TITULO: ANTITUMOR EFFICACY, PHARMACOKINETIC AND BIODISTRIBUTION STUDIES OF THE NEW ANTICANCER PEPTIDE CIGB-552 IN MOUSE MODELS

Authors: Brizaida Oliva, Gilmara Pimentel, Ania Cabrales-Rico, Julio Garza, Osmani Mendoza, Yolanda Gomez, Tais Basaco, Iraida Sánchez, Carlos Calderón, Juan C. Rodriguez, Maria Rivera Markelova, Iduna Fichtner, Soledad Astrada, Mariela Bollati-Fogolín, Hilda E. Garay , Osvaldo Reyes and Maribel G. Vallespí

Introduction

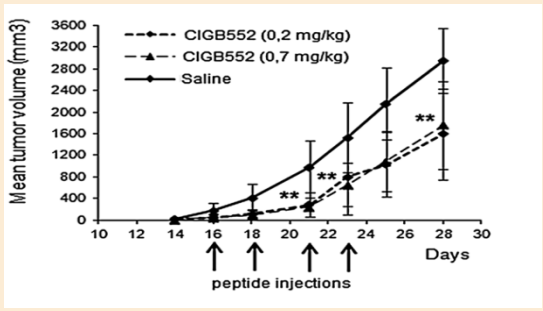
By screening a peptide library corresponding to the Ala-scanning of the antimicrobial peptide LALF32–51 [18,19], a novel antitumor peptide (L-2) that lacks the ability to bind LPS and exhibits cytotoxic activity on tumor cells was identified. By modification in the primary structure of L-2, a second-generation peptide (CIGB-552) was developed. The cytotoxic activity of the peptide CIGB-552 in cancer cells involves an increase in the levels of the protein COMMD1 and a negative regulation of the pathway of NF-κB. In this study, the antitumor efficacy, pharmacokinetic and biodistribution of CIGB-552 in mouse tumor models has been explored.

Methods

We investigated the pharmacokinetic and biodistribution of the peptide ^{131}I-iodine labeled-CIGB-552 by subcutaneous administration of this peptide in a therapeutic schedule in murine model of tumor CT-26 in BALB/c mice. Also, the histological analysis of the kidney and liver tissues after subcutaneous CIGB-552 administration was performed in mice as preliminary toxicological criteria. Further, for evaluating the anticancer effect of CIGB-552 *in vivo* conditions, we administrated the peptide CIGB-552 in both syngeneic murine tumors and patient-derived xenograft models

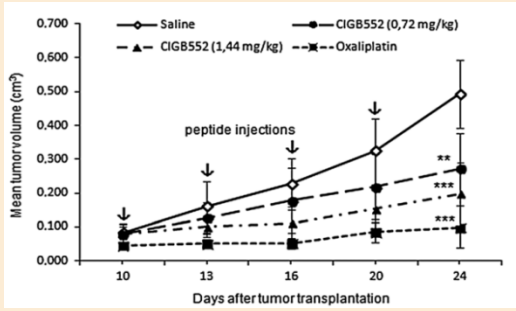
Results

Antitumor Effect of CIGB-552 in the murine CT-26 model



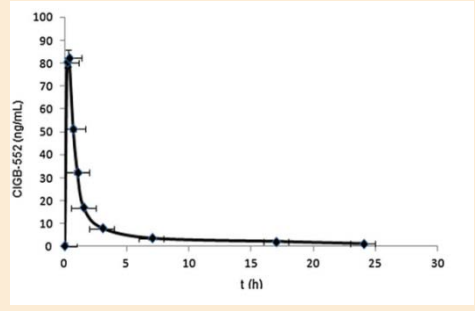
Different doses of CIGB-552 or saline were systemically administered s.c. for 2 weeks (represented by arrows). The mean of tumor mass volume registered until day 47. The respective standard deviations of the mean of tumor mass volume are represented.

Antitumor Effect of CIGB-552 in human HT29 model

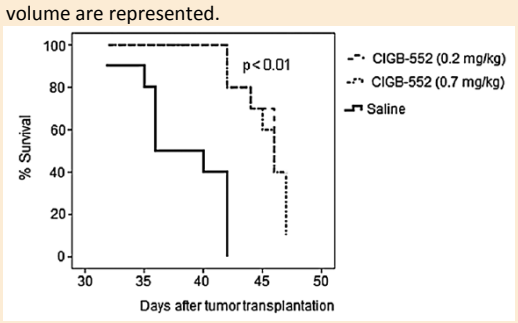


Different doses of CIGB-552 or saline were systemically administered s.c. for 2 weeks (represented by arrows). The mean of tumor mass volume and the respective standard deviation from the human HT-29/nude tumor model.

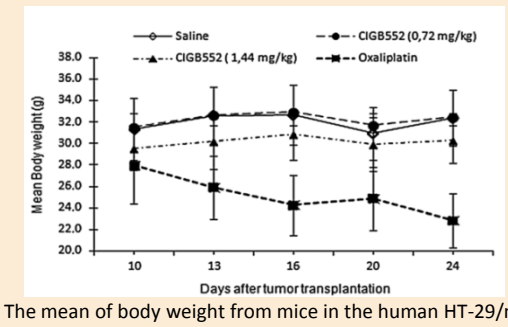
Pharmacokinetic and biodistribution of CIGB-552



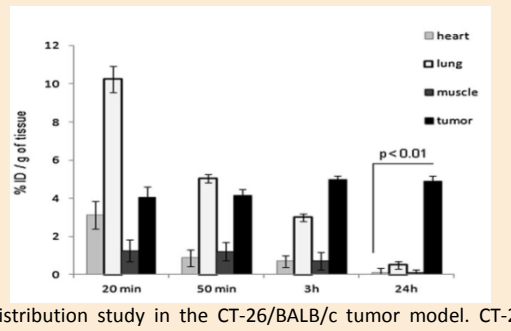
Blood concentration versus time profile following subcutaneous administration of 5 µg of ^{131}I-iodine labeled-CIGB-552. The values represent the mean SD of n = 3 for all time points.



Kaplan–Meier curves of survival registered until day 47 from the murine CT-26 model



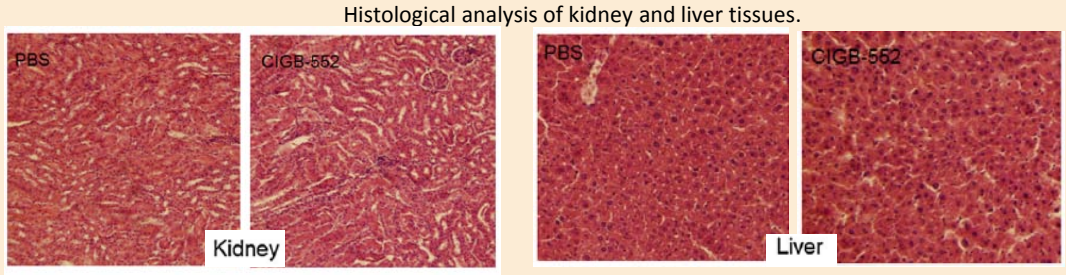
The mean of body weight from mice in the human HT-29/nude tumor model.



Biodistribution study in the CT-26/BALB/c tumor model. CT-26 tumors in BALB/c mice were allowed to growth to a volume of 100 mm3, and 0.2ml of CIGB-552 (0.2 mg/kg) labeled with ^{131}I was injected via s.c.

Elimination of the radiopeptide appeared to be performed through the kidney and liver. CIGB-552 treatment did not alter the architecture of the kidney and liver tissues, which suggests that the transient CIGB-552 deposit in these organs is innocuous.

Histological analysis of kidney and liver tissues.



Three BALB/c mice received one injection of CIGB-552 (5 µg) or PBS. The kidney, liver and other organs were collected, immediately fixed in 10% formalin (pH 7), paraffin embedded and sectioned into 5 µm for histochemical analysis. Subsequently, the dewaxed and alcohol-hydrated sections were stained with hematoxylin–eosin, dehydrated and mounted in Histomount (Zymed Laboratories, San Francisco)

Conclusions

Our data provide a proof of concept that this cytotoxic peptide behaves as antineoplasic agent when it is systemically administered in both human and murine tumors implanted in mice. Furthermore, the pharmacokinetic and biodistribution studies demonstrate a relatively significant in vivo stability that may represent an advantage for its potential systemic administration. Thus, this report becomes the first of its kind describing the antitumor effect elicited by a peptide that targets COMMD1 for stabilization and supports the potential of CIGB-552 for targeted anticancer therapy.

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