RADIOBIOLOGY WITH DNA LIGANDS

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LABELLING OF DNA LIGANDS AND OTHER TUMOUR-AFFINIC COMPOUNDS WITH 4.15-d ^{124}I

Halogenated pyrimidine nucleosides are useful for studying the metabolic pathways of pyrimidine nucleoside incorporation into DNA and RNA for measuring cell proliferation. Thus, in cooperation with the PET program, [^{124}I]5-Iodo-2'-deoxyuridine ([^{124}I]-IUdR) was labelled routinely for PET investigation of brain tumours.

The radiochemical quality control of about 20 syntheses, measured by both TLC and HPLC, showed that the overall yield is between 65 and 75 % and that the amount of *in vitro* cleaved ^{124}I does not exceed 7 % before injection. The long-term stability showed the following trend: 1 day after synthesis the metabolites on average displayed a 1 % increase in ^{124}I activity, the later increase was smaller. In the course of the trial, concentration-dependent radiolytic effects were found which reduced the yield. Consequently, the solution volume was kept at not less than 8 ml. In the following, the purity could be enhanced to more than 95 %.

Hoechst 33258 and 33342 are bisbenzimidazoles with high affinity to the A-T base pairs of DNA. When labelled with a short-range radioactive or activable nuclide and transported into the cell plasma, both at-tach very rapidly to DNA and are stably bound to its small groove. The extremely close proximity of DNA and the Auger electron emitting nuclide should pro-duce high-LET double strand breaks which affect the cell proliferation.

For the first time, both compounds were labelled with ^{124}I by the method mentioned above; the radiochemical yield being > 95 % for both compounds, before ster-ile filtration. For biological comparison, they were also labelled with ^{125}I and ^{131}I. The introduction of the IodoGen method markedly improved the yields and gives access to a large-scale routine production of radioiodinated Hoechst compounds for *in vitro* and *in vivo* investigations.

A so far unsolved problem in Boron Neutron Capture Therapy (BNCT) is the quantitative information about the distribution of boronated drugs in the living body. Radioimaging techniques could solve this problem. Since no radioisotope of boron is suitable for *in vivo* imaging of tumours, however, the boronated drugs must be slightly modified, by introduction of a longer-lived positron emitter like ^{124}I. Consequently, [^{124}I]Iodoboronophenylalanine ([^{124}I]IBPA) was labelled for the first time for potential application in BNCT.

The labelling yield is around 50 %. The borono group proved to be a steric hindrance factor for labelling but not as strong as expected. After determination of the labelling position, this compound may be dispensed to several BNCT groups.

Tyrosine has a high affinity for a transport system in the blood-brain barrier, and this affinity remains when tyrosine is iodinated. Thus, radioiodinated tyrosine derivatives might be useful for functional tumour imaging, and we synthesized L-3-[^{124}I]iodo-α-methyl-tyrosine ([^{124}I]IMT) by the same method. The yield is > 80 % and reflects the reported data remarkably well. [^{124}I]IMT can be produced without difficulties for clinical studies.

RADIOTOXICITY OF HOECHST 33258 AND 33342 AND OF IODINATED HOECHST 33258 IN CELL CULTURES

We previously reported that treatment with the DNA-binding bisbenzimidazoles Hoechst 33258 and Hoechst 33342 can affect the radiosensitivity of tumour cell populations depending on concentration and tumour type. This effect could be important because the DNA is believed to be the ultimate and most important target for radiation. Thus, our aim is to examine possibilities for damaging the DNA in tumour cells by short-range Auger electrons while effectively saving normal cells.

In the present study we used Hoechst 33258 and Hoechst 33342 labelled with 4.2-d ^{124}I, 60-d ^{125}I, and inactive iodine, the human adenocarcinoma cell line Du 145 from prostate and nontransformed fibroblast hamster cells, V79. The cells were grown as monolayers in Optimen medium plus 10% fetal calf serum and antibiotics at 37° C, in 5% CO_2 air. The effect of non-iodinated and iodinated Hoechst 33258 on the cell growth was similar at a concentration range from 0.9 to 9.0 mM. Both derivatives stimulate the cell growth of each cell line and are radioprotectors. The uptake of the dye was very rapid (30-60 min) into all cell lines that were studied and remained in the cells for at least one week.

The fluorescence remained constant only during the first four days, before the cells became confluent or began to detach from the growing surface. The retention of the Hoechst compounds was sufficiently strong to allow cell sorting and microscopic observation several days after treatment.

The ^{124}I and ^{125}I activities were measured with a microplate scintillation TopCounter. The cells were cultivated in a 96-well microplate and pulsed with

1 - 3 mCi for 2h. Than the supernatant was transferred to another microplate. The scintillation cocktail was dispensed in the microplates and the plates were sealed and counted on a TopCount immediately after incubation time (3h, 6h and 24h) .

Attached cells in logarithmic phase of growth, 15-25x10^3 per well (well area 1.3 cm^2) were exposed to Hoechst 33258, Hoechst 33342 and IodoHoechst 33258 (3µg/ml) in 24-well plates under standard culture conditions, at 37 °C for 2h. After the treatment, the cells were carefully washed once with warmed PBS. Then the plates were analyzed for fluorescence while cells were covered with medium. After this treatment, the cells were maintained in a drug-free, complete culture medium for 5 days without additional medium change. Every 24 h duplicate samples were withdrawn: the cells of one plate were detached with trypsin/EDTA for counting the total cell number, and the cells of the other plate were fluorometrically analyzed by a Cytofluor reader (Millipore), which gave a printout of fluorescence per well. Excitation wavelength of the reader was 365 nm with an emission filter collecting fluorescent light in the band 460 nm for the Hoechst compound, 530 nm excitation and 590 nm emission for Propidium Iodide.

It could be shown that the radioactivity of the conjugates remained cell-associated for more than 48 hrs. The labelled IodoHoechst was internalized more slowly into cancer cells than into hamster fibroblasts and remained there longer. This may be explained by the shorter cell cycle. The growth decrease of treated cells after 72 hours of incubation was interpreted as cell inactivation due to energy deposition in the cellular DNA. It is known that bisbenzimidazoles attach to the DNA in a very stable form and cause double-strand breaks there.

We investigated the different behaviour of ^{124}I and ^{125}I at the level of cell growth decrease. Preliminary experiments showed that, after the same incubation period, the [^{124}I]IodoHoechst 33258-labelled cells displayed higher radioactivity in fibroblasts than the cells labelled with the Hoechst 33342 derivative. This effect is opposite in Du 145 cancer cells. Differences were also found in the uptake of unlabelled H 33258 and H 33342 in the cell lines: V79 cells showed a strong difference in the uptake of both IodoHoechst derivatives whereas cancer Du 145 cells did not. This may be interpreted as specificity of the IodoHoechst compounds for tumour cells.

The radiotoxicity of [^{124}I]IodoHoechst proved to be similar to that of the ^{125}I derivative. In conclusion, the results demonstrate that the radioactively labelled bisbenzimidazoles [^{124}I]- and [^{125}I]IodoHoechst were capable of sterilizing cultivated tumour cells. This effect can be interpreted as radiobiological effectiveness of Auger electrons.

PREPARATION OF ^{76}Br-, ^{123}I-, AND ^{211}At-LABELLED 5-HALO-2'-DEOXYURIDINE

7.2-d ^{211}At is of potentially high radiobiological effectiveness within a range of a couple of cell diameters. Thus, we tried to label a DNA ligand with ^{211}At, under reaction conditions which are generally known from its homologous elements bromine and iodine. ^{211}At was prepared at the PSI Injector I cyclotron via the nuclear reaction

$$^{209}Bi(\alpha,2n)^{211}At$$

by irradiation of bismuth metal prepared onto a tantalum backing, with 28 MeV α-particles, followed by thermodistillation of the formed ^{211}At. The yield of 18.5 MBq/µAh (0.5 mCi/µAh) known from literature could be confirmed. The labelling was accomplished by oxidation of the halogenide with Iodogen for ^{123}I and ^{211}At, and with Chloramine-T for ^{76}Br, followed by halodestannylation of 5-trimethylstannyl-2'-deoxyuridine. The reaction takes 1 minute, the labelling yield with all three radiohalogens being > 90 %. Our method is faster than reported in the literature and easy to perform so that this reaction may be used in radiobiological routine investigations.

CHEMICAL SYNTHESES OF BORON DERIVATIVES OF HOECHST 33258. III.

The aim of our work is the preparation of carborane derivatives of Hoechst 33258, useful for boron neutron capture therapy (BNCT).

In a multistep synthesis, all intermediate compounds could be synthesized in high yields. The obtained carborane derivative, however, was synthesized only in traces. The reason for this may be decomposition effects. Using a completely new route, the synthesis could be performed under more mild conditions. MS and ^{11}B-NMR of the desired compound and in all intermediate steps are in agreement with the expected structures. To date, purification on a preparative scale employing chromatography techniques is in development. In parallel, new Hoechst 33258 derivatives labelled with o-carborane will be synthesized in cooperation with the University of Zurich.

GADOLINIUM NEUTRON CAPTURE THERAPY

A further topic of the NCT-DNA ligand programme is the development of macrocyclic Gadolinium-Hoechst conjugates. Their radiobiological potential is based on the high neutron capture cross-section of ^{157}Gd (255'000 barn, 66 times that of ^{10}B) and of the range of Auger electron cascades in the order of DNA dimensions.

The actual work consists in the preparation and purification of several macrocyclic ligands which form stable non-ionic complexes with Gd^{3+} and which may be coupled either to Hoechst intermediates by convergent synthesis routes or to the final Hoechst derivatives, respectively. In the last step, the complexation of Gd in the macrocycles will be performed.

TEACHING ACTIVITIES AND PUBLICATIONS

TEACHING ACTIVITIES AND LECTURES

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N.E.A. Crompton: *"Rapid characterization of cell specimens from cancer patients".* Tumor Biology and Treatment Workshop, PSI, 15.1.96.

N.E.A. Crompton: *"Prediction of cytotoxic therapy response: apoptosis, nekrosis and p53 in tumor and healthy tissue".* Gynäkologische Forschung Seminar. Unispital Zürich, 23.1.96.

N.E.A. Crompton: *"Massively frequent radiation events, instability in the genome, and another advantage of proton therapy".* Biochem. Zellbiol. Kolloquium. PSI, 28.2.96.

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N.E.A. Crompton: *"Telomere: Funktion bei Altern und Krebs".* Gynäkologische Forschung Seminar. Unispital Zürich, 5.11.96.

N.E.A. Crompton: *"A rapid, sensitive assay of intrinsic radiation response based on apoptosis in human CD4 and CD8 T-lymphocytes".* Seminar. Bundesamt für Strahlenschutz, München, Germany. 19.11.96.

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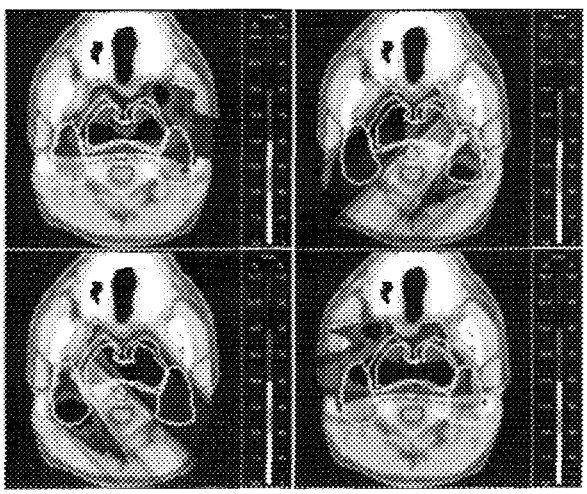
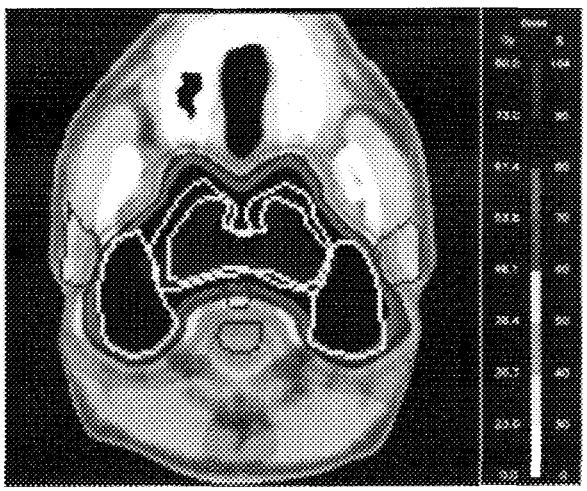
3-d intensity modulated plan for a nasopharynx tumour

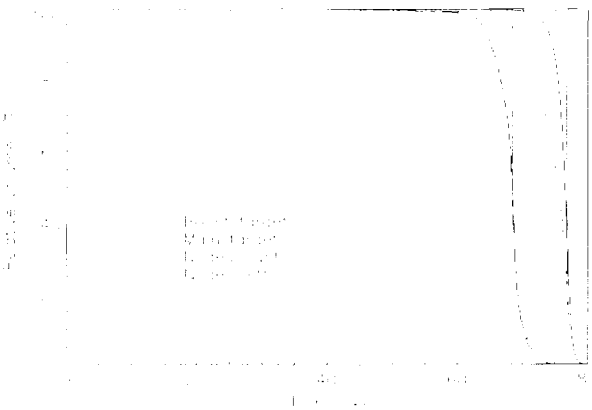
- Inner target prescription dose 76,8 Gy (yellow outlines)
- Outer target and nodes, 68.4 Gy (yellow outlines)
- Critical structures, brain stem and parotid glands (red outlines)
- Four field plan - right and left, lateral and posterior oblique fields



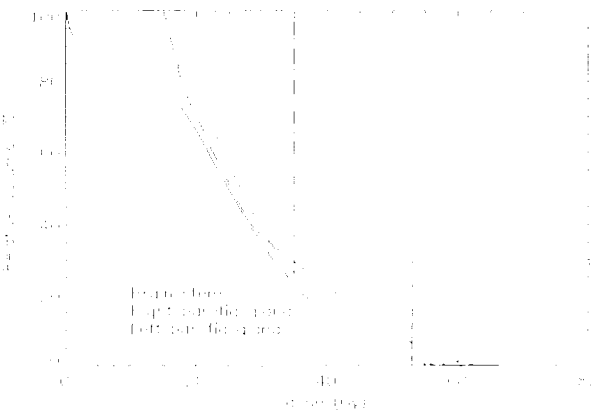
Individual fields clockwise from top right: left posterior oblique, right posterior oblique, left lateral, right lateral.



Resultant dose distribution for all field



DVHs for all target VOIs. Vertical lines indicate the prescription doses. Solid line - boost volume; broken line - main target and nodes.



DVHs for the brain stem and parotid glands Vertical lines indicate dose limits. Solid line brain stem (to centre); broken line - parotid glands (dose limit to 50% of volume)

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