Detection and improvement of anti-angiogenic therapeutic efficacy by using Hemodynamic Response Imaging in mice

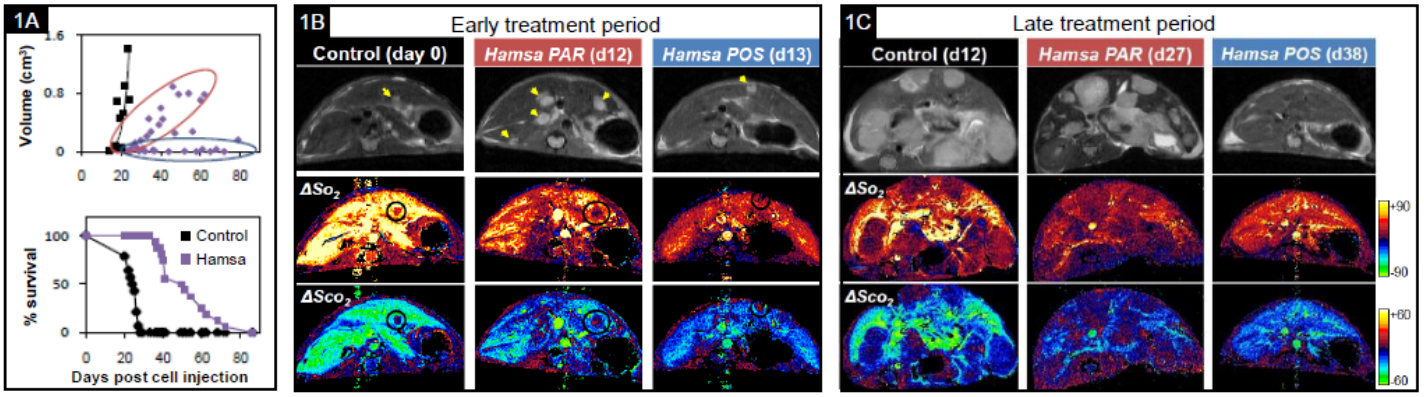
Y. Edrei[1,2], E. Gross[3], N. Corchia[1], E. Dery[1], S. Ben-Sasson[4], and R. Abramovitch[1,2]

[1]The Goldyn Savad Inst. for Gene Therapy, Hadassah Hebrew University Medical Center, Jerusalem, Israel, [2]MRI/MRS lab HBRC, Hadassah Hebrew University Medical Center, Jerusalem, Israel, [3]Pediatric Surgery, Hadassah Hebrew University Medical Center, [4]Experimental Medicine & Cancer Research, The Hebrew Universioty Hadassah Medical School

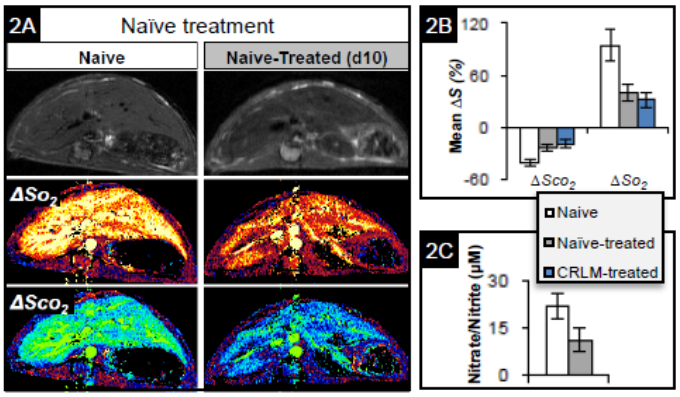
Background & Aims Tumor response to therapy is usually assessed by measurements of tumor size. Since anti-angiogenic therapies may not lead to substantial tumor mass reduction, their effect is better imaged using perfusion sensitive techniques. Furthermore, patients frequently have markedly different responses to the same therapy. Therefore, identification of new noninvasive monitoring techniques for assessing tumor response earlier is a major need in this field. Recently, we demonstrated the feasibility of *Hemodynamic Response Imaging* (*HRI*), an fMRI method combined with hypercapnia and hyperoxia, for monitoring changes in liver perfusion and hemodynamics[1,2]. In the present study, we aimed to understand the early vascular and perfusion changes involved in colorectal liver metastases (CRLM) during a novel anti-angiogenic therapy (*Hamsa*), in order to assess the therapeutic efficacy earlier and to further improve the therapeutic potency of the anti-angiogenic therapy accordingly.

Methods: CB6F1 mice underwent splenic injection with CT-26 colon cancer cells to generate liver metastases. Mice were treated by daily i.p. injections of "*Hamsa",* a novel treatment based on the combination of low-dose cytotoxic agent, COX1 inhibitor, a histamine type-2 receptor antagonist and hypoxia-like inducing agent. Treatment was started on the day of tumor appearance in T_2W images (day 15±2). Tumor progression was monitored by MRI on a 4.7T Bruker Biospec spectrometer. Tumor assessment was done using T_2W FSE images (TR/TE=2000/40ms). Changes in hepatic hemodynamics were evaluated from T_2*W GE (TR/TE=147/10ms) images acquired during breathing of air, air-CO_2 (5%), and carbogen as described[1]. Data analysis was performed using IDL software. *HRI* maps are given as the percentage of signal intensity change (ΔS)[1].

Results: Previously, we demonstrated the feasibility of *HRI* for monitoring changes in liver perfusion during CRLM development[3]. Analysis of tumor growth kinetics showed that *Hamsa* treatment delayed tumor progression and prolonged mouse survival significantly (Fig 1A). The *Hamsa*-treated group could be separated into two patterns of response: (*i*) partial response (PAR) and (*ii*) positive response (POS) (Fig. 1A). In the PAR-group, tumor progression was delayed for a period of 20 days in average (Fig. 1A). Subsequently, the metastases started to grow and additional CRLM developed. In the POS-group, the CRLM were eradicated for more than two months. The hemodynamic changes that occurred during *Hamsa* therapy were assessed using *HRI*. During the first 2 weeks of *Hamsa*-therapy, in the PAR-group, the ΔS values in the tumors were similar to those observed in the control-treated mice (Fig 1B), while in the liver parenchyma, a slight decrease of the ΔS values was observed. In contrast, in the POS-group, an acute decrease of the ΔS values in the entire liver was observed (Fig. 1B). During the late tumor growth phase, in the control-treated mice, *HRI* maps clearly highlighted the metastases from the remaining liver (Fig. 1C). In contrast, in the PAR-group, the lesion borders became blurred and there was a significant decrease in ΔS values in the entire liver[4]. In the POS-group, during the prolonged chronic treatment, the *HRI* maps of the entire liver remained attenuated (Fig. 1C).



The mechanisim for the differential effects of *Hamsa* therapy, seems to be related to the reduced perfusion in the entire liver parenchyma. Thus, we treated naive mice (without tumors) with *Hamsa* and assessed liver hemodynamic using *HRI*, and DCE-MRI. In the *HRI* maps an acute decrease of the ΔS values in the entire liver was observed after 10 days of treatment and remained low for at least month. This attenuation resembled the *HRI* of POS-group (Fig.2A,B,1C). Results from DCE-MRI revealed delay of the contrast agent kinetic parameters in the liver's big vessels. We suspected that *Hamsa* can affect nitric oxide (NO) levels. Indeed, significant decrease of NO serum levels was revealed in the *Hamsa*-treated mice compared to naive mice (Fig. 2C).



Conclusions In this study, we have shown that "*Hamsa"* treatment reduced tumor growth and thus prolonged mice survival. Moreover, the *HRI* method helped to distinguish between two types of treatment response and thereby assist to understand the underlying mechanisim of *Hamsa* which will help to improve the therapeutic potency of *Hamsa.*

References: *[1]Baras H, Radiology 243(3),2007; [2]Barash H, Hepatology 48(4) 2008; [3]Edrei, #1752, ISMRM[2006]; [4]Edrei, #1027, ISMRM[2009];*