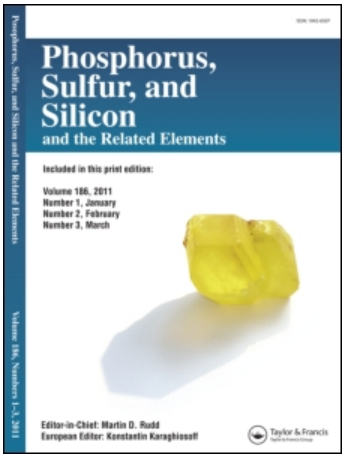

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Cyclophosphazenes and Relatives as Anticancer Drugs

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CYCLOPHOSPHAZENES AND RELATIVES AS ANTICANCER DRUGS

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Aziridinocyclophosphazenes $N_3P_3Az_6$ (code name MYKO 63), $N_4P_4Az_8$ (code name MYKO 83) and relatives constituted the first generation of anticancer drugs whose efficiency on several rodent neoplasms was made conspicuous in a quantitative manner from 1976 to 1978 both in our Laboratory and by EORTC Screening Pharmacology Groups[1]. MYKO 63 appeared at that time as a promising drug for industrial development owing to its wide spectrum of activity and its very low mutagenicity[2]. However, this hope failed as a consequence of a cumulative toxicity which occurs upon heavy polyinjections schedules. In other words, MYKO 63 exhibits an uncomfortable kinetics of action on the tumor - and, consequently, of excretion - presumably due (it was our assumption) to a too high chemical stability of the molecule.

Thus, by using our knowhow about electronic structure and relative stability of inorganic systems as calculated by quantum chemistry[3], we could design suitable derivatives of MYKO 63 without any cumulative toxicity by replacing endocyclic P atoms by S atoms step by step. Pentaziridinocyclodiphosphathiazene $N_3P_2SO_4X$ (code names : SOF for X = F, SOPHi for X = Ph and SOAz for X = Az) were found in this way as exhibiting antitumor properties quite similar to the ones of MYKO 63 without any significant cumulative toxicity[4]. These results were patented by ANVAR on July 4, 1979 (Patent n° 79-17336, World extension July 4, 1980)[5] and licensed to OTSUKA Chemical Co. (Osaka, Japan) and Roger BELLON SA (Paris, France) within a joint-

venture. The pre-clinical file, including acute + sub-acute + chronical toxicity on rats + dogs + monkeys, anatomo-pathology, pharmacokinetics, mode of action, absorption, distribution, excretion, xenographs, nature of metabolites and so on, was achieved by industrial partners for SOAz. Parallely, we were in charge of investigating X-Ray structures of the various drugs from genuine and clathrated single crystals[6], way of fragmentation by mass spectrometry[7], real conformations in physiological serum both by Raman spectroscopy[8] and by micro-computing systems[9] as well as sites of interaction on DNA[10]. The biological behaviour of SOAz was also studied in vitro and in vivo versus constituents of malignant cells membrane (neutral and acidic phospholipids, glycoproteins), oligo-elements (Cu,Zn) of cytoplasm and several antigens and haptens.

Then, Phase I human trials could be performed[11] showing that the MTD (maximal tolerated dose) value under single injection protocols is equal to 8 mg/kg for humans. These human tests indicated that SOAz does not induce any nephro-, hepato- and/or cardio-toxicity, any necrosis or phlebitis when injected by intra-veinous route, any alopecia or nauseas or diarrheas, the unique penalizing side-effect for SOAz being thrombopenia. Phase II human trials are now in progress for evaluating the best directions for its use in clinics.

Whatever the potentiality of SOAz as anticancer agent is, pharmacokinetics proved that 60% of the amount of drug injected to animals and humans is excreted through urins (without any metabolization) during the 24 hours after injection. In other words, a large part of the drug does not reach the tumor and is actually spread out all over the body without any therapeutical efficiency.

Thus, the driving idea we got early 1982 was the following: would it be possible to increase the specificity of our drugs to-

wards malignant cells in targeting them through suitable covalent linkages to some molecular vectors (rockets) having a very high affinity for some components of such cells.

New vectorized anticancer drugs were prepared in this way and tested successfully by EORTC on standard rodent tumors : the rate of the amount of drug injected which reaches the tumor is indeed 60 times larger than for SOAz and therapeutic index TI of the new drugs, defined as the ratio of the highest non-lethal dose, LD_0 , over the minimal dose giving a significant activity, is about 15, that is exceptionally large.

The determinant role of the vector is made conspicuous when comparing proper activities of "drugs themselves" to the ones of the vectorized drugs. The targeting benefit through such vectors is then clearly demonstrated.

This discovery was covered on November 25, 1982, by the CNRS patent n° 82-19768[12].

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