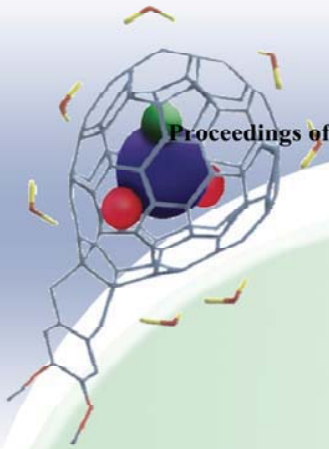

Book of Abstracts

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Effect of local sonication on biological distribution of micellar Doxorubicin: In vivo study

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Goals: To overcome side effects of *Doxorubicin* administrated systemically, nanosized polymeric micelles formed by *Pluronic P-105* copolymer were used in combination with dual frequency ultrasonic irradiation. Then *Doxorubicin* distribution in murine breast adenocarcinoma model was assessed. These micelles release drug because of acoustic cavitation which is enhanced in dual frequency ultrasonic fields.

Background: The systemic administration of many anticancer agents often results in an unsatisfactory therapeutic effect because of the narrow therapeutic window of these drugs. Nanosized colloidal drug carriers such as polymeric micelles have been shown an increased accumulation in tumors via the *EPR (*Enhanced Penetration and Retention*)* effect and the exposure of chemotherapeutic drugs to healthy tissues is reduced.

Methods and Materials: In order to be a drug carrier, Pluronic micelles require stabilization to prevent degradation caused by dilution accompanying *IV* injection. These micelles have a spherical, core-shell structure. To form micelles *Pluronic P-105* copolymer was used and *Doxorubicin* was physically loaded into stabilized micelles (*d~14nm*). To increase cavitation yield, a *3 MHz* sonication system with intensity of *2 W/cm*^{2} and a *28 kHz* system with intensity *0.04 W/cm*^{2} were used (I_{SATA}). The spontaneous tumor of breast adenocarcinoma in *Balb/C* mice was used which was histopathologically verified for type and grading. In this study, sixteen adult female mice were randomly divided into four groups as control, *Doxorubicin* injection, micellar *Doxorubicin* with sonication and micellar *Doxorubicin* without sonication. When the tumor diameter was in the range of 8-10 mm, except control group, animals were injected with a dose

of 0.03 mg of *Doxorubicin* or micellar *Doxorubicin* and the sonication group was irradiated with above protocol 20 min after injection. 24 h after injection, animals were sacrificed and their tumor, heart, spleen, liver, kidneys and plasma were separated and homogenized. After some biochemically procedures, using *UV-VIS* spectrometry, their drug content was extracted as their fluorescence light; 350nm excitation and 560 nm emissions that determined previously for *Doxorubicin*. For each tissue, a standard curve of drug in that tissue was obtained and drug content in each tissue was obtained from the standard curve in mg.

Results: The results show that in micellar *Doxorubicin* with sonication group, drug concentration in tumor tissue was significantly higher than other groups (more than six times of *Doxorubicin* injection group and more than two times of micellar *Doxorubicin* injection group without sonication). Drug concentration in other tissues studied was significantly lower in micellar *Doxorubicin* with sonication group relative to the other two groups (0.3-0.5 times of *Doxorubicin* injection group and micellar *Doxorubicin* injection group) ($p\text{-value}<0.05$).

Conclusion: It was concluded that sonication with dual frequency sonication protocol that was physically showed an enhanced cavitation activity, results in a higher drug uptake in tumor tissue due to drug release in tumor via cavitation and enhanced tumor uptake from *Doxorubicin* due to sonoporation. This system of drug delivery causes an increased treatment gain and reduced systemic side effects due to drug uptake in other tissues. One of the merits of using ultrasound as a drug activator is non-ionizing nature of these waves which enables them to be used in different conditions.

Keywords: Acoustic cavitation, Sonoporation, Breast adenocarcinoma, Doxorubicin, Polymeric micelles