Molecular basis of modulated electro-hyperthermia combination with radio- and chemo-therapies

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Introduction: Hyperthermia is mostly a complimentary therapy applied together with conventional radio- and chemotherapies. Our objective is to show the molecular basis of the selectively applied hyperthermia and its interaction with radiotherapy and chemotherapy drugs.

Method: Modulated electro-hyperthermia (mEHT, trade name: oncothermia) is a complementary treatment to conventional tumor-therapies. The impedance-controlled radiofrequency current is amplitude modulated and maximized to selective targeting of the tumor-cells. Biophysical differences between the malignant and healthy cells allow the selective energy absorption in the tumor-volume. There are numerous molecular evidences proving the extreme capability of mEHT to kill the malignant cells while the healthy cells are unharmed. Additional simple compounds like Quercetin, Methotrexate, or Salicylic acid were combined with mEHT.

Results: The applied chemotherapies show synergic combination with the molecular processes of mEHT, and the radiation therapy also show synergy for cell-destruction. Significant tumor-cell death is shown by TUNEL caused by mEHT. Immunohistochemistry and apoptosis protein array proved elevated hsp70 and hsp90 expression extracellularly. The set of molecules in the measured apoptotic processes concluding to immunogenic cell-death (ICD). The abscopal effect is proven by the in-vivo experiment using an intratumoral dendritic cell (DC) injection together with the mEHT. The systemic antitumor effects are proven. The abscopal effect with mEHT works like vaccination. The ionizing radiation combined with mEHT increases the apoptosis significantly (20%) higher than in case of conventional heating, while the autophagy changes 5 times. The oxygenation of the tumor were significantly higher when mEHT was applied with radiation, than in conventional heating. All the combined application with chemo-agents had shown significantly better apoptosis than the same drugs with conventional heating did on the same temperature. The Quercetin helped the caspase independent apoptotic pathway significantly increasing the apoptosis inducing factor and the salicylic acid improved the abscopal effect of melanoma to lung. The preclinical experiments with liposomal doxorubicin also shown significant advantage of mEHT.

Conclusion: Complementary application of mEHT with chemotherapies and radiation therapy showed its significant advantages in preclinical experiments.

ESHO

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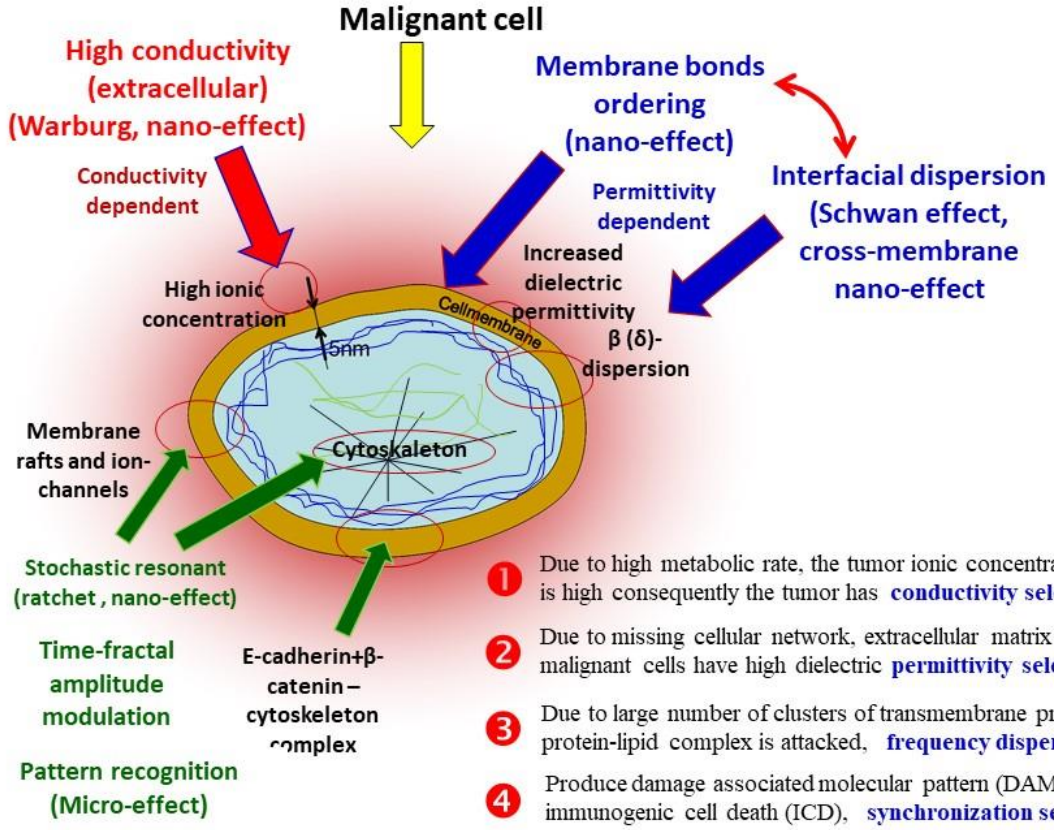
Possible conflict of interest and expertise:

- CEO of company Oncotherm (1988)
- Private docent (associate professor) at Biotechnics Department of St.Istvan University

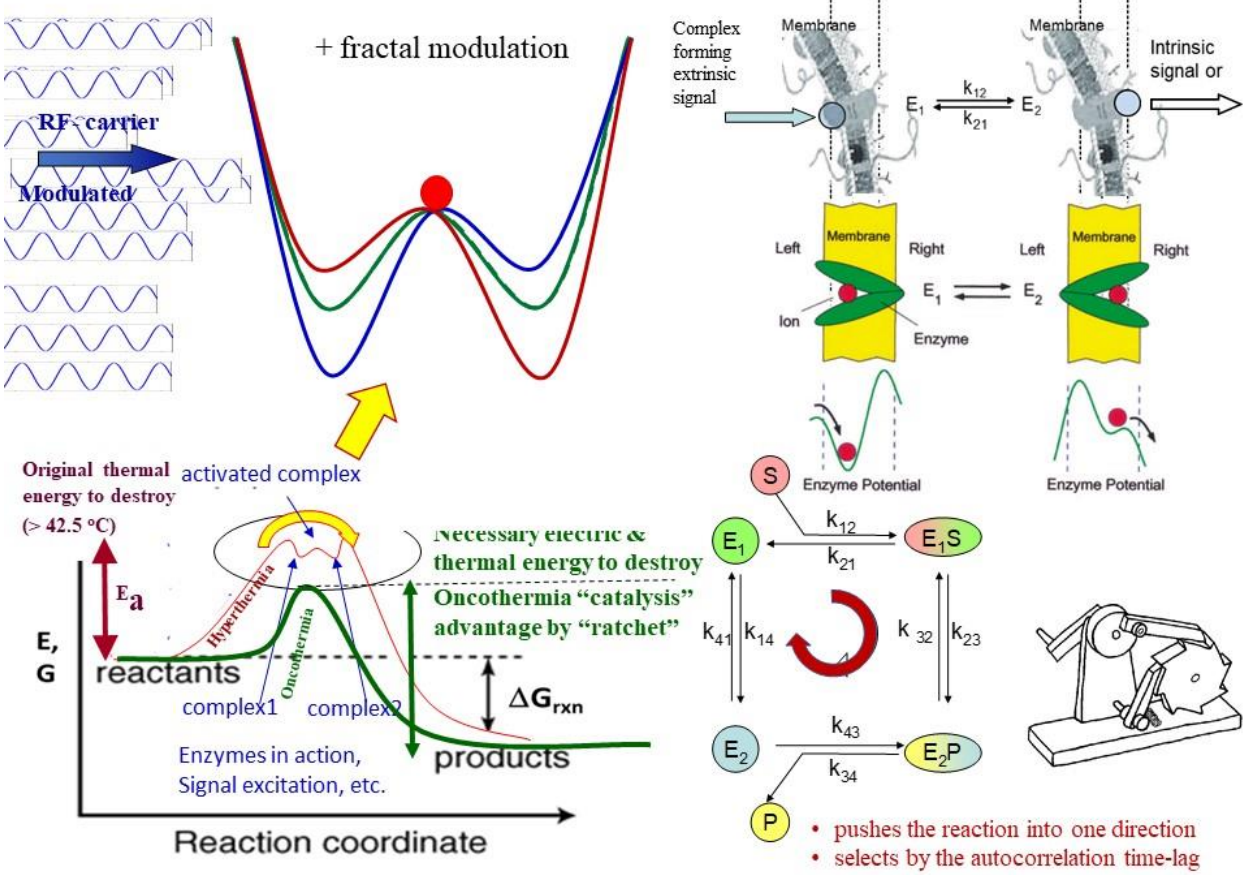
Outline

- ❑ Cellular selection
- ❑ Molecular selection
- ❑ Complementary synergy

Effects of modulated electrohyperthermia (mEHT)



Stochastic resonant "ratchet"



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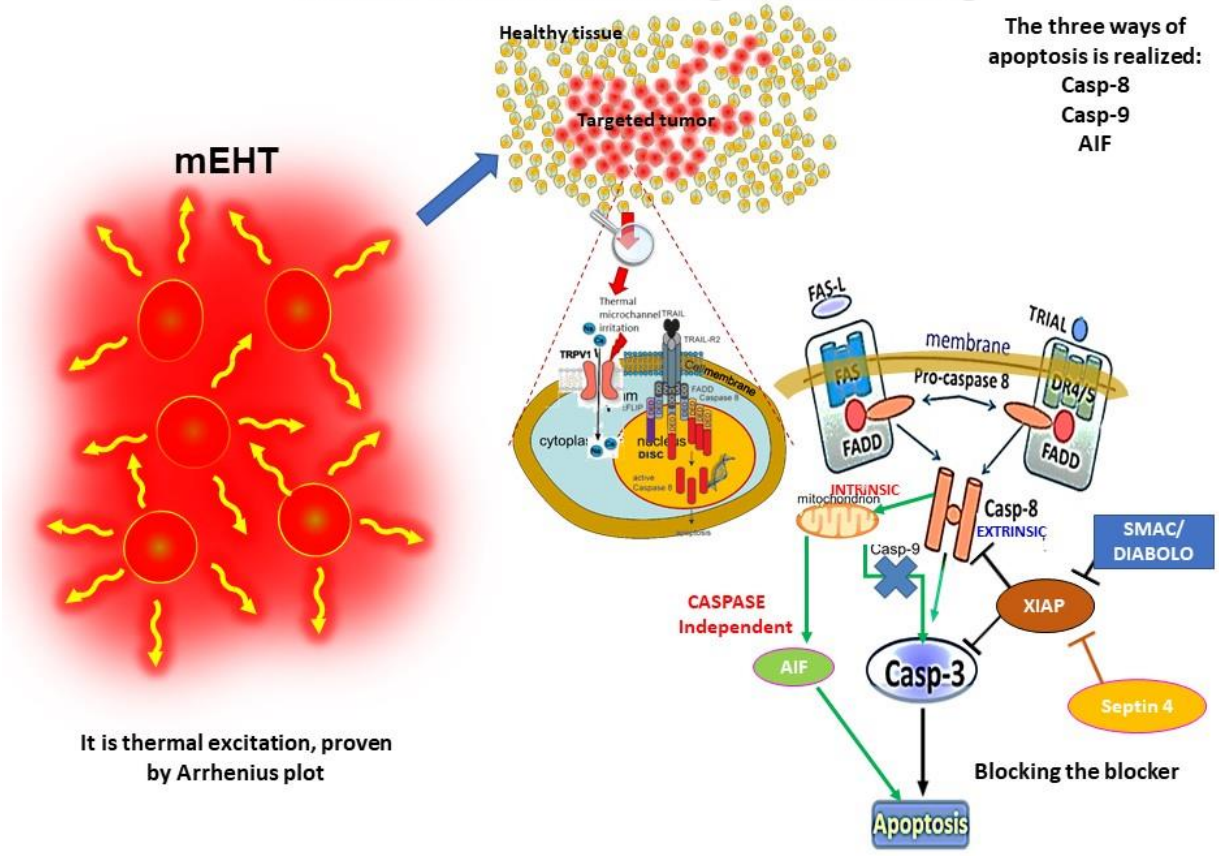
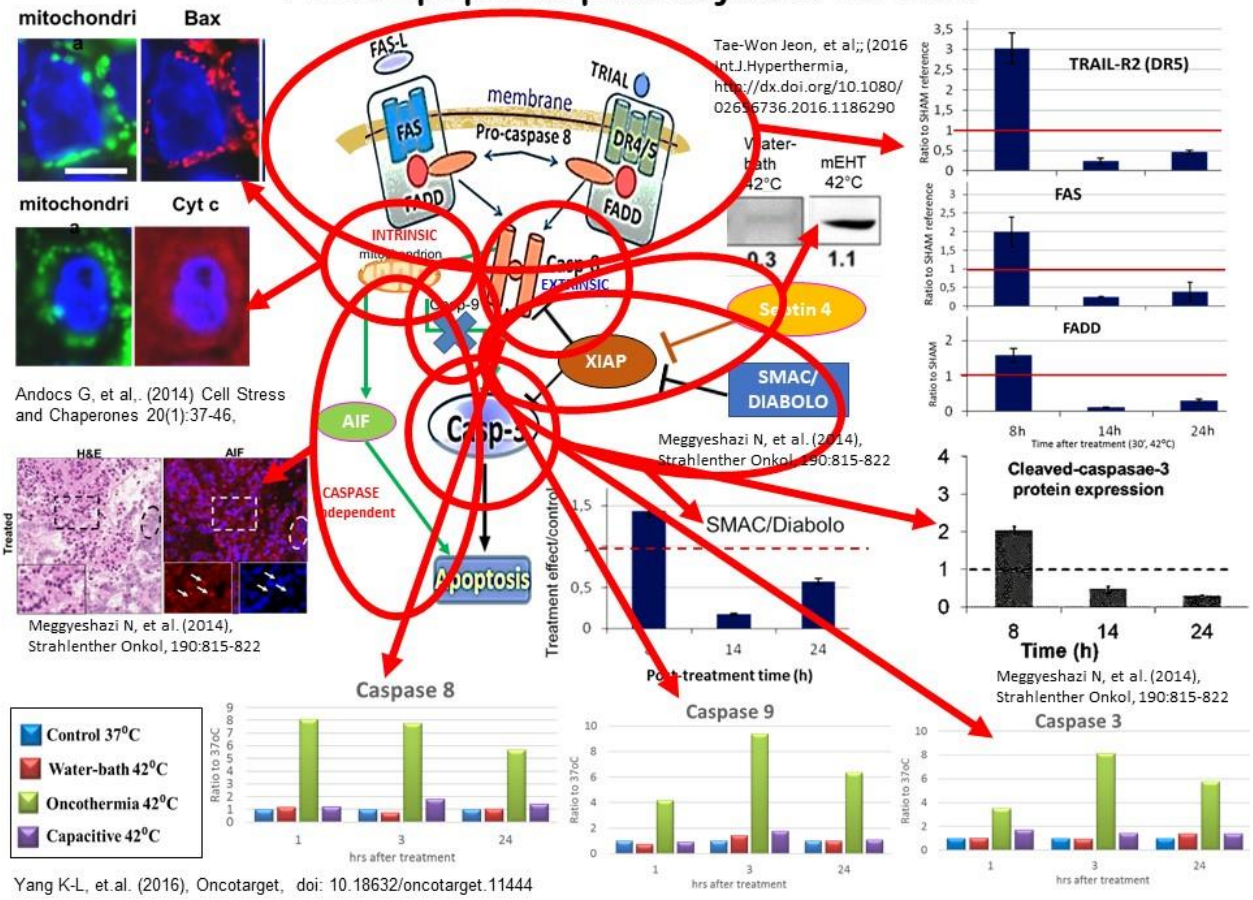
Cellular selective, heterogeneous heating

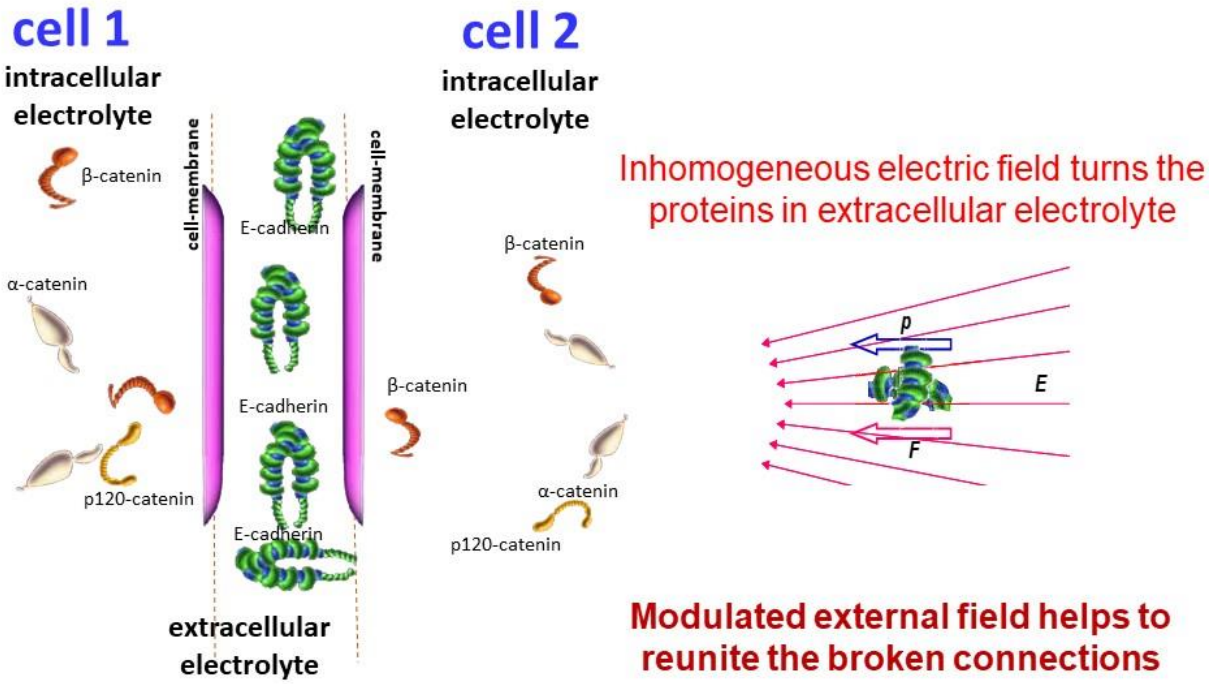


Three apoptotic pathways are verified



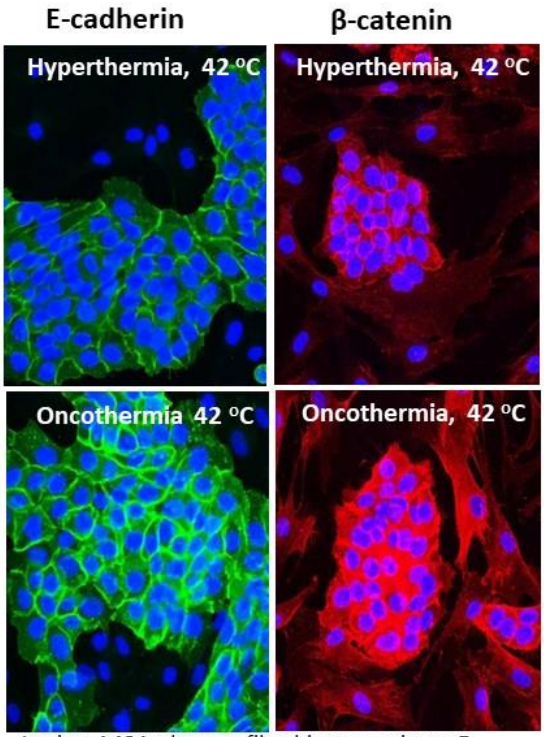
Yang K-L, et.al. (2016), Oncotarget, doi: 10.18632/oncotarget.11444

Challenges in invasion/dissemination



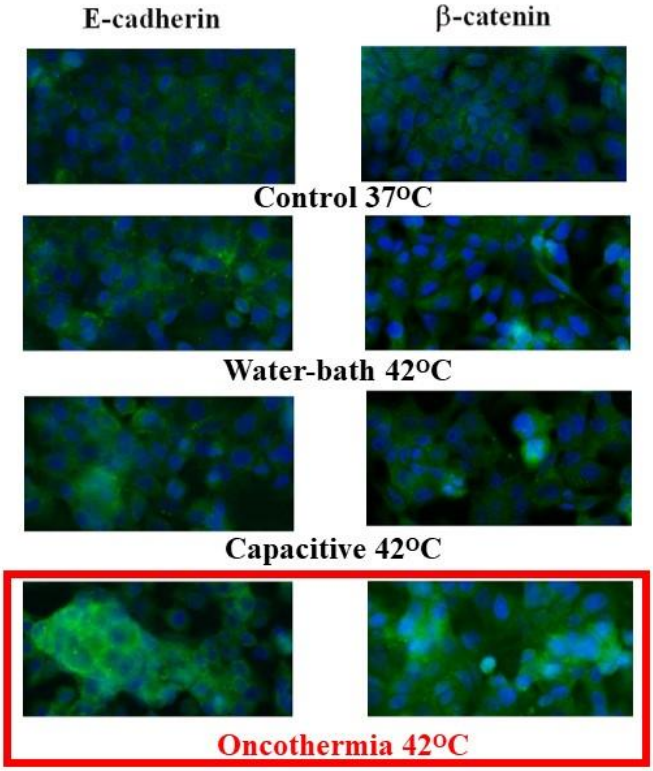
Malignant autonomy

Block the invasion and dissemination



In vitro A431 + human fibroblast co-culture, E-cadherine and β-catenin; 24h after the treatments

Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148–165



Yang K-L, Huang C-C, Chi M-S, Chiang H-C, Wang Y-S, Andocs G, et.al. (2016) In vitro comparison of conventional hyperthermia and modulated electro-hyperthermia, Oncotarget, oi: 10.18632/oncotarget.11444

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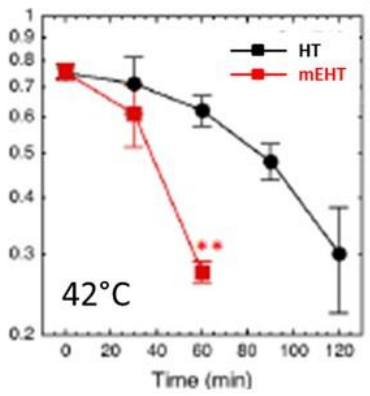
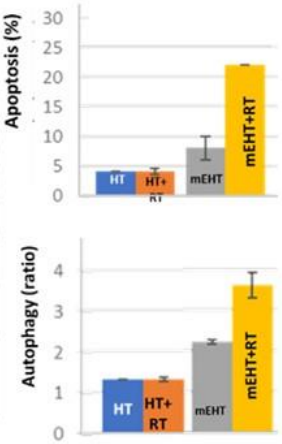
Radiation with mEHT

In vitro SCCVII (SCC7), a mouse head and neck carcinoma cell line

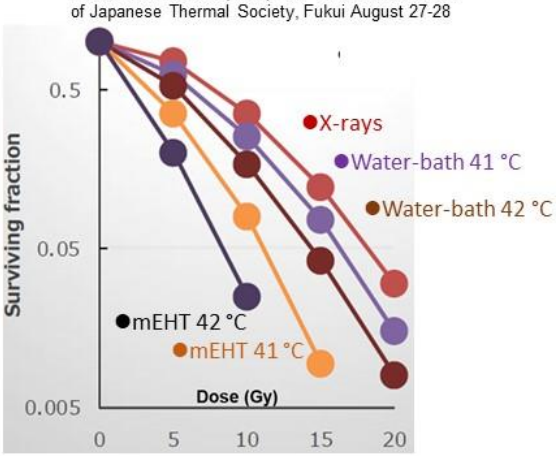
Airi OTA et al.(2017) Conf. JHA of Cancer



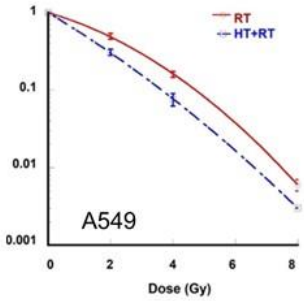


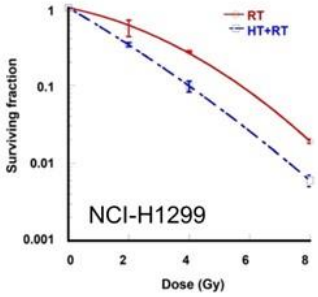
In vivo oral-cancer (SAS) cell-line

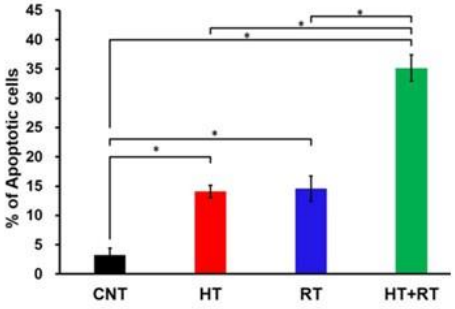
Matsumoto Y. et al. (2018), 35th Annual conference of Japanese Thermal Society, Fukui August 27-28



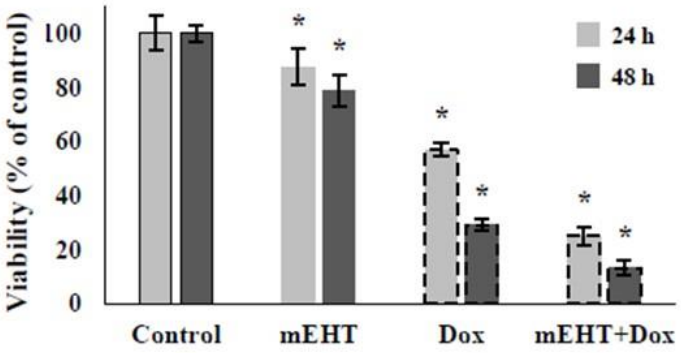
In vivo lung tumor (A549 and HCI-H1299 cell-lines; Bibin Prasad, et al; (2019); Scientific reports *9:3942;* www.nature.com/scientificreports

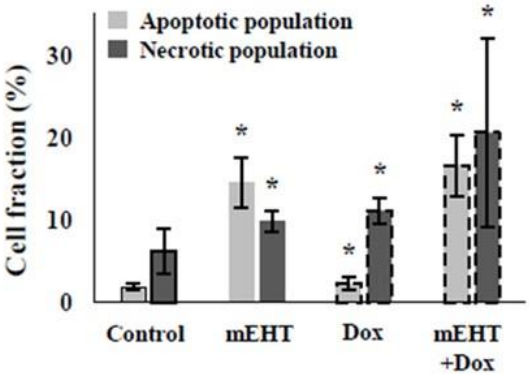






mEHT with doxorubicin chemotherapy (Poster P01)





Vancsik T et al (2019) Modulated electro-hyperthermia induced p53 driven apoptosis and cell cycle arrest additively support doxorubicin chemotherapy of colorectal cancer *in vitro,*

Thank you very much

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associate professor

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