Final Progress Report for Grant Number DE-FG02-93ER61657

Receptor Specific Ligands for Spect Imaging
Dr. Hank F. Kung, Principal Investigator
University of Pennsylvania

Attached is the text for DOE report:

In past funding period we have concentrated in developing new ^{99m}Tc labeled MIBG analogs. Basic chemistry of ligand synthesis, radiochemistry of Re and ^{99m}Tc complex formation, separation of stereoisomers and *in vitro* stability were investigated. We have prepared a number of new MIBG derivatives containing chelating moiety N2S2 and additional groups to increase lipophilicity. Unfortunately none of the new ^{99m}Tc labeled MIBG analogs showed promise as an imaging agent for myocardial neuronal function. Radioactive-iodine-labeled meta-iodobenzylguanidine (MIBG) is currently being used as an *in vivo* imaging agent to evaluate neuroendocrine tumors as well as the myocardial sympathetic nervous system in patients with myocardial infarct and cardiomyopathy. It is generally accepted that MIBG is an analog of norepinephrine and its uptake in the heart corresponds to the distribution of norepinephrine and the density of sympathetic neurons. A series of MIBG derivatives containing suitable chelating functional groups N2S2 for the formation of $[\text{TcVO}] + 3\text{N2S2}$ complex was successfully synthesized and the ^{99m}Tc -labeled complexes were prepared and tested in rats. One of the compounds, $[\text{99mTc}]\text{M2}$, tested showed significant, albeit lower, heart uptakes post iv injection in rats (0.18% dose/organ at 4 hours) as compared to $[\text{125I}]\text{MIBG}$ (1.4% dose/organ at 4 hours). The heart uptake of the ^{99m}Tc -labeled complex, $[\text{99mTc}]\text{M2}$, appears to be specific and can be reduced by coinjection with nonradioactive MIBG or by pretreatment with desipramine, a selective norepinephrine transporter inhibitor. Further evaluation of the *in vitro* uptake of $[\text{99mTc}]\text{M2}$ in cultured neuroblastoma cells displayed consistently lower, but measurable uptake (app. 10% of that for $[\text{125I}]\text{MIBG}$, see Appendix 11). These preliminary results suggested that the mechanisms of heart uptake of $[\text{99mTc}]\text{M2}$ may be related to those for $[\text{125I}]\text{MIBG}$ uptake. To improve the heart uptake of the MIBG derivatives we have developed chemistry related to the preparation of new ligands, M4 and M5. The radiolabeling was successful, but the biodistribution of the new MIBG derivatives did not showed any improvements in heart uptake. Our effort in this area has met with only limited success. Unfortunately, the new $[\text{99mTc}]\text{labeled MIBG derivatives showed lower uptake in the heart in biodistribution study.}$

2/25/2003

DOE Patent Clearance Granted

Mark P. Dvorscak

Mark P. Dvorscak

(630) 252-2393

E-mail: mark.dvorscak@ch.doe.gov

Office of Intellectual Property Law

DOE Chicago Operations Office

5-29-03
Date