

PhD Project Description

School/Department:	Department of Pathology Erasmus MC
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Project Title:	Evaluation of immune stimulatory effect of heat and chemotherapy in hyperthermia triggered drug delivery
Abstract:	<p>Liposomes have shown great capability in formulation, reduction of side effects and enhancing pharmacokinetics of chemotherapeutics by stable encapsulation of chemotherapeutics and long circulating properties. However, effective drug delivery at the cellular level by means of such preparations is still unsatisfactory (1-3). One promising approach is using spatiotemporal drug release by means of liposomes with the capacity for content release triggered by internal or external stimuli (1). Among different stimuli, interests to application of external heat, hyperthermia, is getting more attention and by means of advanced liposomal preparations and heating technologies high level of control over application of heat and drug release could be achieved. Mild hyperthermia (41-43 oC) not only can enhance drug delivery by triggering the release or increasing permeation and distribution of drugs into tumor interstitium (4) but also sensitizes tumor cells to the therapy. In addition to these local mild hyperthermia can also induce immune responses that could be used against tumor. On the other hand most of the commonly used cytotoxic chemotherapeutics also invade tumors by inducing immunologic cell death. In fact, this is under argue whether the direct toxic effect of chemotherapeutics is responsible for the antitumor effect or it is the induced immune response that eliminate cancer cells. Therefore, in treatment of tumor by temperature sensitive liposomes (TSL), there are two different stimuli that stimulate immune response by different pathways and importantly different timings. While in our previous studies we enhanced the antitumor activity of TSL+ hyperthermia by optimizing liposomal preparations or heat application (5-8) in this project we want to evaluate how immune system could be harnessed in favor of tumor regression and not tumor growth and progression. We argue that immune responses induces by each arm may interfere with each other and therefore, their combination may not necessarily be synergistic or even additive. For example while immunogenic cell death mediated by therapeutic agents is in favor of anti-tumor immune response, suppression of immune system followed by administration of high dose of chemotherapeutics may results in opposite responses favoring tumor growth. Therefore, knowing the pathways, mediators and timing of immune</p>

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	<p>responses provoked by these stimuli and when combined with each other enable proper control over treatments of tumor. Additionally, knowing these pathways suggests what kind of immunomodulatory agents can boost the overall therapeutic effect and to achieve such impact when is best to prescribe. In this project we want to evaluate the local and systemic immune reactions followed by treating mouse model of melanoma tumor by either local mild hyperthermia alone or TSL containing doxorubicin or idarubicin plus local application of heat. And later improve the therapeutic activity by adjusting drug dose, dose schedule, duration of hyperthermia and finally using immune modulators. This could be done in two in vitro and in vivo settings using protein analysis techniques such as SDS-PAGE, western blotting and proteomic analysis. immunohistochemistry analysis of treated tumors, confocal microscopy and intravital imaging.</p>
Requirements of candidate:	<ul style="list-style-type: none">• We are looking for a highly motivated, hardworking student to join our very international team. Our strength is in using team work to tackle large scientific questions and thus requires a student with good communication skills.• Master degree or MD• Scholarship that will, at least, cover subsistence allowance and international air plane ticket (we could help with the scientific part of your scholarship proposal)• English language requirement:• <i>English speaking countries & Netherlands:</i> no requirement• <i>Other countries:</i> IELTS 7.0 (<i>min 6.0 for all subs</i>), TOEFL 100 (<i>min 20 for all subs</i>)

Application requirements & Deadlines:

<https://www.eur.nl/en/about-eur/erasmus-university-china-centre/csc-scholarship>

Erasmus MC, ranked world

* No.32 for Clinical Medicine US News 2020:

<https://www.usnews.com/education/best-global-universities/clinical-medicine?page=3>

* No. 30 Nature Index for Biomedical Sciences 2019:

<https://www.natureindex.com/supplements/nature-index-2019-biomedical-sciences/tables/healthcare>