

MRI-guided focused ultrasound  
hyperthermia:  
Translation to a clinical platform and potential  
applications

Rajiv Chopra

Radiology, UT Southwestern Medical Center, Dallas, TX

Acknowledgements

Funding

Cancer Prevention and Research Initiative of Texas (CPRIT, R1308)  
National Institutes of Health (1R01CA199937)  
Evelyn and MR Hudson Foundation

Research Collaborators

Ted Laetsch (Pediatric Oncology), Robert Staruch (Philips Healthcare), Noelle Williams (Biochemistry)

Research Staff

Chenchen Bing, Joris Nofiele, Cecil Futch, Debra Szczepanski, Sumbul Shaikh, Yonatan Chatzinoff, Imalka Munaweera

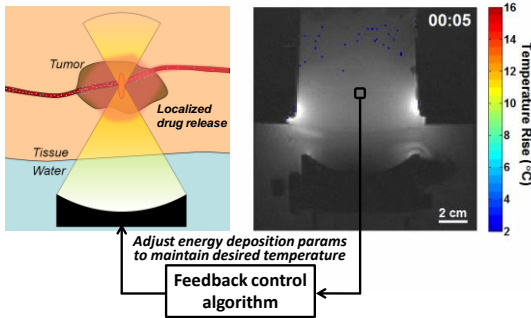
Academic Collaborators

Kullervo Hynynen, Sunnybrook Research Institute

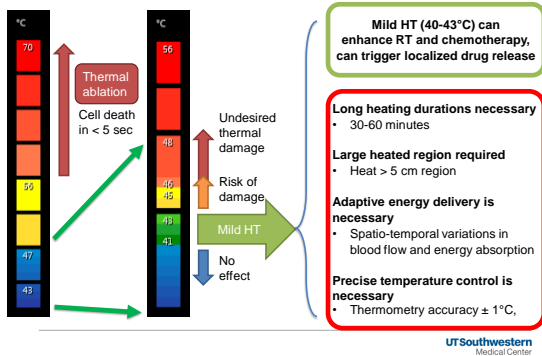
Industrial Partners

Philips Healthcare – on-site personnel, hyperthermia platform  
Celsion Inc – Thermobox®

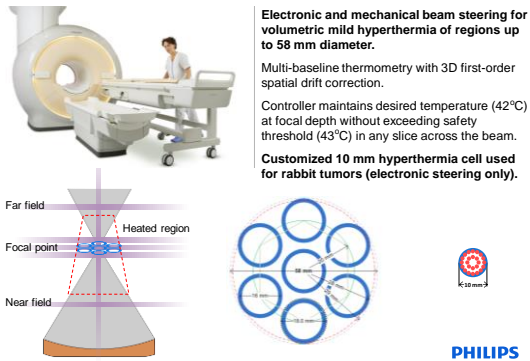
Hyperthermia delivered with MR-HIFU



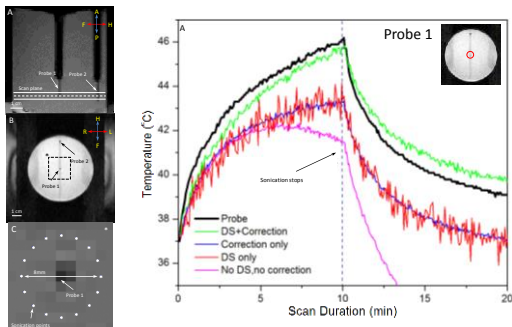
### Benefits and challenges of mild hyperthermia



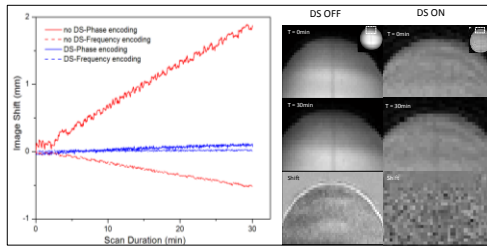
### Clinical hyperthermia platform using MR-HIFU



### Pushing MR thermometry to the limit!

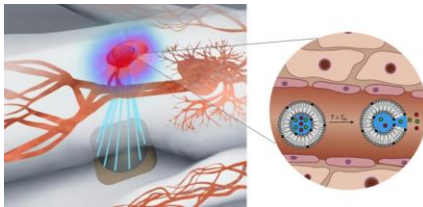


### Pushing MR thermometry to the limit!



- Monitoring of hyperthermia with MR thermometry is feasible
- Existing correction algorithms for ablation are NOT sufficient for HT
- Combination of prospective corrections (for image shift) and retrospective higher order polynomial drift corrections are necessary to achieve accuracy within 1°C
- Pre-heating the magnet with a 5-10 minute acquisition improves performance of corrections!

### Application: Hyperthermia mediated drug delivery



Thermosensitive liposomes containing anticancer drugs (I.e. Thermodox)

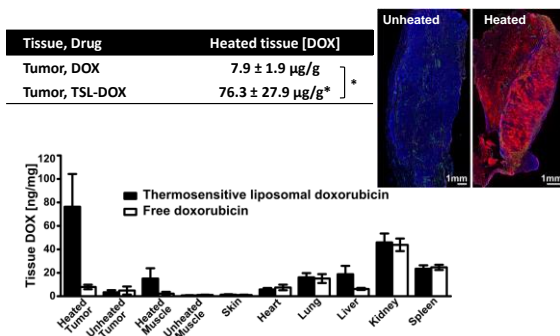
Relatively stable for 1-2 hours in bloodstream,

Rapidly release drug when passing through tissue heated above 41°C,

Prolonged heating allows continuous release for enhanced cellular uptake.

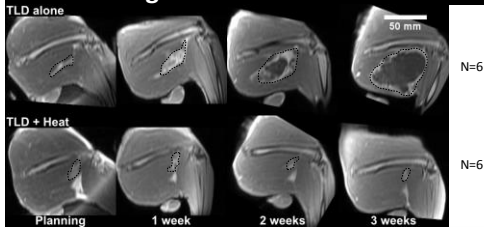
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### Enhanced drug deposition in heated tissue

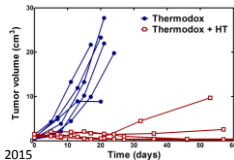


Staruch et al 2010, 2012

## VX2 tumor growth after Thermodox + HT



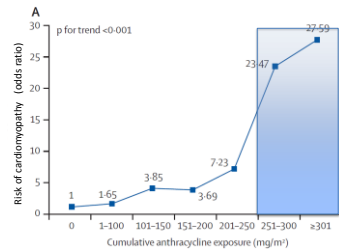
1.67 mg/kg of Thermodox (TLD), administered only once!



Staruch et al, International Journal of Hyperthermia 2015

## Applying localized drug delivery to pediatric cancer

- Doxorubicin is used for the treatment of vast majority of pediatric solid tumors
- Often used prior to surgery or radiation for local control
- 40% of childhood cancer survivors have severe or life-threatening health disorders
- Cardiac toxicity is one of the most common and debilitating of these side effects



Blanco et al, J Clin Oncology 2015

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## Preclinical studies on HT-mediated drug delivery

Does longer heating time increase DOX in tumor more than heart?

Does lower injected dose reduce DOX in heart more than tumor?

Can MR-HIFU safely deliver mild HT to soft tissue and bone?

## Study Methods

Rabbit bilateral Vx2 tumor model

Thermodox®, 2.5 mg/kg infused over 5-6 minutes at start of heating

Exposure durations of 10, 20, 40 minutes of mild hyperthermia (42°C)

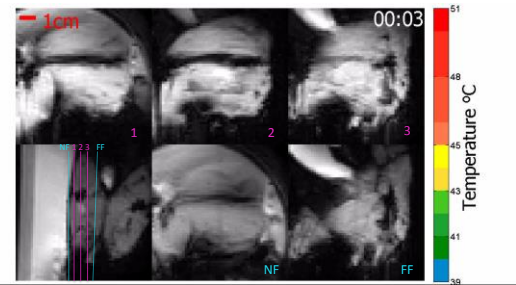
All hyperthermia performed using the clinical platform

Animals sacrificed 30 minutes after end of heating and perfused to remove free drug

DOX measured using fluorimetry

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MR-HIFU hyperthermia in rabbit tumor

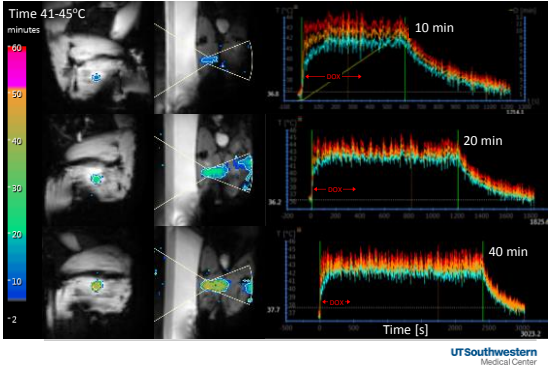


Temperature in 10 mm diameter region kept at 42°C for 40 minutes (1.2 MHz, 60W).  
Temperature-sensitive liposomal doxorubicin infused during first 6 minutes.

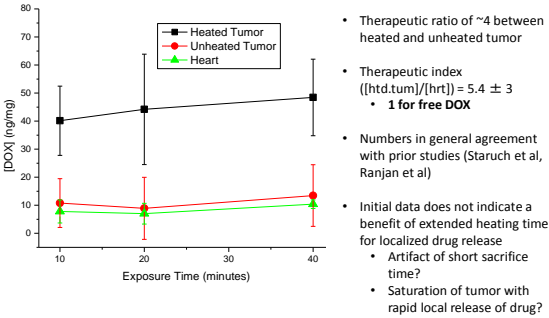
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Heating results: 10, 20, and 40 minutes



Influence of exposure time



## Discussion

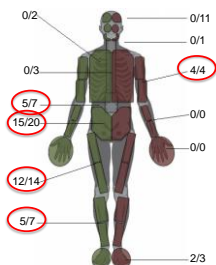
Localized DOX delivery in pediatric cancers could be an important measure to reduce long term cardiac toxicity

Acceptable heating quality for hyperthermia can be achieved using a clinical MR-HIFU hyperthermia system

Localized DOX delivery possible using clinical MR-HIFU system and ThermoDox® in rabbit VX2 model

Stable hyperthermia achieved at 10, 20 and 40 minutes

- Initial analysis suggests longer heating durations do not improve the therapeutic index of DOX



72 Total Tumors, 60% in Treatable Location  
5 year retrospective case review

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Thermosensitive liposomal doxorubicin										
	Heated Tumor	Unheated Tumor	Heated Muscle	Unheated Muscle	Skin	Heart	Lung	Liver	Kidney	Spleen
Rabbit 1-7 HIFU+TSL 2.5mg/kg Ketamine +perfusion										
Larger heating	44.8	2.0	1.1	0.8	-	4.1	11.2	21.6	33.9	23.2
2 hours after heating	78.0	4.0	21.4	1.0	-	5.9	14.7	11.4	51.5	26.1
	71.2	3.8	19.7	0.5	1.1	6.0	22.9	18.7	41.4	18.1
	53.1	2.5	10.5	0.6	1.8	5.7	14.3	15.8	41.6	26.2
	66.4	1.1	10.9	0.4	1.7	4.4	17.5	19.2	45.9	21.8
HIFU+TSL (n=5)	129.1	6.6	27.9	0.9	0.7	7.4	16.4	12.4	56.0	25.3
	91.7	4.1	14.3	0.9	1.3	7.3	15.8	32.7	51.2	23.7
TSL (n=5)										
5mg/kg	76.3 ± 27.9	3.4 ± 1.8	15.1 ± 8.8	0.7 ± 0.2	1.3 ± 0.4	5.8 ± 1.3	16.1 ± 3.6	18.8 ± 7.1	45.9 ± 7.6	23.5 ± 2.9
isoflurane-perfusion	30 ± 9	-	0.7 ± 0.1	2.3 ± 1.3	7 ± 4	11 ± 2	19.8 ± 0.9	6.9 ± 0.2	27 ± 2	27 ± 3
Smaller heating	-	8.8 ± 1.4	-	2.0 ± 0.6	2.1 ± 0.5	7.1 ± 0.4	13.0 ± 0.3	7.8 ± 1.2	47 ± 14	24 ± 4
4 hours after heating										

Ranjan et al, 2012 (5mg/kg, t=4h, partial tumor heating with MR-HIFU)