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Seventh international symposium on Neutron Capture Therapy for cancer

September 4-7, 1996, Zurich

The Symposium was organized by the Paul Sherer Institute and University of Zurich on behalf of the International Society for Neutron Capture Therapy and has gathered some 300 scientists and clinicians from some 30 countries. Due to the very selected topic of the symposium, the majority of the presentations either oral or posters were devoted to different aspects of Neutron Capture Therapy (NCT). The scientists were gathered dealing with physical, chemical, biological and clinical problems associated with NCT.

In its principle NCT is bimodal therapy. It is based on selective accumulation of the agents which become cytotoxic only when activated by some form of radiation. Therapy could be confined to the chosen region of the activating irradiation, independent of the distribution of the targeting agent. The best known example of this principle is boron neutron capture therapy (BNCT). The beginnings of BNCT are in 1936 when Lochner suggested that neutron capture reaction on boron-10 could be used in cancer treatment. Boron-10, which is a stable isotope could be linked or incorporated into a substance that has affinity to the tumor cells and the tumor area irradiated with thermal neutrons. The neutron capture reaction in boron leads to the prompt emission of lithium and helium particles, which release their kinetic energy with less than 10 mm from the reaction site. Hence, if boron carrier with high tumor-specific uptake can be found, this technique may provide a "magic bullet" that kills only the tumor cells with boron uptake, while sparing the surrounding boron-free healthy tissue.

According to these principles of NCT it is evident which are the major obstacles to broader clinical application of the therapy. Major problems are tumor targeting of the boron-10 containing substances and their activation with adequate neutron sources.

From the centers that are involved in NCT Japanese have the most experience. They have performed already several clinical trials and demonstrated that NCT is feasible for treatment of neuroblastoma and malignant melanoma tumors. Following their pioneering work, centers in USA and in Petten in Europe have done a lot of work in this field, which has or will soon lead into the treatment of the first patients on trans-national scale. However, except these reactors already mentioned there are 11 centers all around the world that have pursued to start with the NCT. Slovenia is also one of them, preparing the TRIGA Mark II reactor for the NCT studies. The aim of the project is to develop some new approaches in targeting the boron-10 containing substances to the tumors, in order to increase therapeutic gain of the NCT.

New developments in preclinical studies on NCT are according to the reports on the symposium in the fields of biology, chemistry and physics. Biology of the NCT is largely dependent on biodistribution of boron containing substances. One of the directions mentioned was to search for new compound that are more specific for tumor cells, such as the boronophenylalanine (BPA). This is a substance that is specific for the melanoma cells, but the problem with the substance is that it is not readily soluble. Therefore, new analogues are sought to find the analogue with high water solubility and good specific accumulation in tumor cells. In treatment of glioma tumors sulfhydril boron hydride (BSH) is already well established. It is well water soluble but still there is not enough its accumulation in the tumor tissue. In order to increase the boron uptake in the brain tumors new strategies are sought. On of them is to invasively approach with intracerebral infusion. This approach was already reported, but with limited success, because distribution within the tumors was not even. The other invasive approach is to disrupt blood brain barrier, which is the major limiting factor for the delivery of boron compounds into the brain tumors. Another possibility is to inject substances into carotid

artery. The pharmacological approach could be to incorporate the boron containing substances into the tumors, or to search for smaller molecules. Neither of the two approaches has produced any positive results. Biology in NCT is directed also to radiation oncology. Predictive assays for the NCT studies are highly needed. Unfortunately in this field, similarly as in radiation biology, many attempts were undertaken but with limited success. Important are also imaging assays, to develop a system that would with high accuracy detect boron distribution in the tumors. This is important because relative biological effectiveness of NCT is proportional to the boron content in the tumors. Some computer programs, coupled to boron detection in the tumors *in vivo*, are already operable. These programs help with treatment planning of the patients and are in essence similar to classical treatment planning in oncology. Very few were the contributions from the field of molecular oncology in NCT. Fortunately our contribution of dr. Đ. Novak was one of them. She has produced monoclonal antibodies with high specificity to breast carcinoma cells, with cross reactivity for melanoma cells. These monoclonal antibodies coupled with BSH proved to be very effective in targeting boron to tumor cells, and also proved effective in NCT study *in vitro*. It was stressed in the symposium that it is necessary to attract more molecular biologists and radiobiologists into the field to further develop this new treatment modality.

In the field of chemistry there were few original contributions. Therefore in the concluding remarks it was stressed that this is the field that is not developing fast enough, and does not follow the needs of the NCT. Search for the analogues of the already known compounds continues, as already mentioned, but there is little effort put into development of new compounds that would be specific also for other tumors.

In the field of physics the following topics were discussed: neutron sources (reactors, accelerators, cyclotrons), dosimetry and microdosimetry, dose planning. The requirements for an acceptable neutron source for NCT are rather scarce in terms of the need to provide sufficient epithermal neutrons (0.4 eV to 10 KeV, flux 0.84 x 10^9 nepi/cm^{2}sec^{-1}) to a patient's accessible location in a reasonable time with minimal thermal neutrons, fast neutrons or gamma ray background. Besides the epithermal neutrons from high flux reactors applied for the medical treatment, thermal neutrons from the much smaller and less expensive low power research reactor (as TRIGA Mark II 250 KW) have an important role in the further development and application of NCT, was stressed in concluding remarks. The research group from Finland reported how they succeeded to adapt TRIGA Mark II research reactor. The neutrons are moderated into the epithermal range using a patented material. The facility does not have any beam shutter between the core and the moderator, so the output of the beam always follows the power of the reactor. Therefore, the alternative looks as follows: simple, cheap, safe reactor of low power with expensive filter or powerful, expensive and potentially more dangerous reactor with simple and cheap filter. For reasonable choice between these variants a deeper technical and economical study is necessary. In the poster session our research group from TRIGA Mark II reactor presented the development of the radiation facility using Monte Carlo simulation code MCNP4A. With information on symposium our project team is encouraged to continue the research with small program corrections.

Clinical aspect of NCT was dominated by the groups that already perform NCT studies. Japanese groups have the treatment already as established treatment modality and are therefore leading groups in this field. They treat both, glioma and melanoma patients, with high success rate. However, the success of the treatment is still not very convincing compared to standard radiotherapy treatment. They have demonstrated that in treatment of malignant melanoma patients they have more success than with glioma patients, especially because the tumor lesions are easier to access with radiation in melanoma patients than in glioma patients, and because of the development of the BPA substance that is highly specific for melanoma cells. The American groups have so far treated 19 cases of glioma tumors. Therefore, their experience in NCT is much smaller, but their clinical trials are more strict and well planned. The discussion about the fractionation in NCT is contradictory. The American groups argue that fractionation is not necessary, however the European study has foreseen in protocol fractionation. In Europe first clinical trial will begin soon in EORTC protocol as phase I clinical trial. Before the first patients will be irradiated in Petten, pharmacological studies on BSH in patients have been done. The purpose of the trial is to treat glioma patients from several centers in Europe in Petten. After tedious administrative obstacles, which

have been overcome lately, the first patients are scheduled to be irradiated in Petten by the end of this year. Slovenia has not succeeded to enter into the phase I trial, but will most probably enter the phase II trial and send some of their patient to be treated in EORTC protocol.

In conclusion, the developments in NCT are predominantly in radiophysics, radiobiology and treatment planning, however less in the chemistry. The NCT is still in its developmental phase but is attracting many new scientists that feel this is an topic which has perspectives. In the light of this developments, also Slovenian project has high hopes to contribute some insights into NCT. We all hope that in the next meeting in USA in 1998, progress in NCT will be seen.

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