologic/behavioral findings</td>
</tr>
<tr>
<td>Pons</td>
<td>5</td>
<td>1.2</td>
<td>Minimal necrosis, moderate inflammation</td>
<td>No neurologic/behavioral findings</td>
</tr>
<tr>
<td>Pons</td>
<td>5</td>
<td>1.8</td>
<td>Moderate necrosis and inflammation</td>
<td>Facial palsy in 2 animals, no weight loss or behavioral change</td>
</tr>
<tr>
<td>Pons</td>
<td>5</td>
<td>2.4</td>
<td>Significant necrosis and inflammation</td>
<td>Hemiparesis and weight loss in all animals</td>
</tr>
<tr>
<td>Pons</td>
<td>5</td>
<td>PBS</td>
<td>Minimal cystic change at infusion site</td>
<td>No neurologic/behavioral findings</td>
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tolerated infusion dose of the immunotoxin was delivered to intracranial U87 xenografts. Tumor implantation was done to the striatum and brain stem with an identical inoculum of $1.0 \times 10^5$ cells, but MRI showed that growth rate was markedly different between the two sites. In the striatum, tumors reached a volume large enough to target with confidence by 1 week (0.002-0.01 cm$^3$) and were treated on day 8 with interstitial infusion of 0.75 μg 8H9scFv-PE38. Tumors in the pons reached this size by 4 weeks and were thus treated on day 29 with 1.8 μg 8H9scFv-PE38.

Survival analysis from time of xenografting was conducted for striatal and pontine tumors. For striatal tumors, mean survival for 8H9scFv-PE38 treated animals was 43.4 days (median, 33 days; range, 24–120 days), with one long-term survivor. Animals in the control PBS arm survived a mean 24.6 days (median, 26 days; range, 11–20 days). t Test comparison failed to reveal a significant difference between survivorship in the two groups ($P = 0.18$), and this statistical result was confirmed by Wilcoxon rank-sum test for comparison of medians ($P = 0.12$). For brain stem tumors, animals who underwent convection-enhanced delivery of 8H9scFv-PE38 survived a mean of 80.6 days (median, 57 days; range, 51–120 days), with two long-term survivors. The controls receiving PBS lived a mean 45.5 days (median, 46 days; range, 32–54 days). This survival benefit was found to be statistically significant by t test and Wilcoxon rank-sum test ($P < 0.05$ for both). Kaplan-Meier analysis of all animals in this series (i.e., both hemispherical and brain stem tumors) revealed a statistically significant difference in survival for 8H9scFv-PE38 and placebo-treated animals ($P < 0.05$; plot shown in Fig. 3).

**Radiographic evaluation**

Following therapy, MRI was done on a weekly basis for striatal tumors and biweekly for pontine tumors to determine radiographic response. Subjective evaluation of posttreatment radiographs suggested tumor response to therapy with 8H9scFv-PE38 (Fig. 4). Tumor volume

![Figure 2. Low magnification hematoxylin and eosin brain stem sections following interstitial infusion of 1.2 (A), 1.8 (B), and 2.4 μg (C) of 8H9scFv-PE38. With increasing dose, necrotic change becomes more evident (encircled).](image)

![Figure 3. Kaplan-Meier survival plot for all animals with U87 xenografts, striatal, and brain stem tumors pooled together, in this series ($n = 28$ total). Red, 8H9scFv-PE38; black, PBS control.](image)
measurements were done, and all comparisons were made by t test. Mean changes in tumor volume 2 weeks following convection-enhanced delivery is depicted in Fig. 5. For striatal tumors before treatment, mean tumor volumes were 0.30 mm$^3$ for 8H9scFv-PE38– and PBS-treated animals. Two weeks following therapy, mean volumes were 4.9 and 14.0 mm$^3$ for 8H9scFv-PE38– and placebo-treated rats, respectively. The fold-change in tumor volume was significantly larger for placebo-treated than 8H9scFv-PE38–treated animals ($P < 0.05$). Mean pretreatment tumor volumes for brain stem tumors were 0.3 mm$^3$ for the 8H9scFv-PE38 and 0.5 mm$^3$ for the PBS control groups. Two weeks post–convection-enhanced delivery, mean volumes were 3.0 and 9.0 mm$^3$ for 8H9scFv-PE38– and PBS-treated animals, respectively. The fold-change in tumor volumes was greater in PBS-treated tumors, but this did not reach statistical significance ($P = 0.2$). Tumor volume measurements therefore showed response in striatal U87 xenografts but failed to reveal a statistically significant difference between 8H9scFv-PE38– and placebo-treated animals in the brain stem.

Discussion

The murine mAb 8H9, developed against a neuroblastoma cell line, recognizes B7H3, an outer membrane protein that exhibits complex interactions with T cells and natural killer cells. Expression of this protein may contribute to tumor resistance to host defenses and has in fact been implicated with tumor aggressiveness in prostate and renal cell carcinoma (22, 23). Recently, B7H3-directed immunotherapy has gained interest for the potential treatment of hepatocellular carcinoma (24). The B7H3 epitope recognized by 8H9 is not expressed by normal neurons or glia, and intrathecal [$^{131}$I]8H9 has already shown encouraging results in salvage therapy for neuroblastoma, another neuroectodermally derived tumor (7–9).

Recombinant immunotoxins use ligands specific for receptors or antigens to substitute for the binding domains of the native toxins (1, 25–29). These molecules have garnered enthusiasm for their potential roles in the treatment of high-grade gliomas. 8H9scFv-PE38 is one such immunotoxin that uses the antigen-binding scFv of...
mAb 8H9 to substitute for the membrane-binding component of the Pseudomonas exotoxin PE38. 8H9scFv-PE38 has shown tumoricidal activity against neuroblastoma, osteosarcoma, and breast cancer cell lines in vitro and in vivo (10). Previous work from our laboratory confirmed the potential to deliver a targeted antibody, 8H9, into immunoreactive solid tumor without sacrificing the distributive properties of this technique (8). This is particularly relevant in cases of unresectable and deep-seated gliomas, which have been considered important potential indications for the clinical use of convection-enhanced delivery techniques (15, 16, 18). The recent phase III PRECISE trial evaluating the efficacy of postresection convection-enhanced delivery of IL13-PE38 for recurrent glioblastoma closed without success. This trial evaluated efficacy in postresection glioblastoma, which may include a large cavity acting as a sink for infused therapy (44). A critical need persists not only to continue to evaluate novel agents that may be delivered by convection-enhanced delivery but also to refine criteria for what patients and which tumors are most likely to be favorably treated.

The current investigation sought to evaluate the anti-glioma properties of 8H9scFv-PE38 and determine whether convection-enhanced delivery of this molecule in orthotopic hemispherical and brain stem tumor models would show therapeutic efficacy. The in vitro studies showed antigen-specific tumoricidal activity against the human glioblastoma cell lines U251 and U87, confirmed by a lack of activity against the nonimmunoreactive F98 glioma cell line. Dose concentrations required were higher than seen in tumor cells of breast or bone origin, and although the IC50 of 8H9scFv-PE38 was higher for U87 than has been seen for other tumor cell lines, it should be noted this concentration is still well below tolerated dose concentrations in the rat brain following convection-enhanced delivery (10). The in vitro tumoricidal activity of 8H9scFv-PE38 against U87 compares favorably with some well-regarded therapeutics for glioblastoma but is lower than that of IL13-PE38, which is roughly 600 ng/mL (29, 45). We cannot preclude the possibility that the antiglioma properties of the recombinant immunotoxin may not be any greater than the pseudomonas exotoxin itself based on the experiments we have done. However, the immunotoxin is used largely to reduce toxicity, thereby potentially increasing the dose deliverable.

In vivo intracerebral tolerance studies in the current investigation do in fact suggest a lower toxicity profile with 8H9scFv-PE38 than with IL13-PE38, whose maximum tolerated infusion dose concentration is ∼100 μg/mL in studies stopped 4 days after infusion (28). The difference in tolerated doses seen with 8H9scFv-PE38 in different brain locations is also worth noting, and this finding should be considered for future locally administered therapies. A higher dose tolerance in the brain stem may result from axonal predominance and less neuronal cell bodies than in the gray matter.

Convection-enhanced delivery of the maximum tolerated infusion doses of 8H9scFv-PE38 to both the striatal and pontine U87 xenografts in rodents resulted in increased survival. Interstitial infusion of 8H9scFv-PE38 also resulted in long-term survival (>120 days) for three animals harboring U87 xenografts. No placebo-treated animal survived >54 days. Tumors recurred in most 8H9scFv-PE38–treated animals, suggesting a possible role for repeat or multiple infusions. Furthermore, using

Figure 5. U87 xenograft volume-fold change (with SE) as determined by MRI done 2 wk following treatment with 8H9-PE38 versus placebo in the striatum (A) and brain stem (B).
8H9dsFv-PE38 (a second generation immunotoxin not available at the time of these experiments) may show increased in vivo stability and produce more durable tumor responses. These therapeutic strategies warrant further investigation. Nonetheless, the results presented here support 8H9-based immunotherapy for malignant glioma, with potential efficacy in unresectable or brain stem glioma.

Radiographic responses were subjectively observed in U87 xenografts following 8H9scFv-PE38 therapy. This observation was corroborated by statistical analysis of posttreatment tumor volumes in striatal but not brain stem tumors. The major shortcoming is small group sample sizes (n = 7 per group). The use of tumor volume measurement was also important in establishing tumor growth in all animals before treatment and confirming that there was no significant difference in the size of tumors in the rodents before therapy. This adjunct supports the validity of the survival differences seen between 8H9scFv-PE38– and placebo-treated animals.

An interesting novel observation concerned the differential growth rate between U87 tumors of the striatum and pons. This may be due in part to greater vascularity and blood flow in the deep hemispherical gray matter than the white matter of the brain stem. This finding is noteworthy for investigators planning the logistics of a preclinical in vivo therapeutic efficacy studies in brain stem models.

The most noteworthy shortcoming of the in vivo experiments centers on the use of U87 xenografts in rodents. Although this cell line is commonly used for preclinical in vivo therapeutic efficacy studies, these tumors grow in a uniformly expansile nature, with clear margins to the normal brain they displace. This is dissimilar to the diffusely infiltrative nature of human malignant glioma. However, because mAb 8H9 recognizes an epitope on B7H3 not conserved or expressed in glioma cell lines derived from rodent lineage (such as F98, C6, or 9L), the use of a more representative glioblastoma model was precluded in this study. Consideration was given to glioblastoma neurosphere implantation, but in our experience to date, these tumors grow inconsistently and slowly, rendering their use somewhat inefficient and impractical. A clear need exists for further development of reliable and representative glioma models that may act as targets for tumor-specific human glioma–targeting therapy (46, 47).

In conclusion, convection-enhanced delivery of anti-glioma mAb 8H9 and 8H9scFv-PE38 show potential for the treatment of supratentorial and infratentorial high-grade glioma. Delivery of this molecule is currently being evaluated for safety in a nonhuman primate model before translation to clinical trial.

Disclosure of Potential Conflicts of Interest
Memorial Sloan-Kettering Cancer Center licensed 8H9 to United Therapeutic.

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References


Correction: Interstitial Infusion of Glioma-Targeted Recombinant Immunotoxin 8H9scFv-PE38

In this article (Mol Cancer Ther 2010;9:1039–46), which was published in the April 2010 issue of Molecular Cancer Therapeutics (1), the name of the fourth author was misspelled. The correct spelling of the name is Ioannis Karampelas. The online article has been changed to reflect this correction and no longer matches the print.

Reference


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Neal Luther, Nai-Kong Cheung, Eleni P. Souliopoulos, et al.


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