
Table of Contents

I. Introduction	22
1. Cancer	22
1.1 Classification	22
1.2 Hallmarks of Cancer.....	23
1.3 Epidemiology	24
2 Childhood Cancer	25
2.1 Overall incidence and mortality	25
2.2 Molecular and genetic basis	26
2.3 Treatment of childhood malignancies	27
3. Rhabdomyosarcoma.....	29
3.1 Pathology and molecular biology.....	29
3.2 Epidemiology and Outcome.....	32
3.3 Hereditary syndromes	32
3.4 Clinical Presentation and risk stratification	33
3.5 Treatment	34
4. Fenretinide	35
4.1 Pharmacology.....	35
4.2 Fenretinide-mediated anti-cancer activity: A literature summary.....	37
5 Reactive Oxygen Species (ROS).....	40
5.1 Biology and sources of reactive oxygen species and their regulation.....	40
5.2 ROS and cancer.....	43
5.3 ROS signalling	44
5.3.1 Pro-tumorigenic Role of ROS.....	44
5.3.1 Anti-tumorigenic Role of ROS	45
5.3.2 Exploiting oxidative stress as a therapeutic option in cancer.....	46
6. Endocytosis	48
6.1 Clathrin mediated endocytosis	49
6.2 Clathrin independent endocytosis	50
6.3 Caveolae-mediated endocytosis	51
6.4 The large GTPase Dynamin	51

7. Cell Death Mechanisms	56
7.1 Apoptosis.....	58
7.1.1 Morphology of apoptosis	59
7.1.2 Extrinsic Apoptosis	60
7.1.2 Intrinsic Apoptosis	61
7.2 Necroptosis.....	63
7.2.1 Morphology of Necroptosis	63
7.2.2 Molecular mechanism	63
7.3 Ferroptosis.....	65
7.3.1 Morphology of Ferroptosis.....	66
7.3.2 Molecular mechanism	66
7.4 Autophagy	67
7.4.1 Morphology of autophagy.....	67
7.4.2 Molecular mechanism	68
7.5 Methuosis	69
7.5.1 Morphology of methuosis	69
7.5.2 Molecular mechanism	70
7.5.2.1 Macropinocytosis during physiological processes.....	70
7.5.2.2 Macropinocytosis during methuosis.....	73
8 Ionizing Radiation	76
8.1 Physics and Chemistry	76
8.2 Five R's of Radiobiology	77
8.3 DNA and Chromosome Damage Repair and cell death.....	78
8.4 Radiation induced toxicity	81
8.5 Types of radiation devices and radiosensitizing agents	82
8.6. Radiation therapy in the treatment of rhabdomyosarcoma	83
Subject of Investigation	85
II. Results	86
Manuscript I	87
Introduction	89
Results	91
Discussion	98
Material and Methods.....	102
References	111

Figures and Figure Legends	115
Supplementary Data and Figures	124
Manuscript II	140
Introduction	142
Material and Methods.....	144
Results	150
Discussion	153
References	156
Figures and Figure Legends	160
III. Discussion	172
1. Activation of a distinct and non-classical cell death pathway	173
2. Trigger to the production of reactive oxygen species	173
3. Accumulation of cytoplasmic vesicles and uptake of fluid phase dyes induction	174
4. Accumulation of early and late endosomes in a dynamin-dependent manner.....	175
5. Fenretinide and radiation therapy combination enhances cell death.....	177
6. Combination with ionizing radiation, ROS-production & vacuolizing cell death.....	180
7. Conclusion.....	182
Acknowledgements	183
References	187