ThermoDox®
A Lyso-Thermosensitive Liposomal Doxorubicin

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The importance of heating time on the local drug deposition during radiofrequency ablation (RFA) in combination with Lyso-thermosensitive liposomal doxorubicin (LTLD) in a porcine model

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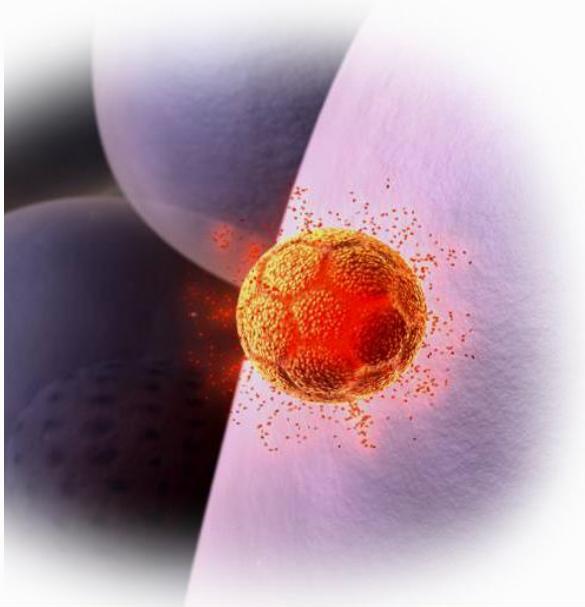
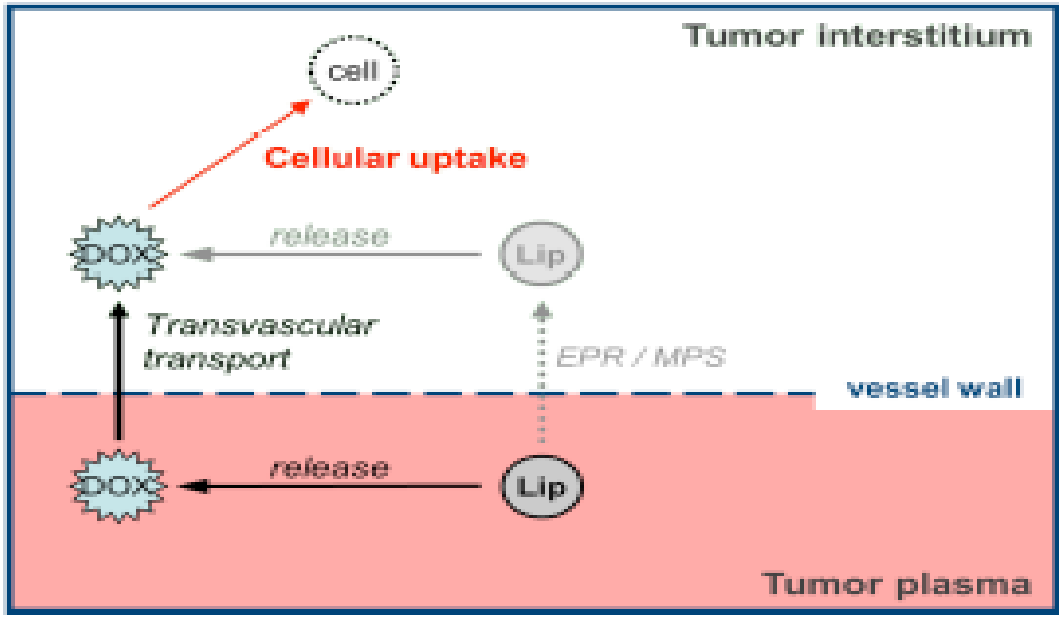
Lyso-Thermosensitive Liposomal Doxorbicin ThermoDox®

- **Nanoparticle** (100nm) which rapidly concentrates in the liver (MPS; Mononuclear Phagocytic System)
- **Enhanced** uptake by tumor due to EPR (Enhanced Permeability & Retention) property of tumors
- **Rapid Diffusion** of cytotoxic doxorubicin into local tissue follows from heating targeted area > 40° C





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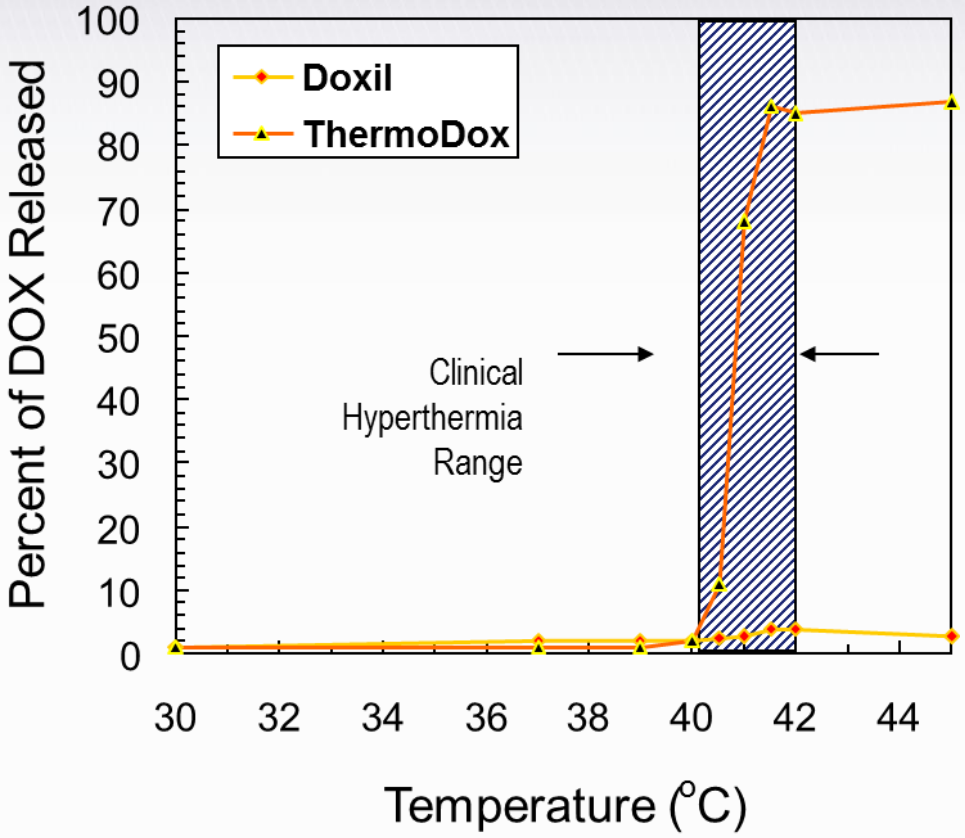
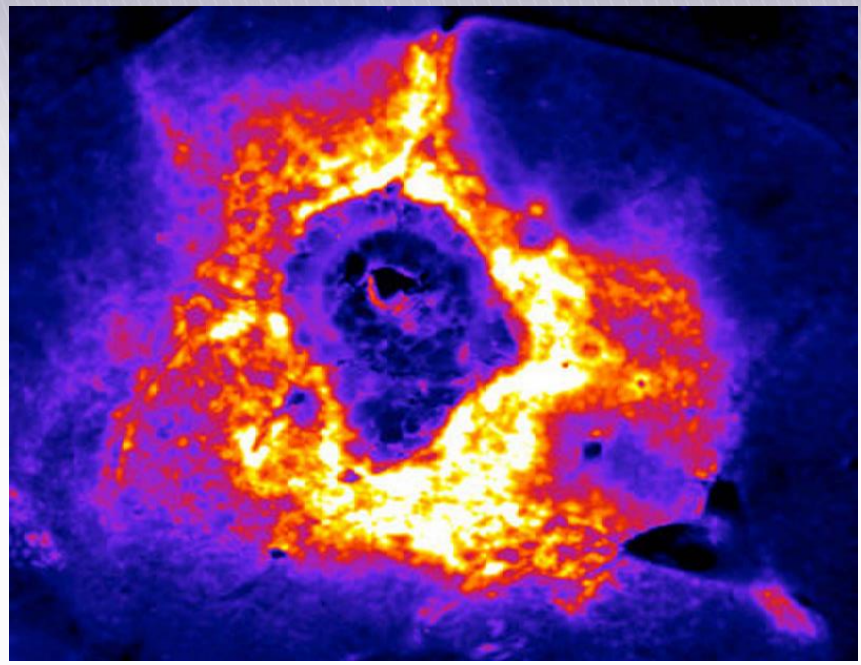
ThermoDox Design Principles In Action





Pig liver single ablation with ThermoDox
Courtesy D. Haemmerich

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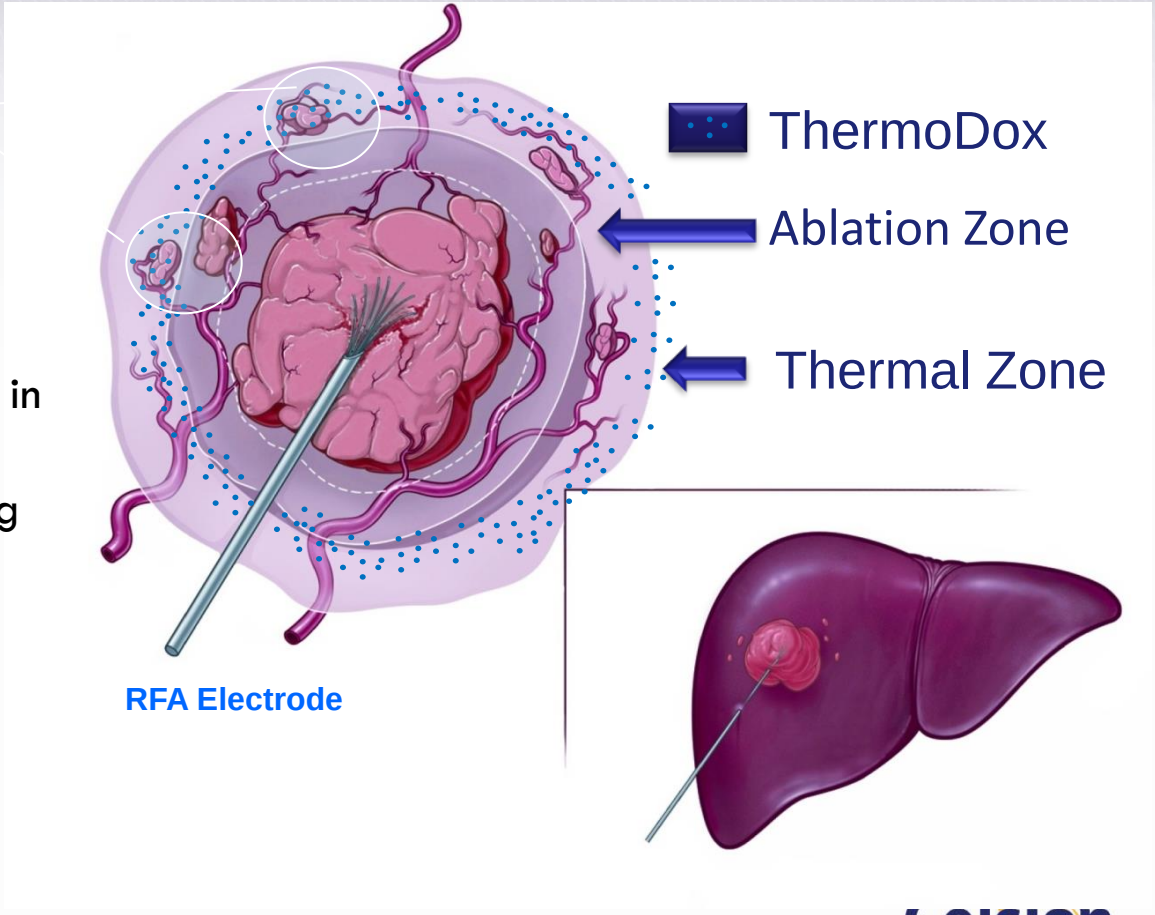
ThermoDox + Liver Ablation

- RFA misses micro-metastases outside ablation zone
- Drug concentrates in the "Thermal Zone"
- Ablation releases doxorubicin in "Thermal Zone" expanding treatment area and destroying micro-metastases



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Methods

Domestic pigs were given a 1.43 mg/kg (~50 mg/m2) iv dose of LTLD and 15 minutes later, the normal liver was subjected to 1, 3 or 6 sequential, overlapping ablations using clinically available RFA generators and probes. This results in RFA dwell times of 15, 45 and 90 minutes respectively. At 15 minutes after the last ablation, the pigs were euthanized and the ablation zones were removed and examined for doxorubicin concentrations by fluorescence imaging.

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Results

Overall, increased heat time from 15 to 45 minutes (and up to 90 minutes) showed an increase in both the amount of doxorubicin deposited (up to ~100 µg/g) and the width of the ablation target margin to which doxorubicin was delivered.

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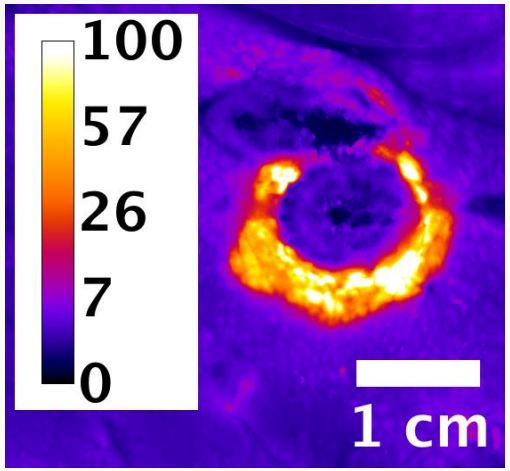
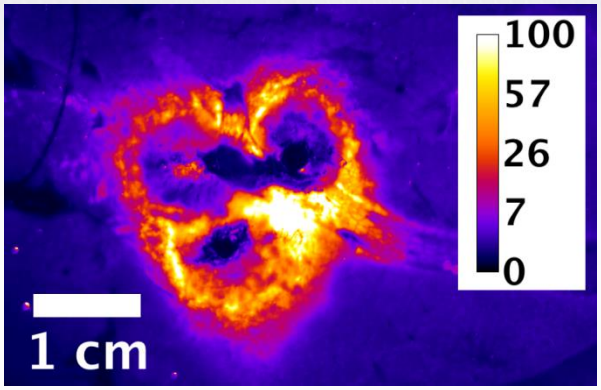
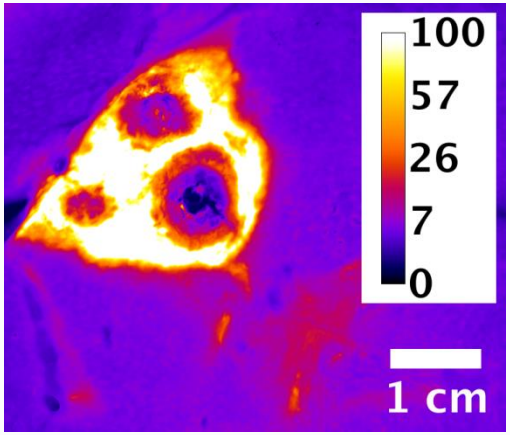
Two Dimensional Fluorescence Mapping of Doxorubicin Distribution in pigs treated with ThermoDox

15 minute

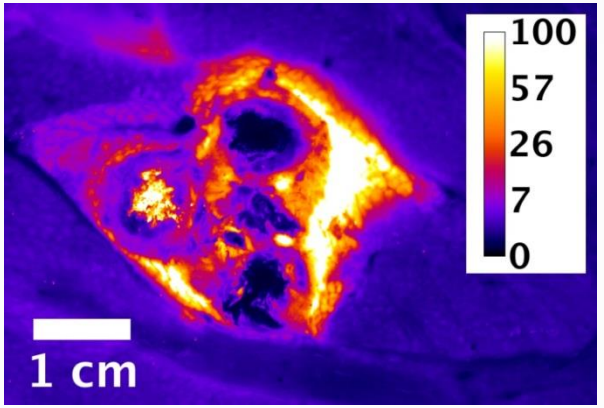


45 minute





90 minute



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Results

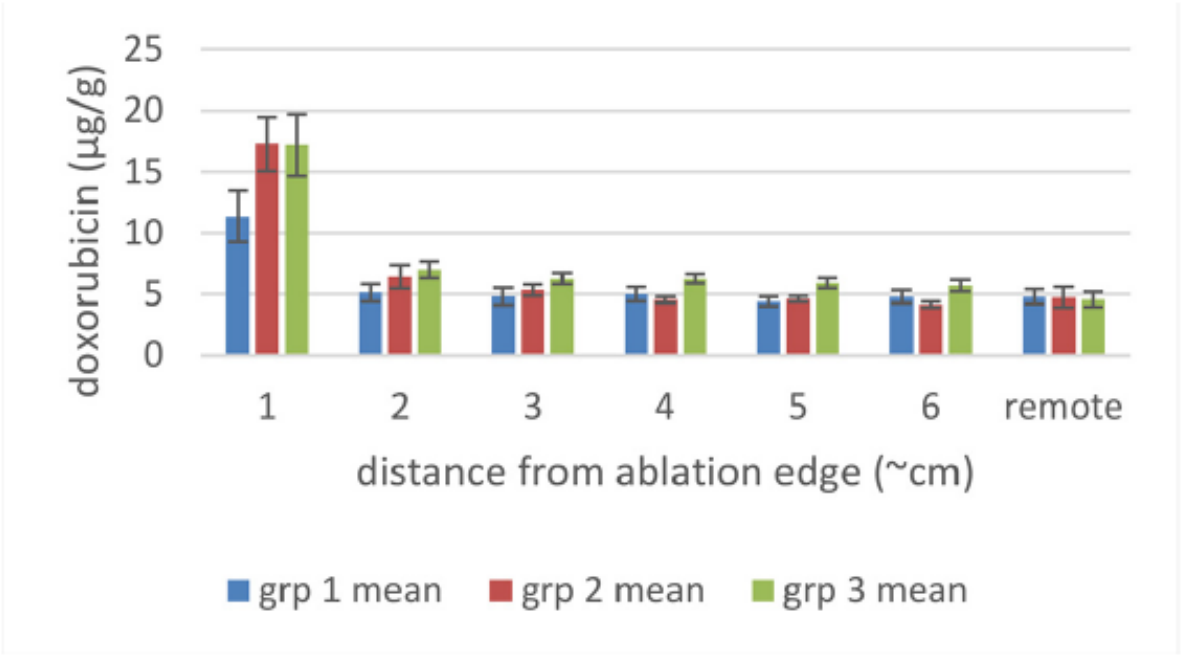
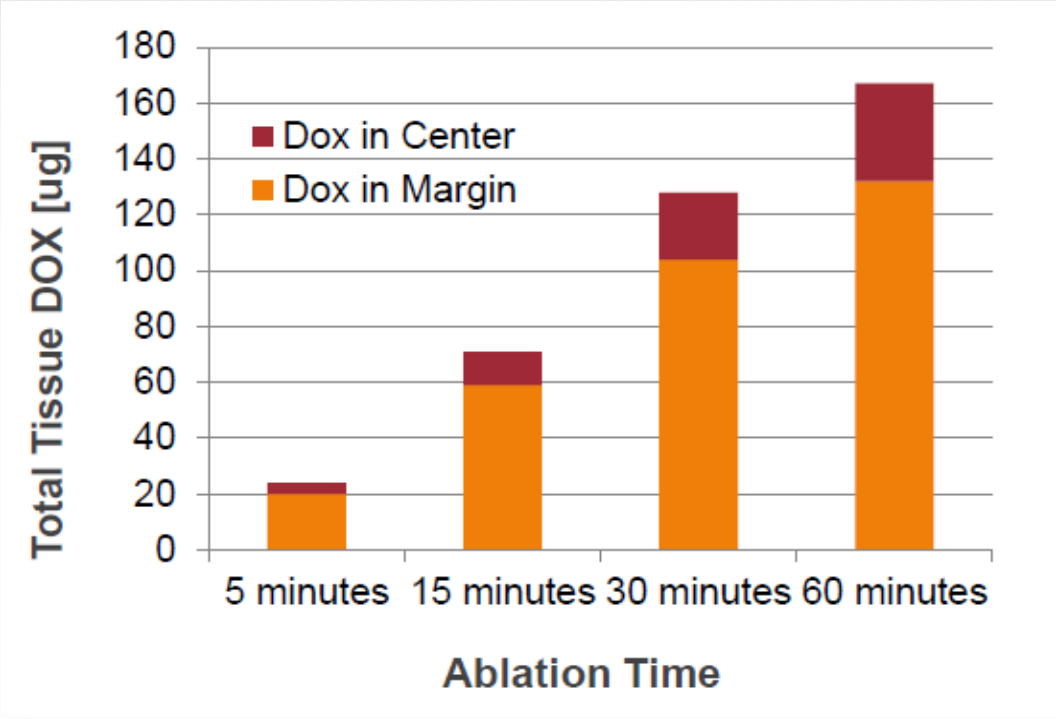


Fig 2. Mean (± SEM) doxorubicin tissue concentrations around the ablation zones of pigs in Study B. Punch biopsies were collected radiating out from the liver ablation zone after 1 (group 1, n = 3), 3 (group 2, n = 3) or 6 (group 3, n = 3) sequential, overlapping ablations using the Covidien device. Distance 1 is just adjacent to the ablation margin and distance 6 is the furthest away from the ablation margin.

Computational Modeling

- Computational model shows that prolonged heating is required in order to achieve optimal tissue concentrations of doxorubicin



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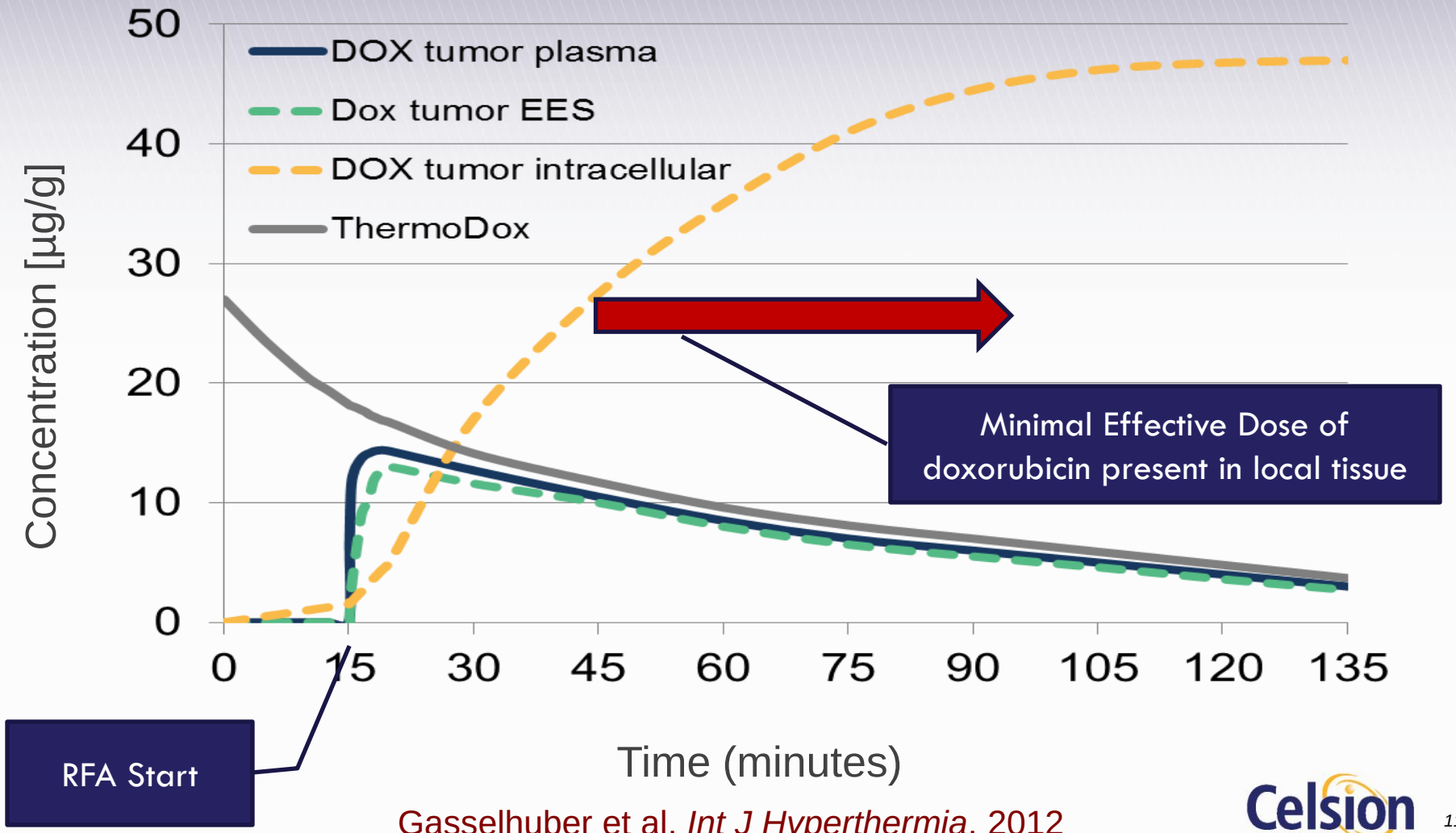
Impact of Mild Hyperthermia on Tissue Deposition



Gasselhuber et al, *Int J Hyperthermia*, 2012

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