Macromolecular antineoplastic iron and platinum co-ordination compounds

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A thesis submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Doctor of Philosophy of Science.

Johannesburg, 2013

DECLARATION

I declare that this dissertation is my own unaided work. It is being submitted for the degree of Doctor of Science, in the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination in any other University.

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_____ day of _____, 2013.

ABSTRACT

Chemotherapy, while representing a vital component of cancer treatment modalities, has so far not fulfilled basic expectations with unsatisfactory cure rates and frequent relapse due to limited effectiveness of the therapeutic drugs, severe side effects and resistance problems. The platinum-containing drugs used in present clinical practice are no exception to this generalized finding. While highly effective against a small number of malignancies, they generally share in the deficiencies of other anticancer agents. To address this issue, intense research is being undertaken to develop novel platinum-compounds offering enhanced therapeutic effectiveness. To accomplish this, several new avenues of development are being pursued world-wide, and one of these involving the binding of monomeric anticancer drug systems to water-soluble, biocompatible and biodegradable polymeric carriers, was utilized in the current research. As part of the ongoing research, this dissertation demonstrates the preparation of several water-soluble polymeric carriers bearing pre-synthesized monomers aimed to anchor the platinum drug. The monomers of interest were aspartic acid, *p*-aminobenzoic acid and *p*-aminosalicylic acid derivatives; while the water-soluble carriers were polyaspartamides, prepared by an aminolytic ring-opening process of polysuccinimide. The platination agents were conjugated to the polymer backbone both *via* amine and *via* leaving-group ligands, such as dihydroxylato, dicarboxylato and carboxylatohydroxylato. In order to demonstrate the multidrug-binding capacity of the carriers, platinum complexes were co-conjugated to polymeric conjugates containing ferrocene. The *in vitro* studies against a human breast cancer (MCF-7) cell line showed IC_{50} values ranging from 48.92 $\mu g.mL^{-1}$ to 281.37 $\mu g.mL^{-1}$ for the platinum conjugates, 13.18 $\mu g.mL^{-1}$ to 149.67 $\mu g.mL^{-1}$ for ferrocene conjugates and 6.22 $\mu g.mL^{-1}$ to 83.86 $\mu g.mL^{-1}$ for platinum/ferrocene co-conjugates; and these values were on average 4 fold more active than the parent drug. The results of these

preliminary tests provide proof of the principle that polymer-drug conjugates can play a role in future cancer therapy.

I will sing to the Lord as long as I will live;
I will sing praise to my God while I have my being.
May my meditation be sweet to Him;
I will be glad in the Lord.
You are He who took me out of the womb;
You made me trust while on my mother's breasts.
I was cast upon You from birth.
From my mother's womb, You have been my God.
Bless the Lord, O my soul;
And all that is within me, bless His holy name!
Bless the Lord, O my soul;
And forget not all His benefits.

Psalm 104:33-34; 22:9-10; 103:1-2 (NKJV)

DEDICATION

To the Lord Almighty God for His unfailing love.

ACKNOWLEDGEMENTS

The author expresses his deepest gratitude to:

- The Lord Almighty God, my creator, for the gift of life.
- Professor Eberhard W. Neuse, for his extreme kindness, guidance, confidence, patience and unending encouragement throughout this project. Professor Neuse's unquenchable passion for science, incredible energy and encyclopedic style is highly communicable. To study under his supervision is a rare fortune I will forever cherish.
- Professor Robyn van Zyl, my co-supervisor, for helpfulness and tireless guidance and for the cell culture testing.
- Dr. M. Tutu, Analytical laboratory, for the atomic absorption analysis.
- Dr. Richard Mampa of the School of Chemistry for the countless NMR spectra scanned for me, and for his kindness and friendship.
- Mr. Chien Teng Chen from the Pharmacology Department for the cell culture testing.
- De Bruyn Spectroscopic Solutions for the Platinum analysis of the free drug and prodrugs.
- Research Office and the School of Chemistry of the University of the Witwatersrand for their financial assistance.
- My colleagues in the Polymer Laboratory, particularly Jacques K. Diainabo, your friendship and sense of humor will always be remembered.
- My parents for being supportive and trusting the Lord God for me to come this far.
- Families Mukaya and Simon, and friends for their love, support and their gift of prayer.
- My spiritual family, your prayers were not worthless.
- Last but not least, my beautiful wife Lydie K. Mukaya, your love, assistance and understanding will always be remembered.

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AEP	2-(2-aminoethyl)pyridine
AF	Activity factor
Asp	Aspartic acid
Calcd	Calculated
d	Day(s)
Dach-Pt	*trans*-1,2-diaminocyclohexanediaquaplatinum(II) dinitrate
DCC	N,N'-dicyclohexylcarbodiimide
DEEA	2-(diethylamino)ethylamine
DHFR	Dihydrofolate reductase
DMEA	2-(dimethylamino)ethylamine
DMF	N,N'-dimethylformamide
DMP	3-(dimethylamino)propylamine
DMSO	Dimethylsulfoxide
DNA	deoxyribonucleic acid
Dopamine	3-Hydroxytyramine (Hydrochloride)
EAB	Ethyl 4-aminobenzoate
EDA	1,2-Diaminoethane
EPR	Enhanced permeability and retention
Et_3N	Triethylamine
IC_{50}	Concentration required to inhibit 50% of the cells
ICP-OES	Inductively coupled plasma-optical emission spectroscopy
IMRT	Intensity modulated radiation therapy
MEA	2-(methoxy)ethylamine
MTD	Maximum tolerated dose
MTT	(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)
MTX	Methotrexate
NMR	Nuclear magnetic resonance
PDA	1,3-diaminopropane
1,2-PDA	1,2-diaminopropane

PEG	Poly(ethylene glycol)
ppm	Parts per million
PSI	Polysuccinimide
RNA	Ribonucleic acid
RT	Room temperature
WHO	World health organization