Radioprotective Effects of ON 01210.Na upon Oral Administration

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ON 01210.Na (Ex-RAD), a chlorobenzylsulfone derivative was investigated for its pharmacologic and radioprotective properties when administered via oral and subcutaneous (SC) routes. The goals of the study were to assess the comparative bioavailability of ON 01210.Na when administered by oral versus SC routes and to demonstrate that the oral drug delivery of ON 01210.Na afforded survival advantage similar to SC dosing. Pharmacokinetics was studied after two doses, 24 h apart, of ON 01210.Na (500 mg/kg) administered to male C3H/Hen mice (7–9 weeks) via SC injection or oral route. The dose response (100 to 750 mg/kg) and survival advantage of ON 01210.Na administered at 24 h and 15 min prior to 7.5 or 8 Gy whole body irradiation from a 137Cs source (dose rate 1 Gy/min) were studied in these mice. Effects on the hematopoietic system were investigated by complete blood count and granulocyte-macrophage colony forming unit assay. A significant survival advantage and hematopoietic protection were observed after prophylactic oral ON 01210.Na and results were comparable to SC administration. These findings correlated well with pharmacokinetic data. Both SC and oral ON 01210.Na showed significant survival advantage against radiation toxicity and ON 01210.Na mediated hematopoietic protection plays key role in enhanced survival of mice. Oral administration holds better clinical promise as an effective countermeasure not only for early-responders in a nuclear accident, but also for the at-risk civilian population.

INTRODUCTION

Apart from accidental exposures, the possibility of non-accidental radiation exposure as a result of malicious, criminal, or terrorist actions has greatly increased in the current world scenario. Military personnel and emergency responders are at a higher risk of being exposed to ionizing radiation doses sufficient to cause acute radiation syndromes (ARS).1,2) Radiation injury intervention can be provided as protection (prophylactic, prior to exposure), mitigation (shortly following exposure, prior to symptoms), or treatment (following display of clinical symptoms).3)

In a radiation accident or a radiological terrorism scenario the immediate concern is to protect emergency responders and the at-risk civilian population.4) Our ability to protect healthy tissues from radiation injury via pre-exposure pharmacological intervention is currently very limited.5) Most of the medical countermeasure approaches aimed at reducing the severity of radiation injury are still experimental and so far none of these agents has received Food and Drug Administration (FDA) approval as radiation countermeasures for use in a disaster scenario. As perceived by both civilian and military agencies, the need for countermeasures to protect from radiation injuries is urgent.6)

The extent of injury from ionizing radiation varies from tissue to tissue and depends on radiation dose and length of exposure.6) The ARS occurs within a short time period (days or weeks) following exposure to high doses of radiation, and lethality occurs mostly due to bone marrow failure. ARS is expected to result from whole-body exposure to radiation doses greater than 1 Gy, and the exhibited syndromes depend on dose and organ system damaged.6) At exposure to
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MATERIALS AND METHODS

Chemicals and reagents

ON 01210.Na (Ex-RAD; 4-carboxystyryl-4-chlorobenzylsulfone) and ON 01910.Na (sodium (E)-2-(2-methoxy-5-[(2,4,6-trimethoxy styrylsulfonyl) methyl] phenylamino) acetate) were provided by Onconova Therapeutics, Inc. (Newtown, PA, USA) and described in detail elsewhere. ON 01919.Na was used as an internal standard for quantitation of ON 01210.Na in plasma samples and was not used in animal experiments. All chemicals and reagents used in this research were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Animals

Seven to nine week old C3H/Hen male mice were purchased from Charles River Laboratories (Wilmington, MA, USA) and were housed in an air and temperature controlled room at the Georgetown University (GU) animal facility. All animals were housed in a room with 12h dark and light cycle maintained at 22°C in 50% humidity. The diet, certified rodent diet #5002 (LabDiet Cat#5002), used in this study was obtained from PMI Nutrition International (St. Louis, MO, USA), and filtered water was supplied to the animals ad libitum. The GU animal facility is an Association for Assessment and Accreditation of Laboratory and Animal Care International (AAALACI) accredited facility. Before starting the experiments, all animals were allowed one week of acclimatization in the facility. The Animal Care and Use Committee at GU approved all the procedures and treatments applied to these mice and the Guide for the Care and Use of Laboratory Animals, prepared by the Institute of Laboratory Animal Resources, National Research Council, and U.S. National Academy of Sciences were used as guidelines for conducting this research.

ON 01210.Na formulation and administration

ON 01210.Na was provided by Onconova as a solution formulation at a concentration of 50 mg/mL in sterile sealed vials. The formulation vehicle consisted of Tris-EDTA buffer and tocophersolan in a mixture of 50% polyethylene glycol 400 and water adjusted to a pH of 8.0. Mice were weighed and an appropriate volume of formulation was administered either by SC injection or orally by gastric gav-
age. For SC injection, a sterile 1 mL insulin syringe with a 25G needle was used, while a 22G × 1” gavage needle was used for oral dosing. For all the studies, 2 doses of ON 01210.Na were administered, 24 h and 15 min before radiation. For the pharmacokinetic studies, no radiation exposure occurred and blood samples were collected at different time points after the second administered dose.

Pharmacokinetic study

The plasma disposition of ON 01210.Na was studied in mice (n = 3) after oral and SC administration. The doses tested were 250 mg/kg and 500 mg/kg. Following two 24 h spaced doses of drug, plasma samples were collected at various time points over a 6 h period (0.083, 0.25, 0.5, 1, 2, 4, and 6 h) starting immediately after the second dose. Terminal anesthesia with CO2 was used for collection of blood samples from mice. Three mice were sampled at each time point.

Plasma concentrations of ON 01210.Na were measured by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay as described previously. Briefly, 10 mL internal standard (ON 01910.Na, 20 μg/mL solution) was spiked into 100 mL plasma samples, and the mixture was extracted by 500 μL acetonitrile (ACN) precipitation. The mixture was then vortexed and centrifuged, and 5 μL of the supernatant was injected into the LC-MS/MS system for quantification.

The LC-MS/MS system consists of an Agilent Triple Quad 6410 mass spectrometer coupled to an Agilent 1200 high performance liquid chromatography (HPLC) system (Agilent Technologies, Santa Clara, CA, USA). The mass spectrometer was operated at negative mode with an electrospray voltage of −4.0 kV and capillary temperature of 350°C. The multiple reaction monitoring (MRM) transition channels were set at 335.0→165.9 for ON 01210.Na and 450.0→418.1 for the internal standard (ON 01910.Na), respectively. The analyses were separated by Agilent Zorbax rapid resolution HT SB C18 cartridge column (2.1 mm × 30 mm; 3.5 μm; Agilent Technologies) under isocratic elution (50% ACN/50% H2O/0.1% formic acid) at a flow rate of 0.5 mL/min. The running time was 2.5 min with a post-run time of 0.5 min. ON 01210.Na eluted at 1.09 min, and the internal standard eluted at 1.00 min.

The samples were diluted 10 fold (SC) or 50 fold (Oral) using blank mouse plasma. Standard curves were generated over a range of drug concentrations from 10 ng/mL to 10000 ng/mL. The within-run precision values were determined in six replicates for low, middle and high quality control (QC) data points at concentrations of 30, 200 and 2000 ng/mL. The between-run precision was determined across the above QC data points in three runs, and the mean concentrations and the coefficients of variation (CV) were calculated. The accuracy of the assay was determined by comparing the nominal concentrations with the corresponding calculated mean concentrations. The extraction recovery of ON 01210.Na at the above QC levels was also evaluated by comparing the area under the curve (AUC) of the analyte after extraction with that prepared in pure solvent without extraction.

Pharmacokinetics data analysis

ON 1210.Na plasma data (concentration vs. time) were analyzed by noncompartmental analysis. The analysis was conducted using the mean plasma concentration (based on data from 3 mice) for each sampling period. Pharmacokinetic parameters were generated through WinNonlin® (version 5.3, Pharsight Corporation, St. Louis, MO, USA). Area under the concentration versus time curve from time 0 to the last experimental time period (Clast) was determined using the linear trapezoidal rule (with extrapolation to infinity using the formula Clast/k where k is the elimination rate constant). Standard pharmacokinetic equations were used to calculate clearance and elimination half-life (0.693/k).

Survival study

Mice were irradiated using a 137Cs source in two steps with 14 mice per group per experimental step. For sample size determination published literature on radioprotection19–21 as well as statistician at Georgetown University’s biostatistics core facility was consulted. During each experimental step mice were placed in a circular pie shaped, well-ventilated plastic mouse holder, which was then placed on a rotating turntable inside the irradiator. The radiation dose was delivered at a rate of 1 Gy/min. For all the survival studies mice were administered two doses of ON 01210.Na either orally or SC. For ON 01210.Na dose response (100, 250, 500, and 750 mg/kg) studies mice were exposed to 7.5 Gy, and for survival advantage studies mice were exposed to 7.5 or 8 Gy of whole body γ-radiation. Survival was monitored for 30 days post-radiation.

Hematopoietic system study

The hematopoietic system was investigated by peripheral white blood cell (WBC) count, platelet count and granulocyte-macrophage colony forming unit (GM-CFU) assay in mice after exposure to 5 Gy whole body radiation. A total of six groups (5 mice per group) were used: untreated control, radiation alone, drug plus radiation, vehicle plus radiation, drug only, and vehicle only. ON 01210.Na was administered either orally or SC 24 h and 15 min before radiation at 500 mg/Kg body weight. The approved animal protocol was followed to euthanize the mice at 7, 14 and 21 days post-exposure. Blood was collected quickly in ethylenediaminetetraacetic acid (EDTA) tubes directly from the heart and the femur bones on either side were dissected out and ends opened using a sharp scalpel blade under aseptic conditions.

While blood was subjected to complete blood count, the
bone marrow cells were flushed using Iscove’s Modified Dulbecco's Media (IMDM) from StemCell Technologies (Vancouver, BC, Canada) supplemented with 5% fetal bovine serum (FBS) followed by filtration through 70 micron mesh from BD Biosciences (Rockville, MD, USA). Isolated cells were counted using the Beckman Coulter counter (Brea, CA, USA), and $2.4 \times 10^4$ cells/mL were plated using Methocult (M3534, StemCell Technologies) medium supplemented with 10 ng/mL granulocyte macrophage-colony stimulating factor (GM-CSF) (StemCell Technologies) in ultra-low attachment 6-well plates from Corning (Corning, NY, USA). The plates were incubated in an incubator maintained at 37°C with 5% CO2 and ≥ 95% humidity for 7 days. Colonies were counted using a dissection microscope (Leica, Wetzlar, Germany) and the results presented as percent of colonies taking numbers in untreated control as 100%. The number of colonies in ON 01210.Na only and vehicle only treated groups were similar to untreated control.

**Statistical analysis**

The statistical significance among survival study groups at 30 days was determined using Fisher’s exact t-test. In the hematopoietic study, a student’s t-test (paired, two-tailed) was performed to determine statistical significance. For all analyses, p < 0.05 was taken as statistically significant.

**RESULTS**

**Pharmacokinetics of ON 01210.Na following oral and SC administration:**

Since drug effects are often dependent on pharmacokinetic behavior, we conducted a comparative study of the pharmacokinetics of ON 01210.Na following SC (Fig. 1A) and oral (Fig. 1B) administration. Plasma exposure of ON 01210.Na increased with increasing dose, and drug absorption was faster following oral administration. ON 01210.Na pharmacokinetic parameters are presented in Table 1. Peak plasma levels (C max) of ON 01210.Na were higher for oral dosing, but area under the curve (AUC) estimates were similar for both routes of administration, indicating comparable bioavailability.

**Comparison of ON 01210.Na mediated radioprotection upon SC and oral administration: dose optimization and survival study**

Different doses of ON 01210.Na were administered either SC or orally to determine the optimal radioprotection dose. Subcutaneous administration of 100, 250, 500, and 750 mg/kg of ON 01210.Na showed significant dose-dependent survival advantage after 7.5 Gy of whole body radiation except for 100 mg/Kg which was not significantly different from radiation only group (p < 0.006 for 250 mg/kg; p < 0.0001 for 500 mg/kg and for 750 mg/kg compared to survival in radiation only group; Fig. 2A). In contrast no significant (p >

**Figure 1.** Pharmacokinetic analysis of oral and subcutaneous (SC) ON 01210.Na. Plot of mean ON 01210.Na plasma concentrations versus time following administration to mice (250 mg/kg or 500 mg/kg). A) SC dosing studies. B) Oral dosing studies. Error bar represents standard deviation.

**Table 1.** Comparison of ON 01210.Na pharmacokinetic parameter estimates following SC versus oral administration*. Numbers in parenthesis represents standard deviation.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dose (mg/kg)</th>
<th>$C_{max}$ (μg/mL)</th>
<th>$t_{1/2}$ (h)</th>
<th>$AUC(0-∞)$ (μg*h/mL)</th>
<th>$Cl/F$ (mL/h/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>250</td>
<td>53.0 (1.30)</td>
<td>1.8 (0.37)</td>
<td>74.8 (8.16)</td>
<td>3370 (392)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>130 (48.9)</td>
<td>3.1 (0.94)</td>
<td>202 (26.4)</td>
<td>2500 (341)</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>250</td>
<td>47.9 (1.06)</td>
<td>1.1 (0.28)</td>
<td>92.4 (27.4)</td>
<td>2880 (891)</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>71.6 (17.1)</td>
<td>2.0 (0.57)</td>
<td>183 (37.6)</td>
<td>2821 (631)</td>
</tr>
</tbody>
</table>

*Three mice were sacrificed at various times post-dose and a sample was collected. The data were pooled and noncompartmental analysis was performed on the mean plasma concentration-time values.
0.05 for all the vehicle groups) difference was observed between radiation only and vehicle plus radiation groups (Fig. 2B). When compared with the vehicle group (Fig. 2C), we did not observe any significant protection at 100 mg/kg dose of ON 01210.Na (42.9% with drug and 28.6% with vehicle; p > 0.05). However, a significant survival advantage was observed with ON 01210.Na at 250 mg/kg (71.4% with drug and 28.6% with vehicle), and 750 mg/kg (92.9% with drug and 28.6% with vehicle) mg/kg (Fig. 2C), when compared to respective vehicle groups (p < 0.02 for 250 mg/kg; p < 0.0003 for 500 mg/kg and for 750 mg/kg).

A dose-dependent survival advantage comparable to SC groups was also observed with oral administration of ON 01210.Na. Compared to the radiation only group, oral ON 01210.Na at 100 mg/kg showed 50% survival (p < 0.03), at 250 mg/kg showed 71.4% survival (p < 0.001), at 500 mg/kg showed 78.6% survival (p < 0.003), and at 750 mg/kg showed 71.4% survival (p < 0.001) (Fig. 3A). None of the oral vehicle treated groups showed a statistically significant survival advantage (survival for vehicle groups: 7.1% for 100 mg/kg, 21.4% for 250 and 500 mg/kg, and 28.6% for 750 mg/kg; p > 0.05 compared to radiation only) (Fig. 3B).

When compared to vehicle treated groups we saw significant protection (Fig. 3C) in all the oral ON 01210.Na doses tested (p < 0.03 for 100 mg/kg, p < 0.02 for 250 mg/Kg, p < 0.007 for 500 mg/kg, an p < 0.05 for 750 mg/kg compared to corresponding vehicle group; Fig. 3C). None of the animal in untreated control group died.

Given that at a dose of 500 mg/kg, ON 01210.Na demonstrated greater radioprotection following administration by SC (92.9% survival) as well as oral (78.6% survival) routes, this dose was chosen for further investigation into the radioprotective properties of ON 01210.Na. When survival was compared between ON 01210.Na (500 mg/Kg) and vehicle treated groups after 7.5 and 8 Gy of whole body radiation, a distinct survival advantage effect of the drug was observed in the SC group (71.4% for 7.5 Gy and 64.3% for 8 Gy; p < 0.006 for 7.5 Gy and p < 0.0006 for 8 Gy compared to respective vehicle groups) (Fig. 4A & B) as well as oral group (71.4% for 7.5 Gy and 57.1% for 8 Gy; p < 0.001 for 7.5 Gy and p < 0.002 for 8 Gy compared to respective vehicle groups) (Fig. 4C & D). These findings clearly demonstrate that the ON 01210.Na-mediated radioprotection is independent of its route of administration.

Comparable protective effect of ON 01210.Na on the hematopoietic system

Peripheral white blood cell (WBC) counts at 7 days after radiation showed similar decreases among the SC experimental groups presented. However, at 14 days significantly (p < 0.02 compared to vehicle treated group) enhanced

![Fig. 2. Dose response of ON 01210.Na after subcutaneous administration. Subcutaneous dose response after 7.5 Gy radiation. A) ON 01210.Na dose response survival plots are compared to survival in radiation only group 30 days post-radiation. B) Survival in vehicle treated groups is compared to radiation only group 30 days post-radiation. C) SC dose response curve of ON 01210.Na and vehicle treated groups.](image-url)
Fig. 3. Dose response of ON 01210.Na after oral administration. Oral dose response after 7.5 Gy radiation. A) ON 01210.Na dose response survival plots are compared to survival in radiation only group 30 days post-radiation. B) Survival in vehicle treated groups is compared to radiation only group 30 days post-radiation. C) Oral dose response curve of ON 01210.Na and vehicle treated groups.

Fig. 4. ON 01210.Na mediated protection from radiation toxicity. Survival after SC or oral ON 01210.Na (500 mg/kg) and exposure to 7.5 Gy or 8 Gy of radiation. A&B) Percent survival at 30 days for SC ON 01210.Na after exposure to 7.5 or 8 Gy of radiation. C&D) Percent survival at 30 days for oral ON 01210.Na after exposure to 7.5 or 8 Gy of radiation. Results are compared to respective vehicle groups.
recovery was observed in the ON 01210.Na treated group and by 21 days about 70% of the normal count (8.01 × 10^3 per μl of blood) was restored in the drug treated group (Fig. 5A). In the vehicle treated group, although we did not see significant protection (p > 0.05 compared to radiation only) at 14 days, we did observe greater recovery than the radiation only group (p < 0.01) at 21 days after radiation. However, WBC counts in the vehicle treated group were significantly (p < 0.01) lower than the ON 01210.Na treated group. A similar trend in WBC count (49 and 60% in ON 01210.Na treated vs. 22 and 47% in vehicle treated at 14 days and 28 days; p < 0.05 for both the time points) was also observed after oral administration of ON 01210.Na (Fig. 5B), and enhanced recovery in WBC count in the oral group was comparable to the SC group.

The degree of reduction in peripheral neutrophil count is directly related to the risk of systemic infection and lethality after exposure to ionizing radiation.22,23 The protective effect of ON 01210.Na was also observed in peripheral absolute neutrophil counts (ANC) and absolute monocyte counts (AMC) (Fig. 5C & D). Compared to the vehicle groups, significantly higher neutrophil (p < 0.02 for SC and oral) and monocyte (p < 0.04 for SC and oral) counts were observed, and the counts were similar in the SC and oral dosing groups both at 7 days and at 14 days. Platelets are important not only for blood clotting but also for innate and adaptive immunity. Both at 7 days (40% in vehicle groups vs. 60% in ON 01210.Na treated mice; p < 0.04) and at 14 days (about 30% in vehicle groups vs. about 47% in ON 01210.Na treated mice; p < 0.05) platelet counts were higher.
in ON 01210.Na treated groups after 5 Gy radiation, and counts showed similar trends for both the SC and the oral treatment groups. Comparative radioprotective properties of SC and oral ON 01210.Na were further confirmed by the GM-CFU assay. The number of colonies in ON 01210.Na administered via either route was similar across all the time points tested (Fig. 6). A significantly higher number of colonies were observed in all the ON 01210.Na treated mice compared to vehicle treated groups (p < 0.05 for 7 days, p < 0.004 for 14 and 21 days compared to respective vehicle groups).

**DISCUSSION**

ON 01210.Na (Ex-RAD) is a novel small molecule being developed by Onconova Therapeutics as a radiation protection agent. The initial indication is for use by first responders and soldiers in the battlefield, as a prophylactic measure in radiation emergencies. In a previous study, the effect of formulation and route of administration on the systemic availability of ON 01210.Na was evaluated across individual species (rat, rabbit, dog, monkey). The results demonstrated that a subcutaneous polyethylene glycol (PEG)-based formulation resulted in high systemic exposure of ON 01210.Na. Furthermore, good oral bioavailability was obtained with this formulation in rabbits, dogs and monkeys, suggesting that development of an orally administered formulation is feasible. Given the distinct advantages of oral delivery for protecting a large at-risk human population, the present investigation evaluates the pharmacokinetic profile and survival advantage of ON 01210.Na upon oral administration and compares the results to SC administration in mice.

Exposure to ionizing radiation and consequent risk to human health may occur from diagnostic and therapeutic procedures as well as from occupational and accidental causes. It has been more than six decades since cysteine was tested as a radioprotector in animals, and yet we do not have an oral agent approved to protect humans from radiation toxicity. The present investigation demonstrated that prophylactic oral administration of ON 01210.Na had similar survival advantage to the SC route of administration in mice exposed to lethal doses of radiation. ON 01210.Na, with potential for prophylactic use against radiation injuries in humans, showed promising results when administered as a SC suspension formulation to mice. Therefore, the current study aims to move from ‘bench to bedside’ with an ON 01210.Na solution formulation that could be administered via the SC or oral route. The results of this study clearly show that oral prophylactic administration of ON 01210.Na provides a survival advantage to mice from lethal effects of ionizing radiation comparable to SC administration. Interestingly, in contrast to SC, oral doses of 100 mg/kg ON 01210.Na were protective when administered 24 h and 15 min before irradiation. We also take note of the fact that even in the vehicle treated group we see some degree of protection from radiation toxicity both in the survival as well as in the blood cell count experiments. This could be because the formulation has polyethylene glycol 400, which has shown to have marginal radioprotective effect. However, it is important to note that in all the experiments the drug (ON 01210.Na) has shown significantly greater protection than the vehicle in both the oral and the SC groups. Taken together, our oral and SC dose response studies clearly demonstrate that the ON 01210.Na doses of 250 mg/kg and 500 mg/kg provide survival advantage when exposed to lethal doses of radiation (7.5 and 8 Gy) and supports earlier observations by Ghosh et al.

The results of radioprotective experiments correlated well with the pharmacokinetic studies, which demonstrated that the current ON 01210.Na formulation was well absorbed following oral and SC dosing. Although the rate of absorption was faster following oral administration, resulting in higher Cmax values, overall exposure (AUC) was comparable for both dosing routes. Overall, this investigation demonstrated that the relative bioavailability of ON 01210.Na was similar following oral and SC administration, and this was associated with comparable survival advantage in mice. These findings suggest, therefore, that the pharmacokinetic profile and drug administration regimen are important determinants of drug efficacy for ON 01210.Na.

Compromised immunity resulting in infection, weakness, and fatigue is associated with whole body radiation doses of 1 Gy and above. This is in part due to a decline in peripheral WBC and platelet count, and death may follow if bone marrow failure occurs due to damage-induced demise of hematopoietic stem cells. The current study employed radiation doses (7.5 and 8 Gy) that were within the hematopoietic toxicity range. Therefore, it is expected that the radioprotectant would exert protective effects on bone marrow cells for a definite survival advantage. Results from additional in vivo studies in the form of WBC and platelet counts and GM-CFU not only support observed survival advantage but also indicate that such benefit is mediated via preferential protection of hematopoietic system by ON 01210.Na administered via either route. It is interesting to note that accelerated recovery in the oral ON 01210.Na groups is of distinct advantage and is comparable to recovery in the SC groups. While additional studies will be required to determine the molecular pathways involved in ON 01210.Na mediated protection of hematopoietic system, our results have the definite indication that the current ON 01210.Na formulation holds better clinical promise as an orally administrable agent. We show for the first time that ON 01210.Na with comparable bioavailability to the SC route and two-dose administration schedule is a viable option as an oral radioprotectant. The availability of ON 01210.Na as an oral radioprotective agent in our arsenal.
against radiation toxicity would not only offer better patient compliance, but would also allow responsible agencies the ease and convenience of distribution among the at-risk population for prophylactic use under conditions of nuclear accidents, warfare, or terrorist threat.

CONFLICT OF INTEREST STATEMENT

Drs. Ramesh Kumar, Manoj Maniar, and Chen Ren are employed at Onconova Therapeutics, Inc. No other authors have financial obligations to Onconova Therapeutics, Inc.

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